2.7.3 SUMMARY OF CLINICAL EFFICACY

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LIST OF ABBREVIATIONS

Abbreviation	Definition
BMI	body mass index
CDC	(US) Centers for Disease Control and Prevention
CI	confidence interval
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
EMA	European Medicines Agency
EUA	Emergency Use Authorization
FDA	(US) Food and Drug Administration
FiO_2	fraction of inspired oxygen
GMFR	geometric mean-fold rise
GMT	geometric mean titer
HIV	human immunodeficiency virus
ICU	intensive care unit
IM	intramuscular
LLOQ	lower limit of quantitation
MAA	Marketing Authorization Application
mRNA	messenger RNA
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein binding
NI	noninferiority
PaO_2	partial pressure of oxygen, arterial
RNA	ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS coronavirus-2; virus causing the disease COVID-19
SCE	summary of clinical efficacy
SPO_2	oxygen saturation as measured by pulse oximetry
USA	United States of America
Th1/Th2	helper T cell type 1/type 2
VE	vaccine efficacy

2.7.3. SUMMARY OF CLINICAL EFFICACY

The prophylactic mRNA-based SARS-CoV-2 vaccine developed by BioNTech and Pfizer (BNT162b2, COMIRNATY) is currently authorized in the EU under a conditional marketing authorization for the prevention of COVID-19 in individuals 16 years of age and older. This Summary of Clinical Efficacy (SCE) supports a Type II variation for use of the vaccine in individuals 12 to 15 years of age. The data supporting the indication in this age group are from Study C4591001 and include results of descriptive efficacy analyses in approximately 2200 participants 12 to 15 years of age with a median follow-up time of at least 2 months after Dose 2 (data cutoff date: 13 March 2021). The submission also includes data demonstrating the noninferiority of the immune response in adolescents 12 to 15 years of age relative to the response in young adults 16 to 25 years of age.

The proposed indication and dosing administration for BNT162b2 (30 µg) are:

- **Proposed indication**: Active immunization to prevent COVID-19 disease caused by SARS-CoV-2, in individuals ≥12 years of age
- **Dosing administration**: single 0.3 mL intramuscular (IM) dose followed by a second 0.3 mL dose 3 weeks later

2.7.3.1. Background and Overview of Clinical Efficacy

A Marketing Authorization Application (MAA) was submitted to the European Medicines Agency (EMA) via a rolling review procedure initiated on 5 October 2020 and completed with submission of clinical modules on 07 December 2020. Conditional marketing authorization was granted by EMA on 21 December 2020 for individuals 16 years of age and older. The conditional approval was based on the following data:

Phase 1/2 Study BNT162-01:

- Phase 1 safety and immunogenicity for both BNT162b1 and BNT162b2 vaccine candidates across adult age groups and dose levels up to 1 month after Dose 2.

Phase 1/2/3 Study C4591001:

- Phase 1 safety and immunogenicity for both BNT162b1 and BNT162b2 vaccine candidates across adult age groups and dose levels up to at least 1 month after Dose 2
- Phase 2 immunogenicity for BNT162b2 (30 µg) in adults up to 1 month after Dose 2
- Phase 2/3 safety for BNT162b2 (30 µg) up to a median follow-up time of at least 2 months after Dose 2 and up to the data cutoff date (14 November 2020) in participants ≥16 years of age
- Phase 2/3 efficacy analysis including prespecified interim analysis of 94 COVID-19 cases (data cutoff date: 04 November 2020) and prespecified final analysis of 170 COVID-19 cases (data cutoff date: 14 November 2020) in participants ≥12 years of age.

Content of the Summary of Clinical Efficacy

This SCE provides an overview of Study C4591001, describing study design and conduct, methods for evaluating vaccine efficacy and immunogenicity, and results from the efficacy and immunogenicity analyses in participants 12 to 15 years of age, as outlined below.

Content	Section
Overview of study design and conduct – Study C4591001	Section 2.7.3.1.1
Methods for the evaluation of efficacy	Section 2.7.3.1.2
Methods for the evaluation of immunogenicity	Section 2.7.3.1.3
Results of efficacy evaluations	Section 2.7.3.2.1
Results of immunogenicity evaluations	Section 2.7.3.2.2

2.7.3.1.1. Overview of the Clinical Development Program

2.7.3.1.1.1. Phase 1 Dose-Ranging Studies – BNT162-01 and C4591001 Phase 1

Two mRNA-based vaccine candidates (BNT162b1 and BNT162b2) were evaluated in a first-in-human dose-ranging study conducted in Germany (Study BNT162-01) and in the Phase 1, dose-ranging portion of Study C4591001, conducted in the United States. The Phase 1 studies evaluated the safety and immunogenicity of escalating dose levels of both vaccine candidates in individuals from 18 through 85 years of age.

In both studies, each vaccine was administered as a 2-dose regimen, given 21 days apart. Blood samples for evaluation of immunogenicity were to be collected at baseline (immediately before Dose 1), at 7 and 21 days after Dose 1, and at several time points after Dose 2, including 7, 14, and 28 days after Dose 2 (in both studies), and at 6, 12, and 24 months after Dose 2 in Study C4591001.

In both studies, immune responses were principally evaluated based on functional antibody titers determined using the SARS-CoV-2 neutralization assay. In addition, in Study BNT162-01, cell-mediated immune response assays were used to characterize T cell responses at baseline and approximately 7 days after Dose 2.

Based on safety and immunogenicity results from both of these studies, as well as nonclinical data, a single candidate and dose level (30 µg BNT162b2) was selected for further development.

2.7.3.1.1.2. Phase 2/3 of Study C4591001

Study Population

Initially, participants enrolled in Phase 2/3 of Study C4591001 were to be 18 to 85 years of age, in 2 age strata: 18 to 55 years ("younger participants") and 56 to 85 years ("older participants"). It was intended that a minimum of 40% of participants would be in the >55-years stratum. The protocol was later amended to lower the minimum age of participants to 16 years and to remove the upper age limit (Protocol Amendment 6, 08 September 2020).

Protocol Amendment 7 (06 October 2020) allowed for enrollment of adolescents 12 to 15 years of age as an additional age stratum. The 12- to 15-year stratum was expected to comprise up to approximately 2000 participants enrolled at selected investigational sites. Note that both of these amendments were implemented after Phase 2 of the study had been fully enrolled (N=360 participants), and therefore the Phase 2 study population included only adults 18 to 85 years of age.

Enrollment criteria for Phase 2/3 were defined to ensure a broad study population representative of the "real-world" populations expected to receive the registered vaccine. Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, were eligible for the study. Individuals were to be, in the judgment of the investigator, at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers). Individuals with medical conditions placing them at high risk of severe COVID-19 or in occupations with high risk of exposure to SARS-CoV-2 were eligible for the study. Also included were individuals with previous clinical or microbiological diagnosis of COVID-19 or with evidence of current or prior infection based on serology or nasal swab. Immunocompromised individuals were excluded, including those receiving immunosuppressive therapy or systemic corticosteroids (inhaled/nebulized corticosteroids were permitted). Initially, known infection with human immunodeficiency virus (HIV), hepatitis C virus, or hepatitis B virus were exclusionary; however, Amendment 6 (08 September 2020) allowed enrollment of individuals with stable HIV, hepatitis B, or hepatitis C. Additional selection criteria are described in the protocol (Module 5.3.5.1 C4591001 Protocol Section 5).

Vaccine Administration and Scheduled Assessments

Participants were randomized in a 1:1 ratio to receive either BNT162b2 (30 µg) or placebo (normal saline). Participants received a 2-dose regimen, administered approximately 21 days apart, at Visit 1 and at Visit 2, with Visit 2 intended to take place 19 to 23 days after Visit 1.

Blood samples were collected from all participants for immunogenicity assessments immediately before Dose 1 and 1 month after Dose 2 (Visit 3). Samples will also be collected at follow-up visits scheduled at 6 months, 12 months, and 24 months after Dose 2.

Nasal (midturbinate) swabs for detection of SARS-CoV-2 were performed at Visit 1 and at Visit 2.

The complete schedule of study activities, including all efficacy, immunogenicity, and safety evaluations is available in the protocol (Module 5.3.5.1 C4591001 Protocol Section 1.3).

Phase 2

Phase 2 of the study comprised the collection and evaluation of safety and immunogenicity data for 360 of the earliest enrollees into the Phase 2/3 portion of the study, selected for balance between the younger (18 to 55 years of age) and older (56 to 85 years of age) protocol-defined strata within each vaccine group (BNT162b2 or placebo). These participants were also included in the efficacy evaluation of the Phase 3 portion of the study.

Phase 3

Phase 3 (which is ongoing) included planned interim analyses of the first primary efficacy endpoint, ongoing efficacy evaluations, and exploratory immunogenicity evaluations in a subset of participants. Phase 3 is being conducted at sites in the United States, Brazil, Argentina, Turkey, South Africa, and Germany.

The protocol-specified interim analysis of efficacy was conducted on an accrued 94 confirmed cases of COVID-19 (data cutoff date: 04 November 2020), and the protocol-specified final analysis of efficacy was conducted on an accrued 170 cases (data cutoff date: 14 November 2020). No additional formal hypothesis testing of clinically confirmed COVID-19 cases is planned.

Results of both the interim and the final analyses demonstrated high efficacy, with ≥95% vaccine efficacy (VE) observed against COVID-19. These data were submitted in support of the MAA for the indication in individuals 16 years of age and older. The long-term persistence of efficacy will be followed-up for at least 2 years and/or until the end of study.

2.7.3.1.2. Methods for the Evaluation of Efficacy in Adolescents 12 to 15 Years of Age

At the time the final analysis of efficacy was conducted, few adolescents (12 to 15 years of age) had enrolled in the study, precluding a meaningful efficacy evaluation. Therefore, to support an indication in adolescents 12 to 15 years of age, an analysis has been performed using data for individuals in this age group collected during blinded follow-up to a data cutoff date of 13 March 2021.

Efficacy Endpoints

The efficacy endpoints analyzed and reported for adolescents 12 to 15 years of age in this Type II variation include the following endpoints:

- COVID-19 incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during the vaccination regimen – cases confirmed ≥7 days after Dose 2

- Severe COVID-19 incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during the vaccination regimen – cases confirmed ≥7 days after Dose 2.

Efficacy Analysis Methods

Evaluations of efficacy in adolescents 12 to 15 years of age include confirmed cases of COVID-19 accrued in blinded follow-up to the data cutoff date of 13 March 2021. Efficacy analyses were conducted for efficacy endpoints using statistical methods described in the study statistical analysis plan. For the descriptive analyses presented in this submission for adolescents 12-15 years of age, the point estimate of VE and the associated 2-sided 95% CI was derived using the Clopper-Pearson method adjusted for surveillance time.

Participants with and without evidence of prior infection were determined by virological testing via NAAT on mid-turbinate swabs and serological testing for SARS-CoV-2 N-binding antibodies. Participants with no serological or virological evidence of SARS-CoV-2 infection prior to 7 days after receipt of the last dose were defined as those who were N-binding antibody negative at Visit 1 and with SARS-CoV-2 not detected by NAAT at Visits 1 and 2 and at any unscheduled visit prior to 7 days after Dose 2.

Surveillance/Definitions /Case Determination for Confirmed COVID-19

Participants who developed any of the potential COVID-19 symptoms listed in the protocol (Module 5.3.5.1 C4591001 Protocol Section 8.13) were to contact the site immediately and, if confirmed, to participate in an in-person or telehealth visit as soon as possible (optimally within 3 days of symptom onset, and at the latest 4 days after symptom resolution). At the visit (or prior to the visit, if a participant utilized a self-swab as permitted per protocol), investigators were to collect clinical information and results from local standard-of-care tests sufficient to confirm a COVID-19 diagnosis.

Confirmation of Infection with SARS-CoV-2: Investigators were to obtain a nasal swab (mid-turbinate) for testing at a central laboratory using a validated reverse transcription–polymerase chain reaction test (Cepheid; EUA200047/A001) to detect SARS-CoV-2. If the evaluation was conducted by telehealth, the participant was to self-collect a nasal swab and ship for assessment at the central laboratory. A local NAAT result was only acceptable if it met protocol-specified criteria and if a central laboratory result was not available.

Confirmed COVID-19 was defined (per FDA guidance)[1] as having a positive SARS-CoV-2 test result per central laboratory or local testing facility (using an acceptable test per protocol only if no central laboratory result was available) and the presence of at least 1 of the following:

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.

Confirmed severe COVID-19 was defined (per FDA guidance)[1] as confirmed COVID-19 and the presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <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 intensive care unit;

– Death.

In addition to the above protocol-specified definition of severe COVID-19, an efficacy analysis was conducted for ***confirmed severe COVID-19 according to the CDC-defined severe symptoms***, ie, COVID-19 illness events that resulted in hospitalization, admission to an intensive care unit, intubation or mechanical ventilation, or death.[2]

2.7.3.1.3. Methods for Evaluation of Immunogenicity

Measurement of the Immune Response

The immunogenicity data included in this submission are based on antibody responses as determined using the SARS-CoV-2 neutralization assay[3,4] and blood samples collected immediately before Dose 1 and 1 month after Dose 2. Details regarding the neutralization assay are available in Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods and 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies.

Immunogenicity Endpoints

In Phase 3, an immunogenicity objective was to demonstrate NI of the immune response to prophylactic BNT162b2 in adolescents 12 to 15 years of age compared to young adults 16 to 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. This NI analysis of neutralizing titers was performed to provide immunobridging between these adolescents and young adults 16 to 25 years of age.

A random sample of 280 participants who received BNT162b2 and 50 participants who received placebo was selected for each of the two age groups (660 participants total) as an immunogenicity subset for immunogenicity assessment. This sample size was originally estimated to provide a power of 90.4% to declare NI in the specified analysis.

Due to a testing laboratory supply limitation of the qualified viral lot used during the validation of the assay and clinical testing of samples, immunogenicity analyses were performed only on samples from participants who had the required tests completed using the same available viral reagent lot. A blinded review of the samples tested at that time suggested a sufficient sample size properly balanced across age groups to perform the planned NI analysis. It was estimated that if the true geometric mean ratio (GMR) is $\geq$0.88, there is approximately 90% power to demonstrate NI using the number of samples currently tested, and >99% power if the true GMR is 1. This approach was mutually agreed with the US FDA.

Immunogenicity endpoints analyzed for SARS-CoV-2 serum neutralizing titers included:

- geometric mean titers (GMTs) at 1 month after Dose 2
- geometric mean-fold rise (GMFR) from before vaccination to 1 month after Dose 2
- percentage of participants with a $\geq$4-fold rise in neutralizing titers from before vaccination to 1 month after Dose 2 (seroresponse rate)

Immunogenicity Analysis Methods

NI was assessed in participants who had no serological or virological evidence of SARS-CoV-2 infection up to 1 month after Dose 2; assessment was based on the geometric mean ratio of SARS-CoV-2 neutralizing titers (GMT in adolescents/GMT in young adults) at 1 month after Dose 2 using a 1.5-fold margin. The GMR and its 2-sided 95% CI were derived by calculating differences in means and CIs on the natural log scale of titers based on Student's t-distribution, then exponentiating the results. The difference in means on the natural log scale was calculated as: (12-15 years of age) – (16-25 years of age). NI was declared if the lower bound of the 2-sided 95% CI for the GMR was >0.67.

A supportive analysis was conducted to assess the seroresponse rate, based on the proportions of participants in each age group with a ≥4-fold rise in neutralizing titers from before vaccination to 1 month after Dose 2. The difference in percentages (% adolescents minus % young adults) and the associated 2-sided 95% CI calculated using the Miettinen and Nurminen method were provided. GMTs and GMFRs of the neutralizing titers were provided with the associated 2-sided 95% CIs calculated with reference to Student's t-distribution.

Immunogenicity results were summarized for all participants with or without serological or virological evidence of SARS-CoV-2 infection before vaccination, and results were also summarized by baseline SARS-CoV-2 status. Positive baseline SARS-CoV-2 status was defined as positive N-binding antibody or positive NAAT at Visit 1, or a medical history of COVID-19; negative baseline SARS-CoV-2 status was defined as negative N-binding antibody and negative NAAT at Visit 1 and no medical history of COVID-19.

2.7.3.2. Summary of Results of Individual Studies

2.7.3.2.1. Efficacy Against Confirmed COVID-19 – Adolescents 12 to 15 Years of Age

2.7.3.2.1.1. Efficacy Populations – Adolescents 12 to 15 Years of Age

The efficacy of BNT162b2 against confirmed cases of COVID-19 in adolescents was evaluated in 3 populations as follows:

- Evaluable efficacy population without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2: N=1005 in the BNT162b2 group and N=978 in the placebo group.
- Evaluable efficacy population with or without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2: N=1119 in the BNT162b2 group and N=1110 in the placebo group.
- Dose 1 all-available efficacy population: N=1131 in the BNT162b2 group and N=1129 in the placebo group.

The all-available efficacy population includes the same number of participants in each group as the safety population, for which demographic characteristics, disposition, and duration of follow-up are described briefly below. Complete details of participant demographics and disposition can be found in Module 5.3.5.1 C4591001 Adolescent (12-15 Years) Interim CSR Section 10.

Demographic Characteristics

A total of 2260 participants 12 to 15 years of age were vaccinated and were included in the safety population (1131 in the BNT162b2 group and 1129 in the placebo group). In the BNT162b2 group, the median age was 14.0 years, and 50.1% were male. Most participants in the BNT162b2 group were White (85.9%), with 4.6% Black participants and 6.4% Asian participants; 11.7% of participants were Hispanic/Latino.

Disposition

The disposition of adolescents (12-15 years of age) was similar in BNT162b2 and placebo groups through 1 month after Dose 2. Among all randomized adolescents, most (≥98.8%) received Dose 1 and Dose 2, and most completed the visit at 1 month after Dose 2 (≥97.5%). Seven adolescents (0.6%) in the BNT162b2 group and 17 (1.5%) in the placebo group discontinued from the vaccination period but continued in the study for safety follow-up; among these, 2 participants in the BNT162b2 group discontinued after Dose 1 but before Dose 2 due to adverse events (one due to pyrexia considered by the investigator as related to study intervention, and one due to anxiety/depression considered not related to study intervention). No adolescents in the BNT162b2 group and 2 in the placebo group withdrew from the study before the 1 month post Dose 2 visit.

Duration of Follow-up

Among the total 2260 participants 12 to 15 years of age, 57.9% had at least 2 months of follow-up after Dose 2, and only 1.7% had <1 month of follow-up after Dose 2 (Table 1).

Table 1. Follow-up Time After Dose 2 – Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N^a=1131) n^b (%)	Placebo (N^a=1129) n^b (%)	Total (N^a=2260) n^b (%)
Subjects (%) with length of follow-up of:			
Total exposure from Dose 2 to cutoff date			
<1 Month	13 (1.1)	25 (2.2)	38 (1.7)
≥1 Month to <2 months	458 (40.5)	456 (40.4)	914 (40.4)
≥2 Months to <3 months	612 (54.1)	599 (53.1)	1211 (53.6)
≥3 Months	48 (4.2)	49 (4.3)	97 (4.3)

Note: Follow-up time was calculated to the cutoff date or the date of unblinding, whichever date was earlier.
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.
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2.7.3.2.1.2. Results of Efficacy Analyses – Adolescents 12 to 15 Years of Age

2.7.3.2.1.2.1. Vaccine Efficacy Against COVID-19

Confirmed Cases of COVID-19 Occurring at Least 7 Days after Dose 2 – Evaluable Efficacy Population

Participants Without Evidence of Infection Before and During Vaccination Regimen

In the evaluable efficacy population, among adolescents 12 to 15 years of age without evidence of SARS-CoV-2 infection before and during the vaccination regimen, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 100% (2-sided 95% CI: 75.3%, 100.0%), with 0 cases in the BNT162b2 group and 16 cases in the placebo group (Table 2).

Table 2. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=1005)		Placebo (N[a]=978)			
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2	0	0.154 (1001)	16	0.147 (972)	100.0	(75.3, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects 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 subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects 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 subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
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(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adc19ef_ve_cov_7pd2_peds_wo_eval

Participants With or Without Evidence of Infection Before and During Vaccination Regimen

Among participants with or without evidence of SARS-CoV-2 infection before and during the vaccination regimen, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 100.0% (2-sided 95% CI: 78.1%, 100.0%), with 0 cases in the BNT162b2 group and 18 cases in the placebo group (Table 3).

Relative to the analysis of cases in participants without evidence of prior SARS-CoV-2 infection (Table 2), 2 additional cases occurred in the placebo group of the evaluable efficacy population with or without evidence of prior SARS-CoV-2 infection before and during vaccine regimen. These 2 cases were reported in participants who had a negative serostatus for SARS-CoV-2 at baseline and had a negative NAAT at Visit 1 (immediately before Dose 1) followed by a positive NAAT (confirmed by the central laboratory) at Visit 2 (immediately before Dose 2).

Table 3. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=1119)		Placebo (N[a]=1110)			
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2	0	0.170 (1109)	18	0.163 (1094)	100.0	(78.1, 100.0)

Abbreviation: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects 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 subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
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(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File:
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All Confirmed Cases of COVID-19 After Dose 1 – All-Available Efficacy Population

A number of confirmed cases of COVID-19 are not captured in the analyses above because the cases either occurred in participants who were excluded from the evaluable efficacy population, or occurred less than 7 days after Dose 2.

All confirmed cases of COVID-19 with onset at any time after Dose 1 are accounted for in Table 4, which provides a summary of confirmed cases for all participants in the Dose 1 all-available efficacy (modified intention-to-treat) population, regardless of evidence of infection before or during the vaccination regimen. Among these participants, 3 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared to 35 cases in the placebo group. The estimated VE against confirmed COVID-19 occurring after Dose 1 was 91.6% (2-sided 95% CI: 73.5%, 98.4%).

From Dose 1 to Dose 2, 3 cases occurred in the BNT162b2 group, compared with 12 cases in the placebo group, giving a VE of 75.0% (2-sided 95% CI: 7.4, 95.5) during this time period. All 3 cases in the BNT162b2 group occurred less than 11 days after Dose 1; therefore, the observed VE was 100.0% for all time periods ≥11 days after Dose 1 (see Table 4).
All 3 cases in the BNT162b2 group occurred in participants who had baseline SARS-CoV-2 negative status.

Table 4. Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=1131)		Placebo (N[a]=1129)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	3	0.257 (1120)	35	0.250 (1119)	91.6	(73.5, 98.4)
After Dose 1 to before Dose 2	3		12		75.0	(7.4, 95.5)
After Dose 1 to <11 days after Dose 1	3		4		25.0	(-343.3, 89.0)
≥11 Days after Dose 1 to before Dose 2	0		8		100.0	(41.4, 100.0)
Dose 2 to 7 days after Dose 2	0		5		100.0	(-9.1, 100.0)
≥7 Days after Dose 2	0		18		100.0	(77.3, 100.0)
≥7 days after Dose 2 to <2 Months after Dose 2	0		16		100.0	(74.1, 100.0)
≥2 Months after Dose 2 to <4 Months after Dose 2	0		2		100.0	(-432.5, 100.0)

Abbreviation: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects 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 subjects 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 overall row).
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(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File:
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2.7.3.2.1.2.2. Vaccine Efficacy Against Severe COVID-19

No severe cases of COVID-19 (per protocol definition or CDC criteria) were reported in adolescents through the data cutoff date of 13 March 2021.

2.7.3.2.1.3. Efficacy Conclusions – Adolescents 12 to 15 Years of Age

Descriptive efficacy analyses were conducted for adolescents 12 to 15 years of age for cases accrued during blinded follow-up period through the data cutoff date of 13 March 2021.

In the evaluable efficacy population, and based on confirmed cases occurring at least 7 days after Dose 2 through the data cutoff date, the observed VE was 100% (95% CI: 75.3%, 100%) for individuals without evidence of SARS-CoV-2 infection before and during the vaccination regimen, and 100% (2-sided 95% CI: 78.1%, 100%) for those with or without evidence of SARS-CoV-2 infection before and during the vaccination regimen.

In the efficacy analysis for the Dose 1 all-available (modified intention-to-treat) population, VE against all cases of COVID-19 reported at any time after Dose 1 was 91.6% (2-sided

95% CI: 73.5%, 98.4%), with 3 cases in the BNT162b2 group and 35 cases in the placebo group. All 3 cases in the BNT162b2 group occurred <11 days after Dose 1. No severe cases were reported in BNT162b2 group as of the data cutoff date.

Overall, these efficacy data strongly support the use of BNT162b2 in adolescents 12 to 15 years of age.

2.7.3.2.2. Immunogenicity Evaluations

All immunogenicity results presented in the SCE are for the evaluable immunogenicity population; results for the all-available immunogenicity population are available in the CSR.

2.7.3.2.2.1. Immunogenicity Populations

Immunogenicity analyses were planned to demonstrate the noninferiority of the immune response among adolescents 12 to 15 years of age as compared with the response among young adults 16 to 25 years of age. For each of the two age groups, a random sample of 280 participants in the BNT162b2 group was selected as the immunogenicity subset for the NI assessment. To maintain blinding of the laboratory personnel, 50 participants in each placebo group were also randomly selected from each of the two age groups for serology testing.

Data Sets Analyzed

The Dose 2 evaluable immunogenicity population included 209 participants in the BNT162b2 group and 36 participants in the placebo group for adolescents 12 to 15 years of age, and included 186 participants in the BNT162b2 group and 32 participants in the placebo group for young adults 16 to 25 years of age. Reasons for participant exclusion from the immunogenicity populations were generally balanced across age and vaccine groups (Table 5). The majority of exclusions were due to participants not having at least 1 valid and determinate immunogenicity result after Dose 2, mostly as the result of testing laboratory supply limitation of the qualified viral lot (refer to Section 2.7.3.1.3).

Table 5. Immunogenicity Populations – Subjects 12 Through 15 and 16 Through 25 Years of Age (Immunogenicity Subset)

	Vaccine Group (as Randomized)			
	BNT162b2 (30 µg)		Placebo	
	12-15 Years n[a] (%)	16-25 Years n[a] (%)	12-15 Years n[a] (%)	16-25 Years n[a] (%)
Randomized[b]	280 (100.0)	280 (100.0)	50 (100.0)	50 (100.0)
Dose 2 all-available immunogenicity population	210 (75.0)	191 (68.2)	36 (72.0)	34 (68.0)
Subjects excluded from Dose 2 all-available immunogenicity population	70 (25.0)	89 (31.8)	14 (28.0)	16 (32.0)
Reason for exclusion				
Did not receive Dose 2	1 (0.4)	0	0	0
Did not have at least 1 valid and determinate immunogenicity result after Dose 2	69 (24.6)	89 (31.8)	14 (28.0)	16 (32.0)
Dose 2 evaluable immunogenicity population	209 (74.6)	186 (66.4)	36 (72.0)	32 (64.0)
Subjects excluded from Dose 2 evaluable immunogenicity population	71 (25.4)	94 (33.6)	14 (28.0)	18 (36.0)
Reason for exclusion[c]				
Did not receive 2 doses of the vaccine to which they were randomly assigned	1 (0.4)	0	0	0
Did not receive Dose 2 within 19-42 days after Dose 1	1 (0.4)	2 (0.7)	0	2 (4.0)
Did not have at least 1 valid and determinate immunogenicity result after Dose 2	69 (24.6)	89 (31.8)	14 (28.0)	16 (32.0)
Did not have blood collection within 28-42 days after Dose 2	3 (1.1)	16 (5.7)	0	3 (6.0)
Had important protocol deviation(s) as determined by the clinician	0	0	0	1 (2.0)

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.
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Demographic Characteristics

In the adolescent (12 to 15 years of age) BNT162b2 group (Dose 2 evaluable immunogenicity population, Table 6), 50.7% of participants were male; 88.0% were White, 7.7% were Black or African American, and 2.4% were Asian; 10.5% were Hispanic/Latino; and the median age was 14 years. Baseline SARS-CoV-2 status was positive for 4.8% of adolescent participants in the BNT162b2 group. Demographics were generally similar between the BNT162b2 and placebo groups, and between adolescents and young adults 16 to 25 years of age.

Table 6. Demographic Characteristics – Subjects 12 Through 15 and 16 Through 25 Years of Age (Immunogenicity Subset) – Dose 2 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)			
	BNT162b2 (30 µg)		Placebo	
	12-15 Years (N^a=209) n^b (%)	16-25 Years (N^a=186) n^b (%)	12-15 Years (N^a=36) n^b (%)	16-25 Years (N^a=32) n^b (%)
Sex				
Male	106 (50.7)	92 (49.5)	21 (58.3)	14 (43.8)
Female	103 (49.3)	94 (50.5)	15 (41.7)	18 (56.3)
Race				
White	184 (88.0)	147 (79.0)	31 (86.1)	28 (87.5)
Black or African American	16 (7.7)	15 (8.1)	3 (8.3)	2 (6.3)
American Indian or Alaska Native	1 (0.5)	3 (1.6)	0	1 (3.1)
Asian	5 (2.4)	10 (5.4)	1 (2.8)	1 (3.1)
Native Hawaiian or other Pacific Islander	0	3 (1.6)	0	0
Multiracial	3 (1.4)	6 (3.2)	1 (2.8)	0
Not reported	0	2 (1.1)	0	0
Racial designation				
Japanese	1 (0.5)	0	0	0
Ethnicity				
Hispanic/Latino	22 (10.5)	31 (16.7)	2 (5.6)	7 (21.9)
Non-Hispanic/non-Latino	187 (89.5)	154 (82.8)	34 (94.4)	25 (78.1)
Not reported	0	1 (0.5)	0	0
Country				
USA	209 (100.0)	186 (100.0)	36 (100.0)	32 (100.0)
Age at vaccination (years)				
Mean (SD)	13.5 (1.12)	20.6 (3.09)	13.4 (1.17)	20.3 (3.05)
Median	14.0	21.0	13.0	19.5
Min, max	(12, 15)	(16, 25)	(12, 15)	(16, 25)
Baseline SARS-CoV-2 status				
Positive[c]	10 (4.8)	8 (4.3)	2 (5.6)	1 (3.1)
Negative[d]	194 (92.8)	178 (95.7)	33 (91.7)	31 (96.9)
Missing	5 (2.4)	0	1 (2.8)	0
Body mass index (BMI) Obese[e]				
Yes	24 (11.5)	43 (23.1)	3 (8.3)	4 (12.5)
No	185 (88.5)	143 (76.9)	33 (91.7)	28 (87.5)

Table 6. Demographic Characteristics – Subjects 12 Through 15 and 16 Through 25 Years of Age (Immunogenicity Subset) – Dose 2 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)			
	BNT162b2 (30 µg)		Placebo	
	12-15 Years (N^a=209) n^b (%)	16-25 Years (N^a=186) n^b (%)	12-15 Years (N^a=36) n^b (%)	16-25 Years (N^a=32) n^b (%)

Abbreviation: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Human immunodeficiency virus (HIV)-positive subjects are included in this summary but analyzed and reported separately.
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. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
d. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
e. For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev htm. For 16 through 25 years age group, obesity is defined as BMI≥30.0 kg/m^2.
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2.7.3.2.2.2. Immunogenicity Results

2.7.3.2.2.2.1. Noninferiority Analyses

Noninferiority of the immune response was evaluated in participants with no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after receipt of the second dose.

Geometric Mean Ratio

The immune response to BNT162b2 in adolescents 12 to 15 years of age was noninferior to that observed in young adults 16 to 25 years of age, based on SARS-CoV-2 50% neutralizing titers at 1 month after Dose 2. The geometric mean ratio (GMR) (GMT in adolescents/GMT in young adults) was 1.76 (2-sided 95% CI: 1.47, 2.10), meeting the 1.5-fold noninferiority criterion (ie, lower bound of the 2-sided 95% CI for GMR >0.67) (Table 7). Of note, the lower bound of the 2-sided 95% CI for the GMR was >1, which indicates that the GMT in adolescents is statistically significantly higher than in young adults.

Seroresponse Rate

High proportions of participants (97.9% of adolescents and 100.0% of young adults) had a ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination to 1 month after

Dose 2 (seroresponse). The difference in the proportions (adolescents – young adults) was -2.1% (2-sided 95% CI: -6.0%, 0.9%) (Table 8).

Table 7. Summary of Geometric Mean Ratio – NT50 – Comparison of Subjects 12 Through 15 Years of Age to Subjects 16 Through 25 Years of Age (Immunogenicity Subset) – Subjects Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)					
		BNT162b2 (30 µg)					
		12-15 Years		16-25 Years		12-15 Years/16-25 Years	
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met Noninferiority Objective[e] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	190	1239.5 (1095.5, 1402.5)	170	705.1 (621.4, 800.2)	1.76 (1.47, 2.10)	Y

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Subjects who had no serological or virological evidence (up to 1 month 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 up to 1 month after Dose 2 were included in the analysis.

a. Protocol-specified timing for blood sample collection.

b. n = Number of subjects with valid and determinate assay results for the specified assay at the given dose/sampling time point.

c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1 [12-15 years] – Group 2 [16-25 years]) and the corresponding CI (based on the Student t distribution).

e. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

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Table 8. Number (%) of Subjects Achieving a ≥4-Fold Rise From Before Vaccination to Each Subsequent Time Point 1 Month After Dose 2 – NT50 – Comparison of Subjects 12 Through 15 Years of Age to Subjects 16 Through 25 Years of Age (Immunogenicity Subset) – Subjects Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)					
		BNT162b2 (30 µg)					
		12-15 Years		16-25 Years		Difference	
Assay	Dose/ Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	%[e]	(95% CI[f])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	143	140 (97.9) (94.0, 99.6)	124	124 (100.0) (97.1, 100.0)	-2.1	(-6.0, 0.9)

Abbreviations: LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subjects who had no serological or virological evidence (up to 1 month 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 up to 1 month after Dose 2 were included in the analysis.
Note: Baseline assay results below the LLOQ were set to LLOQ in the analysis.
a. Protocol-specified timing for blood sample collection.
b. N = number of subjects with valid and determinate assay results for the specified assay both before vaccination and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of subjects with ≥4-fold rise from before vaccination for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (12-15 years – 16-25 years).
f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
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2.7.3.2.2.2.2. SARS-CoV-2 Neutralizing Titers

Immunogenicity results were summarized for all participants with or without serological or virological evidence of SARS-CoV-2 infection before vaccination, and results were also summarized by baseline SARS-CoV-2 status. Positive baseline SARS-CoV-2 status was defined as positive N-binding antibody or positive NAAT at Visit 1, or a medical history of COVID-19; negative baseline SARS-CoV-2 status was defined as negative N-binding antibody and negative NAAT at Visit 1 and no medical history of COVID-19.

Geometric Mean Titers (GMTs)

At 1 month after Dose 2 of BNT162b2, SARS-CoV-2 50% neutralizing GMTs were substantially increased from baseline in both age groups, but were higher among adolescents than among young adults (GMT 95% CIs were not overlapping) (Table 9). The neutralizing GMT in adolescents at 1 month after Dose 2 was approximately 1.76-fold that of the young adult group.

At 1 month after Dose 2 of BNT162b2, adolescents who had been seropositive at baseline had SARS-CoV-2 50% neutralizing GMTs approximately 1.89-fold that of adolescents who had been seronegative at baseline (Table 9). A similar pattern was observed for baseline SARS-CoV-2 positive versus negative young adults.

Geometric Mean Fold-Rise (GMFR) in Titers

GMFRs in SARS-CoV-2 50% serum neutralizing titers from before vaccination to 1 month after Dose 2 of BNT162b2 were robust, with a greater magnitude of rise in the adolescent group (118.3) compared with the young adult group (71.2) (Table 10).

In both age groups, GMFRs were numerically higher in individuals who had been seronegative at baseline than in those who had been seropositive at baseline.

Seroresponse Rate

The proportions of participants with a ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination to 1 month after Dose 2 of BNT162b2 (seroresponse rate) were similar in adolescents (98.1%) and young adults (99.3%) (Table 11).

Seroresponse rates were similar in adolescents who had been seropositive at baseline (100.0%) and in those who had been seronegative (97.9%) (Table 11).

Table 9. Summary of Geometric Mean Titers, by Baseline SARS-CoV-2 Status – NT50 – Subjects 12 Through 15 and 16 Through 25 Years of Age (Immunogenicity Subset) – Dose 2 Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2 (30 µg)				Placebo			
			12-15 Years		16-25 Years		12-15 Years		16-25 Years	
Assay	Dose/ Sampling Time Point[a]	Baseline SARS-CoV-2 Status[b]	n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])
SARS-CoV-2 neutralization assay - NT50 (titer)	1/Prevax	ALL	155	11.2 (10.3, 12.3)	136	10.5 (9.9, 11.2)	29	11.2 (8.9, 14.0)	24	10.0 (10.0, 10.0)
		POS	8	54.1 (19.7, 148.7)	5	38.6 (6.4, 232.9)	1	251.0 (NE, NE)	0	NE (NE, NE)
		NEG	146	10.3 (9.7, 10.9)	131	10.0 (10.0, 10.0)	27	10.0 (10.0, 10.0)	24	10.0 (10.0, 10.0)
	2/1 Month	ALL	207	1283.0 (1139.6, 1444.5)	185	730.8 (646.7, 825.8)	36	15.1 (10.7, 21.4)	32	10.7 (9.3, 12.4)
		POS	10	2342.2 (1308.7, 4191.8)	8	1439.2 (727.1, 2848.7)	2	191.0 (1.2, 30873.6)	1	10.0 (NE, NE)
		NEG	192	1239.2 (1096.6, 1400.5)	177	708.7 (626.4, 802.0)	33	13.1 (9.7, 17.7)	31	10.8 (9.3, 12.5)

Table 9. Summary of Geometric Mean Titers, by Baseline SARS-CoV-2 Status – NT50 – Subjects 12 Through 15 and 16 Through 25 Years of Age (Immunogenicity Subset) – Dose 2 Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2 (30 µg)				Placebo			
			12-15 Years		16-25 Years		12-15 Years		16-25 Years	
Assay	Dose/ Sampling Time Point[a]	Baseline SARS-CoV-2 Status[b]	n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])

Abbreviations: COVID-19 = coronavirus disease 2019; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NE = not estimable; NEG = negative; NT50 = 50% neutralizing titer; POS = positive; Prevax = before vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. Protocol-specified timing for blood sample collection.

b. POS = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. NEG = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19. ALL = irrespective of baseline SARS-CoV-2 status, including missing baseline status.

c. n = Number of subjects with valid and determinate assay results for the specified assay at the given dose/sampling time point.

d. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

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(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2 unblinded/C4591001 BLA/adva s001 gm ped eval

Table 10. Summary of Geometric Mean Fold Rise From Before Vaccination to Each Subsequent Time Point, by Baseline SARS-CoV-2 Status – NT50 – Subjects 12 Through 15 and 16 Through 25 Years of Age (Immunogenicity Subset) – Dose 2 Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2 (30 µg)				Placebo			
			12-15 Years		16-25 Years		12-15 Years		16-25 Years	
Assay	Dose/ Sampling Time Point[a]	Baseline SARS-CoV-2 Status[b]	n[c]	GMFR[d] (95% CI[d])	n[c]	GMFR[d] (95% CI[d])	n[c]	GMFR[d] (95% CI[d])	n[c]	GMFR[d] (95% CI[d])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	ALL	154	118.3 (101.4, 137.9)	135	71.2 (61.3, 82.7)	29	1.4 (1.0, 1.9)	24	1.1 (0.9, 1.3)
		POS	8	47.6 (26.4, 86.0)	5	47.1 (3.1, 721.4)	1	1.1 (NE, NE)	0	NE (NE, NE)
		NEG	145	125.0 (106.9, 146.2)	130	72.3 (62.9, 83.2)	27	1.4 (1.0, 2.0)	24	1.1 (0.9, 1.3)

Abbreviations: COVID-19 = coronavirus disease 2019; GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NE = not estimable; NEG = negative; NT50 = 50% neutralizing titer; POS = positive; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. Protocol-specified timing for blood sample collection.

b. POS = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. NEG = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19. ALL = irrespective of baseline SARS-CoV-2 status, including missing baseline status.

c. n = Number of subjects with valid and determinate assay results for the specified assay both prevaccination time points and at the given dose/sampling time point.

d. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

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Table 11. Number (%) of Subjects Achieving a ≥4-Fold Rise From Before Vaccination to Each Subsequent Time Point, by Baseline SARS-CoV-2 Status – NT50 – Subjects 12 Through 15 and 16 Through 25 Years of Age (Immunogenicity Subset) – Dose 2 Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2 (30 µg)				Placebo			
			12-15 Years		16-25 Years		12-15 Years		16-25 Years	
Assay	Dose/ Sampling Time Point[a]	Baseline SARS-CoV-2 Status[b]	N[c]	n[d] (%) (95% CI[e])	N[c]	n[d] (%) (95% CI[e])	N[c]	n[d] (%) (95% CI[e])	N[c]	n[d] (%) (95% CI[e])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	ALL	154	151 (98.1) (94.4, 99.6)	135	134 (99.3) (95.9, 100.0)	29	1 (3.4) (0.1, 17.8)	24	1 (4.2) (0.1, 21.1)
		POS	8	8 (100.0) (63.1, 100.0)	5	4 (80.0) (28.4, 99.5)	1	0 (0.0) (0.0, 97.5)	0	0 (NE) (NE, NE)
		NEG	145	142 (97.9) (94.1, 99.6)	130	130 (100.0) (97.2, 100.0)	27	1 (3.7) (0.1, 19.0)	24	1 (4.2) (0.1, 21.1)

Abbreviations: LLOQ = lower limit of quantitation; NE = not estimable; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Baseline assay results below the LLOQ were set to LLOQ in the analysis.
a. Protocol-specified timing for blood sample collection.
b. POS = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. NEG = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19. ALL = irrespective of baseline SARS-CoV-2 status, including missing baseline status
c. N = number of subjects with valid and determinate assay results for the specified assay both before vaccination and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
d. n = Number of subjects with ≥4-fold rise from before vaccination for the given assay at the given dose/sampling time point.
e. Exact 2-sided CI based on the Clopper and Pearson method.
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2.7.3.2.2.3. Immunogenicity Conclusions

The immune response to BNT162b2 in adolescents 12 to 15 years of age was noninferior to the immune response in young adults 16 to 25 years of age, as measured by SARS-CoV-2 50% neutralizing titers at 1 month after Dose 2. In both age groups, substantial increases over baseline in neutralizing GMTs and high seroresponse rates were observed, both in individuals who had been seronegative and in those who had been seropositive at baseline.

2.7.3.3. Comparison and Analyses of Results Across Studies

Not applicable.

2.7.3.4. Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable. The dose regimen (2 doses of 30 µg BNT162b2, administered 21 days apart), was determined in Phase 1 studies, which were conducted in individuals ≥18 years of age.

2.7.3.5. Persistence of Efficacy and/or Tolerance Effects

In Study C4591001, participants will be followed for occurrences of COVID-19 through 24 months after Dose 2, and these data will be reported at study completion. The study also includes evaluations of functional neutralizing antibody titers at 6, 12, and 24 months after Dose 2 of study vaccine. These data will be provided in future submissions.

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