2.7.3 SUMMARY OF CLINICAL EFFICACY

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Abbreviation	Definition
ALT	alanine aminotransferase
ARDS	adult respiratory distress syndrome
BiPaP	bilevel positive airway pressure
BNP	brain natriuretic peptide
BP	blood pressure
CDC	(US) Centers for Disease Control and Prevention
CI	confidence interval
CPaP	continuous positive airway pressure
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CRF	case report form
CSR	clinical study report
CVA	cerebrovascular accident
ECMO	extracorporeal membrane oxygenation
EMA	European Medicines Agency
ESR	erythrocyte sedimentation rate
EUA	Emergency Use Authorization
FDA	(US) Food and Drug Administration
FiO2	fraction of inspired oxygen
GMFR	geometric mean-fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
ICU	intensive care unit
IgG	immunoglobulin G
IL-6	interleukin 6
IRR	illness rate ratio
IM	intramuscular
IRC	internal review committee
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
MAA	Marketing Authorization Application
MIS-C	multisystem inflammatory syndrome in children
mRNA	messenger RNA
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein binding
NT50	neutralizing titer 50
PaO2	partial pressure of oxygen, arterial
RNA	ribonucleic acid
RT-PCR	reverse transcription–polymerase chain reaction

Abbreviation	Definition
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS coronavirus-2; virus causing the disease COVID-19
SBP	systolic blood pressure
SCE	summary of clinical efficacy
SpO2	oxygen saturation as measured by pulse oximetry
ULN	upper limit of normal
US	United States
VE	vaccine efficacy

2.7.3. SUMMARY OF CLINICAL EFFICACY

This Summary of Clinical Efficacy (SCE) describes clinical data for a prophylactic, RNA-based SARS CoV-2 vaccine, BNT162b2 (COMIRNATY), developed by BioNTech and Pfizer.

This submission supports an extension for use of the vaccine in children 5 to <12 years of age. The data supporting the indication in this age group are from Study C4591007 and include immunogenicity results from the Phase 1 open-label, dose-finding portion of the study, which, along with results of safety and tolerability assessments, led to selection of a dose of 10 µg BNT162b2 as the optimal dose to take forward for evaluation in children 5 to <12 years of age in Phase 2/3 of the study. Results are also presented from the Phase 2/3 double-blind portion of the study that demonstrate immunobridging of the response elicited by 10 µg BNT162b2 in children 5 to <12 years of age to the response elicited by 30 µg BNT162b2 in young adults 16 to 25 years of age in Study C4591001 (the pivotal study that established the safety and efficacy of BNT162b2 [30 µg] in individuals 12 years of age and older). Although Phase 2/3 of Study C4591007 includes evaluation of the efficacy of BNT162b2 in preventing COVID-19, results from the efficacy analyses are not yet available, as a sufficient number of confirmed COVID-19 cases have not yet accrued.

Content of the Summary of Clinical Efficacy

This SCE provides an overview of Study C4591007, describing study design and conduct, methods for evaluating immunogenicity and planned supportive vaccine efficacy. Results are presented for immunogenicity analyses, which includes immunobridging data comparing immune responses of pediatric participants 5 to <12 years of age in C4591007 to those of young adult participants 16 to 25 years of age in C4591001 at 1 month after Dose 2. This scope of methods and results is outlined below.

Content	Section
Overview of study design and conduct – Study C4591007	Section 2.7.3.1.1
Methods for the planned supportive evaluation of efficacy	Section 2.7.3.1.1.2
Methods for the evaluation of immunogenicity	Section 2.7.3.1.1.1
Results of immunogenicity evaluations	Section 2.7.3.2.1

2.7.3.1. Background and Overview of Clinical Efficacy

2.7.3.1.1. Phase 1/2/3 Pediatric Study C4591007

Study C4591007 is an ongoing, randomized, placebo-controlled, Phase 1/2/3 study in healthy children from 6 months to <12 years of age. The study was designed to evaluate BNT162b2 vaccination in an age de-escalation Phase 1 dose finding part and Phase 2/3 selected dose part, in protocol defined age groups 5 to <12 years, 2 to <5 years, and 6 months to <2 years of age. Initiation of the pediatric study with the oldest pediatric group (5 to <12 years of age) was based on acceptable safety and tolerability demonstrated in adolescents (12 to 15 years of age) in Study C4591001. Because this submission includes data only for the 5 to <12 years of age group, only methods and evaluations relevant to this age group will be described in this SCE. Details of the study design and conduct for all age groups are provided in the C4591007 Protocol.

Phase 1 of Study C4591007 was conducted in the United States, while Phase 2/3 is being conducted at sites in the United States, Finland, Poland, and Spain.

Study Eligibility Criteria

In Phase 1, the protocol defined age groups were studied separately: 5 to <12 years of age, 2 to <5 years of age, and 6 months to <2 years of age. The study population includes male and female participants deemed healthy as determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study. Exclusions included screened individuals with clinically important prior medical or psychiatric illness or laboratory abnormalities, past diagnosis MIS-C, serological evidence of prior SARS-CoV-2 infection or current SARS-CoV-2 infection as measured by PCR.

In Phase 2/3, participants were enrolled into protocol defined age groups to evaluate the dose level of BNT162b2 selected for each age group in the Phase 1 dose-finding part of the study. Eligibility in Phase 2/3 permitted enrollment of participants with medical conditions such as stable Type 1 diabetes or hypothyroidism; stable and controlled HIV, HCV, or HBV infection; and past serological or microbiological evidence of prior (not active) SARS-CoV-2 infection.

Phase 1 Design and Conduct

The Phase 1, open-label, dose-finding portion of the study was designed to evaluate escalating dose levels of BNT162b2 within each age group in Study C4591007 and, based on results of safety, tolerability, and immunogenicity assessments, determine the optimal dose level of BNT162b2 for each age group to take forward for evaluation in Phase 2/3.

Children 5 to <12 years of age were to receive escalating dose levels of BNT162b2 (10 µg, 20 µg, or 30 µg) administered as a 2-dose series 21 days apart, with progression to higher dose levels based on recommendations from an IRC. Each dose level was planned to be administered to 16 participants, for a total of 48 vaccinated children 5 to <12 years of age. However, although 16 participants received their first dose at the 30-µg dose level, after 4 participants had received their second 30-µg dose, the IRC recommended that a second dose of 30 µg not be administered due to reactogenicity for these 4 participants. The

remaining 12 participants in this group instead received a second dose of BNT162b2 at the 10-µg dose level.

Blood samples for immunogenicity assessments were collected from all Phase 1 participants immediately before Dose 1, immediately before Dose 2, and at the 7-day follow-up visit (6 to 8 days after Dose 2). Participants in Phase 1 were followed for cases of COVID-19 or MIS-C but did not contribute to the efficacy assessment. Safety follow-up visits occurred at 1 month and 6 months after Dose 2 for collection of AEs and/or SAEs, and surveillance for COVID-19 or MIS-C continued through 24 months after Dose 2.

Phase 2/3 Design and Conduct

Based upon review of safety and immunogenicity results from the Phase 1 portion of the study, the BNT162b2 dose level selected for further evaluation in Phase 2/3 was 10 µg for the 5 to <12 years age group.

In Phase 2/3, the efficacy of BNT162b2 was planned to be established by immunobridging of the SARS-CoV-2 neutralizing antibody response in pediatric participants aged 5 to <12 years of age group in Study C4591007 to the response in young adult participants 16 to 25 years of age in Phase 2/3 efficacy study C4591001. A supportive vaccine efficacy analysis is planned to be conducted when at least 22 confirmed cases of COVID-19 had accrued in the 5 to <12 years of age group among participants without serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection and if success criteria for immunobridging in this age group had first been met.

Vaccine Administration and Scheduled Assessments

In the 5 to <12 years of age group, a total of ~2250 participants were initially planned to be enrolled (randomized 2:1; 1500 to BNT162b2 10 µg: 750 to placebo). An additional 2250 participants 5 to <12 years of age (randomized 2:1 BNT162b2 10 µg: placebo) are being enrolled for a total of 4500 participants in this age group. Only data from the initial ~2250 participants in this age group are reported in the current submission.

All participants were to receive 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. The study staff administering the study interventions were unblinded. All other study and site personnel, including the investigator and the participants were blinded to study intervention.

Blood samples were collected from all participants at baseline for determination of N-binding IgG antibody to establish serological evidence of prior exposure to SARS-CoV-2.

Nasal (anterior nares) swabs for detection of SARS-CoV-2 were performed at Visit 1 and at Visit 2 to assess for potential current infection with SARS-CoV-2.

Blood samples for assessment of the immune response to vaccination were to be collected from approximately 450 participants in the 5 to <12 years of age group (300 in the active vaccine group and 150 in the placebo group) immediately before Dose 1, approximately 1 month after Dose 2 (for the immunobridging analysis), and approximately 6 months after

dose 2 (for assessment of persistence of the immune response). In addition, blood samples are to be collected from a subset of approximately 70 participants originally randomized to BNT162b2 for evaluation of antibody persistence at 12 months and 24 months after Dose 2.

At 6 months after Dose 2, blood samples for determination of N-binding antibody are to be collected from the approximately 2250 participants originally enrolled in the 5 to <12 years of age group (1500 in the BNT162b2 group and 750 in the placebo group). The purpose of this testing is to detect potential seroconversion in participants who had been seronegative (negative for N-binding IgG) at baseline. Seroconversion without any COVID-19 symptoms is an indicator of asymptomatic infection with COVID-19 after vaccination and is to be used in analyses of efficacy against asymptomatic infection.

Surveillance for Confirmed COVID-19 (including Severe COVID-19 and MIS-C)

If a participant developed any of the symptoms of potential COVID-19 or MIS-C listed in the protocol (Protocol Section 8.13), the participant's parent(s)/legal guardian was to contact the site, and an in-person or telehealth visit was to occur as soon as possible. The assessments were to include a nasal (anterior nares) swab sample collection either by site staff personnel (if a clinic visit) or by a participant's parent/legal guardian (if a telehealth visit), which was to be tested by RT-PCR or other equivalent NAAT to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests sufficient were to be collected to confirm a COVID-19 diagnosis. Definitions for case determination are described in Section 2.7.3.1.1.2.

The complete schedule of study activities in Phase 2/3 of the study, including all efficacy, immunogenicity, and safety evaluations, is available in the protocol (C4591001 Protocol Section 1.3).

Data Presented in this SCE

The data presented in this SCE are for pediatric participants in the 5 to <12 years of age group only, and include results from Study C4591007 for:

- Phase 1 dose-finding among BNT162b2 dose levels of 10, 20, and 30 μg (N=16 per group), including immunogenicity at 7 days after Dose 2;
- Phase 2/3 at the selected dose of BNT162b2 10 μg:
  - Immunogenicity results for the immunogenicity subset of approximately 450 participants (300 in the active vaccine group and 150 in the placebo group) including immunobridging and other immunogenicity analyses at 1 month after Dose 2

Other age groups and/or objectives in Study C4591007 will be reported at a later time.

2.7.3.1.1.1. Methods for Evaluation of Immunogenicity in Children 5 to <12 Years of Age

Immunogenicity data are included in this submission for the 5 to <12 years of age group only.

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, which has been described previously.[1,2] 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 1, immunogenicity was analyzed and reported for SARS-CoV-2 50% neutralizing titers for C4591007 participants 5 to <12 years of age by dose level at 7 days after Dose 2. These results were used to inform dose level selection to proceed to Phase 2/3 evaluation. Phase 1 data are presented to the 7 days post-Dose 2 time point, for participants without serological or virological evidence of SARS-CoV-2 infection up to 7 days post-Dose 2.

In Phase 2/3, the primary immunogenicity objective was to demonstrate immunobridging of the immune response elicited by prophylactic BNT162b2 in Phase 2/3 participants without serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing children in the 5 to <12 years of age group who received BNT162b2 10 µg to young adult participants 16 to 25 years of age from Phase 2/3 of the C4591001 efficacy study who received BNT162b2 30 µg. Phase 2/3 immunogenicity results were reported as:

- SARS-CoV-2 neutralizing geometric mean titers (GMTs) by vaccine/age group
- geometric mean ratio (GMR) of SARS-CoV-2 neutralizing titers for children vs young adults
- percentages/difference in percentages of children vs young adults with seroresponse
- geometric mean-fold rises (GMFRs) of SARS-CoV-2 neutralizing titers by vaccine/age group

Immunogenicity Analysis Methods

In Phase 1, SARS-CoV-2 50% neutralizing titers were assessed to 7 days after Dose 2 and summarized as GMTs.

In Phase 2/3, immunobridging was based on SARS-CoV-2 50% neutralizing titers at 1 month after Dose 2, comparing Phase 2/3 C4591007 participants 5 to <12 years of age to Phase 2/3 C4591001 participants 16 to 25 years of age, for GMR and seroresponse assessed sequentially (ie, seroresponse was evaluated only after the prespecified GMR criteria for immunobridging were met).

- GMR was calculated as the mean of the difference of logarithmically transformed titers and exponentiating the mean. The associated 2-sided 95% CIs were obtained by constructing CIs using Student's t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. Immunobridging success for the GMR was declared if the lower bound of the 2-sided 95% CI for the GMR was >0.67 and the GMR point estimate was ≥0.8 (as prespecified in the protocol) or ≥1 (as requested by FDA)*

  * Note that the FDA requested GMR point estimate was considered in a post hoc manner for this analysis as the database release was in progress at the time of the FDA request.

- Seroresponse was defined as achieving a ≥4-fold rise in SARS-CoV-2 neutralizing titers from before Dose 1. If the baseline measurement was below the LLOQ, the postvaccination measure of ≥4 × LLOQ was considered seroresponse. The difference in percentages and the associated 2-sided 95% CI calculated using the Miettinen and Nurminen method were provided. Immunobridging success for seroresponse was declared if the lower limit of the 2-sided 95% CI for the difference in seroresponse rate was greater than -10%, provided that the immunobridging success criterion based on the GMR was achieved.

GMTs and GMFRs were provided with associated 2-sided 95% CIs calculated with reference to Student's t-distribution. Comparative analyses of immunogenicity data were performed for participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 2. Two-sided 95% CIs were obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t-distribution, and then exponentiating the confidence limits. The exact 2-sided 95% CI for binary endpoints for each group was computed using the F distribution (Clopper-Pearson). Titers below the LLOQ were set to 0.5 × LLOQ for all other analyses except for seroresponse.

Immunobridging Subset Sample Size

In Phase 2/3, primary immunobridging assessments had an immunobridging subset sample size of 225 evaluable participants in Study C4591007 (5 to <12 years of age) and corresponding randomly selected comparator group in Study C4591001 (16 to 25 years of age), providing 90.4% and 92.6% power to declare immunobridging success based on GMR and seroresponse difference, respectively.

Subgroup Analyses

In Phase 2/3, subgroup analyses of immunogenicity endpoints were planned to be conducted based on demographics (sex, race, ethnicity) and SARS-CoV-2 baseline status (positive or negative).

2.7.3.1.1.2. Methods for the Evaluation of Efficacy in Children 5 to <12 Years of Age

Efficacy analyses in the 5 to <12 years of age group were prespecified to be conducted when at least 22 confirmed COVID-19 cases had accrued in participants without serological or virological evidence of past SARS-CoV-2 infection prior to 7 days post-Dose 2 and immunobridging success criteria had first been met (refer to Section 2.7.3.1.1.1).

The event-driven, supportive efficacy analysis was not conducted as an insufficient number of confirmed COVID-19 cases accrued by the data cutoff date of 06 September 2021. Efficacy endpoints, criteria, and analysis methods are provided below, for reference, regarding ongoing case evaluation.

Case surveillance and Criteria

In Study C4591007 participants 5 to <12 years of age, efficacy against confirmed COVID-19 was assessed by continuous surveillance for potential cases of COVID-19 (overall and those meeting criteria as severe or MIS-C). If a study participant developed an acute illness, it was considered to potentially be COVID-19 and the participant's parent/legal guardian was to contact the site to arrange an in-person or telehealth visit. Per protocol, illness visit assessments included nasal (anterior nares) swab sample collection either by site staff personnel (clinical visit) or by a participant's parent/legal guardian, for RT-PCR test (Cepheid; US FDA-authorized under EUA) or other equivalent nucleic acid amplification-based test (ie, NAAT), to detect SARS-CoV-2. Clinical information and results from local standard-of-care tests were also assessed. The central laboratory NAAT result was used for case definition; if no central laboratory result was available, a local NAAT result could be used if it was obtained using one of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche Cobas SARS-CoV-2 Real-Time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001).

Two definitions (first and second definitions) of SARS-CoV-2–related cases, SARS-CoV-2-related severe cases and MIS-C, were considered in case assessments. In all cases, the onset date of the case was the date that symptoms were first experienced by the participant; if new symptoms were reported within 4 days after resolution of all previous symptoms, they were considered as part of a single illness.

SARS-CoV-2–Related Cases: Confirmed COVID-19

First definition (per protocol criteria) - Presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test), which triggers a potential COVID-19 illness visit:

- 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, as defined by ≥3 loose stools/day
- Vomiting
- Inability to eat/poor feeding in participants <5 years of age.

Second definition (per CDC criteria): Could include the following additional symptoms defined by the CDC[3], but did not trigger a potential COVID-19 illness visit unless deemed necessary in the opinion of the investigator: fatigue, headache, nasal congestion or runny nose, nausea or abdominal pain[4], and/or lethargy.

SARS-CoV-2–related hospitalization definition: Confirmed COVID-19 and hospitalization.

SARS-CoV-2–related severe case definition: Confirmed COVID-19 and presence of at least 1 of the following triggers a potential COVID-19 illness visit:

- Clinical signs at rest indicative of severe systemic illness:
  - Respiratory rate (breaths/min) and heart rate (beats/min) outside of normal range[5]
  - SpO2 ≤92% on room air, >50% FiO2 to maintain ≥92%, or PaO2/FiO2 <300 mm Hg
- Respiratory failure: defined as needing high-flow oxygen, including CPaP, BiPaP, noninvasive ventilation, mechanical ventilation, or ECMO
- Evidence of shock or cardiac failure:
  - Systolic blood pressure (mm Hg); <70 + (age in years × 2) for age up to 10 years, <90 for age ≥10 years; or requiring vasoactive drugs to maintain BP in the normal range
- Significant acute renal failure:
  - Serum creatinine ≥2 times ULN for age or 2-fold increase in baseline creatinine
- Significant gastrointestinal/hepatic failure:
  - Total bilirubin ≥4 mg/dL or ALT 2 times ULN for age
- Significant neurological dysfunction:
  - Glasgow Coma Scale score ≤11, or acute change in mental status with a decrease in Glasgow Coma Scale score ≥3 points from abnormal baseline[6]
- Admission to an intensive care unit
- Death

Confirmed MIS-C definition[7] (per the CDC MIS-C case definition):

- An individual <21 years of age presenting with fever (≥38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours); AND

- Laboratory evidence of inflammation (based on local laboratory ranges) including, but not limited to, 1 or more of the following: Elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, and low albumin; AND

- Evidence of clinically severe illness requiring hospitalization (definition as noted above for severe disease), with multisystem (≥2) organ involvement:
  - Cardiac (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia)
  - Renal (eg, acute kidney injury)
  - Respiratory (eg, pneumonia, ARDS, pulmonary embolism)
  - Hematologic (eg, elevated D-dimers, thrombophilia, or thrombocytopenia)
  - GI/hepatic (eg, elevated bilirubin, elevated liver enzymes, or diarrhea)
  - Dermatologic (eg, rash, mucocutaneous lesions)
  - Neurological (eg, CVA, aseptic meningitis, encephalopathy); AND

- No alternative plausible diagnoses; AND

- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; OR

- COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

Serological definition: Used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: Positive N-binding antibody result in a participant with a prior negative N-binding antibody result

- Current or recent exposure established by SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

- Past serological and virological status is established by SARS-CoV-2 PCR or history of reported COVID-19.

Efficacy Endpoints

The secondary endpoints for estimation of vaccine efficacy (VE) against confirmed COVID-19 in Phase 2/3 participants, if success criteria for immunobridging were successful, are:

- Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of follow-up in evaluable participants without serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection.

- Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of follow-up in evaluable participants with or without serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection.

Exploratory endpoints to describe COVID-19 cases in participants without, and with and without, evidence of past SARS CoV-2 infection included confirmed COVID-19 cases; confirmed severe COVID-19 cases; and confirmed MIS-C cases per CDC criteria.

Efficacy Analysis Methods

Efficacy against confirmed COVID-19 is planned to be evaluated as a supportive analysis only if at least 22 cases accrued in participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen and success criteria were met for immunobridging in the 5 to <12 years of age group.

Vaccine efficacy (VE) against confirmed COVID-19 from 7 days after Dose 2 is estimated by $100 \times (1 - IRR)$, where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of blinded follow-up in the active vaccine group to the corresponding illness rate in the placebo group. VE and the associated 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time are included with efficacy analyses.

In addition to the analyses of VE performed using the per protocol case definition, descriptive statistics (counts, percentages, and the associated Clopper-Pearson 95% CIs) are planned to be provided for severe COVID-19 cases (as defined by FDA), for all cases (regardless of severity) and severe COVID-19 cases as defined by CDC.[8]

2.7.3.1.2. Pivotal Study in Adolescents and Adults >12 Years of Age – C4591001

Study C4591001, the pivotal study that established the safety, efficacy, and immunogenicity of BNT162b2 in individuals 12 years of age and older, provides immunogenicity data (SARS-CoV-2 neutralizing titers) for immunobridging comparisons. The data for immunobridging are from a randomly selected subset of participants 16 to 25 years of age who received BNT162b2 (30 μg) or placebo in Study C4591001.

Study design and conduct for C4591001 were similar to those described above for Study C4591007 and have been described previously in the CSR for the final efficacy analysis, which was submitted for the adult MAA (Module 5.3.5.1 Study C4591001 Final Analysis Interim CSR).

2.7.3.2. Summary of Results of Individual Studies (Study C4591007)

2.7.3.2.1. Immunogenicity Evaluations

In this section, immunogenicity results are first summarized for Phase 1 participants by BNT162b2 dose level (Section 2.7.3.2.1.1). Subsequently, results are presented for participants who received the selected dose level of BNT162b2 or placebo in Phase 2/3 of the study (Section 2.7.3.2.1.2).

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

Immunogenicity data are detailed in Module 5.3.5.1 C4591007 (5 to <12 Years) Interim CSR Section 10 (study populations) and Section 11 (immunogenicity analysis results).

2.7.3.2.1.1. Phase 1

2.7.3.2.1.1.1. Data Sets Analyzed and Demographic Characteristics – Phase 1

Data Sets Analyzed – Phase 1

In Phase 1 participants 5 to <12 years of age, the immunogenicity populations (all-available and evaluable) were comprised of enrolled participants who received vaccine at the 10 and 20 µg dose levels. One additional participant was assigned to the 20-µg dose level group but did not receive BNT162b2 and was therefore excluded from immunogenicity populations and analyses. One participant in the 10-µg dose level group did not have a post-vaccination assay result available.

All 16 participants assigned to the 30-µg dose level group were excluded from the all-available and evaluable immunogenicity populations. In the 10 and 20 µg dose level groups, a total of 2 participants (n=1 each per dose level) were excluded for the following reasons:

- All-available immunogenicity population: did not have at least 1 valid and determinate immunogenicity result after vaccination; did not receive any dose of study intervention
- Evaluable immunogenicity population: did not receive two doses of vaccine as assigned; did not have at least 1 valid and determinate immunogenicity result within 6 to 8 days after Dose 2

Demographics (Evaluable Immunogenicity Population) – Phase 1

Most Phase 1 participants 5 to <12 years of age in the evaluable immunogenicity population were White (74.2%), with 9.7% Black or African American participants and 12.9% Asian participants, and other racial groups were 3.2%. There were 6.5% Hispanic/Latino participants. The median age was 9.0 years and 48.4% of participants were male Table 1.

Table 1. Demographic Characteristics – Phase 1 – 5 to <12 Years of Age – Evaluable Immunogenicity Population

	Vaccine Group (as Assigned)		
	10 µg (N[a]=15) n[b] (%)	20 µg (N[a]=16) n[b] (%)	Total (N[a]=31) n[b] (%)
Sex			
Male	5 (33.3)	10 (62.5)	15 (48.4)
Female	10 (66.7)	6 (37.5)	16 (51.6)
Race			
White	10 (66.7)	13 (81.3)	23 (74.2)
Black or African American	3 (20.0)	0	3 (9.7)
American Indian or Alaska Native	0	1 (6.3)	1 (3.2)
Asian	2 (13.3)	2 (12.5)	4 (12.9)
Ethnicity			
Hispanic/Latino	2 (13.3)	0	2 (6.5)
Non-Hispanic/non-Latino	13 (86.7)	16 (100.0)	29 (93.5)
Age at vaccination (years)			
Mean (SD)	8.0 (1.89)	8.0 (1.97)	8.0 (1.90)
Median	9.0	8.5	9.0
Min, max	(5, 11)	(5, 10)	(5, 11)

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.
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(Cutoff Date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: ./nda3/C4591007_Phase1_EUA/adsl_s005_demo_p1_12_evl

2.7.3.2.1.1.2. Immunogenicity Results – Phase 1

SARS-CoV-2 Neutralizing Titers

C4591007 Phase 1 immunogenicity data are summarized for participants 5 to <12 years of age group who were without evidence of SARS-CoV-2 infection in the evaluable immunogenicity population, for 10 and 20 µg dose levels. Results for the all-available immunogenicity population were similar to those of the evaluable population.

At Day 7 post-Dose 2, the GMTs were similar across the tested dose levels: 4162.6 (95% CI: 2584.7, 6704.0) in the 10-µg group and 4583.4 (95% CI: 2802.9, 7494.8) in the 20-µg group (Table 2).

Table 2. Summary of Geometric Mean Titers – Participants Without Evidence of Infection – Phase 1 – 5 to <12 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Assigned)					
		10 µg			20 µg		
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/Day 7	15	4162.6	(2584.7, 6704.0)	15	4583.4	(2802.9, 7494.8)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to the Visit 3 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visits 1, 2, and 3, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result
at any unscheduled visit prior to the Visit 3 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants 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.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: adva Table Generation: 17AUG2021 (19:51)
(Cutoff Date: 16JUL2021, Snapshot Date: 11AUG2021) Output File:
./nda3/C4591007 Phase1 EUA/adva s001 gmt p1 12 evl

2.7.3.2.1.1.3. Immunogenicity Conclusions and Dose Selection – Phase 1

BNT162b2 elicited robust SARS-CoV-2 50% neutralizing titers at 7 days after Dose 2 at both tested dose levels (10 and 20 µg) when administered to healthy children 5 to <12 years of age who were without evidence of SARS-CoV-2 infection. The Day 7 post-Dose 2 GMTs were similar across the 10 and 20 µg dose level groups tested in Phase 1.

The similarity in post-vaccination immunogenicity as reflected in Day 7 post-Dose 2 GMTs across 10 µg and 20 µg dose levels, along with the most favorable reactogenicity profile observed in the 10 µg dose level, led to the selection of BNT162b2 at the 10 µg dose level to proceed to Phase 2/3 evaluation for participants 5 to <12 years of age.

2.7.3.2.1.2. Phase 2/3

2.7.3.2.1.2.1. Data Sets Analyzed and Demographic Characteristics – Phase 2/3

Immunogenicity Populations

Immunogenicity data from Phase 2/3 pediatric participants 5 to <12 years of age in Study C4591007 (who received BNT162b2 at the 10-µg dose level or placebo) were compared with Phase 2/3 young adults 16 to 25 years of age in Study C4591001 (who received BNT162b2 at the 30-µg dose level or placebo). Samples for comparison from each age group/study were tested contemporaneously in the same assay.

In Phase 2/3, immunogenicity data were evaluated for children 5 to <12 years of age who had had the protocol-specified blood draws for immunogenicity testing (ie, the immunobridging subset: approximately 300 participants in the BNT162b2 group and 150 participants in the placebo group). Data for comparison in immunobridging analyses were from a randomly selected subset of participants 16 to 25 years of age from Study C4591001 (approximately 300 participants in the BNT162b2 group and 50 participants in the placebo group).

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.

The Phase 2/3 evaluable immunogenicity population for participants 5 to <12 years of age included 294 participants in the BNT162b2 group and 147 participants in the placebo group, and for Study C4591001 participants 16 to 25 years of age included 273 participants in the BNT162b2 group and 47 participants in the placebo group (Table 3). Exclusions from the evaluable immunogenicity population were generally balanced across vaccine groups, and the most common reason for exclusion was participants not having at least 1 valid and determinate immunogenicity result within 28-42 days after Dose 2.

The evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2 for the group of children 5 to <12 years of age was comprised of 264 participants in the BNT162b2 group and 130 participants in the placebo group, and for young adults 16 to 25 years of age was comprised of 253 participants in the BNT162b2 group and 45 participants in the placebo group (Table 3).

Table 3. Immunogenicity Populations – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age

	Vaccine Group (as Randomized)			
	BNT162b2		Placebo	
	10 µg 5 to <12 Years (C4591007)	30 µg 16-25 Years (C4591001)	5 to <12 Years (C4591007)	16-25 Years (C4591001)
	n[a] (%)	n[a] (%)	n[a] (%)	n[a] (%)
Randomized[b]	322 (100.0)	300 (100.0)	163 (100.0)	50 (100.0)
All-available immunogenicity population	311 (96.6)	286 (95.3)	156 (95.7)	49 (98.0)
Participants excluded from all-available immunogenicity population	11 (3.4)	14 (4.7)	7 (4.3)	1 (2.0)
Reason for exclusion				
Did not have at least 1 valid and determinate immunogenicity result after vaccination	11 (3.4)	13 (4.3)	7 (4.3)	1 (2.0)
Unreliable data due to lack of PI oversight	0	1 (0.3)	0	0
Evaluable immunogenicity population	294 (91.3)	273 (91.0)	147 (90.2)	47 (94.0)
Without evidence of infection up to 1 month after Dose 2[c]	264 (82.0)	253 (84.3)	130 (79.8)	45 (90.0)
Participants excluded from evaluable immunogenicity population	28 (8.7)	27 (9.0)	16 (9.8)	3 (6.0)
Reason for exclusion[d]				
Did not receive 2 doses of the vaccine as randomized	3 (0.9)	0	1 (0.6)	0
Did not receive Dose 2 within the 19-42 days after Dose 1	3 (0.9)	3 (1.0)	2 (1.2)	1 (2.0)
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after Dose 2	13 (4.0)	21 (7.0)	14 (8.6)	3 (6.0)
Did not have blood draw at 1 month after Dose 2 visit	7 (2.2)	8 (2.7)	6 (3.7)	0
1 Month after Dose 2 blood draw outside of window (28-42 days after Dose 2)	6 (1.9)	8 (2.7)	8 (4.9)	2 (4.0)
Had blood draw within the window but no valid and determinate immunogenicity result obtained in lab	0	5 (1.7)	0	1 (2.0)
Had important protocol deviation(s) as determined by the clinician	10 (3.1)	4 (1.3)	1 (0.6)	0
Unreliable data due to lack of PI oversight	0	1 (0.3)	0	0

Table 3. Immunogenicity Populations – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age

	Vaccine Group (as Randomized)			
	BNT162b2		Placebo	
	10 µg 5 to <12 Years (C4591007)	30 µg 16-25 Years (C4591001)	5 to <12 Years (C4591007)	16-25 Years (C4591001)
	n[a] (%)	n[a] (%)	n[a] (%)	n[a] (%)

Abbreviations: COVID-19 = coronavirus disease 2019; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding;
PI = principal investigator; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. n = Number of participants with the specified characteristic, or the total sample.
b. These values are the denominators for the percentage calculations.
c. Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
d. Participants may have been excluded for more than 1 reason.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 17SEP2021 (09:12)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File:
./nda2 ubped/C4591007 P23 5 12 Bridging/adva s008 immu pop p2 12

Disposition

Disposition of participants in each age group who were included in the immunobridging subset, is summarized in Module 5.3.5.1 C4591007 (5 to <12 Years) Interim CSR Table 14.2. The disposition of Phase 2/3 pediatric participants 5 to <12 years of age in the immunobridging subset through 1 month after Dose 2 (Module 5.3.5.1 C4591007 (5 to <12 Years) Interim CSR Table 14.2) was similar to that of all randomized participants (Module 5.3.5.1 C4591007 (5 to <12 Years) Interim CSR Table 5) for the BNT162b2 and placebo groups. Most participants across both groups completed the visit at 1 month after Dose 2 (≥97.7%). There were no meaningful differences in the discontinuation or withdrawal categories in this subset.

Within the immunobridging subset, most participants randomized in both age groups (≥99.1%) received Dose 1 and Dose 2. Most participants across age groups completed the visit at 1 month after Dose 2 (≥97.7%).

Demographic Characteristics

In C4591007 Phase 2/3 pediatric participants 5 to <12 years of age in the evaluable immunogenicity population without evidence of infection up to 1 month after Dose 2, in the BNT162b2 group 53.0% of participants were male; 78.0% were White, 6.4% were Black or African American, 8.0% were Asian; 14.8% were Hispanic/Latino; the median age was 8.0 years (Table 4). Baseline SARS-CoV-2 status was positive for 7.1% and 8.8% of participants in the BNT162b2 and placebo groups, respectively (Module 5.3.5.1 C4591007 (5 to <12 Years) Interim CSR Table 14.15). Obese children (based on age- and sex-specific BMI) made up 8.0% and 11.5% of participants in the BNT162b2 and placebo groups, respectively (Table 4).

In C4591001 Phase 2/3 young adult participants 16 to 25 years of age in the evaluable immunogenicity population without evidence of infection up to 1 month after Dose 2, in the BNT162b2 group 49.8% of participants were male; 76.7% were White, 10.7% were Black or African American, 6.3% were Asian; 37.5% were Hispanic/Latino; the median age was 21.0 years (Table 4). Baseline SARS-CoV-2 status was positive for 4.8% and 2.1% of participants in the BNT162b2 and placebo groups, respectively (Module 5.3.5.1 C4591007 (5 to <12 Years) Interim CSR Table 14.15). Obese adults made up 15.8% and 31.1% of participants in the BNT162b2 and placebo groups, respectively (Table 4).

Table 4. Demographic Characteristics – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)			
	BNT162b2		Placebo	
	10 µg 5 to <12 Years (C4591007) (N^a=264) n^b (%)	30 µg 16-25 Years (C4591001) (N^a=253) n^b (%)	5 to <12 Years (C4591007) (N^a=130) n^b (%)	16-25 Years (C4591001) (N^a=45) n^b (%)
Sex				
Male	140 (53.0)	126 (49.8)	72 (55.4)	16 (35.6)
Female	124 (47.0)	127 (50.2)	58 (44.6)	29 (64.4)
Race				
White	206 (78.0)	194 (76.7)	103 (79.2)	29 (64.4)
Black or African American	17 (6.4)	27 (10.7)	5 (3.8)	11 (24.4)
American Indian or Alaska Native	0	3 (1.2)	0	1 (2.2)
Asian	21 (8.0)	16 (6.3)	14 (10.8)	2 (4.4)
Native Hawaiian or other Pacific Islander	1 (0.4)	0	0	0

Table 4. Demographic Characteristics – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)			
	BNT162b2		Placebo	
	10 µg 5 to <12 Years (C4591007) (N[a]=264) n[b] (%)	30 µg 16-25 Years (C4591001) (N[a]=253) n[b] (%)	5 to <12 Years (C4591007) (N[a]=130) n[b] (%)	16-25 Years (C4591001) (N[a]=45) n[b] (%)
Multiracial	16 (6.1)	11 (4.3)	6 (4.6)	1 (2.2)
Not reported	3 (1.1)	2 (0.8)	2 (1.5)	1 (2.2)
Ethnicity				
Hispanic/Latino	39 (14.8)	95 (37.5)	20 (15.4)	12 (26.7)
Non-Hispanic/non-Latino	223 (84.5)	158 (62.5)	110 (84.6)	32 (71.1)
Not reported	2 (0.8)	0	0	1 (2.2)
Age at vaccination (years)				
Mean (SD)	8.3 (1.85)	20.9 (3.02)	8.3 (2.04)	20.8 (3.10)
Median	8.0	21.0	9.0	22.0
Min, max	(5, 11)	(16, 25)	(5, 11)	(16, 25)
Obese[c]				
Yes	21 (8.0)	40 (15.8)	15 (11.5)	14 (31.1)
No	243 (92.0)	213 (84.2)	115 (88.5)	31 (68.9)

Abbreviations: COVID-19 = coronavirus disease 2019; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding;
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
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. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart for 5 to <12 years of age or BMI ≥30 kg/m^2 for 16 to 25 years of age.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 16SEP2021 (15:29)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File:
./nda2_ubped/C4591007_P23_5_12_Bridging/adsl_s005_demo_p2_12_weoi_evl

2.7.3.2.1.2.2. Immunogenicity Results

2.7.3.2.1.2.2.1. Immunobridging Analyses

Geometric Mean Ratio (GMR) of Neutralizing Titers

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the ratio of the SARS-CoV-2 50% neutralizing GMT in children 5 to <12 years of age (who received the 10-µg dose level) to that of young adults 16 to 25 years of age (who received the 30-µg dose level) was 1.04 (2-sided 95% CI: 0.93, 1.18) (Table 5).

The lower bound of the 2 sided 95% CI for GMR was >0.67 and the GMR point estimate was ≥0.8, which meets the prespecified 1.5-fold margin and success criteria (see Section 2.7.3.1.1.1). Therefore, immunobridging based on GMR was achieved. Note that the observed GMR point estimate meets the requested criterion from the FDA of ≥1.

Table 5. Summary of Geometric Mean Ratios – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)								
		BNT162b2								
		10 µg 5 to <12 Years (C4591007)			30 µg 16-25 Years (C4591001)			5 to <12 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 Immunobridging Objective[e] (Yes/No)
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	264	1197.6	(1106.1, 1296.6)	253	1146.5	(1045.5, 1257.2)	1.04	(0.93, 1.18)	Yes

Abbreviations: COVID-19 = coronavirus disease 2019; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = SARS-CoV-2 serum neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.

a. Protocol-specified timing for blood sample collection.

b. n = Number of participants 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 ([5 to <12 years] - [16-25 years]) and the corresponding CI (based on the Student t distribution).

e. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.8.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 16SEP2021 (18:27)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File: ./nda2 ubped/C4591007 P23 5 12 Bridging/adva s004 gmr p2 12 evl

Difference in Seroresponse Rate

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, high and equal proportions (99.2% each of children 5 to <12 years of age and young adults 16 to 25 years of age) achieved a seroresponse (as defined in Section 2.7.3.1.1.1 from before vaccination to 1 month after Dose 2. The difference in the proportions of participants who had seroresponse between the 2 age groups (children – young adults) was 0.0% (2-sided 95% CI: -2.0%, 2.2%) (Table 6).

Since immunobridging based on GMR was achieved, hypothesis of immunobridging based on seroresponse rate was tested subsequently (refer to analysis methods in Section 2.7.3.1.1.1). The lower limit of the 95% CI for the difference in seroresponse rate was -2.0%, which is greater than the prespecified margin of -10%. Therefore, immunobridging based on seroresponse rate was achieved.

Table 6. Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – Comparison of 5 to <12 Years of Age to Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)							
		BNT162b2							
		10 µg 5 to <12 Years (C4591007)			30 µg 16-25 Years (C4591001)			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	264	262 (99.2)	(97.3, 99.9)	253	251 (99.2)	(97.2, 99.9)	0.0	(-2.0, 2.2)

Abbreviations: COVID-19 = coronavirus disease 2019; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = SARS-CoV-2 serum neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.

a. Protocol-specified timing for blood sample collection.

b. N = number of participants 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 participants with seroresponse 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 (5 to <12 years – 16-25 years).

f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 16SEP2021 (15:31)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File: ./nda2_ubped/C4591007_P23_5_12_Bridging/adva_s003_diff_sero_p2_12_evl

2.7.3.2.1.2.2.2. SARS-CoV-2 Neutralizing Titers

SARS-CoV-2 neutralizing titer data for children 5 to <12 years of age and young adults 16 to 25 years of age are summarized below for the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2.

Results for the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2 were generally similar to those in the evaluable and all-available immunogenicity populations with or without prior evidence of SARS-CoV-2 infection.

Geometric Mean Titers (GMTs)

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, at 1 month after Dose 2 (Day 52) of BNT162b2 vaccination there were substantial and comparable increases in SARS-CoV-2 50% neutralizing GMTs in both children 5 to <12 years of age (who received 10-µg dose level) and young adults 16 to 25 years of age (who received the 30-µg dose level) (Figure 1, Figure 2, Table 7)

The neutralizing GMTs observed at 1 month after Dose 2 was 1197.6 in children 5 to <12 years of age compared to 1146.5 in young adults 16 to 25 years of age. As expected, the neutralizing GMTs were low in placebo groups for both age groups.

Subgroup Analysis

SARS-CoV-2 50% neutralizing titers (GMTs) were evaluated by demographic and baseline SARS-CoV-2 status subgroups. Subgroups of pediatric participants 5 to <12 years of age and young adults 16 to 25 years of age (with or without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2) had similar patterns of GMTs at before vaccination and 1 month after Dose 2 across the BNT162b2 and placebo groups when evaluated by sex, race, and ethnicity (Table 10 in Appendix A).

Several subgroups included a limited number of participants, and their results should be interpreted with caution. There were no meaningful differences in the neutralizing titers on the basis of demographic subgroups within each age group, or between the age groups. Participants who were SARS-CoV-2 baseline status positive had higher GMTs at both before vaccination and 1 month after Dose 2 compared to those negative at baseline, in both age groups.

All subgroups are summarized below.

Sex

The GMTs at 1 month post-Dose 2 were similar for male and female participants in the 5 to <12 years of age group who received BNT162b2 10 µg (1218.5 vs 1395.3). Likewise, the GMTs at 1 month post-Dose 2 were similar for male and female participants in the 16 to 25 years of age group who received BNT162b2 30 µg (1081.8 vs 1308.3).

Race

The GMTs at 1 month post-Dose 2 were similar across participants in different race subgroups in the 5 to <12 years of age group who received BNT162b2 10 µg (White: 1299.4 vs Black or African American: 1171.2 vs Asian: 1219.4). Likewise, the GMTs at 1 month post-Dose 2 were similar across participants in different race subgroups in the 16 to 25 years of age group who received BNT162b2 30 µg (White: 1225.6 vs Black or African American: 1010.3 vs Asian: 967.9). Due to the limited number of participants in the Black or African American and Asian subgroups, these differences should be interpreted with caution.

Ethnicity

The GMTs at 1 month post-Dose 2 were similar for Hispanic/Latino and non-Hispanic/Non-Latino participants in the 5 to <12 years of age group who received BNT162b2 10 µg (1412.3 vs 1276.9). Likewise, the GMTs at 1 month post-Dose 2 were similar for Hispanic/Latino and non-Hispanic/Non-Latino participants in the 16 to 25 years of age group who received BNT162b2 30 µg (1179.2 vs 1200.2).

Baseline SARS-CoV-2 Status

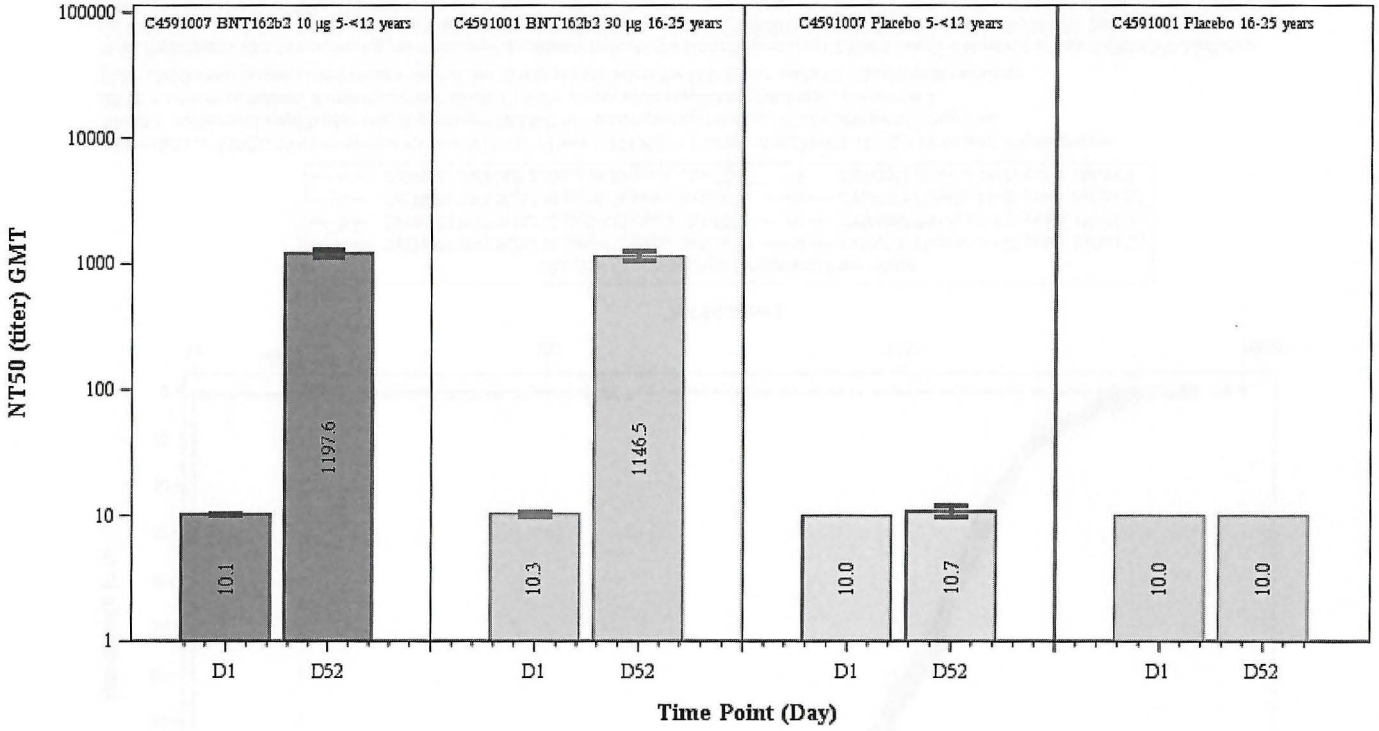
Vaccination with BNT162b2 induced an increased immune response at 1 month after Dose 2 for all participants, regardless of baseline SARS-CoV-2 status. In the BNT162b2 group, children 5 to <12 years of age who were baseline SARS-CoV-2 positive (n=21) had SARS-CoV-2 50% neutralizing GMTs approximately 2.7-fold that of children who were baseline negative (n=273) (3270.0 vs 1211.3).

A similar pattern was observed for baseline SARS-CoV-2 positive (n=13) versus negative (n=259) young adults in the BNT162b2 group, with baseline positive participants GMTs 1.96-fold that of negative participants (2253.8 vs 1151.2).

Notably, the GMTs and fold-increase in GMTs among baseline SARS-CoV-2 positive participants was higher in the pediatric group 5 to <12 years of age who received BNT162b2 10 µg compared with the young adult group 16 to 25 years of age who received BNT162b2 30 µg.

Due to the limited number of baseline positive participants in either age group, these differences should be interpreted with caution.

Figure 1. Geometric Mean Titers and 95% CIs: SARS-CoV-2 Neutralization Assay – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population



Abbreviations: COVID-19 = coronavirus disease 2019; D = day; GMT = geometric mean titer; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Number within each bar denotes geometric mean.

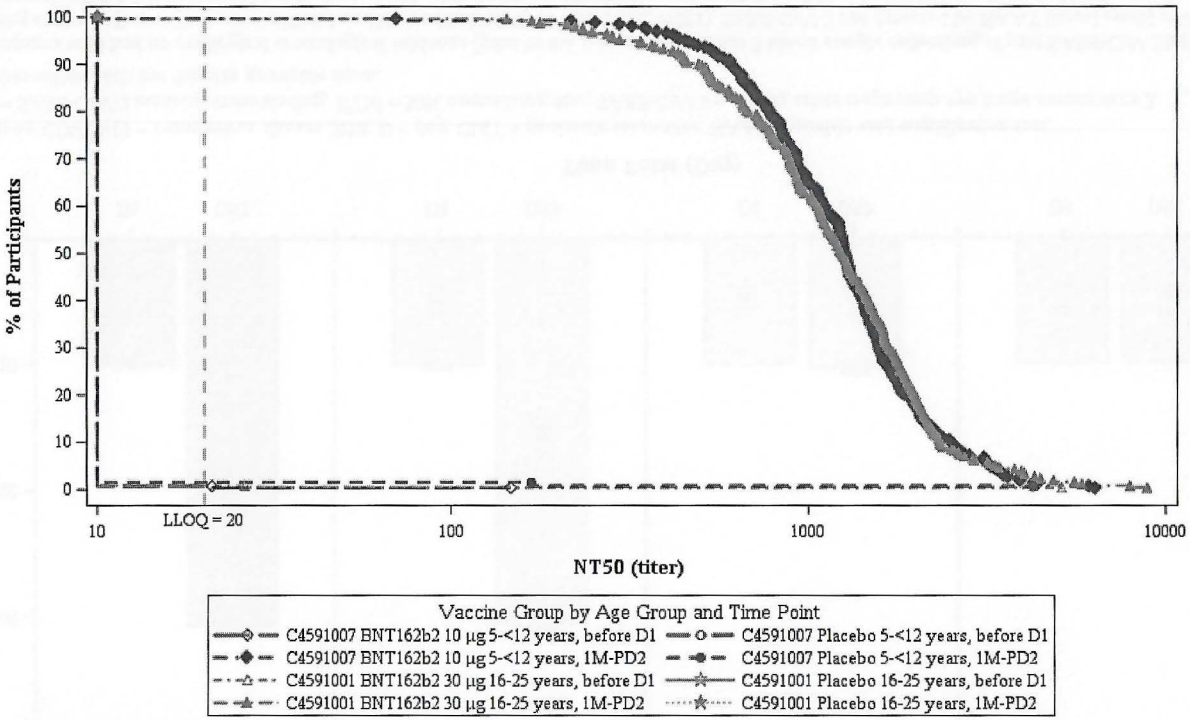
Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.

PFIZER CONFIDENTIAL Source Data: adva Date of Generation: 16SEP2021 (16:11)

(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021])

Output File: ./nda2_ubped/C4591007_P23_5_12_Bridging/adva_f002_sars_50_p2_12_evl

Figure 2. Reverse Cumulative Distribution Curves, SARS-CoV-2 Neutralization Assay – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population



Abbreviations: COVID-19 = coronavirus disease 2019; D1 = Dose 1; 1M-PD2 = 1 month after Dose 2; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titer; RCDC = reverse cumulative distribution curve; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: LLOQ value is represented using a vertical line. Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.

PFIZER CONFIDENTIAL Source Data: adva Date of Generation: 16SEP2021 (16:11)

(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021])

Output File: ./nda2_ubped/C4591007_P23_5_12_Bridging/adva_f003_sars_50_p2_12_evl

Table 7. Summary of Geometric Mean Titers – NT50 – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)											
		BNT162b2						Placebo					
		10 µg 5 to <12 Years (C4591007)			30 µg 16-25 Years (C4591001)			5 to <12 Years (C4591007)			16-25 Years (C4591001)		
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	1/Prevax	264	10.1	(9.9, 10.3)	253	10.3	(9.8, 10.8)	130	10.0	(10.0, 10.0)	45	10.0	(10.0, 10.0)
	2/1 Month	264	1197.6	(1106.1, 1296.6)	253	1146.5	(1045.5, 1257.2)	130	10.7	(9.7, 11.8)	45	10.0	(10.0, 10.0)

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; NT50 = 50% neutralizing titer; Prevax = before vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.

a. Protocol-specified timing for blood sample collection.

b. n = Number of participants 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.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 16SEP2021 (15:33)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File: ./nda2_ubped/C4591007_P23_5_12_Bridging/adva_s001_gmt_p2_12_evl

Geometric Mean Fold-Rise (GMFR) in Titers

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the GMFRs of SARS-CoV-2 50% serum neutralizing titers from before vaccination to 1 month after Dose 2 of BNT162b2 were robust. There was a similar magnitude of rise in the pediatric 5 to <12 years of age group (118.2) compared with the young adult 16 to 25 years of age group (111.4) for BNT162b2 group (Table 8). GMFRs for placebo participants in either age group were very low (1.0 to 1.1).

Subgroup Analysis

The fold-rises in SARS-CoV-2 50% neutralizing titers (GMFRs) were evaluated by baseline SARS-CoV-2 status subgroups, among participants 5 to <12 years of age and young adults 16 to 25 years of age (with or without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2). Within each age group in the BNT162b2 groups, baseline negative participant subgroups had a greater magnitude of rise in titers from before vaccination to 1 month after Dose 2 as compared to baseline positive participants.

Baseline SARS-CoV-2 Status

The GMFRs were overall slightly higher in the pediatric BNT162b2 group compared to the young adult BNT162b2 group at 1 month after the second dose, regardless of baseline SARS-CoV-2 status (Table 11 in Appendix A).

Taking into account the limited sample size for those SARS-CoV-2 status positive at baseline, the GMFRs were numerically higher in those who were SARS-CoV-2 status negative than in those who were baseline positive, in both age groups.

Among children 5 to <12 years of age who were baseline status positive (n=21) or negative (n=273), GMFRs in the BNT162b2 group were 54.7 versus 119.6, showing a greater magnitude of rise in titers for the baseline negative subgroup. Similarly, among young adults 16 to 25 years of age who were baseline positive (n=13) or negative (n=259), the GMFRs in the BNT162b2 group were 24.7 versus 112.0 (Table 11 in Appendix A).

Table 8. Summary of Geometric Mean Fold Rises From Before Vaccination to Each Subsequent Time Point – NT50 – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)							
		BNT162b2				Placebo			
		10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
Assay	Dose/ Sampling Time Point[a]	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	264	118.2 (109.2, 127.9)	253	111.4 (101.2, 122.7)	130	1.1 (1.0, 1.2)	45	1.0 (1.0, 1.0)

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; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.

a. Protocol-specified timing for blood sample collection.

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

c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the 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.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 16SEP2021 (15:31)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File: ./nda2_ubped/C4591007_P23_5_12_Bridging/advas_s001_gmfr_p2_12_weoi_evl

Seroresponse Rate

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, proportions of participants who achieved seroresponse (as defined in Section 2.7.3.1.1.1) in SARS-CoV-2 50% neutralizing titers 1 month after Dose 2 of BNT162b2 was the same (99.2%) in children 5 to <12 years of age and young adults 16 to 25 years of age (Table 9). Very few placebo participants in either age group reached seroresponse based on SARS-CoV-2 neutralizing titers at 1 month after Dose 2.

Subgroup Analysis

Seroresponse rates were evaluated by demographic and baseline SARS-CoV-2 status subgroups. Subgroups of pediatric participants 5 to <12 years of age and young adults 16 to 25 years of age (with or without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2) had similar patterns of seroresponse rates at 1 month after Dose 2 in the BNT162b2 group when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status (Table 12 in Appendix A). Seroresponse rates in the BNT162b2 groups were overall high with no meaningful differences between any subgroups. These subgroups are summarized below.

Sex

In the BNT162b2 groups, the seroresponse rates at 1 month post-Dose 2 were similar for male and female participants in the 5 to <12 years of age group (100% vs 98.6%) and in the 16 to 25 years of age group (98.5% vs 100%)

Race

In the BNT162b2 groups, the seroresponse rates at 1 month post-Dose 2 were similar across participants in different race subgroups in the 5 to <12 years of age group (range: 99.1% to 100%) and in the 16 to 25 years of age group (range: 93.8% to 100%).

Ethnicity

In the BNT162b2 groups, the seroresponse rates at 1 month post-Dose 2 were similar for Hispanic/Latino and non-Hispanic/non-Latino participants in the 5 to <12 years of age group (100% vs 99.2%) and in the 16 to 25 years of age group (100% vs 98.9%).

Baseline SARS-CoV-2 Status

In the BNT162b2 groups, children 5 to <12 years of age who were baseline status SARS-CoV-2 positive (n=21) or negative (n=273) had similar seroresponse rates (100% vs 99.3%), as did young adults 16 to 25 years of age who were baseline positive (n=13) or negative (n=259) (100% vs 99.2%).

Table 9. Number (%) of Participants With Seroresponse – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)							
		BNT162b2				Placebo			
		10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
Assay	Dose/ Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	264	262 (99.2) (97.3, 99.9)	253	251 (99.2) (97.2, 99.9)	130	2 (1.5) (0.2, 5.4)	45	0 (0.0) (0.0, 7.9)

Abbreviations: COVID-19 = coronavirus disease 2019; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.

a. Protocol-specified timing for blood sample collection.

b. N = number of participants 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 participants with seroresponse for the given assay at the given dose/sampling time point.

d. Exact 2-sided CI based on the Clopper and Pearson method.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 16SEP2021 (15:31)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File: ./nda2_ubped/C4591007_P23_5_12_Bridging/adva_s003_fr4_p2_12_wout_evl

2.7.3.2.1.2.3. Immunogenicity Conclusions

Based on immune response to the 10-µg dose level of BNT162b2 in SARS-CoV-2 50% neutralizing titers in participants without prior evidence of SARS-COV-2 infection up to 1 month after Dose 2, children 5 to <12 years of age met success criteria for immunobridging to young adults 16 to 25 years of age who received BNT162b2 at the 30-µg dose level, for both GMR and difference in seroresponse rates. The success criteria for GMR comparing children 5 to <12 years of age to young adults 16 to 25 years of age included a lower bound of the 2-sided 95% CI for GMR >0.67 and GMR point estimate ≥0.8, and for seroresponse rate was the lower limit of the 2-sided 95% CI for the difference in seroresponse rate of greater than -10%. Criteria for both endpoints were met with a GMR of 1.04 (2-sided 95% CI: 0.93, 1.18) and difference in seroresponse rate of 0.0% (2-sided 95% CI: -2.0%, 2.2%), therefore, immunobridging based on both GMR and difference in seroresponse rates was achieved for the 5 to <12 years of age group in C4591007. Note that the observed GMR point estimate meets the requested criterion from the FDA of ≥1.

Substantial and comparable increases over baseline (pre-vaccination) in neutralizing GMTs, GMFRs, and high seroresponse rates were observed at 1 month after Dose 2 of BNT162b2 in both age groups. The vast majority of BNT162b2 recipients in both age groups achieved a seroresponse 1 month after Dose 2.

Subgroup analyses of GMTs and seroresponse rates suggested no meaningful differences in neutralizing immune response based on participant demographics, within either age group, given that some subgroups included a limited number of participants. Participants who were baseline SARS-CoV-2 status positive had higher SARS-CoV-2 50% neutralizing titers at 1 month after Dose 2, and those who were baseline status negative had a greater magnitude of rise in titers from before vaccination to 1 month after Dose 2; seroresponse was high and not differentiated by baseline SARS-CoV-2 status.

Overall, based on SARS-CoV-2 50% neutralizing titers at 1 month after Dose 2, children 5 to <12 years of age had a similar immune response to the two-dose primary series of BNT162b2 10 µg compared to young adults 16 to 25 years of age who received two doses of BNT162b2 30 µg.

2.7.3.2.2. Efficacy Against Confirmed COVID-19 – Children 5 to <12 Years of Age

Efficacy analyses for the 5 to <12 years of age group are planned to be conducted only when at least 22 confirmed cases of COVID-19 had accrued in participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen and success criteria for immunobridging have already been met (see results in Section 2.7.3.2.1.2.2.1). These will be supportive data in addition to the primary immunobridging analyses.

As of the data cutoff date (06 September 2021), the prespecified number of at least 22 confirmed COVID-19 cases had not been reached in this age group (refer to analysis methods in Section 2.7.3.1.1.2), and no VE analysis was conducted. At the time of this submission data cutoff date, 13 confirmed cases of COVID-19 meeting evaluability criteria had accrued in this age group. Efficacy results will be reported at a later time, when a sufficient number of cases have accrued to conduct the event-driven analysis.

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

The dose level of 10 µg BNT162b2 was selected for use in children 5 to <12 years of age based, in part, on the results of immunogenicity results from Phase 1 of Study C4591007, as described in Section 2.7.3.2.1.1.

2.7.3.5. Persistence of Efficacy and/or Tolerance Effects

At the time of data summary for this submission, immunogenicity data demonstrating the immune response to 10 µg BNT162b2 administered to children 5 to <12 years of age were available only for the 1-month post Dose 2 time point in Study C4591007. 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.

Results of efficacy analyses will be provided once a sufficient number of COVID-19 cases have accumulated to conduct the event-driven analysis.

2.7.3.6. APPENDICES

2.7.3.6.1. Appendix A: Phase 2/3 Study C4591007, Post-text Tables

2.7.3.6.1.1. Immunogenicity (Phase 2/3 Study C4591007, Post-text Tables)

Table 10. Summary of Geometric Mean Titers, by Subgroup – NT50 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2				Placebo			
			10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
Assay	Dose/ Sampling Time Point[a]	Subgroup	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	294	11.5 (10.7, 12.3)	272	11.4 (10.6, 12.3)	147	12.4 (11.0, 14.0)	47	10.0 (10.0, 10.0)
		Sex								
		Male	153	10.8 (10.1, 11.6)	133	11.4 (10.1, 12.9)	84	12.6 (10.7, 14.8)	17	10.0 (10.0, 10.0)
		Female	141	12.3 (10.9, 13.8)	139	11.5 (10.4, 12.6)	63	12.2 (10.2, 14.6)	30	10.0 (10.0, 10.0)
		Race								
		White	232	11.8 (10.9, 12.9)	204	10.4 (9.9, 11.0)	120	13.0 (11.3, 15.0)	29	10.0 (10.0, 10.0)
		Black or African American	18	10.0 (10.0, 10.0)	32	16.4 (10.5, 25.6)	5	10.0 (10.0, 10.0)	12	10.0 (10.0, 10.0)
		American Indian or Alaska Native	0	NE (NE, NE)	4	22.1 (1.8, 277.4)	0	NE (NE, NE)	1	10.0 (NE, NE)
		Asian	23	11.0 (9.5, 12.8)	17	13.0 (7.5, 22.5)	14	10.0 (10.0, 10.0)	3	10.0 (10.0, 10.0)

Table 10. Summary of Geometric Mean Titers, by Subgroup – NT50 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2				Placebo			
			10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
Assay	Dose/ Sampling Time Point[a]	Subgroup	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])
		Native Hawaiian or other Pacific Islander	1	10.0 (NE, NE)	1	42.0 (NE, NE)	0	NE (NE, NE)	0	NE (NE, NE)
		Multiracial	17	10.0 (10.0, 10.0)	12	12.3 (7.8, 19.2)	6	10.0 (10.0, 10.0)	1	10.0 (NE, NE)
		Not reported	3	10.0 (10.0, 10.0)	2	10.0 (10.0, 10.0)	2	10.0 (10.0, 10.0)	1	10.0 (NE, NE)
		Ethnicity								
		Hispanic/Latino	46	14.3 (10.8, 19.0)	98	10.6 (9.7, 11.6)	26	19.4 (11.6, 32.5)	12	10.0 (10.0, 10.0)
		Non-Hispanic/non-Latino	246	11.0 (10.4, 11.7)	174	11.9 (10.6, 13.3)	121	11.3 (10.3, 12.3)	34	10.0 (10.0, 10.0)
		Not reported	2	10.0 (10.0, 10.0)	0	NE (NE, NE)	0	NE (NE, NE)	1	10.0 (NE, NE)
		Baseline SARS-CoV-2 Status[b]								
		POS	21	59.8 (33.5, 106.5)	13	91.3 (45.1, 184.7)	13	114.5 (71.6, 183.0)	1	10.0 (NE, NE)
		NEG	273	10.1 (9.9, 10.3)	259	10.3 (9.8, 10.8)	134	10.0 (10.0, 10.0)	46	10.0 (10.0, 10.0)

Table 10. Summary of Geometric Mean Titers, by Subgroup – NT50 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2				Placebo			
			10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
Assay	Dose/ Sampling Time Point[a]	Subgroup	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])
	2/1 Month	All	294	1300.3 (1195.9, 1413.8)	273	1192.6 (1089.7, 1305.2)	147	13.5 (11.6, 15.8)	47	10.3 (9.7, 10.9)
		Sex								
		Male	153	1218.5 (1102.8, 1346.3)	133	1081.8 (939.2, 1245.9)	84	14.5 (11.5, 18.3)	17	10.0 (10.0, 10.0)
		Female	141	1395.3 (1216.4, 1600.6)	140	1308.3 (1168.1, 1465.5)	63	12.3 (10.2, 14.8)	30	10.4 (9.6, 11.4)
		Race								
		White	232	1299.4 (1178.8, 1432.4)	205	1225.6 (1120.7, 1340.3)	120	14.5 (12.0, 17.4)	29	10.0 (10.0, 10.0)
		Black or African American	18	1171.2 (823.7, 1665.4)	32	1010.3 (657.3, 1552.9)	5	10.0 (10.0, 10.0)	12	11.2 (8.8, 14.2)
		American Indian or Alaska Native	0	NE (NE, NE)	4	1905.7 (724.8, 5011.0)	0	NE (NE, NE)	1	10.0 (NE, NE)
		Asian	23	1219.4 (918.6, 1618.6)	17	967.9 (641.0, 1461.3)	14	10.0 (10.0, 10.0)	3	10.0 (10.0, 10.0)
		Native Hawaiian or other Pacific Islander	1	3921.0 (NE, NE)	1	1063.0 (NE, NE)	0	NE (NE, NE)	0	NE (NE, NE)
		Multiracial	17	1435.8 (1086.7, 1896.9)	12	1236.8 (649.5, 2354.8)	6	10.0 (10.0, 10.0)	1	10.0 (NE, NE)

Table 10. Summary of Geometric Mean Titers, by Subgroup – NT50 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2				Placebo			
			10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
Assay	Dose/ Sampling Time Point[a]	Subgroup	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])
		Not reported	3	1659.9 (616.0, 4472.4)	2	2028.7 (715.8, 5749.2)	2	10.0 (10.0, 10.0)	1	10.0 (NE, NE)
		Ethnicity								
		Hispanic/Latino	46	1412.3 (1118.1, 1783.9)	98	1179.2 (1046.6, 1328.6)	26	20.0 (11.7, 34.3)	12	10.0 (10.0, 10.0)
		Non-Hispanic/non-Latino	246	1276.9 (1166.4, 1397.9)	175	1200.2 (1059.4, 1359.6)	121	12.4 (10.7, 14.4)	34	10.4 (9.6, 11.2)
		Not reported	2	1823.3 (432.2, 7691.5)	0	NE (NE, NE)	0	NE (NE, NE)	1	10.0 (NE, NE)
		Baseline SARS-CoV-2 Status[b]								
		POS	21	3270.0 (2032.1, 5261.8)	13	2253.8 (1497.7, 3391.5)	13	133.2 (81.0, 219.0)	1	37.0 (NE, NE)
		NEG	273	1211.3 (1121.1, 1308.7)	259	1151.2 (1050.5, 1261.5)	134	10.8 (9.8, 12.0)	46	10.0 (10.0, 10.0)

Table 10. Summary of Geometric Mean Titers, by Subgroup – NT50 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2				Placebo			
			10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
Assay	Dose/ Sampling Time Point[a]	Subgroup	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. Participants whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included.

c. n = Number of participants 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.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 16SEP2021 (15:33)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File: ./nda2_ubped/C4591007_P23_5_12_Bridging/adva_s001_gmt_sub_p2_12_evl

Table 11. Summary of Geometric Mean Fold Rises From Before Vaccination to Each Subsequent Time Point, by Baseline SARS-CoV-2 Status – NT50 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2				Placebo			
			10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
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	294	113.1 (104.4, 122.6)	272	104.2 (94.1, 115.3)	147	1.1 (1.0, 1.2)	47	1.0 (1.0, 1.1)
		POS	21	54.7 (35.3, 84.7)	13	24.7 (13.9, 43.8)	13	1.2 (0.9, 1.5)	1	3.7 (NE, NE)
		NEG	273	119.6 (110.8, 129.2)	259	112.0 (101.7, 123.2)	134	1.1 (1.0, 1.2)	46	1.0 (1.0, 1.0)

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 participants with valid and determinate assay results for the specified assay at 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 the 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.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 16SEP2021 (15:31)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File: ./nda2 ubped/C4591007 P23 5 12 Bridging/advas s001 gmfr p2 12 evl

Table 12. Number (%) of Participants With Seroresponse, by Subgroup – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2				Placebo			
			10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
Assay	Dose/ Sampling Time Point[a]	Subgroup	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	294	292 (99.3) (97.6, 99.9)	272	270 (99.3) (97.4, 99.9)	147	2 (1.4) (0.2, 4.8)	47	0 (0.0) (0.0, 7.5)
		Sex								
		Male	153	153 (100.0) (97.6, 100.0)	133	131 (98.5) (94.7, 99.8)	84	2 (2.4) (0.3, 8.3)	17	0 (0.0) (0.0, 19.5)
		Female	141	139 (98.6) (95.0, 99.8)	139	139 (100.0) (97.4, 100.0)	63	0 (0.0) (0.0, 5.7)	30	0 (0.0) (0.0, 11.6)
		Race								
		White	232	230 (99.1) (96.9, 99.9)	204	204 (100.0) (98.2, 100.0)	120	2 (1.7) (0.2, 5.9)	29	0 (0.0) (0.0, 11.9)
		Black or African American	18	18 (100.0) (81.5, 100.0)	32	30 (93.8) (79.2, 99.2)	5	0 (0.0) (0.0, 52.2)	12	0 (0.0) (0.0, 26.5)
		American Indian or Alaska Native	0	0 (NE) (NE, NE)	4	4 (100.0) (39.8, 100.0)	0	0 (NE) (NE, NE)	1	0 (0.0) (0.0, 97.5)
		Asian	23	23 (100.0) (85.2, 100.0)	17	17 (100.0) (80.5, 100.0)	14	0 (0.0) (0.0, 23.2)	3	0 (0.0) (0.0, 70.8)
		Native Hawaiian or other Pacific Islander	1	1 (100.0) (2.5, 100.0)	1	1 (100.0) (2.5, 100.0)	0	0 (NE) (NE, NE)	0	0 (NE) (NE, NE)

Table 12. Number (%) of Participants With Seroresponse, by Subgroup – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2				Placebo			
			10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
Assay	Dose/ Sampling Time Point[a]	Subgroup	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])
		Multiracial	17	17 (100.0) (80.5, 100.0)	12	12 (100.0) (73.5, 100.0)	6	0 (0.0) (0.0, 45.9)	1	0 (0.0) (0.0, 97.5)
		Not reported	3	3 (100.0) (29.2, 100.0)	2	2 (100.0) (15.8, 100.0)	2	0 (0.0) (0.0, 84.2)	1	0 (0.0) (0.0, 97.5)
		Ethnicity								
		Hispanic/Latino	46	46 (100.0) (92.3, 100.0)	98	98 (100.0) (96.3, 100.0)	26	0 (0.0) (0.0, 13.2)	12	0 (0.0) (0.0, 26.5)
		Non-Hispanic/non-Latino	246	244 (99.2) (97.1, 99.9)	174	172 (98.9) (95.9, 99.9)	121	2 (1.7) (0.2, 5.8)	34	0 (0.0) (0.0, 10.3)
		Not reported	2	2 (100.0) (15.8, 100.0)	0	0 (NE) (NE, NE)	0	0 (NE) (NE, NE)	1	0 (0.0) (0.0, 97.5)
		Baseline SARS-CoV-2 Status[b]								
		POS	21	21 (100.0) (83.9, 100.0)	13	13 (100.0) (75.3, 100.0)	13	0 (0.0) (0.0, 24.7)	1	0 (0.0) (0.0, 97.5)
		NEG	273	271 (99.3) (97.4, 99.9)	259	257 (99.2) (97.2, 99.9)	134	2 (1.5) (0.2, 5.3)	46	0 (0.0) (0.0, 7.7)

Table 12. Number (%) of Participants With Seroresponse, by Subgroup – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2				Placebo			
			10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
Assay	Dose/ Sampling Time Point[a]	Subgroup	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])

Abbreviations: COVID-19 = coronavirus disease 2019; 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.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

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.

c. N = number of participants 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 participants with seroresponse 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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(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File: ./nda2 ubped/C4591007 P23 5 12 Bridging/adva s003 fr4 p2 12 sub evl

2.7.3.7. REFERENCES

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