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sBLA Clinical Review Memorandum

Application Type	Supplemental Biologics License Application (sBLA)
STN	125742/45
CBER Received Date	December 16, 2021
PDUFA Goal Date	June 17, 2022
Division / Office	DVRPA / OVRR
Priority Review (Yes/No)	Yes
Reviewer Name	Susan K. Wollersheim, MD
Review Completion Date / Stamped Date	July 8, 2022
Supervisory Concurrence	Lucia Lee, M.D.; Team Leader CRB1/DVRPA/OVRR Maria Allende, M.D.; Chief, CRB1/DVRPA/OVRR
Applicant	BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.)
Established Name	COVID-19 Vaccine, mRNA
(Proposed) Trade Name	Comirnaty
Pharmacologic Class	Vaccine
Formulation, including Adjuvants	Each 0.3 mL dose contains 30 µg modified mRNA encoding SARS-CoV-2 spike glycoprotein, encapsulated in lipid nanoparticles (LNP)
Dosage Form and Route of Administration	Suspension for intramuscular injection
Dosing Regimen	Two 0.3 mL doses, 3 weeks apart
Indication(s) and Intended Population(s)	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 through 15 years of age
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

GLOSSARY

AE	adverse event
AESI	adverse event of special interest
BLA	Biologics License Application
BNT162b2	Pfizer-BioNTech COVID-19 Vaccine
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COVID-19	coronavirus disease 2019
EUA	emergency use authorization
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
ICU	intensive care unit
IND	investigational new drug application
LNP	lipid nanoparticle
MIS-C	multisystem inflammatory syndrome in children
NAAT	nucleic acid amplification-based test
PREA	Pediatric Research Equity Act
PT	Preferred Term
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
sBLA	supplemental Biologics License Application
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	System Organ Class
US	United States
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
WHO	World Health Organization

1. Executive Summary

On December 16, 2021, BioNTech Manufacturing GmbH, Inc. submitted a supplemental Biologics License Application (sBLA) for Comirnaty (COVID-19 Vaccine, mRNA; also referred to as BNT162b2 during clinical development and the Pfizer-BioNTech COVID-19 Vaccine as authorized under EUA) to extend the currently approved indication for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to include individuals 12 through 15 (hereafter 12-15) years of age. The primary immunization series consists of 2 intramuscular doses (30 µg each dose) administered 3 weeks apart. Comirnaty contains SARS-CoV-2 spike glycoprotein (S) antigens encoded in RNA formulated in lipid nanoparticles (LNPs). Encapsulation of the vaccine mRNA into LNPs protects the RNA from degradation by RNases and enables transfection of host cells after intramuscular delivery.

Study C4591001, the main study to support the safety and effectiveness of BNT162b2, is an ongoing randomized clinical trial which has enrolled a total of 2260 participants (1131 BNT162b2, 1129 saline placebo) 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 190 participants 12-15 years of age with those of 170 young adults 16 through 25 (hereafter 16-25) years of age (the most clinically relevant subgroup of the study population in whom vaccine efficacy [VE] has been demonstrated). Descriptive analyses of VE were also conducted in participants 12-15 years of age to evaluate the efficacy of BNT162b2 to prevent laboratory-confirmed symptomatic COVID-19 occurring ≥7 days after Dose 2 in participants without serological or virological evidence of past SARS-CoV-2 infection before and during the vaccination regimen. Planned safety analyses in all participants 12-15 years of age included evaluation of: 1) local reactions, systemic events, and antipyretic/pain medication use from Day 1 through Day 7 after each dose; 2) non-serious unsolicited adverse events (AEs) from Dose 1 through 1 month after Dose 2; 3) serious adverse events (SAEs) from Dose 1 through 6 months after Dose 2; and deaths and serious adverse events from Dose 1 through the end of the study.

Effectiveness and safety data accumulated in the study through March 13, 2021, which included median follow-up of 2 months after Dose 2, supported FDA's May 10, 2021 issuance of an emergency use authorization (EUA) for use of BNT162b2 in individuals 12-15 years of age. Following issuance of the EUA, study participants 12-15 years of age were progressively unblinded to their treatment assignment (when eligible for vaccination per national and local public health prioritization recommendations), and placebo recipients could choose to receive BNT162b2 with continued active unblinded/open-label follow-up in the study. This sBLA submission included updated efficacy analyses of COVID-19 cases accrued during blinded placebo-controlled follow-up through September 2, 2021, representing up to 6 months of follow up after Dose 2 for participants in the safety population. A total of 99.4% participants received 2 doses in the study. The median follow-up for both safety and efficacy after Dose 2 of adolescent participants in the blinded placebo-controlled period was 4.4 months. Updated safety analyses included in the sBLA submission evaluated data accumulated in both blinded and unblinded follow-up through September 2, 2021. The sBLA safety database included 1113 study participants originally randomized to BNT162b2 who completed at least 6 months of total (blinded and open label) safety follow-up after Dose 2, with a median total follow-up duration of 8.4 months.

In the planned immunobridging analysis, based on the March 13, 2021 data cutoff, the geometric mean ratio (GMR) of neutralizing antibody titers (adolescents to young adults) was 1.77 (95% CI: 1.50, 2.09), meeting the success criterion (lower bound of the 95% CI for the GMR >0.67). In the updated descriptive efficacy analyses, based on the September 2, 2021 data cutoff including a median of 4.4 months blinded placebo-controlled follow-up, vaccine efficacy after 7 days post Dose 2 was assessed. Among a total of 28 confirmed symptomatic cases of COVID-19 in the trial in participants without evidence of prior infection with SARS-CoV-2, all cases of COVID-19 were in the placebo group (n=1129), and no cases were in the Pfizer-BioNTech vaccine group (n=1131). Vaccine efficacy was 100%, (95% CI: 86.8, 100.0). There were no cases of severe COVID-19 accrued during blinded, placebo-controlled follow-up. The SARS-CoV-2 variants of concern identified from COVID-19 cases in this age group from the September 2, 2021 data cutoff included B.1.1.7 (Alpha); all cases were accrued prior to the emergence of the Delta and Omicron variants.

The safety population from the September 2, 2021 data cutoff included 1131 BNT162b2 recipients and 1129 placebo recipients 12-15 years of age with up to 6 months of safety follow-up post-dose 2 during the blinded placebo-controlled time period. During the placebo-controlled phase, the most commonly reported solicited adverse reactions in the BNT162b2 group were pain, redness and swelling at the injection site, fatigue, and headache. Adverse reactions other than solicited reactogenicity events identified from the clinical trial data include myocarditis, lymphadenopathy in regional proximity to the vaccination site, and nausea. One (1) adolescent who had myocarditis after Dose 2 of BNT162b2 had resolution of symptoms with conservative management. In the additional safety follow-up data submitted in this sBLA, between the two data cutoff dates (March 13, 2021 and September 2, 2021), there were otherwise no notable patterns between treatment groups for specific categories of serious or non-serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2. There were no reported deaths or pregnancies in participants 12-15 years of age.

Despite more recent real-world evidence from the Omicron predominant period indicating decreased vaccine effectiveness and waning effectiveness against more mild COVID-19 compared to that demonstrated in clinical trials during circulation of previous variants, available evidence indicates a 2-dose series continues to provide substantial protection against more severe COVID-19 and its serious outcomes caused by currently circulating SARS-CoV-2 variants. Consequently, the World Health Organization (WHO) and national regulatory and public health authorities continue to endorse use of currently available COVID-19 vaccines for use in primary vaccination. The risk profile of Comirnaty is now informed by intensive post-authorization and post-approval safety surveillance following hundreds of millions of doses, including post-authorization safety surveillance in millions of adolescents 12-15 years of age. Post-authorization and post-approval safety surveillance and observational studies to date have not identified any new serious adverse reactions; anaphylaxis, myocarditis and pericarditis remain the important identified risks associated with Comirnaty. Based on evidence from passive surveillance and observational studies, the risk of myocarditis/pericarditis is greatest following Dose 2 of the vaccine series and is greater among males 16-17 years of age (currently included in the population approved for use of Comirnaty) compared to females and compared to older and younger males.

The clinical data submitted in this application, and benefit-risk considerations as outlined above, support approval of Comirnaty for use in individuals 12-15 years of age for active immunization to prevent symptomatic coronavirus disease 2019 (COVID 19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The table below summarizes demographic representation of study participants 12-15 years of age who enrolled in the Phase 3 portion of the ongoing study C4591001 and were randomized to a two-dose series of BNT162b2 or placebo.

Table 1. Randomized Participants 12-15 Years of Age, by Subgroup, Study C4591001

Subgroup	BNT162b2	Placebo	Total
Total 12-15 years of age	1131	1129	2260
Gender: Female	564	544	1108
Gender: Male	567	585	1152
Ethnicity: Hispanic/Latino	132	130	262
Ethnicity: Non-Hispanic/Non-Latino	997	996	1993
Ethnicity: Not reported	2	3	5
Race: White	970	962	1932
Race: Black/African American	52	57	109
Race: All others	109	110	219

Source: FDA-generated table.

The demographic characteristics of the safety and efficacy populations were 85.5% White, 51.0% male, and 88.2% non-Hispanic/non-Latino ethnicity. Subgroup analyses of vaccine effectiveness (although limited by small numbers in some subgroups) did not suggest meaningful differences in effectiveness across genders, ethnic groups, geographies, or for participants with obesity or medical comorbidities associated with high risk of severe COVID-19. No clinically meaningful differences in the occurrence of solicited AEs, unsolicited AEs or SAEs were observed by ethnicity, race, or sex subgroups.

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	N/A
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death. Symptoms associated with SARS-CoV-2 infection in individuals less than 18 years of age are similar to those in adults, but are generally milder, with fever and cough most commonly reported (Irfan et al. 2021; Liguoro et al. 2020). Other symptoms in children include nausea and vomiting, diarrhea, dyspnea, nasal symptoms, rashes, fatigue and abdominal pain (Irfan et al. 2021). Most children with COVID-19 recover within 1 to 2 weeks. Estimates of asymptomatic infection in children vary from 15 to 50% of infections (Assaker et al. 2020; Poline et al. 2021). However, COVID-19 associated

hospitalizations and deaths have occurred in adolescents (see below), and for some children, COVID-19 symptoms may continue for weeks to months after their initial illness (Office of National Statistics 2021).

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of July 6, 2022, has caused over 551 million cases of COVID-19, including 6.3 million deaths worldwide (Johns Hopkins Coronavirus Resource Center 2021). In the US, more than 87 million cases and 1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC) (CDC 2021a; CDC 2021b). Of the total COVID-19 cases reported in the US to date, 4.7% occurred among individuals 12-15 years of age (CDC 2021c).

Following EUA of the first COVID-19 vaccine in December 2020, COVID-19 cases and deaths in the US declined sharply during the first half of 2021. The emergence of the Delta variant, variable implementation of public health measures designed to control spread, and continued transmission among unvaccinated individuals were major factors in the resurgence of COVID-19 in the US, leading to the Delta variant-associated peak in September of 2021 and the more recent surge in cases attributed to the Omicron variant. As of the week ending July 2, 2022, the Omicron variant BA.4/BA.5 sub-lineages comprised the majority of the tested strains in the US (CDC 2021d). Among cases of COVID-19 in individuals less than 18 years of age from the COVID-NET network, approximately 8597 have resulted in hospitalization. (CDC 2021e). As of July 6, 2022, 408 deaths from COVID-19 have been reported in the US in the 12–15-year age group (CDC 2021c).

The most common underlying medical conditions among hospitalized children were obesity (31.9%), neurologic disorders (14.8%), and asthma (14.5%). Obesity was associated with increased risk of severe disease. Available evidence suggests that highest risk groups include children with special healthcare needs, including genetic, neurologic, metabolic conditions, or with congenital heart disease (CDC 2021f). As in the adult population, COVID-19 in children disproportionally affects underrepresented racial and ethnic groups, with hospitalizations and deaths more frequent among Native American/Alaskan, Hispanic or Latin American, and non-Hispanic Black children than among White children (McCormick et al. 2021; Kim et al. 2020).

Following observation of an increased incidence of myocarditis in 2020 compared with 2019, several studies have suggested an association between COVID-19 and myocarditis (Murk et al. 2021; Daugherty et al. 2021). While the overall incidence of myocarditis following COVID-19 infection is low, persons with COVID-19 have a nearly 16-fold increase in risk for myocarditis, compared to individuals without COVID-19. Myocarditis may also present as part of the multisystem inflammatory syndrome in children (MIS-C), usually 3 to 5 weeks after a SARS-CoV-2 infection. MIS-C is a rare but serious COVID-19-associated condition that occurs in less than 1% of children with confirmed SARS-CoV-2 infection (Dufort et al. 2020). MIS-C presents with persistent fever, laboratory evidence of inflammation, and at least 2 affected organs. In severe cases, hypotension and shock can occur. Between May 2020 and May 31, 2022, the CDC received reports of 8525 cases and 96 deaths that met the definition for MIS-C; the median age of participants was 9 years with 19.2% of the cases occurring in adolescents 12-15 years of age. Males comprised 61% of cases, and 57% were reported in children who were reported as Hispanic or Black (CDC 2021g). Up to 66.7% of patients with MIS-C had cardiac involvement (Feldstein et al. 2021), including left

ventricular dysfunction, mitral or tricuspid regurgitation, coronary artery aneurysms, and/or arrhythmias (Farooqi et al. 2021). One study of outcomes in children with MIS-C followed up to 9 months found that while 76% children with MIS-C required intensive care unit (ICU) admission and therapy with inotropes or pressors, most symptoms, including cardiovascular manifestations, resolved within 1 to 4 weeks (Farooqi et al. 2021). Limited data are available on long-term outcomes in MIS-C.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

The antiviral remdesivir is currently approved by the FDA for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 testing who are hospitalized, or who are not hospitalized and have mild-to-moderate COVID-19 and are at high risk for severe COVID-19. Additionally, the immune modulator baricitinib is approved by the FDA for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Other pharmacological products for pre-exposure prophylaxis of COVID-19, post-exposure prophylaxis and/or treatment of COVID-19 that have received emergency use authorization are as follows:

Antivirals: Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) is authorized under EUA 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) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Molnupiravir is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.

SARS-CoV-2-targeting monoclonal antibodies: Bebtelovimab is authorized under EUA 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 with positive results of direct SARS-CoV-2 testing, who are at high risk for progression to severe COVID-19 and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. Tixagevimab co-packaged with cilgavimab is authorized under EUA as pre-exposure prophylaxis for prevention of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg).

Immune modulators: Baricitinib is authorized for the treatment of COVID-19 in hospitalized patients 2 to less than 18 years of age who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Tocilizumab is authorized for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

COVID-19 convalescent plasma with high antibody titer is authorized for emergency use as a treatment for patients with COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings.

2.3 Safety and Efficacy of Pharmacologically Related Products

On August 23, 2021, the Pfizer-BioNTech COVID-19 vaccine (Comirnaty) was approved for use as a two-dose primary series for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. Additionally, the Pfizer-BioNTech COVID-19 Vaccine is authorized for emergency use as a: three-dose primary series for individuals 6 months through 4 years of age, a two-dose primary series for individuals 5 years of age and older, a third primary series dose for individuals 5 years of age and older with certain types of immunocompromise. The Pfizer-BioNTech COVID-19 vaccine is also authorized as: a first booster dose in individuals 5-17 years of age and older to be administered at least 5 months after completion of a primary series, a first booster dose in individuals 18 years of age and older after completion of primary vaccination with any authorized or approved COVID-19 vaccine (with the same interval as authorized for a booster dose with the vaccine used for primary vaccination), and a second booster dose at least four months after a first booster dose of any authorized or approved COVID-19 vaccine in individuals 50 years of age and older and individuals 12-49 years of age with certain types of immunocompromise. Each of the authorized and approved primary series and booster doses are administered according to the age group: 3 µg for 6 months through 4 years of age, 10 µg for 5 through 11 years of age, and 30 µg for 12 years old and older. Safety and efficacy data supporting approval (Comirnaty) and authorizations for Pfizer-BioNTech COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

On January 31, 2022, FDA approved the Moderna COVID-19 vaccine (Spikevax) for use as a two-dose primary series for active immunization to prevent COVID-19 in individuals 18 years of age and older. Additionally, the Moderna COVID-19 vaccine is authorized for emergency use as a: 2 dose primary series for individuals 6 months of age and older, third primary series dose for individuals 6 months of age and older with certain types of immunocompromise, homologous or heterologous first booster dose administered after completion of primary vaccination to individuals 18 years of age and older (the authorized dosing interval for a homologous booster is at least 5 months after completion of a primary series, and the authorized interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination), and homologous or heterologous second booster dose administered at least 4 months after the first booster dose to individuals 50 years of age and older and individuals 18-49 years of age with certain types of immunocompromise. Safety and efficacy data supporting approval (Spikevax) and authorizations for Moderna COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

The Janssen COVID-19 Vaccine is authorized for use in individuals 18 years of age and older for whom other FDA-authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, or who elect to receive the Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine. Safety and efficacy data supporting authorization for the Jannsen COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website. The vaccine is authorized for use in these individuals as a single primary vaccination dose and as a single

homologous or heterologous booster dose (the dosing interval for a homologous booster is at least 2 months after the single primary vaccination dose, and the dosing interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Clinical trial experience

EUA of the Pfizer-BioNTech COVID-19 Vaccine (also referred to as BNT162b2) was based on the following data: In individuals ≥16 years of age enrolled in a Phase 2/3 portion of an ongoing study (n=~22000 vaccine, n=~22000 placebo), vaccine efficacy (VE) was 95% to prevent PCR-confirmed COVID-19 occurring at least 7 days after completion of a 2-dose series. Common solicited adverse reactions after vaccination were injection site reactions, fatigue, headache, muscle pain, chills, and joint pain, which were generally mild to moderate and lasted a few days. Adverse reactions other than solicited reactogenicity events identified from the clinical trial data include lymphadenopathy in regional proximity to the vaccination site and potentially Bell's Palsy (the latter from a small numerical imbalance of temporally associated events). Vaccine effectiveness in participants 12-15 years of age (n=1131 vaccine, n=1129 placebo) was inferred by immunobridging, based on a comparison of SARS-CoV-2 50% neutralization antibody titers (SARS-CoV-2 mNG microneutralization assay) at 1 month after Dose 2, to participants 16-25 years of age, and supported by a supplemental efficacy analysis showing VE after 7 days post Dose 2 was 100% (95% CI: 75.3; 100.0) in study participants without evidence of prior SARS-CoV-2 infection and 100% (95% CI: 78.1; 100.0) in participants with or without evidence of prior SARS-CoV-2 infection. Common solicited adverse reactions after vaccination were injection site reactions, fatigue, headache, muscle pain, chills, and joint pain, which were generally mild to moderate and lasted a few days. Of the unsolicited adverse events (AEs) reported (5.8% from each treatment group), lymphadenopathy was considered related to the vaccine, which was also observed in older age groups. Serious adverse events, while uncommon (<0.5%), represented medical events expected to occur among individuals in this age group, and available data did not suggest a causal relationship to vaccine.

Post-EUA

As discussed in Section 2.1 above, since the issuance of the EUA, published observational studies have supported the effectiveness of BNT162b2 to prevent COVID-19, including high-level protection against severe disease, hospitalization, and death, although recent evidence indicates decreased primary series (2-dose) vaccine effectiveness since emergence of Omicron variant and its sub-lineages in the US (CDC 2022). Despite decreased effectiveness against Omicron compared with previous variants, authorized and approved COVID-19 vaccines based on the ancestral (Wuhan) strain continue to provide substantial protection against severe COVID-19 and associated serious outcomes, and the World Health Organization and various national regulatory and public health authorities, including FDA, continue to endorse their use for primary series vaccination in COVID-19 vaccine-naïve individuals (EMA 2022; FDA 2022; WHO 2022).

During the post-EUA surveillance period, cases of myocarditis and pericarditis were reported after vaccination, as well as rare cases of anaphylaxis (see Section 4.6).

Please see CBER pharmacovigilance reviewer's memorandum for a more detailed review of post-authorization myocarditis/pericarditis risk and details about the Applicant's ongoing post-authorization studies.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Prior to sBLA submission

- EUA 27034
  - November 20, 2020: Submission of EUA request for individuals ≥16 years of age
  - December 11, 2020: Issuance of EUA for individuals ≥16 years of age
  - April 9, 2021: Submission of EUA request for individuals 12-15 years of age
  - May 10, 2021: Issuance of EUA amendment to include individuals 12-15 years of age
  - June 25, 2021: EUA amendment to include warning statement and associated information regarding myocarditis and pericarditis in the Fact Sheet for Vaccination Providers and the Fact Sheet for Recipients and Caregivers

- IND 19736 major milestones in advance of this sBLA submission
  - April 22, 2020: IND 19736 submission, first subject enrolled on April 29, 2020
  - October 15, 2020: first subject 12-15 years of age enrolled to Study C4591001
  - November 18, 2020-April 2, 2021: Request for Comments and Advice re: Study C4591001 Placebo Recipients
  - August 3, 2021: Request for Comments and Advice re: submission of an sBLA to extend the indication to include adolescents 12-15 years of age

2.6 Other Relevant Background Information

In June 2020, FDA published guidance on the Development and Licensure of Vaccines to Prevent COVID-19 . In October 2020, FDA published guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19 (revised February 2021) .

On October 22, 2020, a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was held to discuss considerations for development, EUA and licensure of vaccines to prevent COVID-19. The VRBPAC endorsed the principles outlined in the June and October FDA guidance documents regarding safety and effectiveness data to support EUA and licensure and expectations for continued post-authorization and post-approval evaluation of COVID-19 vaccines.

On June 10, 2021, a VRBPAC meeting was held to discuss considerations for EUA and licensure of COVID-19 vaccines in pediatric age groups. The VRBPAC endorsed the use of immunobridging to infer effectiveness of COVID-19 vaccines in pediatric age groups and pediatric safety databases of at least 500-1500 vaccine recipients per age

group, depending on the age group being evaluated, with at least 6 months of follow-up to support licensure.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Sponsor responsibilities were transferred from BioNTech SE to Pfizer Inc. for the conduct of clinical study C4591001, including compliance with Good Clinical Practice as per 21 CFR 312. Bioresearch Monitoring inspections of three clinical sites in study C4591001 did not identify deficiencies that would affect the integrity of the clinical data submitted in this sBLA.

3.3 Financial Disclosures

Study C4591001 Disclosure start date: April 29, 2020. Disclosure Cut-off Date: November 3, 2021
Was a list of clinical investigators provided? ☑ Yes ☐ No
Total number of investigators identified: 340
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 2 Is an attachment provided with details of the disclosable financial interests/arrangements? ☑ Yes ☐ No Is a description of the steps taken to minimize potential bias provided? ☑ Yes ☐ No
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 4 Is an attachment provided with the reason? ☑ Yes ☐ No

The investigators with disclosable financial interests represented 0.9% (n=3/340) of the total investigators who participated in covered clinical studies.

Efforts reported to eliminate bias for the covered studies consisted of the following:

- Randomized, double-blind and multicenter study design as well as pre-specified statistical methods as per the statistical analysis plan
- Frequent monitoring of investigator trial sites and auditing of study sites
- Validity of data collected was confirmed by standard monitoring procedures
- Data processing involved cleaning checks (querying data through electronic edit checks) to ensure that errors were identified and corrected
- Data were reviewed by clinicians and queries were generated in case of inconsistencies during the course of the trial
- The study report underwent review by the project team and Quality Control; and
- Study sites performing safety evaluations were determined acceptable based on appropriate certification or historical performance and/or qualifications and credentials.

  Reviewer Comment: The Applicant satisfactorily addressed possible study investigator financial interests that could impact clinical data quality.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

The CBER CMC reviewer identified no issues that would impact the conclusions of the clinical review.

4.2 Assay Validation

The SARS-CoV-2 mNG microneutralization assay measures neutralizing antibodies (50% inhibition titers) against SARS-CoV-2 using Vero cell monolayers in a 96-well plate format. The SARS-CoV-2 mNG virus is derived from the USA_WA1/2020 strain that had been rescued by reverse genetics and engineered to express a fluorescent reporter gene (mNeonGreen) upon productive infection of cells. The validation protocol (that includes evaluation of dilutional linearity, precision, limits of quantification, and limit of detection) and the results of the validation study, executed at Pfizer Hackensack Meridian Health Center (Nutley, New Jersey), were submitted to support the suitability of the assay for testing of clinical trial immunogenicity samples.

Two clinical diagnostic assays (Cepheid Xpert Xpress reverse transcription-polymerase chain reaction [RT-PCR] assay for the detection of SARS-CoV-2 in clinical specimens and Roche Elecsys Anti-SARS-CoV-2 assay for the evaluation of serostatus to SARS-CoV-2) were used to assess clinical endpoints. Both assays have received FDA authorization under EUA. The Cepheid Xpert Xpress RT-PCR assay is used to assess viral infection of the subjects before vaccination and to confirm COVID-19 cases during study follow-up. The Roche Elecsys Anti-SARS-CoV-2 assay is used to assess serostatus of the subjects before vaccination. Data were submitted to support the suitability of both the Cepheid Xpert Xpress assay and the Roche Elecsys Anti-SARS-CoV-2 assay for their intended use in Phase 2/3 clinical studies when performed at Pfizer's testing facility (Pfizer Vaccine Research and Development; Pearl River, NY).

4.3 Nonclinical Pharmacology/Toxicology

No toxicology studies were submitted to this sBLA.

4.5 Statistical

No major statistical issues were identified by CBER statistical reviewers in this application. The key statistical analyses for safety and efficacy were confirmed by CBER statistical reviewers.

4.6 Pharmacovigilance

Post-authorization safety surveillance has not identified any new serious adverse reactions associated with BNT162b2, including among individuals 12-15 years of age who received the vaccine under EUA, other than anaphylaxis, myocarditis and pericarditis. The risk of anaphylaxis associated with BNT162b2 appears to be similar in magnitude to the risk of anaphylaxis following approved preventive vaccines in general and can be managed with standard vaccination practices. The risk of myocarditis/pericarditis appears to be greatest in individuals under the age of 40, in particular in males following Dose 2, and have been highest in males 12 through 17 years of age (~70.2 verified cases per million doses within 7-days following dose 2 administration among males ages 16-17 years and 45.7 verified cases per million doses within 7-days following dose 2 among males ages 12-15 years as per CDC presentation to the ACIP on January 5, 2022). Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae.

Please see the CBER Pharmacovigilance Plan review memorandum for further details.

4.7 Risk-Benefit Assessment

FDA conducted a quantitative benefit-risk assessment of the myocarditis risk to inform the review of Pfizer and BioNTech's supplemental Biological Licensure Application (sBLA) for use of mRNA COVID-19 vaccines in individuals 12-15 years of age. For myocarditis risk, the real-world data suggests a rate ranging from 46-71 per million post 2nd dose (see Appendix C for an extended list of studies) among individuals 12-15 years of age, and Vaccine Adverse Event Reporting System (VAERS) data suggests a lower risk compared to individuals 16-17 years of age, who are included in the age group for which Comirnaty is already approved for use. The FDA benefit-risk assessment concluded that the benefit-risk balance of the Comirnaty 2-dose primary series is favorable in individuals 12-15 years of age and supports licensure of the vaccine for use in this age group.

For further details, please refer to the review memorandum from the Analytics and Benefit-Risk Assessment Team, Office of Biostatistics and Epidemiology, CBER.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

Clinical data that were available as of March 13, 2021 from Phase 3 Study C4591001 participants 12-15 years of age enrolled from October 15, 2020 were previously submitted in support of an EUA request and reviewed by FDA. See the Adolescent EUA Review Memorandum for the Pfizer COVID-19 Vaccine.

This sBLA contains new clinical data, as follows:
Study C4591001

- Phase 3
  For participants 12-15 years of age:
  - Safety to ≥6 months after Dose 2 among study participants with follow-up during the blinded placebo-controlled and/or open-label follow-up periods
  - Updated efficacy for all participants in the efficacy analysis populations with confirmed COVID-19 cases during the blinded placebo-controlled follow-up period through September 2, 2021.

Only safety and effectiveness data in individuals 12-15 years of age, the population for intended use, who received the final vaccine formulation (BNT162b2 30 µg) are presented in this clinical memorandum.

Post-authorization effectiveness data from observational studies referenced in Section 2 and Section 11 are limited to published literature and were not submitted as part of the licensure application. Therefore, FDA has not independently reviewed and confirmed the data or assessed the study designs for potential sources of bias.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The primary source of data considered for review of this investigational vaccine were documents submitted to STN 125742/0. The following sections were reviewed in support of this application:
Module 1, all sections: Administrative Information and Prescribing Information
Section 2.2 Introduction
Section 2.5 Clinical Overview
Section 5.2 Tabular Listing of All Clinical Studies
Section 5.3.5.1 Clinical Study Reports

During the sBLA review period, the Applicant submitted a total of 5 amendments in response to CBER's requests for clinical information.

Table 2. Amendments to the sBLA 125742/45 (submitted December 16, 2021)

Amendment Number	Date Submitted	Description
2	February 2, 2022	Response to 1/19/22 re: datasets
4	March 11, 2022	Response to 3/7/22 clinical-statistical comments re: updated immunobridging analyses and solicited adverse reaction frequencies.
8	April 29, 2021	Response to 4/20/22 first set of labeling comments
11	May 9, 2022	Response to 5/4/22 clinical-statistical comments re: nausea events
12	May 10, 2022	Labeling comments

Source: FDA-generated table.

The amendments satisfactorily addressed all clinical requests sent during the review period, and salient responses from the amendments were incorporated into this memorandum.

Supportive information from EUA 27034/132 and clinical study protocols reviewed under IND 19736 were also referenced during the review cycle.

5.3 Overview of Clinical Studies

An interim report from one ongoing clinical study was submitted on December 16, 2021, to support approval and licensure of Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) in individual 12-15 years of age. Study C4591001 is a multicenter Phase 1/2/3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study.

Table 3. Study C4591001, Participants 12 Through 15 Years of Age

Study Number/ Countries	Description	BNT162b2 (30 µg) N	Placebo (Saline) N	Study Status
C4591001 USA	Phase 1/2/3, randomized, placebo-controlled, observer-blind; to evaluate safety, immunogenicity and efficacy of COVID-19 vaccine	Total: 1131	Total: 1129	Ongoing

N=Number of randomized participants as of September 2, 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).

5.4 Consultations

5.4.1 Advisory Committee Meeting

The most critical issues involving data to support safety and effectiveness of this vaccine were covered in the October 2020, December 2020, and June 2021 VRBPAC meetings. More complete information concerning the risk of myocarditis/pericarditis has become available in post-EUA surveillance and observational studies. FDA's assessment of this information did not impact the overall benefit/risk considerations to an extent that VRBPAC input was needed to guide a licensure decision for use in individuals 12-15 years of age.

5.5 Literature Reviewed

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study C4591001

NCT04368728

Title: Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Reviewer Comment: The protocol for this ongoing study has been amended over time to add study populations, interventions, and analyses not included in the original design and not pertinent to this sBLA. The study design as described herein reflects objectives, endpoints, and monitoring pertaining to safety, immunogenicity, and efficacy evaluations in individuals 12-15 years of age following a 2-dose BNT162b2 primary series, according to protocol amendment 18, which was the version implemented at the time of the September 2, 2021 data cutoff. Secondary/exploratory objectives pertaining to booster vaccination (e.g., 3rd BNT162b2 dose), and evaluation of modified BNT162b2 vaccine formulations were beyond the scope of this sBLA, and therefore not presented in this clinical review. Additionally, the sBLA submission did not include data to address vaccine effectiveness against asymptomatic COVID-19 infection, based on seroconversion or surveillance PCR testing; thus, study objectives pertaining to asymptomatic infection are not presented.

6.1.1 Objectives and Endpoints

The objectives and endpoints are presented below are for the adolescent population enrolled into the Phase 3 portion of the study.

Secondary Immunogenicity objective: To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12-15 years of age compared to participants 16-25 years of age.

Endpoint: SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection

Primary safety objective: To characterize the safety of BNT162b2.

Endpoints: solicited local adverse reactions (injection site pain, redness, swelling), solicited systemic AEs (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), AEs, SAEs

Descriptive efficacy objectives

1. To evaluate the efficacy of BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 in participants without evidence of SARS-CoV-2 infection before vaccination.

   Endpoint: COVID-19 incidence per 1000 person-years of follow-up based on laboratory-confirmed nucleic acid amplification-based test (NAAT) in participants with no serological or virological evidence (up to 7 days after Dose 2) of past SARS-CoV-2 infection

2. To evaluate the efficacy of BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 in participants with and without evidence of SARS-CoV-2 infection before vaccination.

   Endpoint: COVID-19 incidence per 1000 person-years of follow-up based on laboratory-confirmed NAAT

For the study objectives described above, NAAT could be confirmed in a central or local laboratory. Evidence of past SARS-CoV-2 infection (before Dose 1) was documented serologically or virologically.

6.1.2 Design Overview

Study C4591001 is an ongoing, randomized, placebo-controlled, Phase 1/2/3 study being conducted in the US, 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 12-15 years of age were added to the protocol during Phase 3, following a review of safety data in young adult participants, and enrollment began in the United States on October 15, 2020.

The protocol-specified evaluation for vaccine effectiveness in participants 12-15 years of age was 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 (the most clinically relevant subgroup of the study population in whom VE has been demonstrated).

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 (see Appendix B for COVID-19 and Severe COVID-19 Case Definitions). The primary efficacy endpoint of Study C4591001 was VE against laboratory-confirmed COVID-19 in participants without prior SARS-CoV-2 infection. A second primary 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 (Pfizer COVID-19 Vaccine EUA Review Memo Dec 2020). Efficacy against COVID-19 disease was assessed with descriptive analyses in study participants 12-15 years of age.

Per protocol, since May 10, 2021, following issuance of the Emergency Use Authorization for the Pfizer-BioNTech COVID-19 Vaccine for individuals 12-15 years of age, Phase 3 participants 12-15 years of age in the vaccine and placebo groups were progressively unblinded to their treatment assignment (when eligible per local recommendations). Participants initially randomized to the placebo group were offered BNT162b2 vaccination at a time no later than the 6-month follow-up visit after the second placebo vaccination. For participants unblinded to his/her vaccine assignment, follow-up evaluations thereafter were conducted in an open-label manner.

> *Reviewer Comment:* During the blinded placebo-controlled time period, study staff who prepared and administered the study interventions were unblinded to the treatment assignment, due to differences in appearance of BNT162b2 and saline placebo, and study investigators/personnel collecting and evaluating safety and efficacy information were blinded to the participants' treatment assignment

(observer-blinded). In the package insert, double-blind refers only to the study investigators/personnel collecting and evaluating safety and efficacy information and the participant.

After BNT162b2 became available for emergency use, participants who elected to receive BNT162b2 were unblinded to their initial study intervention assignment. The Applicant and site personnel who are responsible for the ongoing conduct of the study remain blinded to the data from participants whose treatment assignment has not been disclosed.

6.1.3 Population

Phase 3
Key inclusion criteria

- Healthy or had pre-existing stable chronic medical conditions
- ≥12 years of age.
- At higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, frontline essential workers).

Key exclusion criteria

- Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19
- Known or suspected immunodeficiency, or received/planning treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt throughout the study
- Women who are pregnant or breastfeeding
- Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Criteria for temporarily delaying enrollment/randomization/study intervention administration

- Current febrile illness (T ≥38°C) or other acute illness within 48 hours before study intervention administration, including symptoms that could represent a potential COVID-19 illness: new or increased cough; new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste/smell, sore throat, diarrhea, vomiting.
- Receipt or planning to receive a seasonal or pandemic influenza vaccine within 14 days, or any other non-study vaccine within 28 days, before or after study vaccination.
- Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The BNT162b2 (30 µg) vaccine candidate was selected for further evaluation in Phase 2/3. BNT162b2 contains a nucleoside-modified messenger RNA that encodes the viral spike (S) glycoprotein of SARS-CoV-2 encapsulated in a lipid nanoparticle. Each dose also includes the following ingredients: lipids ((4-hydroxybutyl)azanediyl)bis(hexane-

6,1-diyl)bis(2-hexyldecanoate), 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

6.1.5 Directions for Use

Two doses of BNT162b2 (0.3 mL per dose) were administered 3 weeks apart. Each dose was injected intramuscularly into the deltoid muscle.

See the full prescribing information for further information regarding preparation of BNT162b2.

6.1.6 Sites and Centers

A total of 29 clinical sites enrolled participants 12-15 years of age for Study C4591001 in the United States.

6.1.7 Surveillance/Monitoring

Efficacy

Efficacy is being assessed throughout a participant's follow-up in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness, an illness visit occurs. Assessments for illness visits include a nasal (midturbinate) swab, which is tested at a central laboratory using an RT-PCR test (e.g., Cepheid; FDA authorized under EUA), or other sufficiently validated NAAT, to detect SARS-CoV-2. Case ascertainment is based on central laboratory NAAT results, unless it is not possible to test the sample at the central laboratory. In that case, the following NAAT results are acceptable: Cepheid Xpert Xpress SARS-CoV-2, Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001), and Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001).

Safety

Solicited AEs (local and systemic reactions, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose) were assessed for all participants 12-15 years of age. Additionally, all unsolicited AEs were collected from Dose 1 to 1 month after the Dose 2, and all SAEs from Dose 1 to 6 months after Dose 2. The planned safety follow-up for currently enrolled adolescents is a maximum of 26 months (i.e., through 24 months after vaccination #2) and will include collection of deaths and related SAEs reported after 6 months post-Dose 2.

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), and antipyretic/pain medication use were recorded in an e-diary.

After BNT162b2 was granted emergency use authorization for this age group (May 10, 2021), unblinding procedures were initiated to vaccinate the placebo group. Please see Section 6.1.10.1 (Population enrolled/analyzed) for additional details.

6.1.8 Endpoints and Criteria for Study Success

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 before and during vaccination regimen.
- Immunobridging success 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.
- Immunobridging also included a descriptive analysis of the difference in seroresponse rates (adolescents minus young adults) among participants without prior evidence of SARS-CoV-2 infection. Seroresponse was defined as a ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination to 1 month after Dose 2.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The estimands to evaluate the immunogenicity objectives were based on evaluable populations for immunogenicity (Section 6.1.10.1). These estimands estimated the vaccine effect in the setting where participants follow the study schedules and protocol requirements as directed. One of the secondary objectives in the Phase 3 part of the study was to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12-15 years of age compared to the response in participants 16-25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population was used for the following hypothesis testing: H_0: $\ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$ where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, $\ln(\mu_2)$ and $\ln(\mu_1)$ are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2. If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) was >0.67, the noninferiority objective was met.

Solicited safety analyses were based on participants who received at least one dose of the vaccine and responded yes or no to any reaction within 7 days of each dose. Unsolicited safety analyses were based on the safety population, which consisted of participants randomized in the Phase 2/3 study who received at least one dose of the vaccine, analyzed according to the vaccine received. Safety endpoints were summarized descriptively for the number of participants within the analysis set reporting at least one event in each category.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The study protocol was revised to allow participants 12-15 years of age who originally received placebo the opportunity to receive BNT162b2 following local or national recommendations or following completion of the active safety surveillance period, following issuance of the EUA (protocol amendment 10). On May 10, 2021, the process of disclosing vaccine assignments for all trial participants 12-15 years of age began (following issuance of the EUA for use of the Pfizer-BioNTech COVID-19 vaccine in individuals 12-15 years of age). Hence, for each trial participant, there are 2 periods in

the study: enrollment into the observer-blind phase until the date of vaccine disclosure and the time in the study after disclosure. Participants who originally were randomized to BNT162b2 are continuing to be followed for safety as specified in the protocol. The safety data for participants who originally were randomized to and received placebo prior to disclosure of vaccine assignment include blinded data that contribute to controlled assessment of safety, immunogenicity, and efficacy compared to individuals who randomly assigned to BNT162b2. After vaccine treatment disclosure and the administration of BNT162b2, the placebo participants can no longer be used for direct comparison with those who originally were randomized to BNT162b2. Even though individuals were unblinded on different days after May 10, 2021, the difference in the total blinded follow-up duration is minor between the treatment arms. Thus, the analysis of the observer-blinded, placebo-controlled portion of the study as well as the open-label portion is reported in frequencies, such that the number of participants within the analysis set reporting at least one event in each category is displayed.

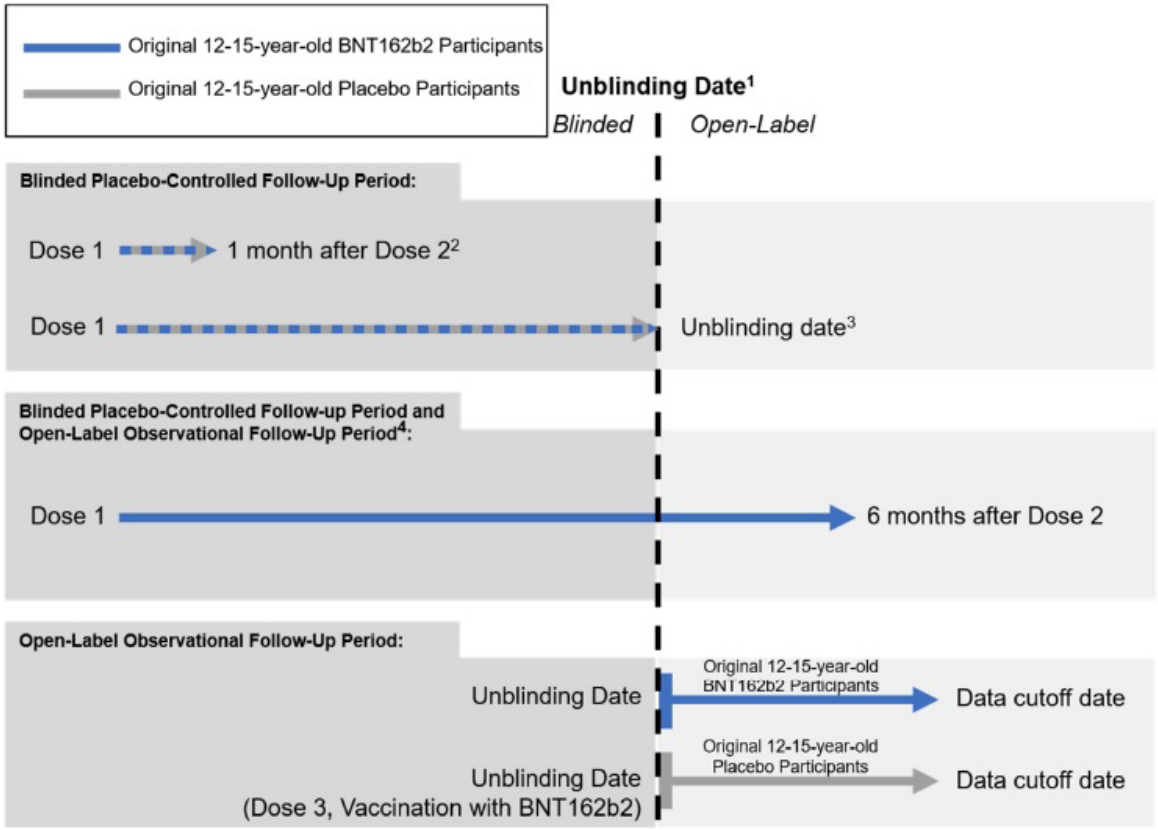
Safety data presented for Phase 3 of Study C4591001, based on the data cutoff date of September 2, 2021, include:

1. Blinded placebo-controlled period: Dose 1 to unblinding date, with a median follow-up duration of 4.4 months:
   - Participants with up to ~6 months of follow-up after Dose 2 (N=2260; BNT162b2 group N=1131 and placebo group N=1129).
2. Open-label observational period: from time of unblinding to data cutoff date, with a median follow-up duration of 4.0 months for both groups:
   - Participants originally randomized to BNT162b2 (N=1107)
   - Participants originally randomized to placebo who then received BNT162b2 (N=1010)
   - Only unsolicited AEs (AEs, SAEs and adverse events of special interest [AESIs]) were assessed during this time period.
3. Cumulative follow-up from Dose 1 to at least 6 months after Dose 2, with a median follow-up duration of 8.4 months after Dose 2.:
   - Participants originally randomized to BNT162b2 (inclusive of blinded data and open-label data through the September 2, 2021 data cutoff). (Total N=1113).

   Reviewer Comment: The safety data from time period of Dose 1 to 1 month post Dose 2 (solicited local and systemic reactions, and unsolicited adverse events from Dose 1 through 1 month post Dose 2) were previously reviewed (Adolescent EUA Review Memo).

A graphic of these three different time periods taken into consideration for the evaluation of the safety data is displayed in Figure 1, below.

Figure 1. Phase 2/3 Safety Analyses: Time Period and Analysis Groups



Source: STN 125742.45 c4591001-ado-mth6-report-body.pdf. Figure 2 (p 78).
1. Will vary by participant. Adverse event data analyzed from Dose 1 to unblinding date, or from unblinding date to data cutoff date.
2. Up to ~6 months after Dose 2.
3. Cumulative BNT162b2 follow-up to at least 6 months after Dose 2.

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.

Data analysis cutoff dates:

- March 13, 2021 (Phase 2/3 immunobridging analysis, exploratory vaccine efficacy analysis and safety follow-up previously reviewed in support of the Pfizer-BioNTech COVID-19 Vaccine EUA amendment for use of a 2-dose primary series in adolescents 12-15 years of age)
- September 2, 2021 (Phase 2/3 updated exploratory vaccine efficacy analysis and safety follow-up)

  Reviewer Comment: All of the COVID-19 cases analyzed through the March 13, 2021 cutoff occurred during the ancestral (Wuhan with D614G mutation) predominant period, while additional cases analyzed through the September 2, 2021 cutoff all occurred during May 2021 or earlier and therefore occurred prior to the emergence of the Delta and Omicron variants.

6.1.10.2 Demographics

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). Please refer to the Adolescent EUA Review Memo for the description of demographics for this population.

The demographic characteristics of the evaluable efficacy population in participants 12-15 years of age for the VE analyses (N=1005 vaccine group, N=978 placebo group) are similar to the baseline characteristics of the Dose 1 all-available efficacy population.

The Dose 1 all-available efficacy population of 12-15-year-olds (BNT162b2 N=1131, placebo N=1129) were the same individuals as the 12-15-year-olds in the safety population (Table 4).

The safety population included 2260 participants 12-15 years of age (1131 in the BNT162b2 group and 1129 in the placebo group). The median age was 14 years, and all participants live in the US. Overall, the safety population was 49.0% female; 85.5% White, 4.8% African American, 6.3% Asian, and <3% from other racial groups; 11.6% of participants were Hispanic/Latino. One or more comorbidities that increase the risk of severe COVID-19 disease were present among 21.7% of participants. Only 4.2% of participants had evidence of prior SARS-CoV-2 infection. The demographics were balanced between the treatment groups. Table 4 presents the specific demographic characteristics in the studied population.

Table 4. Demographics and Other Baseline Characteristics, Participants 12 Through 15 Years of Age, Safety Population (Data Cutoff September 2, 2021)

Characteristic	BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	Placebo (N[a]=1129) n[b] (%)	Total (N[a]=2260) n[b] (%)
Sex: Female	564 (49.9)	544 (48.2)	1108 (49.0)
Sex: Male	567 (50.1)	585 (51.8)	1152 (51.0)
Age at Vaccination: Mean years (SD)	13.6 (1.11)	13.6 (1.11)	13.6 (1.11)
Age at Vaccination: Median (years)	14.0	14.0	14.0
Age at Vaccination: Min, max (years)	(12, 15)	(12, 15)	(12, 15)
Race: American Indian or Alaska Native	4 (0.4)	3 (0.3)	7 (0.3)

Characteristic	BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	Placebo (N[a]=1129) n[b] (%)	Total (N[a]=2260) n[b] (%)
Race: Asian	72 (6.4)	71 (6.3)	143 (6.3)
Race: Black or African American	52 (4.6)	57 (5.0)	109 (4.8)
Race: Native Hawaiian or Other Pacific Islander	3 (0.3)	0	3 (0.1)
Race: White	970 (85.8)	962 (85.2)	1932 (85.5)
Race: Multiracial	24 (2.1)	29 (2.6)	53 (2.3)
Race: Not reported	6 (0.5)	7 (0.6)	13 (0.6)
Ethnicity: Hispanic or Latino	132 (11.7)	130 (11.5)	262 (11.6)
Ethnicity: Not Hispanic or Latino	997 (88.2)	996 (88.2)	1993 (88.2)
Ethnicity: Not reported	2 (0.2)	3 (0.3)	5 (0.2)
Obesity: Yes[c]	143 (12.6)	128 (11.3)	271 (12.0)
Obesity: No	988 (87.4)	1001 (88.7)	1989 (88.0)
Comorbidities: Yes[d]	249 (22.0)	242 (21.4)	491 (21.7)
Comorbidities: No	882 (78.0)	887 (78.6)	1769 (78.3)
Baseline evidence of prior SARS-CoV-2 infection: Negative[e]	1083 (95.8)	1078 (95.5)	2161 (95.6)
Baseline evidence of prior SARS-CoV-2 infection: Positive[f]	46 (4.1)	50 (4.4)	96 (4.2)
Baseline evidence of prior SARS-CoV-2 infection: Missing	2 (0.2)	1 (0.1)	3 (0.1)
Country: United States of America	1131 (100.0)	1129 (100.0)	2260 (100.0)

Source: STN 125742.45 c4591001-508-compliant tables-12-15 years.doc, Table F, Pages 10-11.
Abbreviation: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Subjects who had a BMI at or above the 95th percentile from the CDC growth chart.
d. Number of subjects who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as subjects who had at least one of the Charlson comorbidity index category or BMI ≥95th percentile.
e. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
f. Negative N-binding ant body result and negative NAAT result at Visit 1 and no medical history of COVID-19.

6.1.10.3 Subject Disposition

The overall study disposition tables are presented below in Table 5 (Blinded Follow-up Time Period) and Table 6 (Open-label Unblinded Follow-up Time Period). Overall, few participants were discontinued or lost to follow-up and these discontinuations were generally balanced between treatment groups.

A total of 4 (0.4%) Phase 2/3 original BNT162b2 participants received Dose 1 of BNT162b2 during the blinded placebo-controlled follow-up period and then received Dose 2 of BNT162b2 during the open-label follow-up period (when they were unblinded). Among all 1107 participants originally randomized to BNT162b2 and included in open-label follow-up, 45 (4.0%) withdrew from the study during open-label follow-up (Table 6), and 21 of the 23 participants who withdrew for “other reasons” were enrolled into Study C4591031 to evaluate a booster dose of BNT162b2.

During the open-label follow-up period, most participants originally randomized to the placebo group for Doses 1 and 2 of study vaccine received BNT162b2 as Doses 3 and 4 (89.4% and 87.8%, respectively) of study vaccine. Most participants who received Dose 3 but not Dose 4 were within the 3-week window between the two doses as of the data cutoff date. There were few participants in this group (n=6; 0.5%) who were withdrawn from the study, and most were due to withdrawals by the participant. The

number of participants originally randomized to the placebo group who were unblinded and received BNT162b2 was 1010.

Table 5. Study Disposition of Phase 2/3 Randomized Participants 12 Through 15 Years of Age, Blinded Follow-Up Period

Disposition	BNT162b2 (30 µg) (N[a]=1134) n[b] (%)	Placebo (N[a]=1130) n[b] (%)	Total (N[a]=2264) n[b] (%)
Randomized	1134 (100.0)	1130 (100.0)	2264 (100.0)
Not vaccinated	3 (0.3)	1 (0.1)	4 (0.2)
Original blinded placebo-controlled follow-up period			
Vaccinated	1131 (99.7)	1129 (99.9)	2260 (99.8)
Dose 1	1131 (99.7)	1129 (99.9)	2260 (99.8)
Dose 2	1124 (99.1)	1117 (98.8)	2241 (99.0)
Discontinued from original blinded placebo-controlled vaccination period[c]	3 (0.3)	14 (1.2)	17 (0.8)
Reason for discontinuation			
No longer meets eligibility criteria	0	7 (0.6)	7 (0.3)
Protocol deviation	0	2 (0.2)	2 (0.1)
Adverse event	1 (0.1)	0	1 (0.0)
Physician decision	1 (0.1)	0	1 (0.0)
Withdrawal by subject	0	1 (0.1)	1 (0.0)
Withdrawal by parent/guardian	0	1 (0.1)	1 (0.0)
Other	1 (0.1)	3 (0.3)	4 (0.2)
Unblinded before 1-month post–Dose 2 visit	12 (1.1)	21 (1.9)	33 (1.5)
Completed 1-month post–Dose 2 visit	1113 (98.1)	1096 (97.0)	2209 (97.6)
Withdrawn from the study	5 (0.4)	14 (1.2)	19 (0.8)
Withdrawn after Dose 1 and before Dose 2	0	0	0
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	0	3 (0.3)	3 (0.1)
Withdrawn after 1-month post–Dose 2 visit	5 (0.4)	11 (1.0)	16 (0.7)
Reason for withdrawal from the study			
Withdrawal by subject	1 (0.1)	7 (0.6)	8 (0.4)
Withdrawal by parent/guardian	1 (0.1)	5 (0.4)	6 (0.3)
Lost to follow-up	3 (0.3)	2 (0.2)	5 (0.2)

Source: STN 125742.45 c4591001-508-compliant tables-12-15 years.doc, Table B, Pages 2-4.
a. N = number of randomized participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Original blinded placebo-controlled vaccination period is defined as the time period from Dose 1 to 1-month post–Dose 2 visit.
d. Open-label vaccination period is defined as the time period from Dose 3 (first dose of BNT162b2 [30 µg]) to 1-month post–Dose 4 (second dose of BNT162b2 [30 µg]) visit.

Table 6. Study Disposition of Phase 2/3 Randomized Participants 12 Through 15 Years of Age, Open-Label (Unblinded) Follow-Up Period

Disposition	BNT162b2 (30 µg) (N[a]=1134) n[b] (%)	Placebo (N[a]=1130) n[b] (%)
Open-label follow-up period		
Originally randomized to BNT162b2	1107 (97.6)	
Received Dose 2/unplanned dose	4 (0.4)	
Completed 1-month post–Dose 2 visit	15 (1.3)	
Completed 6-month post–Dose 2 visit	1065 (93.9)	

Disposition	BNT162b2 (30 µg) (N[a]=1134) n[b] (%)	Placebo (N[a]=1130) n[b] (%)
Withdrawn from the study	45 (4.0)	
Withdrawn before 6-month post–Dose 2 visit	25 (2.2)	
Withdrawn after 6-month post–Dose 2 visit	20 (1.8)	
Reason for withdrawal from the study		
Withdrawal by subject	7 (0.6)	
Withdrawal by parent/guardian	7 (0.6)	
Lost to follow-up	6 (0.5)	
Protocol deviation	1 (0.1)	
No longer meets eligibility criteria	1 (0.1)	
Other	23 (2.0)	
Originally randomized to placebo		1108 (98.1)
Withdrawn from the study after unblinding and before Dose 3		47 (4.2)
Received Dose 3 (first dose of BNT162b2 [30 µg])		1010 (89.4)
Received Dose 4 (second dose of BNT162b2 [30 µg])		992 (87.8)
Discontinued from open-label vaccination period[d]		5 (0.4)
Reason for discontinuation from open-label vaccination period		
Protocol deviation		4 (0.4)
Withdrawal by subject		1 (0.1)
Completed 1-month post–Dose 4 visit		933 (82.6)
Withdrawn from the study		6 (0.5)
Withdrawn after Dose 3 and before Dose 4		5 (0.4)
Withdrawn after Dose 4 and before 1-month post–Dose 4 visit		0
Withdrawn after 1-month post–Dose 4 visit		1 (0.1)
Reason for withdrawal from the study		
Withdrawal by subject		3 (0.3)
Lost to follow-up		2 (0.2)
Protocol deviation		1 (0.1)

Source: STN 125742.45 c4591001-508-compliant tables-12-15 years.doc, Table B, Pages 2-4.
a. N = number of randomized participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Original blinded placebo-controlled vaccination period is defined as the time period from Dose 1 to 1-month post–Dose 2 visit.
d. Open-label vaccination period is defined as the time period from Dose 3 (first dose of BNT162b2 [30 µg]) to 1-month post–Dose 4 (second dose of BNT162b2 [30 µg]) visit.

The duration of blinded follow-up after completion of the 2-dose vaccine series in the safety population is displayed in Table 7. Because this study is ongoing, and participants were unblinded to their study intervention following issuance of the EUA Amendment in May 2021 or at their 6-month follow-up visit, the number of participants with blinded follow-up decreases beyond 6 months, as expected.

Table 7. Blinded Follow-up Duration After Dose 2, Participants 12-15 Years of Age, Safety Population

Length of Follow-up[c]	Vaccine Group (as Administered) BNT162b2 N[a] =1131 n[b] (%)	Vaccine Group (as Administered) Placebo N[a] =1129 n[b] (%)	Total N[a] =2260 n[b] (%)
<4 Months	345 (30.5)	356 (31.5)	701 (31.0)
≥4 Month to <5 months	528 (46.7)	532 (47.1)	1060 (46.9)
≥5 Months to <6 months	106 (9.4)	97 (8.6)	203 (9.0)
≥6 Months	152 (13.4)	144 (12.8)	296 (13.1)

Source: STN 125742.45 c4591001-508-compliant tables-12-15 years.doc, Table A, page 1
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = number of participants with the specified characteristic.
c. Length of follow-up is the total exposure from Dose 2 to cutoff date or the date of unblinding, whichever date was earlier.

The number of original BNT162b2 recipients in the safety population with ≥6 months duration of total (blinded and open-label) follow-up from Dose 2 to the data cutoff date for was 1113 (98.4%).

Disposition is further presented below in Table 8 (efficacy analysis populations) and Table 9 (Safety population). Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups.

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. Please refer to the Adolescent EUA Review Memo for the description of disposition for this population.

For the evaluable efficacy population, most participants who were excluded from the analysis had not received all vaccinations as randomized or did not receive Dose 2 within the predefined window (i.e., 19 to 42 days after Dose 1).

Table 8. Disposition of Participants 12 Through 15 Years of Age, Efficacy Population (Data Cutoff September 2, 2021)

Disposition	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	1134 (100.0)	1130 (100.0)	2264 (100.0)
Dose 1 all-available efficacy population	1131 (99.7)	1129 (99.9)	2260 (99.8)
Subjects without evidence of infection before Dose 1	1083 (95.5)	1078 (95.4)	2161 (95.5)
Subjects excluded from Dose 1 all-available efficacy population	3 (0.3)	1 (0.1)	4 (0.2)
Reason for exclusion[c]			
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)
Subjects without evidence of infection prior to 7 days after Dose 2	1061 (93.6)	1037 (91.8)	2098 (92.7)

Disposition	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Subjects excluded from Dose 2 all-available efficacy population	11 (1.0)	13 (1.2)	24 (1.1)
Reason for exclusion[c]			
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)	1109 (98.1)	2228 (98.4)
Subjects without evidence of infection prior to 7 days after Dose 2	1057 (93.2)	1030 (91.2)	2087 (92.2)
Subjects excluded from evaluable efficacy (7 days) population	15 (1.3)	21 (1.9)	36 (1.6)
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria	1 (0.1)	1 (0.1)	2 (0.1)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	14 (1.2)	19 (1.7)	33 (1.5)
Unblinded prior to 7 days after Dose 2	1 (0.1)	0	1 (0.0)
Had other important protocol deviations on or prior to 7 days after Dose 2	0	3 (0.3)	3 (0.1)

Source: STN 125742.45 c4591001-508-compliant tables-12-15 years.doc, Table E, Pages 8-9.
a. n = Number of subjects with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Subjects may have been excluded for more than 1 reason.

The safety population included a total of 2260 participants: 1131 participants in the BNT162b2 group and 1129 participants in the placebo group.

Table 9. Disposition of Participants 12 Through 15 Years of Age, Safety Population (Data Cutoff September 2, 2021)

Disposition	BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	Placebo (N[a]=1129) n[b] (%)	Total (N[a]=2260) n[b] (%)
Vaccinated	1131 (100.0)	1129 (100.0)	2260 (100.0)
Completed 1 dose	1131 (100.0)	1129 (100.0)	2260 (100.0)
Completed 2 doses	1124 (99.4)	1117 (98.9)	2241 (99.2)
Safety population	1131 (100.0)	1129 (100.0)	2260 (100.0)
Participants excluded from safety population	-	-	4
Reason for exclusion			
Participant did not receive study vaccine	-	-	4
Completed at least 6 months follow-up after Dose 2 in blinded placebo-controlled follow-up period	152 (13.4)	144 (12.8)	296 (13.1)
Completed at least 6 months follow-up after Dose 2 in blinded and open-label follow-up period	1113 (98.4)	-	-
Completed 1-month post–Dose 2 visit (vaccination period)	1113 (98.4)	1096 (97.1)	2209 (97.7)

Disposition	BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	Placebo (N[a]=1129) n[b] (%)	Total (N[a]=2260) n[b] (%)
Discontinued from vaccination period but continued in the study up to 1-month post–Dose 2 visit	3 (0.3)	14 (1.2)	17 (0.8)
Discontinued after Dose 1 and before Dose 2	3 (0.3)	10 (0.9)	13 (0.6)
Discontinued after Dose 2 and before 1-month post–Dose 2 visit	0	4 (0.4)	4 (0.2)
Reason for discontinuation from vaccination period			
No longer meets eligibility criteria	0	7 (0.6)	7 (0.3)
Protocol deviation	0	2 (0.2)	2 (0.1)
Adverse event	1 (0.1)	0	1 (0.0)
Physician decision	1 (0.1)	0	1 (0.0)
Withdrawal by subject	0	1 (0.1)	1 (0.0)
Withdrawal by parent/guardian	0	1 (0.1)	1 (0.0)
Other	1 (0.1)	3 (0.3)	4 (0.2)
Withdrawn from study before 1-month post–Dose 2 visit	0	3 (0.3)	3 (0.1)
Withdrawn after Dose 1 and before Dose 2	0	0	0
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	0	3 (0.3)	3 (0.1)
Reason for withdrawal			
Withdrawal by parent/guardian	0	2 (0.2)	2 (0.1)
Withdrawal by subject	0	1 (0.1)	1 (0.0)

Source: STN 125742.45 c4591001-508-compliant tables-12-15 years.doc, Table D, Pages 6-7.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.

6.1.11 Vaccine Effectiveness

6.1.11.1 Analyses of Secondary Endpoint

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 1.77 (2-sided 95% CI: 1.5, 2.09), meeting the 1.5-fold non-inferiority criterion (i.e., lower bound of the 2-sided 95% CI for GMR >0.67).

Table 10. Geometric Mean SARS-CoV-2 Neutralizing Titers (NT50)[a] 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[b]
BNT162b2	1253.6 (1117.7, 1406.1)	708.1 (625.9, 801.1)	1.77 (1.50, 2.09)	Yes

Source: STN 125742.45 amendment 4. Appendix 1-immunobridging-data-c4591001.pdf. Page 8.
a. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.
b. 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

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 evaluate by protocol-specified methods.

Please refer to the Adolescent EUA Review Memo for additional analyses of the immunogenicity results.

> *Reviewer Comment:* The GMT calculations for the analyses presented above are based on the SARS-CoV-2 mNeonGreen Virus Microneutralization lower level of quantification titer of 41. The GMT analyses for the EUA submission for this age group were based on the limit of detection for the assay, which is a titer of (b) (4), as the lower range cutoff. The clinical reviewer's conclusions, based on the updated immunogenicity analyses presented in this sBLA, are unchanged from the conclusions in the Adolescent EUA review memo.

Vaccine Efficacy

For the VE evaluation of BNT162b2 against confirmed COVID-19 was evaluated in participants without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. Cases were counted from 7 days after Dose 2. Descriptive analyses of VE in adolescents 12-15 years of age were conducted with all cases accrued during blinded follow-up to a data cutoff date of March 13, 2021 to support issuance of the EUA Amendment for use of the Pfizer-BioNTech COVID-19 Vaccine in this age group on May 10, 2021. For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 100.0% (95% CI: 75.3, 100.0). The case split was 0 COVID-19 cases in the BNT162b2 group compared to 16 COVID-19 cases in the placebo group. Please refer to the Adolescent EUA Review Memo for additional details from that analysis time point.

Updated efficacy analyses

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up through September 2, 2021, representing a median of 6 months of follow-up after Dose 2 for participants in the efficacy population. All of the following updated primary and secondary VE analyses are from this blinded placebo-controlled follow-up period through the September 2, 2021 data cutoff.

For the first updated efficacy endpoint, VE against confirmed COVID-19 was evaluated in participants without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. For the second updated efficacy endpoint, VE against confirmed COVID-19 was evaluated in participants with and without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. Cases were counted from 7 days after Dose 2 for both endpoints.

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, the updated 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 28 COVID-19 cases in the placebo group (Table 11).

Table 11. Updated Vaccine Efficacy Against Confirmed COVID-19 in Participants Without Evidence of Prior SARS-CoV-2 Infection, Participants 12-15 Years of Age, Evaluable Efficacy Population (Data Cutoff September 2, 2021)

Endpoint	BNT162b2 (N[a] =1057) Cases n1[b] Surveillance Time[c] (n2[d])	Placebo (N[a] =1030) Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 Occurrence from 7 days after Dose 2	0 0.343 (1043)	28 0.322 (1019)	100.0 (86.8, 100.0)

Source: STN 125742.45 c4591001-interim-ado-mth6-report-body.pdf, Table 12, Page 67
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. 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.
d. n2 = Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

For participants with and without evidence of SARS-CoV-2 infection before and during vaccination regimen, the updated VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 100.0%, with 0 and 30 cases in the BNT162b2 and placebo groups, respectively (Table 12).

Table 12. Updated Vaccine Efficacy Against Confirmed COVID-19 in Participants With or Without Evidence of Prior SARS-CoV-2 Infection, Participants 12-15 Years of Age, Evaluable Efficacy Population (Data Cutoff September 2, 2021)

Endpoint	BNT162b2 (N[a] =1119) Cases n1[b] Surveillance Time[c] (n2[d])	Placebo (N[a] =1109) Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 Occurrence from 7 days after Dose 2	0 0.362 (1098)	30 0.345 (1088)	100.0 (87.5, 100.0)

Source: STN 125742.45 c4591001-interim-ado-mth6-report-body.pdf, Table 13, Page 69

Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. 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.
d. n2 = Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Multiple Cases of COVID-19

One participant in the placebo group had two positive central laboratory COVID-19 NAAT results with corresponding COVID-19 illness visits. Baseline SARS CoV-2 NAAT testing at Visit 1 was positive, with a corresponding negative serology for N-binding antibody.

Subgroup Analyses of VE

Because there were no confirmed COVID-19 cases in the BNT162b2 group, all VE estimates are 100%, with varying 95% confidence interval lower bounds, depending upon the case split for the specific subgroup. The low total number of cases, all of which occurred in the placebo group, limits the interpretability of the VE results because of the wide confidence intervals, but are displayed for completeness.

Table 13. Subgroup Analyses of Vaccine Efficacy by Demographic and Baseline Characteristics: Updated Vaccine Efficacy Against Confirmed COVID-19 in Participants With or Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population

Subgroup	BNT162b2 (N[a] =1119) Cases n1[b] Surveillance Time[c] (n2[d])	Placebo (N[a] =1109) Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy (%) (95% CI[e])
Overall	0 0.362 (1098)	30 0.345 (1088)	100.0 (87.5, 100.0)
Age group: 12-13 years	0 0.180 (521)	13 0.168 (503)	100.0 (69.3, 100.0)
Age group: 14-15 years	0 0.183 (577)	17 0.178 (585)	100.0 (76.5, 100.0)
Sex: Female	0 0.179 (548)	12 0.169 (527)	100.0 (66.1, 100.0)
Sex: Male	0 0.183 (550)	18 0.177 (561)	100.0 (78.0, 100.0)
Ethnicity: Hispanic or Latino	0 0.045 (127)	7 0.040 (125)	100.0 (37.8, 100.0)
Ethnicity: Not Hispanic or Latino	0 0.317 (969)	23 0.304 (960)	100.0 (83.3, 100.0)
Race: Black or African American	0 0.019 (47)	2 0.021 (56)	100.0 (-492.9, 100.0)
Race: White	0 0.309 (945)	28 0.291 (926)	100.0 (86.8, 100.0)
Country: United States	0 0.362 (1098)	30 0.345 (1088)	100.0 (87.5, 100.0)

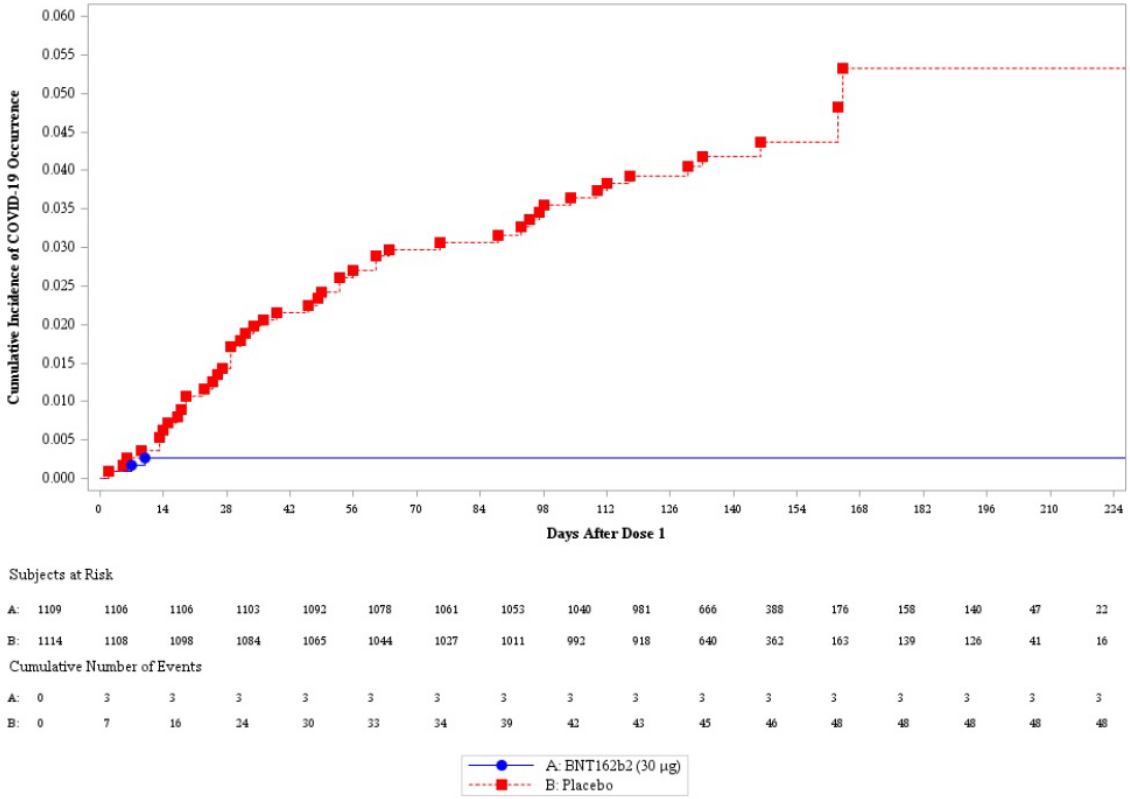
Source: STN 125742.45 c4591001-508-efficacy tables-12-15, Table L, Page 20
Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.

c. 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.
d. n2 = Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Cumulative incidence curves

Based on the cumulative incidence curve for the all-available efficacy population after Dose 1, (Figure 2), COVID-19 disease onset appears to occur similarly for both BNT162b2 and placebo groups until approximately 14 days after Dose 1, at which time point, the curves diverge.

Figure 2. Updated Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, All-Available Efficacy Population (data cutoff September 2, 2021)



Source: Adapted from STN 125742.45 c4591001-interim-ado-mth6-report-body.pdf, Figure 1, Page 73

An updated analysis of the number of confirmed COVID-19 cases following Dose 1 was conducted with the all-available efficacy population, for all participants regardless of evidence of prior infection through 7 days after Dose 2, and at time intervals following completion of the vaccine series (Table 14).

Table 14. Updated Vaccine Efficacy after Dose 1, Dose 1 All-Available Efficacy Population

Efficacy Endpoint Subgroup	BNT162b2 (N[a] =1131) Cases n1[b] Surveillance Time[c] (n2[d])	Placebo (N[a] =1129) Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence after Dose 1	3 0.450 (1109)	48 0.434 (1114)	94.0 (81.3, 98.8)
After Dose 1 to before Dose 2	3 0.065 (1109)	12 0.065 (1114)	75.1 (7.6, 95.5)
Dose 2 to 7 days after Dose 2	0 0.021 (1103)	5 0.021 (1100)	100.0 (-8.7, 100.0)
≥7 Days after Dose 2	0 0.364 (1102)	31 0.348 (1095)	100.0 (87.9, 100.0)
≥7 Days after Dose 2 to <2 Months after Dose 2	0 0.146 (1102)	17 0.142 (1095)	100.0 (76.3, 100.0)
≥2 Months after Dose 2 to 4 Months after Dose 2	0 0.156 (1065)	10 0.149 (1029)	100.0 (57.3, 100.0)
≥4 Months after Dose 2	0 0.062 (770)	4 0.056 (732)	100.0 (-37.7, 100.0)

Source: STN 125742.45 c4591001-interim-ado-mth6-report-body.pdf, Table 15, Page 72
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. 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.
d. n2 = Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

The VE estimate for the prevention of COVID-19 disease after Dose 1 in the all-available efficacy population is 94.0%. Based on the number of cases accumulated after Dose 1 and before Dose 2, there does seem to be some protection against COVID-19 disease following one dose; however, these data do not provide information about longer term protection beyond 3 weeks after a single dose, especially given the small number of total confirmed COVID-19 cases overall.

6.1.11.2 Analyses of Secondary Endpoints

There were no reports of severe COVID-19 cases (and no cases of MIS-C) in participants 12-15 years of age.

6.1.11.4 Dropouts and/or Discontinuations

The number of participants who dropped out and/or discontinued from the study did not affect the interpretation of the vaccine efficacy outcomes. Refer to Section 6.1.12.7 for details regarding dropouts and/or discontinuations.

6.1.11.5 Exploratory and Post Hoc Analyses

Sequencing Data from Centrally Confirmed COVID-19 Cases

Enrollment of adolescents 12-15 year of age in the Phase 3 portion of Study C4591001 was from October 15, 2020 through the data cutoff date of September 2, 2021. Sequence data were available for 29 of 30 SARS-CoV-2 variants identified from COVID-19 cases; 7 were B.1.1.7 (Alpha) and 29 were categorized as Other.

Reviewer Comment: All confirmed COVID-19 cases in the updated efficacy analyses occurred between November 2020 and May 2021, prior to the circulation of the B.1.61.2 (Delta) and B.1.1.529 (Omicron) variants in the US.

6.1.12 Safety Analyses

The Phase 2/3 safety data presented in this section are categorized in following time periods:

1. Blinded placebo-controlled period: Dose 1 to unblinding date, with a median follow-up duration of 4.4 months:
   - Participants with up to ~6 months after Dose 2 (N=2260; BNT162b2 group N=1131 and placebo group N=1129).
   - Solicited local and systemic Adverse Reactions were assessed for 7 days following vaccination in all participants.
2. Open-label observational period: from time of unblinding to data cutoff date, with a median follow-up duration of 4.0 months for both groups:
   - Participants originally randomized to BNT162b2 (N=1107)
   - Participants originally randomized to placebo who then received BNT162b2 (N=1010)
   - Only unsolicited AEs (AEs, SAEs and adverse events of special interest [AESIs]) were assessed during this time period.
3. Cumulative follow-up from Dose 1 to at least 6 months after Dose 2, with a median follow-up duration of 8.4 months after Dose 2.::
   - Participants originally randomized to BNT162b2 (inclusive of blinded data and open-label data through the September 2, 2021 data cutoff). (N=1113*)*

Reviewer Comment: Interpretation of safety data from the open-label observational period are limited because there was no longer a placebo group for safety comparisons in the unblinded portion of the study.

6.1.12.1 Methods

Please see Section 6.1.7.

6.1.12.2 Overview of Adverse Events

Overview of adverse events

Table 15 below presents an overview of adverse events reported, which includes immediate unsolicited adverse events, solicited local and systemic reactions, unsolicited adverse events reported from Dose 1 to 1 month after Dose 2 and from Dose 1 to the September 2, 2021 data cutoff or participant unblinding, whichever was earlier, in the safety population.

Table 15. Safety Overview, Participants 12-15 Years of Age, Safety Population

Event	BNT162b2 n[a]/N[b] (%)	Placebo n[a]/N[b] (%)
Immediate unsolicited AE within 30 minutes after vaccination		
Dose 1	0/1131 (0.0)	4/1129 (0.4)
Dose 2	2/1124 (0.2)	3/1117 (0.3)
Solicited injection site reaction within 7 days[a]		

Event	BNT162b2 n[a]/N[b] (%)	Placebo n[a]/N[b] (%)
Dose 1	976/1127 (86.6)	271/1127 (24.0)
Dose 2	872/1097 (79.5)	198/1078 (18.4)
Solicited systemic AE within 7 days[a]		
Dose 1	877/1127 (77.8)	636/1127 (56.4)
Dose 2	904/1097 (82.4)	440/1078 (40.7)
Dose 1 through 1 Month after Dose 2[b]		
Unsolicited non-serious AE	72/1131 (6.4)	76/1129 (6.7)
SAE	4/1131 (0.4)	1/1129 (0.1)
Dose 1 to data cutoff or participant unblinding (whichever is earlier)[b]		
Any unsolicited AE	95/1131 (8.4)	113/1129 (10.0)
SAE	10/1131 (0.9)	2/1129 (0.2)
Withdrawal due to AE	1/1131 (0.1)	0
Death	0	0

Source: STN 125742.45 c4591001-508-compliant-tables 12-15 years.pdf, Table P, page 25 and STN 125742.45.7 response-14march2022.pdf, Table 2, pages 5-8.
Note: Medical Dictionary for Regulatory Activities (v24.0) coding dictionary applied.
Note: Immediate AE refers to an AE reported in the 30-minute observation period after vaccination.
a. N: number of participants in the specified age group in the reactogenicity subset of the safety population with data available for the adverse event.
b. N: number of participants in the safety population.

> *Reviewer Comment:* Since the last data cutoff on March 13, 2021 (described in the Adolescent EUA Review Memo) to this September 2, 2021 data cutoff, there have been no additional reports of immediate unsolicited AEs or local or systemic reactions. A total of 16 new unsolicited non-serious AEs were reported from Dose 1 through 1 month after Dose 2 (n=6 and n=10 in the BNT162b2 and placebo groups, respectively), none of which were serious or led to withdrawal. These new reported non-serious AEs were consistent with events described in the EUA Review Memo. Please refer to the Adolescent EUA Review Memo for details.

Immediate AEs

The immediate AEs that occurred were consistent with solicited reactions/events (injection site pain, headache, dizziness, fatigue, chills) reported among participants in the reactogenicity subset during the first 7 days following vaccination.

One (1) BNT162b2 recipient and 1 placebo recipient reported symptoms on the day of vaccination that were consistent with pre-syncope (after BNT162b2 Dose 2 and after placebo dose 1, respectively). Vasovagal reactions are not uncommon in adolescents following vaccinations and other medical procedures involving needlesticks; the Prescribing Information and Fact Sheet for Healthcare Providers for the authorized Pfizer-BioNTech COVID-19 Vaccine include a warning about measures to avoid injury following vasovagal/syncopal episodes in the immediate post-vaccination period.

Anaphylaxis

No anaphylactic reactions to BNT162b2 were reported through the cutoff date of September 2, 2021.

Solicited local reactions and systemic adverse events

Solicited Local Reactions

For BNT162b2 recipients 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. Injection site reactions following both doses were mostly mild to moderate. Injection site reactions were more frequent in the BNT162b2 group than in the placebo group.

Table 16. Frequency of Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose, Participants 12 Through 15 Years of Age, Safety Population[a]

	BNT162b2 Dose 1 N =1127 n (%)	Placebo Dose 1 N =1127 n (%)	BNT162b2 Dose 2 N =1097 n (%)	Placebo Dose 2 N =1078 n (%)
Pain at the injection site[b]				
Any[d]	971 (86.2)	263 (23.3)	866 (78.9)	193 (17.9)
Mild	467 (41.4)	227 (20.1)	466 (42.5)	164 (15.2)
Moderate	493 (43.7)	36 (3.2)	393 (35.8)	29 (2.7)
Severe	11 (1.0)	0	7 (0.6)	0
Redness[c]				
Any[d]	65 (5.8)	12 (1.1)	55 (5.0)	10 (0.9)
Mild	44 (3.9)	11 (1.0)	29 (2.6)	8 (0.7)
Moderate	20 (1.8)	1 (0.1)	26 (2.4)	2 (0.2)
Severe	1 (0.1)	0	0	0
Swelling[c]				
Any[d]	78 (6.9)	11 (1.0)	54 (4.9)	6 (0.6)
Mild	55 (4.9)	9 (0.8)	36 (3.3)	4 (0.4)
Moderate	23 (2.0)	2 (0.2)	18 (1.6)	2 (0.2)
Severe	0	0	0	0

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Tables R and R.1, pages 18-19.
Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.
%: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.
a. All randomized participants in the reactogenicity subset who received at least 1 dose of the study intervention.
b. Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
c. Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.
d. Any local reaction: any redness >2.0 cm, any swelling >2.0 cm, or any pain at the injection site.

Solicited Systemic Reactions

Among BNT162b2 recipients 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. Solicited systemic AEs following both doses were mostly mild to moderate. 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. Systemic AEs were more frequently reported in BNT162b2 recipients than in the placebo group.

Table 17. Frequency of Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose, Participants 12 Through 15 Years of Age, Safety Population[a]

	BNT162b2 Dose 1 N =1127 n (%)	Placebo Dose 1 N =1127 n (%)	BNT162b2 Dose 2 N =1097 n (%)	Placebo Dose 2 N =1078 n (%)
Fever				
≥38.0℃	114 (10.1)	12 (1.1)	215 (19.6)	7 (0.6)
≥38.0℃ to 38.4℃	74 (6.6)	8 (0.7)	107 (9.8)	5 (0.5)
>38.4℃ to 38.9℃	29 (2.6)	2 (0.2)	83 (7.6)	1 (0.1)
>38.9℃ to 40.0℃	10 (0.9)	2 (0.2)	25 (2.3)	1 (0.1)
≥40.0℃	1 (0.1)	0	0	0
Fatigue[b]				
Any[e]	677 (60.1)	457 (40.6)	726 (66.2)	264 (24.5)
Mild	278 (24.7)	250 (22.2)	232 (21.1)	133 (12.3)
Moderate	384 (34.1)	199 (17.7)	468 (42.7)	127 (11.8)
Severe	15 (1.3)	8 (0.7)	26 (2.4)	4 (0.4)
Headache[b]				
Any[e]	623 (55.3)	396 (35.1)	708 (64.5)	264 (24.5)
Mild	361 (32.0)	256 (22.7)	302 (27.5)	170 (15.8)
Moderate	251 (22.3)	131 (11.6)	384 (35.0)	93 (8.6)
Severe	11 (1.0)	9 (0.8)	22 (2.0)	1 (0.1)
Chills[b]				
Any[e]	311 (27.6)	109 (9.7)	455 (41.5)	74 (6.9)
Mild	195 (17.3)	82 (7.3)	221 (20.1)	53 (4.9)
Moderate	111 (9.8)	25 (2.2)	214 (19.5)	21 (1.9)
Severe	5 (0.4)	2 (0.2)	20 (1.8)	0
Vomiting[c]				
Any[e]	31 (2.8)	10 (0.9)	29 (2.6)	12 (1.1)
Mild	30 (2.7)	8 (0.7)	25 (2.3)	11 (1.0)
Moderate	0	2 (0.2)	4 (0.4)	1 (0.1)
Severe	1 (0.1)	0	0	0
Diarrhea[d]				
Any[e]	90 (8.0)	82 (7.3)	65 (5.9)	44 (4.1)
Mild	77 (6.8)	72 (6.4)	59 (5.4)	39 (3.6)
Moderate	13 (1.2)	10 (0.9)	6 (0.5)	5 (0.5)
Severe	0	0	0	0
New or worsened muscle pain[b]				
Any[e]	272 (24.1)	148 (13.1)	355 (32.4)	90 (8.3)
Mild	125 (11.1)	88 (7.8)	152 (13.9)	51 (4.7)
Moderate	145 (12.9)	60 (5.3)	197 (18.0)	37 (3.4)
Severe	2 (0.2)	0	6 (0.5)	2 (0.2)
New or worsened joint pain[b]				
Any[e]	109 (9.7)	77 (6.8)	173 (15.8)	51 (4.7)
Mild	66 (5.9)	50 (4.4)	91 (8.3)	30 (2.8)
Moderate	42 (3.7)	27 (2.4)	78 (7.1)	21 (1.9)
Severe	1 (0.1)	0	4 (0.4)	0
Use of antipyretic or pain medication[f]	413 (36.6)	111 (9.8)	557 (50.8)	95 (8.8)

Source: STN 125742.45.7 response-14march2022.pdf, Table 2, pages 5-8.
Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.

%: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.
a All randomized participants in the reactogenicity subset who received at least 1 dose of the study intervention.
b Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.
c Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.
d 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.
e Any systemic event: any fever ≥38.0° C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
f Severity was not collected for use of antipyretic or pain medication.

> *Reviewer comment:* Minor revisions were made to the solicited systemic reactions since the EUA was issued for this age group in May 2021, because of a delayed data synchronization for e-diary data upload from one placebo recipient. This resulted in no changes to local reactions and minor changes for headache, chills and diarrhea (n=1 for each) for systemic reactions. Conclusions regarding reactogenicity were unchanged.

Subgroup analyses
Among 12-15-year-old BNT162b2 recipients, the frequencies of solicited local and systemic reactions were generally similar among males and females.

After Dose 2, Hispanic/Latino vaccine recipients reported notably lower rates for certain systemic AEs and higher rates for certain local reactions than non-Hispanic/non-Latino vaccine recipients.

- any fever: 9.4% (95%CI 4.9, 15.8) vs. 21.0% (95% CI 18.5, 23.7)
- any headache: 51.6% (95%CI 42.6, 60.5) vs. 66.3% (95% CI 63.2, 69.3)

These findings were accompanied by less antipyretic use after Dose 2 among Hispanic/Latino vaccine recipients compared with non-Hispanic/Latino vaccine recipients.

- any injection site swelling: 11.4% (95%CI 6.5, 18.0) vs. 4.7% (95% CI 3.4, 6.2)
- any injection site pain: 89.4% (95%CI 82.8, 94.1) vs. 79.1% (95% CI 76.4, 81.6)

Reactogenicity after Dose 1 was similar among Hispanic/Latino and non-Hispanic/non-Latino vaccine recipients.

The frequencies of solicited local reactions and systemic AEs were generally similar by race. While the proportions of African American, Asian and other racial groups in the study were reflective of the general distribution in the US population, the numbers of BNT162b2 recipients in these racial groups are too small (total n=157) to make definitive conclusions.

Reactogenicity in BNT162b2 recipients who were SARS-CoV-2 positive prior to Dose 1 (n=46) was similar to the overall population of vaccine recipients, but the number of subjects was too small to make definitive conclusions.

Unsolicited Non-serious AEs
Dose 1 through 1 month after Dose 2
Overall, among 12-15-year-olds, approximately 6.5% and 6.8% of participants in each treatment group (BNT162b2 and placebo, respectively) reported at least 1 non-serious AE from Dose 1 through 1 month after Dose 2 in ongoing follow-up. Differences in

frequencies of AEs between the vaccine and placebo groups were notable for fever with onset within 7 days after vaccination, nausea and lymphadenopathy.

Reactogenicity
Five (0.4%) BNT162b2 and 0 placebo recipients reported fever. AEs in the Medical Dictionary for Regulatory Activities System Organ Class (SOC) General disorders and administration site conditions were most frequently reported of all non-serious, unsolicited AEs in the BNT162b2 and placebo groups, of which injection site pain (0.6% BNT162b2, 0.6% placebo) and fatigue (0.6% BNT162b2, 0.4% placebo) were most common.

Nausea
Five (0.4%) BNT162b2 and 2 (0.2%) placebo recipient reported nausea. AEs in the Medical Dictionary for Regulatory Activities System Organ Class (SOC) Gastrointestinal Disorders were the second most frequently reported of all non-serious, unsolicited AEs in the BNT162b2 and placebo groups, of which nausea (0.4% BNT162b2, 0.2% placebo) and diarrhea (0.3% BNT162b2, 0.1% placebo) were most common.

Lymphadenopathy
A total of 9 (0.7%) BNT162b2 recipients and 2 (0.2%) placebo recipients reported lymphadenopathy. Of those, 7 (0.6%) BNT162b2 recipients and 1 (0.1%) placebo recipient were considered related to study intervention by the investigator; all of the events occurred within 2-10 days after study intervention and were located mainly in the arm/neck (axillary, cervical, supraclavicular lymph nodes). The majority of events were mild, with one moderate event reported in the BNT162b2 group. The median onset of lymphadenopathy following BNT162b2 was 5 days after Dose 1, with a shorter median onset of 4 days following Dose 2 of BNT162b2. Median duration of lymphadenopathy was 6 days in the BNT162b2 group and 25.5 days in the placebo group. Three additional reports of lymphadenopathy (2 BNT162b2 recipients and 1 placebo recipient) were assessed as unrelated by the study investigator due to onset 28 days after Dose 2 in the 2 BNT162b2 recipients and concurrent infectious mononucleosis in the placebo recipient. FDA agrees with the investigator's assessments.

A total of 16 new unsolicited non-serious AEs occurred since the time of the EUA for this age group from Dose 1 through 1 month after Dose 2 (n=6 and n=10 in the BNT162b2 and placebo groups, respectively), none of which were serious or led to withdrawal. These new reported non-serious AEs in BNT162b2 recipients were consistent with reactogenicity events (chills, fatigue, injection site pain, injection site swelling, pyrexia) or common events for this age group (sports injuries, infections, acne).

<u>Dose 1 to data cutoff date or participant's unblinding date (whichever was earlier)</u>
Other than reactogenicity, nausea and lymphadenopathy reported from Dose 1 through 1 month after Dose 2, there were no other notable patterns between treatment groups for specific categories (SOC and Preferred Term (PT)) of non-serious adverse events, including Bell's palsy, facial paralysis/paresis, other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to BNT162b2 vaccine.

Open-label observational follow-up: from participant unblinding to the September 2, 2021 data cutoff

Original BNT162b2 recipients

Overall, 1107 original BNT162b2 recipients were followed after unblinding. Of these, 18 (1.6%) participants reported any adverse event; 4 (0.4%) participants had at least 1 occurrence of an event that was considered related to the vaccine, and 3 (0.3%) participants had at least 1 occurrence of an event that was graded as severe.

Overall, the rates of AEs in all System Organ Classes (SOCs) after the unblinding date decreased or remained similar to those in the blinded placebo-controlled period. The most commonly reported events occurred in the SOC of General disorders and administration site conditions with 4 (0.4%) participants reporting at least 1 event, and the Preferred Term (PT) Injection site pain had the highest number of participants (n=3).

Of the 4 participants who reported at least 1 event considered related to the vaccine, the events were similar to reactogenicity events, reflecting AEs within 7 days of vaccination or events reported more than 7 days from vaccination indicating either recurrent or prolonged reactogenicity symptoms. Note that one participant can report multiple events.

The most common SOCs and PTs are listed below:

- 4 participants reported at least 1 event in the SOC General disorders and administration site conditions: Injection site pain (3), Fatigue (2), Pyrexia (2) and Pain (1).
- 2 participants reported at least 1 event in the SOC Nervous system disorders: Headache (2) and Dizziness (1).

Placebo recipients who were unblinded and received BNT162b2

Overall, 1010 original placebo participants were unblinded and received BNT162b2. The number of participants reporting any AE and at least 1 related AE were 265 (26.2%) and 242 (24.0%), respectively. The number of participants reporting severe AEs was 12 (1.2%).

After participants who originally received placebo were unblinded and then received BNT162b2, events related to reactogenicity were not reported using an e-diary but were reported as unsolicited AEs. Because an e-diary was not used after original placebo recipients received open-label BNT162b2, in comparison to participants randomized to BNT162b2 from Dose 1 to the unblinding date, the frequencies for any AE and at least 1 related AE for participants who originally received placebo and then received BNT162b2 are greater (26.2% and 24.0%) than the frequencies (8.4% and 3.2%) for participants who originally received BNT162b2, respectively. However, the frequencies for severe AEs were similar (1.2% versus 1.1%).

Immediate adverse events after either BNT162b2 dose (Dose 3 or 4, for original placebo recipients), were low in frequency (n=7 [0.7%]) Most immediate AEs after BNT162b2 were primarily injection site reactions, with injection site pain (n=6 [0.6%]) most frequently reported and 1 participant with injection site erythema.

Most AEs reported from Dose 3 (first dose of BNT162b2) to the data cutoff were in SOCs with reactogenicity events.

- general disorders and administration site conditions (225 [22.3%])

- nervous system disorders (75 [7.4%])
- musculoskeletal and connective tissue disorders (48 [4.8%])
- gastrointestinal disorders (20 [2.0%])

The most frequently reported AEs were injection site pain (15.5%), fatigue (10.3%), headache (7.0%), pyrexia (6.3%), chills (4.5%), myalgia (3.8%), pain (3.5%), nausea (1.2%), pain in extremity (0.9%), vomiting (0.7%), malaise (0.7%), and injection site erythema (0.5%).

To examine the time period for collection of reactogenicity events, an analysis of AEs reported within 7 days after each vaccine dose was evaluated. Preferred terms (PTs) reported from Dose 3 to 7 days after Dose 3 and from Dose 4 to 7 days after Dose 4 were in the SOCs of general disorders and administration site conditions (injection site pain, fatigue, chills, pyrexia, and pain), nervous system disorders (headache), musculoskeletal and connective tissue disorders (myalgia), and gastrointestinal disorders (nausea) and represented the majority of PTs reported in those SOCs. These events appear to be attributable to common local and systemic reactions known to occur after receipt of BNT162b2. One participant reported a nonserious AE of right axillary lymphadenitis on Day 6 after Dose 3, which was moderate in severity and resolved after 24 days. The investigator assessed this AE as related to the study intervention, and FDA agrees with the investigator assessment.

Placebo-controlled and Open-label follow up from Dose 1 to 6 Months after Dose 2: Original BNT162b2 Participants

A total of 1113 participants who originally received BNT162b2 had at least 6 months of follow-up post-Dose 2. Of these, 98 (8.8%) participants reported at least 1 AE, and 34 (3.1%) participants reported at least 1 related AE. The most frequently reported AEs were reactogenicity events: General disorders and administration site conditions reported in 16 (1.4%), Musculoskeletal and connective tissue disorders reported in 8 (0.7%), Nervous system disorders reported in 16 (1.4%) and Gastrointestinal disorders reported in 16 (1.4%). Additionally, all 9 of the reports of lymphadenopathy occurred from Dose 1 to 1 month after Dose 2 and none were reported from 1 month to 6 months after Dose 2.

When frequencies of AEs for participants with at least 6 months of follow-up time are examined by time since the second dose, the frequency of AEs and related AEs is 6.3% and 3.1% through 1 month after Dose 2 compared with 3.1% and no related events from 1 month after Dose 2 to 6 months after Dose 2.

Subgroup Analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of solicited or unsolicited in these subgroups were generally consistent with the overall study population.

6.1.12.3 Deaths

There were no deaths during the reporting period of Dose 1 to the September 2, 2021 data cutoff date.

6.1.12.4 All Serious Adverse Events (SAEs)

Dose 1 through 1 month after Dose 2

SAEs from Dose 1 through up to 30 days after Dose were reported by 4 (0.4%) BNT162b2 recipients and 1 (0.1%) placebo recipients, all of whom were SARS-CoV-2 negative at baseline.

BNT162b2 group:

- 3 participants, all with pre-existing anxiety and depression, were hospitalized for medical management of depression exacerbation that started 7 days after Dose 1, 1 day after Dose 2, and 15 days after Dose 1, respectively. All 3 participants reported treatment with a selective serotonin reuptake inhibitor (SSRI) that began within 1-2 months prior to vaccination. Worsening suicidal ideas with initial SSRI treatment in adolescents is a recognized risk and provides a reasonable alternative explanation for depression exacerbation in these BNT162b2 recipients.
- One participant experienced an SAE reported as generalized neuralgia, and also reported 3 concurrent non-serious AEs (abdominal pain, abscess, gastritis) and 1 concurrent SAE (constipation) within the same week. The participant was eventually diagnosed with functional abdominal pain. The event was reported as ongoing at the time of the cutoff date.

Placebo group:

- One participant was hospitalized for appendicitis 19 days after Dose 2. The event resolved after 2 days, and the participant continued in the study.

Dose 1 to data cutoff date or participant's unblinding date (whichever was earlier)

SAEs were reported by 10 (0.9%) and 2 (0.2%) of participants in the BNT162b2 and placebo groups, respectively. Since the time of the EUA data cutoff, 6/10 of these SAEs were reported by BNT162b2 recipients and none were reported by placebo recipients; the events were similar in nature to those that occurred from Dose 1 through 1 month after Dose 2, described above , but the 6 new SAEs (anal abscess, femur fracture, conversion disorder, suicidal ideation [n=3]) occurred at longer time intervals since vaccination which further decreases the likelihood of relatedness to BNT162b2. All SAEs were assessed by the investigator as not related to study intervention and FDA agrees with the assessment that the SAEs were unlikely to be related to study intervention.

Open-label follow-up: from participant unblinding to the September 2, 2021 data cutoff

Original BNT162b2 recipients

Overall, 1107 original BNT162b2 recipients were followed after unblinding. Of these, 4 (0.4%) participants reported at least 1 SAE, none of which were considered related to vaccination and FDA agrees with those assessments. Two participants experienced appendicitis 148 and 177 days after Dose 2, 1 participant experienced an upper limb fracture and 1 participant reported syringomelia.

Placebo recipients who were unblinded and received BNT162b2

Overall, 1010 original placebo recipients were unblinded and received BNT162b2. The number of participants reporting SAEs was 6/1010 (0.6%), four of which were considered not related by the investigator (epilepsy in participant with family history of epilepsy, traumatic renal injury, major depression, somnolence) and two of which were considered related to vaccination by the investigator:

- One participant had myocarditis 3 days after Dose 4 (second BNT162b2 dose), which presented with acute chest pain and recent cough, runny nose and low grade fever. The participant was evaluated in an emergency room, found to have EKG findings consistent with myocarditis, elevated troponin levels and a positive respiratory PCR panel result for rhinovirus (negative for enterovirus, Parvovirus B19 and SARS CoV-2 PCR). The participant was hospitalized for pain management until troponin levels normalized after 2 days. The participant has since returned to normal physical activities and continues outpatient follow up with a cardiologist. FDA agrees that this SAE was possibly related to vaccination; myocarditis is a known identified risk following BNT162b2 vaccination.
- One participant had appendicitis 4 days after Dose 4 (second BNT162b2 dose) which resolved within a day following appendectomy. While this SAE occurred within several days of vaccination, FDA considers this event as unrelated to vaccine because there is no clear basis upon which to suspect that cases of appendicitis represent a vaccine-related event. Additionally, postmarketing safety surveillance comparing appendicitis incidence in vaccinated versus unvaccinated individuals has not supported appendicitis as an adverse reaction.

Placebo-controlled and Open-label follow up from Dose 1 to 6 Months after Dose 2: Original BNT162b2 Participants

A total of 1113 participants who originally received BNT162b2 had at least 6 months of follow-up post-Dose 2. SAEs were reported by 10 (0.9%) participants.
In the first month after Dose 2, 0.3% participants reported SAEs. From 1 month post Dose 2 to 6 months after Dose 2, the frequency of SAEs was 0.8%. The following SOCs did not occur from Dose 1 through 1 month after Dose 2, but were reported from 1 month after Dose 2 to 6 months after Dose 2:

- Infections and infestations (anal abscess and appendicitis: 0 vs 2 (0.2%)
- Congenital, familial and genetic disorders (syringomelia): 0 vs 1 (0.1%)
- Injury, poisoning, and procedural complications (femur fracture): 0 vs 1 (0.1%)
- Gastrointestinal disorders (abdominal pain, constipation in the same participant): 0 vs 1 (0.1%)

The frequency of SAEs reported in the psychiatric disorders SOC was similar from Dose 1 to 1 month after Dose 2 (n=3) versus 1 month after Dose 2 to 6 months after Dose 2 (n=4). None of these SAEs were considered related to the study intervention, and FDA agrees with the investigator's assessment.

No AEs leading to withdrawal were reported during the blinded and open-label follow-up periods in the group of original BNT162b2 recipients with at least 6 months of follow-up after Dose 2.

Subgroup Analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of non-fatal serious adverse events in these subgroups were generally consistent with the overall study population.

6.1.12.7 Dropouts and/or Discontinuations

Dose 1 to data cutoff date or participant's unblinding date (whichever was earlier)

From Dose 1 to the unblinding date, 1 (0.1%) participant in the BNT162b2 group had an AE of pyrexia (104.7ºF 1 day after Dose 1) leading to withdrawal that was assessed by the investigator as related to study intervention. FDA agrees with the investigator assessment.

Open-label follow-up: from participant unblinding to the September 2, 2021 data cutoff
Placebo recipients who unblinded to receive BNT162b2
From Dose 3 (first dose of BNT162b2 30 µg) administration to the data cutoff date, there were no original placebo recipients who were withdrawn because of AEs.

Original BNT162b2 Participants
From the unblinding date to the data cutoff date, there were no original BNT162b2 recipients who were withdrawn because of AEs.

Placebo-controlled and Open-label follow up from Dose 1 to 6 Months after Dose 2: Original BNT162b2 Participants
From Dose 1 to 6 months after Dose 2 during the blinded and open-label follow-up time periods, no participants with at least 6 months of follow-up time after Dose 2 withdrew because of AEs.

6.1.13 Study Summary and Conclusions

This randomized, blinded, placebo-controlled multinational clinical trial evaluated the safety, immunogenicity, and efficacy of a two-dose primary series of BNT162b2 in a total of 2260 participants 12-15 years of age. A total of 99.4% participants received 2 doses, and the median duration of follow-up after Dose 2 in the blinded placebo-controlled period was 4.4 months. A total of 1010 original placebo recipients were unblinded and received BNT162b2, with a median open-label follow-up duration of 4.0 months after unblinding. A total of 1113 original BNT162b2 recipients had total (blinded and open-label) follow-up duration of at least 6 months after Dose 2, with a median total follow-up duration of 8.4 months after Dose 2.

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 (the most clinically relevant subgroup of the study population in whom VE has been demonstrated). In the planned immunobridging analyses, the GMR of neutralizing antibody titers (adolescents to young adults) was 1.77 (95% CI: 1.50, 2.09), meeting the success criterion (lower bound of the 95% CI for the GMR >0.67). Immunogenicity outcomes were consistent across demographic subgroups. In the updated descriptive efficacy analyses, VE after 7 days post Dose 2 was 100%, (95% CI: 86.8; 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. There were no cases of severe COVID-19.

Local and/or systemic solicited reactions following vaccination were generally of short duration and occurred more commonly in the BNT162b2 group than the placebo group, which included pain at the injection site (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%). Overall, SAEs were infrequently reported by participants in both groups. Adverse reactions other than solicited reactogenicity events identified from the clinical trial data include myocarditis,

lymphadenopathy and nausea (the latter from a small numerical imbalance of temporally associated events, likely consistent with reactogenicity). There were no reported deaths or pregnancies. Study conclusions are somewhat limited by the small sample size and exclusion of participants with certain types of immunocompromise.

7. Integrated Overview of Efficacy

Not applicable (only 1 study included in this sBLA)

8. Integrated Overview of Safety

Not applicable (only 1 study included in this sBLA)

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There were no pregnancies reported from participants 12-15 years of age. As part of the postmarketing surveillance, the Applicant will perform a pregnancy registry study to assess pregnancy and infant outcomes after exposure to BNT162b2 during pregnancy among pregnant women aged 18 years or older who reside in the US or Canada. (Study C4591022). Additionally, a randomized controlled trial in pregnant women (Study C4591015) is ongoing.

9.1.2 Use During Lactation

It is not known if BNT162b2 is secreted in human breast milk. Data are not available to assess the effects of BNT162b2 on the breastfed infant or on milk production.

9.1.3 Pediatric Use and PREA Considerations

The safety and effectiveness data from study C4591001 participants 12-15 years of age fulfill the Pediatric Research Equity Act (PREA) requirement for assessment of the vaccine in this age group. As a condition of the August 2021 FDA approval of Comirnaty for use in individuals 16 years of age and older, the Applicant must also complete and submit results of assessments of the vaccine in pediatric age groups from birth through <12 years.

9.1.4 Immunocompromised Individuals

Similar to other preventive vaccines, a 2-dose primary series of Comirnaty may have decreased effectiveness in immunocompromised individuals compared with healthy individuals. Based on published reports of low antibody responses and breakthrough infections among significantly immunocompromised individuals (mainly solid organ transplant recipients) who received the two-dose vaccination series under EUA, the EUA for the Pfizer COVID-19 Vaccine allows for a third dose, at least 28 days following the second dose, in individuals at least 5 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

9.1.5 Geriatric Use

Comirnaty is approved for use in individuals 65 years of age and older, and geriatric use is not relevant to the review of this BLA supplement. Older adult participants were also enrolled to Study C4591001, and the data were reviewed with the original BLA submission (see BLA Clinical Review Memo). Among all participants (N=22026) who were originally randomized to BNT162b2 in this study and included in the safety population, 20.7% (n=4552) were 65 years of age and older and 4.2% (n=925) were 75 years of age and older. The effectiveness in geriatric participants was consistent with that seen in younger adult participants, and no safety concerns specific to the geriatric age group were identified. The reported frequencies of adverse reactions, including myocarditis/pericarditis, are lower in the geriatric age group compared with younger adults and adolescents.

10. CONCLUSIONS

The clinical data submitted to the sBLA include results of a randomized, blinded, placebo-controlled clinical trial that evaluated the safety and efficacy of BNT162b2 in 2260 participants 12-15 years of age. The immunobridging analysis results show that the immune response following receipt of 2 doses of BNT162b2, given 3 weeks apart, in participants 12-15 years of age was non-inferior to immune responses in participants 16-25 years of age (the most clinically relevant subgroup of the study population in whom VE has been demonstrated). In updated descriptive efficacy analyses, VE after 7 days post Dose 2 was 100% (95% CI: 86.8; 100.0) in participants 12-15 years of age without prior evidence of SARS-CoV-2 infection and 100% (95% CI: 87.5, 100.0) in participants with or without prior infection. Although based on a small number of cases in descriptive analyses, the supplementary VE data provide compelling direct evidence of clinical benefit in addition to the immunobridging data.

The clinical safety data submitted represent at least 1000 participants in the 12-15 years of age group with at least 6 months of total safety follow-up and met FDA expectations for an acceptable pre-licensure safety database. In the clinical trial, local and/or systemic solicited reactions following vaccination were generally of short duration and occurred more commonly in the BNT162b2 group than the placebo group. Overall, SAEs were infrequently reported by participants in both groups. Adverse reactions other than solicited reactogenicity events identified from the clinical trial data include myocarditis, lymphadenopathy and nausea (the latter from a small numerical imbalance of temporally associated events, likely consistent with reactogenicity). These imbalances support labeling of both lymphadenopathy and nausea as potential adverse reactions.

Post-authorization safety surveillance has already identified additional clinically important but infrequent adverse reactions: anaphylaxis and myocarditis/pericarditis. The risk of myocarditis, observed as highest in males 12 through 17 years of age, is being addressed by labeling in the Warnings and Precautions Section of the US package insert, by ongoing monitoring through active and passive surveillance, and by postmarketing studies to be conducted by the Applicant, US Government agencies, and other healthcare stakeholders to further evaluate and understand these risks.

Data from numerous published observational studies of real-world use of the vaccine, although not independently reviewed and confirmed by FDA, appear to corroborate the clinical benefit supported by the clinical trial results, most notably against COVID-19

associated hospitalization and death. Despite more recent real-world evidence from the Omicron predominant period indicating decreased vaccine effectiveness and waning effectiveness against more mild COVID-19 compared to that demonstrated in clinical trials during circulation of previous variants, available evidence indicates a 2-dose series continues to provide substantial protection against more severe COVID-19 and its serious outcomes caused by currently circulating SARS-CoV-2 variants; consequently, the WHO and national regulatory and public health authorities continue to endorse use of currently available COVID-19 vaccines for use in primary vaccination.

Based on the totality of data and the benefit-risk considerations as described in Section 11 below, the clinical reviewer concludes that the clinical trial data submitted in this application, and complemented by available post-authorization data and plans for post-licensure studies, support approval of BNT162b2 for the indication of active immunization to prevent symptomatic coronavirus disease 2019 (COVID 19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12-15 years of age.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 18. STN125742: Risk -Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• SARS CoV-2, a novel respiratory coronavirus causing COVID-19, is currently responsible for a global pandemic that has significantly disrupted human activity on a global scale. • COVID-19 is associated with significant morbidity, mortality (>6.3 million deaths worldwide to date) and long-term sequelae among survivors. In the US, COVID-19 has been responsible for >4.9 million hospitalizations and >1 million deaths to date. • Multiple variants of the virus are circulating and continue to emerge. Evidence of an increase in transmissibility, shorter incubation periods and/or more severe disease (e.g., increased hospitalizations or deaths) has been associated with some of these variants. • Uncertainties include: lack of complete understanding of mechanisms of pathogenesis and individual risk for severe disease; evolving epidemiology of the pandemic; and potential for emergence of SARS-CoV-2 variants with altered infectivity, virulence, and/or capacity to evade immunity from natural infection or vaccination.	• Since the beginning of the COVID-19 pandemic in early 2020, SARS-CoV-2 remains a cause of significant morbidity and mortality in the US and worldwide.
Unmet Medical Need	• Remdesivir is the only drug approved for the treatment of COVID-19, and approved use is limited to hospitalized adults and pediatric patients [12 years of age and older and weighing at least 40 kilograms (about 88 pounds)]. • Paxlovid is authorized for the treatment of mild-moderate COVID-19 in adults and children 12 years of age and older, weighing at least 40 kilograms, with positive results of direct SARS-CoV-2 testing and who are at high risk for progression to severe COVID-19. • Monoclonal antibodies are available under EUA for treatment and post-exposure prophylaxis but not for pre-exposure prophylaxis. • Comirnaty is one of two COVID-19 vaccines approved for the prevention of COVID-19. Currently, no vaccines are FDA-approved for the prevention of COVID-19 in individuals <16 years of age. This has been cited as a reason for vaccine hesitancy and refusal of some individuals to receive approved and/or EUA vaccines.	• Public health measures of social distancing and masking are helpful but do not prevent all transmission of the virus. • There is an unmet medical need in individuals <16 years of age for an FDA-approved vaccine to prevent COVID-19 caused by SARS-CoV-2.

	• Non-pharmacologic measures to prevent transmission of SARS-CoV-2 include masks, social distancing, and avoidance of high-risk situations. These actions do not prevent all infections. • Uncertainties include to what extent the recent increased incidence of new infections in the US is due to waning immunity from natural infection or vaccination, the emergence of new variants, or a combination of these factors.	
Clinical Benefit	• The immunobridging analysis results from Study C4591001 show that the immune response following receipt of 2 doses of BNT162b2, given 3 weeks apart, in participants 12-15 years of age is comparable to immune response in participants 16-25 years of age, for whom efficacy of the vaccine was previously demonstrated. • In descriptive efficacy analyses, vaccine efficacy after 7 days post Dose 2 was 100% (95% CI: 86.8; 100.0) in participants 12-15 years of age without prior evidence of SARS-CoV-2 infection. However, COVID-19 cases included in this efficacy analyses were accrued prior to emergence of currently circulating variants whose spike protein mutations are known to adversely impact effectiveness of the vaccine. • Uncertainties in clinical benefit include longer-term duration of protection; effectiveness in certain populations (e.g., significantly immunocompromised) not well represented in the clinical trial; and effectiveness against SARS-CoV-2 variants that may emerge in the future.	• The evidence for clinical benefit meets the evidentiary standards (i.e., substantial evidence of effectiveness) for approval of Comirnaty for use in individuals 12-15 years of age. • Despite real-world evidence indicating decreased vaccine effectiveness and waning effectiveness against more mild COVID-19 compared to that demonstrated in clinical trials, available evidence indicates a 2-dose series continues to provide substantial protection against more severe COVID-19 and its serious outcomes caused by currently circulating SARS-CoV-2 variants; consequently, the WHO and national regulatory and public health authorities continue to endorse use of currently available COVID-19 vaccines for use in primary vaccination. • Additional data from post-approval studies are needed to further address uncertainties in clinical benefit.

Risk	• The most frequently reported adverse reactions in the ongoing placebo-controlled trial were solicited injection site reactions (redness, swelling, and pain) and systemic adverse reactions (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain). • Among unsolicited adverse events reported in the trial, an imbalance in self-limited lymphadenopathy (9 events in vaccine recipients, mostly ipsilateral and regional to the injection site, vs. 2 events in placebo recipients) and nausea (5 events in vaccine recipients and 2 event in a placebo recipient) supports a causal association with the vaccine, consistent with events observed in older age groups. • Similar to other preventive vaccines, hypersensitivity reactions, including anaphylaxis rarely, are a known risk associated with Comirnaty. • One case of myocarditis occurred on Day 3 post Dose 2 in an adolescent participant in this trial, with resolution of symptoms with conservative management. Myocarditis and pericarditis are known to be risks associated with Comirnaty, with most cases characterized by resolution of symptoms with conservative management and return to normal activities among individuals with at least 90 days of follow-up. The risk of myocarditis/pericarditis is greatest following Dose 2 of the vaccine series and is greatest among males 12-17 years of age compared to females and compared to older and younger males. • Uncertainties related to risks of myocarditis and pericarditis include lack of precise estimates for excess risk across various age and gender subgroups (accounting for background cases of COVID-19-associated myocarditis and pericarditis that would be prevented by vaccination), whether and how frequently subclinical cases occur, and longer-term outcomes and prognoses. • The risk profile of Comirnaty is now informed by intensive post-authorization and post-approval safety surveillance following hundreds of millions of doses, including post-authorization safety surveillance in millions of adolescents 12-15 years of age. While this safety surveillance has not identified risks other than those summarized above, it is possible that additional rare but clinically important risks could be identified in the future.	• The most commonly manifested risks are mild to moderate, self-limited injection site and systemic adverse reactions. • Less commonly manifested but potentially serious risks include severe allergic reactions and myocarditis/pericarditis. Additional data are needed to better quantify the risks of myocarditis and pericarditis and to more fully understand long-term prognoses for vaccine-associated myocarditis and pericarditis.

Risk Management	• Labeling for Comirnaty describes the common and uncommon (but potentially serious) risks associated with the vaccine. The labeling includes warning statements for severe allergic reactions and myocarditis/pericarditis. • Safety surveillance efforts by the Applicant and led by US public health agencies (FDA and CDC) will continue following approval of Comirnaty for use in adolescents 12-15 years of age. • The Applicant will be required to conduct post-approval studies to further evaluate vaccine safety and effectiveness, and specifically to better understand the identified risks of vaccine-associated myocarditis and pericarditis and their long-term sequelae.	• Risk mitigation strategies for Comirnaty for use in individuals 12 years of age and older include communication of risks and benefits through labeling, directed counseling prior to vaccination according to individual risks and benefits, and a pharmacovigilance plan to further evaluate risks. • Ongoing monitoring of COVID-19 epidemiology (including emergence of variants) and vaccine effectiveness will also be critical to updating benefit risk assessments and risk mitigation strategies as the pandemic evolves over time.

11.2 Risk-Benefit Summary and Assessment

COVID-19 caused by SARS-CoV-2 is associated with a wide spectrum of manifestations, including mild illness in some individuals but severe morbidity (in some cases with long-term sequelae) and/or mortality in others. Over 6.3 million deaths attributable to COVID-19 have been reported worldwide since the beginning of the pandemic in late 2019, with >1 million US deaths since the beginning of the pandemic and >4.9 million US hospitalizations from August 2020 to the week ending on July 2, 2022. Currently, the surge of COVID-19 associated with widespread transmission of the SARS-CoV-2 Omicron variant has reached a plateau phase. While the greatest risk of severe or fatal COVID-19 is in individuals >65 years of age and those with comorbid conditions (e.g., obesity, diabetes, immunocompromising conditions), significant morbidity and mortality and long-term sequelae from COVID-19 has occurred in healthy individuals of all ages, including adolescents 12-15 years of age. In addition to individual-level morbidity and mortality, the COVID-19 pandemic has overwhelmed healthcare systems during periods of high incidence, and the effects of SARS-CoV-2 infection, COVID-19 disease, and the necessary public health measures implemented to prevent infection and illness have severely disrupted human activities on a global scale. While two COVID-19 vaccines have been approved for the prevention of COVID-19 caused by SARS-CoV-2, and emergency use authorization of the Pfizer-BioNTech COVID-19 Vaccine is available for individuals 6 months of age and older, full approval of a COVID-19 vaccine in the adolescent age group represents an important step in addressing the unmet need for approved pharmacologic interventions for the prevention of COVID-19 in pediatric age groups.

A randomized, blinded, multinational placebo-controlled trial (C4591001) that enrolled 2260 participants 12-15 years of age demonstrated the clinical benefit of Comirnaty in this age group by successful immunobridging analyses 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 (the most clinically relevant subgroup of the study population in whom vaccine efficacy has been demonstrated). Additionally, descriptive VE analyses, the VE after 7 days post Dose 2 was 100% (95% CI: 86.8; 100.0) in participants 12-15 years of age without prior evidence of SARS-CoV-2 infection and provided compelling direct evidence of clinical benefit in addition to the immunobridging results.

Data from numerous published observational studies of real-world use of the vaccine, although not independently reviewed and confirmed by FDA, appear to corroborate the clinical benefit supported by the clinical trial results, most notably against COVID-19 associated hospitalization and death. Despite more recent real-world evidence from the Omicron predominant period indicating decreased vaccine effectiveness and waning effectiveness against more mild COVID-19 compared to that demonstrated in clinical trials during circulation of previous variants, available evidence indicates a 2-dose series continues to provide substantial protection against more severe COVID-19 and its serious outcomes caused by currently circulating SARS-CoV-2 variants; consequently, the WHO and national regulatory and public health authorities continue to endorse use of currently available COVID-19 vaccines for use in primary vaccination. Remaining uncertainties regarding the clinical benefits of Comirnaty in individuals 12-15 years of age include effectiveness against asymptomatic infection and transmission of SARS-CoV-2, confirmation of more robust estimates of effectiveness in certain populations not

well represented in the clinical trial, and vaccine effectiveness against future emerging variants.

Risks associated with Comirnaty in individuals 12-15 years of age include common self-limited local and systemic adverse reactions characterized in the clinical trial, which are mostly mild to moderate and short-lived, and rare but more serious risks of anaphylaxis and myocarditis/pericarditis as detected through post-authorization safety surveillance. Although some cases of vaccine-associated myocarditis/pericarditis required intensive care support (with several suspected fatal cases under CDC investigation but not confirmed to be vaccine-associated myocarditis at the time of this review), available data from short-term follow-up suggest that most individuals affected by vaccine-associated myocarditis/pericarditis have had resolution of symptoms with conservative management and return to normal activities among individuals with at least 90 days of follow-up. Information is not yet available to further evaluate potential long-term sequelae and outcomes in affected individuals, and additional uncertainties regarding the risk of myocarditis/pericarditis include: whether and to what extent subclinical cases might occur, and if they do what are the long-term outcomes; the mechanism of pathogenesis; and individual factors conferring increased risk for vaccine-associated myocarditis/pericarditis. Based on evidence from passive surveillance and observational studies, the risk of myocarditis/pericarditis is greatest following Dose 2 of the vaccine series and is greatest among males 12-17 years of age compared to females and compared to older and younger males. Despite adolescent males 12-15 years of age being included in the age group at greatest risk for vaccine-associated myocarditis, the risk and consequences of vaccine-associated myocarditis appear to be less than the risk and consequences of cardiac complications associated with COVID-19, and the risk of vaccine-associated myocarditis is clearly offset by the benefits of the vaccine.

The risk profile of Comirnaty is now informed by intensive post-authorization and post-approval safety surveillance following hundreds of millions of doses, including post-authorization safety surveillance in millions of adolescents 12-15 years of age. While this safety surveillance has not identified risks other than those summarized above, it is possible that additional rare but clinically important risks could be identified in the future. More robust characterization of the safety profile through active safety surveillance and/or controlled observational studies should include specific populations (e.g., individuals with prior COVID-19, pregnant women, and significantly immunocompromised individuals). Nonetheless, currently available data support a benefit-risk balance that is clearly favorable for approving Comirnaty for use in individuals 12-15 years of age. Mitigation of the observed risks and associated uncertainties will be accomplished through labeling (including warning statements regarding risks of allergic reactions and vaccine-associated myocarditis/pericarditis) and through continued safety surveillance and postmarketing studies to further assess and understand these risks.

11.3 Discussion of Regulatory Options

The Pfizer-BioNTech COVID-19 Vaccine is authorized for use in individuals 6 months of age and older; Comirnaty is approved for use in individuals 16 years of age and older. Approval of Comirnaty for use in individuals as young as 12 years of age would enable this vaccine to be used under non-emergency conditions.

11.4 Recommendations on Regulatory Actions

This clinical reviewer recommends approval of Comirnaty for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

11.5 Labeling Review and Recommendations

The information in the package insert was reviewed, and requested revisions were communicated to the Applicant. The revised label is accurate, not misleading, and appropriate for the proposed use of the vaccine. The WARNINGS AND PRECAUTIONS section describes the occurrence of myocarditis and pericarditis in subjects who receive Comirnaty, and the increased risk observed for adolescents and young adult males.

11.6 Recommendations on Postmarketing Actions

There is no change to the currently required post-marketing studies as outlined in the Comirnaty Approval Letter from August 23, 2021.

APPENDIX A CHARLSON COMORBIDITY INDEX

This index is based on a list of 19 conditions identified from diagnoses in hospital and physician data. Each condition is assigned a weight from 1 to 6. The index score is the sum of the weights for all identified conditions (Charlson et al., 1987). An index score of 0 indicates no comorbid conditions, while higher scores indicate a greater level of comorbidity.

Charlson Index Diagnoses: Cancer, Chronic Pulmonary Disease, Diabetes without Complications, Congestive Heart Failure, Cerebrovascular Disease, Dementia, Renal Disease, Peripheral Vascular Disease, Myocardial Infarction, Diabetes with Complications, Paraplegia and Hemiplegia, Connective Tissue Disease-Rheumatic Disease, Peptic Ulcer Disease, Mild Liver Disease, Metastatic Carcinoma, Moderate or Severe Liver Disease, /AIDS.

Reference: Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373– 383. [PubMed: 3558716]

APPENDIX B COVID-19 AND SEVERE COVID-19 CASE DEFINITIONS

The case definition for a confirmed case of COVID-19 for the primary efficacy endpoint, was the presence of at least one of the following symptoms and a positive SARS-CoV-2 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

The case definition for severe COVID-19 case included a confirmed COVID-19 case with at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2≤93% on room air at sea level, or PaO2/FiO_2<300 mm Hg)
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation)
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to an ICU
- Death

APPENDIX C COMIRNATY-ATTRIBUTABLE MYOCARDITIS/PERICARDITIS RISKS

Table 19. International and US Data on Comirnaty-Attributable Myocarditis/Pericarditis Risks

Study	Age group	Risk of myocarditis/pericarditis (cases per 1 million doses administered)	Notes	Reference
US, VAERS	12-15	45.7 post Dose 2	Male only, 7-Day risk window, Not background rate adjusted	Su
US, VSD	12-17	70.8 post Dose 2	Male and Female, 7-day risk window, Background rate adjusted	Klein
US, BEST Data Partner	12-15	32 combined doses, females 179 combined doses, males	7-day risk window, Background rate adjusted	Unpublished data.
Israel Ministry of Health	12-15	59 post Dose 2	Male only, 21/30-Day risk window, Not background rate adjusted	Milo
South Korea	~16-18	18 [95% CI: 8,35] in one dose recipients 43 [95% CI: 26,67] in two dose recipients	12th graders (age is not accurate) Risk window- days between dose 1 and 2 and 30-days post second dose	Choe et al.

Su, John R. "COVID-19 vaccine safety updates: Primary series in children and adolescents ages 5–11 and 12–15 years, and booster doses in adolescents ages 16–24 years" Advisory Committee on Immunization Practices. January 5, 2022. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-01-05/02-COVID-Su-508.pdf

Klein, Nicola. "Vaccine Safety Datalink Rapid Cycle Analyses: Uptake and Safety of COVID-19 Vaccines in 5–11 and 12–17-Year-Olds". Advisory Committee on Immunization Practices. January 5, 2022. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-01-05/04-COVID-Klein-508.pdf

Milo, Ron, "Protection by 4th dose of BNT162b2 against Omicron in Israel", April 6th, FDA Vaccines and Related Biological Products Advisory Committee Meeting, Retrieved from https://www.fda.gov/media/157492/download on May 4, 2022.

Choe, Young June, et al. "Safety and effectiveness of BNT162b2 mRNA Covid-19 vaccine in adolescents." *Vaccine* 40.5 (2022): 691-694.