2.5 CLINICAL OVERVIEW

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ABBREVIATIONS

Abbreviation	Definition
ADR	adverse reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ARDS	acute respiratory distress syndrome
BiPaP	bilevel positive airway pressure
BLA	(US FDA) Biologics License Application
BMI	body mass index
BNP	B-type natriuretic peptide
CBER	(US FDA) Center for Biologics Evaluation and Research
CDC	(US) Centers for Disease Control and Prevention
CFR	case fatality rate
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CPaP	continuous positive airway pressure
CRP	C-reactive protein
CSR	Clinical Study Report
CVA	cerebrovascular accident
DART	developmental and reproductive toxicity
ECMO	extracorporeal membrane oxygenation
e-diary	electronic diary
EMA	European Medicines Agency
ESR	erythrocyte sedimentation rate
EU	European Union
EUA	Emergency Use Application
FDA	(US) Food and Drug Administration
FIH	first-in-human
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMFR	geometric mean-fold rise
GMT	geometric mean titer
HIV	human immunodeficiency virus
ICH	International Council on Harmonisation
ICU	intensive care unit
IFNγ	interferon-gamma
IL-6	Interleukin 6
IM	intramuscular(ly)
IND	Investigational New Drug application
iPSP	initial Pediatric Study Plan
IRC	(US Study) Internal Review Committee
IRR	illness rate ratio
LDH	lactate dehydrogenase
LLN	lower limit of normal

Abbreviation	Definition
LNP	lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger RNA
mRNA	messenger RNA
NAAT	nucleic acid amplification testing
NHP	non-human primate
P2 S	SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein
PaO_2	partial pressure of oxygen
PDCO	Paediatric Committee
PCR	polymerase chain reaction
PIP	Paediatric Investigational Plan
PSP	Pediatric Study Plan
PT	Preferred Term
RBD	receptor binding domain
RNA-LNP	RNA lipid nanoparticle
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
SBP	systolic blood pressure
S glycoprotein, S	spike glycoprotein
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA query
SOC	System Organ Class
SpO_2	peripheral oxygen saturation
SRC	(German Study BNT162-01) Safety Review Committee
TME	targeted medical event
UK	United Kingdom
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
VAE(R)D	vaccine-associated enhanced (respiratory) disease
VE	vaccine efficacy
WHO	World Health Organization

2.5. CLINICAL OVERVIEW

This Clinical Overview (CO) describes clinical data for a prophylactic, RNA-based SARS-CoV-2 vaccine, BNT162b2 (COMIRNATY), developed by BioNTech and Pfizer. BNT162b2 is administered intramuscularly (IM) as a primary series of two doses given 3 weeks apart.

A Marketing Authorization Application (MAA) was submitted to the European Medicines Agency (EMA) via a rolling review procedure that completed on 07 December 2020. Conditional marketing authorization was granted by EMA on 21 December 2020 for individuals ≥16 years of age and was subsequently expanded on 28 May 2021 to include individuals ≥12 years of age.

A Biologics License Application (BLA) was submitted to the United States (US) Food and Drug Administration (FDA) on 18 May 2021. Licensure was granted by the FDA on 23 August 2021 for individuals ≥16 years of age.

The present submission supports an extension of the indication to children 5 to <12 years of age, based on Phase 1 dose finding (BNT162b2 10, 20, or 30 µg) and Phase 2/3 selected dose (BNT162b2 10 µg) data on safety and immunobridging data in children 5 to <12 years of age with at least 2 months of follow-up after receiving Dose 2 of BNT162b2 in Study C4591007. The clinical data are supplemented by a Chemistry, Manufacturing and Controls (CMC) package supporting a line extension for the 10-µg Tris/Sucrose presentation to enable pediatric dosing.

2.5.1. Product Development Rationale

2.5.1.1. Therapeutic Context

2.5.1.1.1. Disease or Condition

COVID-19 is caused by SARS-CoV-2, a zoonotic virus that first emerged as a human pathogen in China and has rapidly spread around the world by human to human transmission.

At the time of this submission, the ongoing pandemic remains a significant challenge to public health and economic stability worldwide, for which for a licensed prophylactic vaccine is a necessary and critical mitigation across all age groups.

2.5.1.1.2. Clinical Features and Epidemiology of COVID-19

COVID-19 presentation is generally with cough and fever, with chest radiography showing ground-glass opacities or patchy shadowing.[1] However, many patients present without fever or radiographic changes, and infections may be asymptomatic which is relevant to controlling transmission. For symptomatic patients, disease progression may lead to acute respiratory distress syndrome requiring ventilation, subsequent multi-organ failure, and death.[1]

Common symptoms in hospitalized patients (in order of highest to lowest frequency) include fever, dry cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhea, headache, weakness, and rhinorrhea.[1] Anosmia (loss of smell) or ageusia (loss of taste) may be the sole presenting symptom in approximately 3% of individuals who have COVID-19.[1]

The US Centers for Disease Control and Prevention (CDC) defined COVID-19 symptoms as including 1 or more of the following:[2] 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, fatigue, headache, nasal congestion or runny nose, or nausea.

All ages may present with the disease, with case fatality rates (CFR) elevated in persons >60 years of age.[3] Comorbidities are associated with increased CFR, including cardiovascular disease, diabetes, hypertension, and chronic respiratory disease.[4] Healthcare workers are over-represented among COVID-19 patients due to occupational exposure to infected.[4]

An increase in the number of COVID-19 cases among children has been observed in recent weeks; for example, at end of September 2021, COVID-19 pediatric cases currently represent 26.7% of total cases reported in the US, and cumulatively since the pandemic began represent 16.0% of reported cases in the US.[5] Similarly, in Europe, new reported COVID-19 cases at the end of September 2021 were highest in children <15 years of age.[6] Although the severity of COVID-19 disease in children appears to be substantially lower compared to adults, concerns have been raised that COVID-19 symptoms may be associated with more severe disease in children with chronic health conditions, and SARS-CoV-2 infection and the ongoing pandemic in general may cause harm to children's long-term physical and mental health.[5,7]

2.5.1.2. Vaccine Clinical Development Program

2.5.1.2.1. Rationale for Development

2.5.1.2.1.1. Current Therapies

Currently available therapies have different benefit-risk considerations depending on the stage of illness and disease manifestations.[1,8] While care for individuals who have COVID-19 has improved with clinical experience, vaccination is the most effective medical countermeasure to decrease risk and mitigate spread of the SARS-CoV-2 virus during the ongoing pandemic.

2.5.1.2.1.2. Unmet Need

At present, community transmission in the vast majority of the US and many regions of the world is high.[9,10] This is the case despite an ongoing global vaccination campaign, in part due to the now-predominant circulation of the highly transmissible B.1.617.2 (Delta) SARS-CoV-2 variant.[11] Fully vaccinated individuals remain highly protected from serious illness owing to the high efficacy of available vaccines including BNT162b2 but unvaccinated individuals continue to serve as a large reservoir for community transmission, which has trended steeply upward since July 2021 and is forecasted to remain high with potential to continue to increase further.[12] Children <12 years of age are presently among the unvaccinated, as they are currently ineligible to receive a COVID-19 vaccine. This occurs at a time when they have returned to school amid this increasing SARS-CoV-2 transmission and a patchwork of mitigations in place depending on regionally disparate government, health department, and school district guidances.

Data from CDC's Coronavirus Disease 2019-Associated Hospitalization Surveillance Network (COVID-NET)[13] show hospitalization rates are currently increasing in the US, including in children. Recent weekly hospitalization rates in children 5 to 11 years of age increased from 0.3 per 100,000 population for the week ending 19 June 2021, up to 0.8 per 100,000 for the week ending 11 September 2021.[13] In Europe, COVID-19 case rates at the end of September 2021 were highest among children <15 years of age, and overall hospitalization rates are forecasted to rise.[6] Of particular concern is the risk of developing multisystem inflammatory syndrome in children (MIS-C), a rare but serious condition associated with COVID-19. In the US, the CDC estimates the number of children who have been diagnosed with MIS-C to be >4600, with a median age of 9 years and half of all cases reported in children 5 to 13 years of age.[14] As the number of COVID-19 cases in children increases, the current available CDC data predict a spike in MIS-C cases could occur.[14]

Authorizing BNT162b2 for use in children <12 years of age will address an urgent public health need, as this population remains vulnerable to COVID-19 and may transmit SARS-CoV-2 virus to others in the ongoing pandemic. Aside from the physical health risks of contracting COVID-19, children have experienced unprecedented prolonged disruption to education and social development for over a year during the COVID-19 pandemic, due to outbreaks in congregate settings and associated quarantines; the immediate downstream impact is significant challenges for families and communities, in particular where the pandemic has exacerbated pre-existing socio-economic disparities.[15,16] Education is a key determinant of health and a driver of economic opportunity. Globally, COVID-19 has caused the largest disruption in education systems in history, affecting nearly 1.6 billion students in >190 countries, and children living in vulnerable situations are also disproportionately affected with regard to long-term health outcomes.[17] Expanding COVID-19 vaccination eligibility to include school-age children 5 to <12 years of age would help protect individuals and communities from an individual and public health standpoint and support a safe return to in-person learning at school.

Approval of BNT162b2 at the 10-µg dose for use in children 5 to <12 years of age, based on demonstrated effectiveness (via immunobridging) and safety data from Study C4591007, would address critical and dual unmet needs for public health and education. The available data suggest the vaccine and dose level is safe and well tolerated, elicits a strong immune response, and presents favorable benefits that outweigh the known and potential risks in the 5 to <12 years of age group.

2.5.1.2.1.3. BNT162b2 Development

Pfizer and BioNTech developed an investigational vaccine that targets SARS-CoV-2, intended to prevent COVID-19, for which BioNTech initiated a FIH study in April 2020 in Germany (BNT162-01) and Pfizer initiated a Phase 1/2/3 study (C4591001) shortly afterwards in the US which expanded to include global sites upon initiation of the Phase 2/3 part of the study. Additional information on Study BNT162-01 is in Section 2.5.1.2.3.2.1, and on Study C4591001 is in Section 2.5.1.2.3.2.2. The Phase 1/2/3 pediatric Study C4591001 commenced after C4591001; additional information is in Section 2.5.1.2.3.2.3.

The vaccine is based on SARS-CoV-2 spike glycoprotein (S) antigens encoded in RNA formulated in lipid nanoparticles (LNPs) and is referred to as BNT162b2 (BioNTech code number BNT162, Pfizer code number PF-07302048). The structural elements of the vector backbones of BNT162 vaccines are optimized for prolonged and strong translation of the antigen-encoding RNA. The potency of RNA vaccines is further optimized by encapsulation of the RNA into LNPs, which protect the RNA from degradation by RNAses and enable transfection of host cells after IM delivery.

2.5.1.2.2. Vaccine Product Information

BioNTech has developed multiple RNA-LNP platforms, including nucleoside-modified RNA (modRNA) which has blunted innate immune sensor activating capacity and thus augmented antigen expression. Each modRNA candidate encodes either a P2 mutant S (P2 S) or the trimerized receptor binding domain (RBD) of S. Each candidate is given a V number to indicate the specific version of the optimized insert genomic sequence.

The licensed vaccine is BNT162b2 (RBP020.2) modRNA encoding P2 S (V9). Vaccine candidates based on other RNA platforms are not discussed further herein.

The current vaccine formulation is described in Section 2.5.2.1.

2.5.1.2.3. Vaccine Development Program

2.5.1.2.3.1. Nonclinical Studies

Key nonclinical evaluations of BNT162b2 included pharmacology (mouse immunogenicity studies, non-human primate [NHP] immunogenicity and challenge studies) and toxicity (two Good Laboratory Practice [GLP] rat repeat-dose toxicity studies) in vitro and in vivo. A developmental and reproductive toxicity (DART) study was completed in rats.

These data supported the clinical development of BNT162b2 and were previously submitted. Additional details of nonclinical studies were provided in Module 2.4 Nonclinical Overview.

2.5.1.2.3.2. Clinical Studies

2.5.1.2.3.2.1. Phase 1/2 Study BNT162-01

Study BNT162-01 is the ongoing, FIH, Phase 1 dose level-finding study, in which healthy younger adults (18 to 55 years of age) and older adults (56 to 85 years of age) all receive active vaccine. This study is evaluating the safety and immunogenicity of several different candidate vaccines at various dose levels. The available Phase 1 safety and immunogenicity data for younger and older adults are reported in this submission.

Multiple vaccine candidates are being evaluated in this study. For each candidate, participants receive escalating dose levels (N=12 per dose level) with progression to subsequent dose levels based on recommendation from a Sponsor Safety Review Committee (SRC).

The study design is detailed in the BNT162-01 Protocol. Available data from both age groups this study have been previously submitted, and there are no new or additional data from this study presented in this CO.

2.5.1.2.3.2.2. Phase 1/2/3 Study C4591001

Study C4591001 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 registration study. It was started as a Phase 1/2 study in adults in the US, was then amended to expand the study to a global Phase 2/3 study planning to enroll enough participants to accrue sufficient COVID-19 cases to conduct a timely efficacy assessment; amended to include older adolescents 16 to 17 years of age, then later amended to include younger adolescents 12 to 15 years of age.

The study design is detailed in C4591001 Protocol. Data from C4591001 participants in all age groups have been previously submitted.

This study contributes only immunogenicity data as an immunobridging comparator group from C4591001 Phase 2/3 participants 16 to 25 years of age (refer to Section 2.5.4.1).

2.5.1.2.3.2.3. Phase 1/2/3 Study C4591007

Study C4591007 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 pediatric 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 in Study C4591001.

This submission contains only the clinical data to support administration of the 10-µg dose of BNT162b2 to individuals 5 to <12 years of age. The study design is detailed in C4591007 Protocol and summarized below.

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 of multisystem inflammatory syndrome in children (MIS-C), serological evidence of prior SARS-CoV-2 infection or current SARS-CoV-2 infection as measured by polymerase chain reaction (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

Phase 1 is the dose-finding portion of the study. Dose levels were tested in sentinel cohorts of children by age de-escalation, starting with the lowest dose level in the oldest age group. For each age group, the dose level identified as safe and tolerable and immunogenic in C4591007 Phase 1 was advanced for further evaluation in Phase 2/3.

Phase 1 of Study C4591007 was conducted in the US. Starting with the oldest age group (5 to <12 years of age), sentinel cohorts in that age group received the lowest dose level (N=16 per dose level) followed by either the progression to subsequent a higher dose level cohort or termination of a dose level based upon the safety evaluation by the IRC. The intent was to evaluate doses up to 30 µg in each age cohort if the safety was acceptable for all the lower doses. Terminated dose cohorts were not to be evaluated further in the age cohort that received the dose and in younger age cohorts. Progression to a subsequent younger age cohort occurred if a dose was judged safe in an older cohort, based upon the safety evaluation of the IRC. Following this schema, the doses tested and selected in each age group during Phase 1 were:

- 5 to <12 years of age: dose levels 10, 20, 30 µg
- 2 to <5 years of age: dose levels 3 and 10 µg
- 6 to <2 years of age: dose level 3 µg

After the initial 4 participants in the 5 to <12 years of age group received the second dose of the highest dose level of BNT162b2 30 µg, the IRC recommended that a second dose of 30 µg not be administered for the remaining participants due to reactogenicity after the second dose for these 4 participants. The remaining 12 participants in this group instead received a second dose of BNT162b2 at the 10-µg dose level based on the dose selected for Phase 2/3, and the 30-µg dose level was discontinued (ie, not administered to any further participants in any age group).

The Sponsor/agent study team was not blinded in Phase 1. Participants who enrolled in Phase 1 are followed for cases of COVID-19 but do not contribute to the planned supportive efficacy assessments. Safety follow-up will continue for at least 2 years and/or end of study.

Based upon review of safety and immunogenicity from the Phase 1 part of the study, the final BNT162b2 dose levels selected were 10 µg for the 5 to <12 years and 3 µg for the 2 to <5 years of age and 6 months to <2 years of age groups.

This submission reports C4591007 Phase 1 dose finding data for the 5 to <12 years of age group only, in support of authorization of the 10-µg dose for this age group. Dose finding data for other pediatric age groups will be reported at a later time.

Phase 2/3

Phase 2/3 of Study C4591007 commenced with the selected vaccine dose for each age group, who were randomized 2:1 to receive vaccine or placebo.

Phase 2/3 is being conducted at sites in the US, Finland, Poland, and Spain. Phase 2/3 (which is ongoing) was planned to evaluate BNT162b2 at the selected dose levels for each age group for safety and tolerability, immunogenicity, and efficacy (depending on meeting success criteria for immunobridging and accrual of a sufficient number of COVID-19 cases). An immunobridging analysis was designed to compare SARS-CoV-2 neutralizing antibody responses in pediatric participants within each age group in Study C4591007 to a group of young adult participants 16 to 25 years of age in the C4591001 efficacy study. 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 <u>and</u> if success criteria for immunobridging in this age group had also been met. Additional objectives are designed to explore lower dose levels and other vaccine immunogenicity evaluations subsets of participants.

Note that an additional 2250 participants 5 to <12 years of age are being enrolled and randomized 2:1 (1500 BNT162b2 at 10 µg and 750 placebo) at the selected dose level in the Phase 2/3 part of C4591007, to obtain a larger safety database to support licensure for this age group (but not included in this present submission). Enrollment for this expansion set of participants started in August 2021. Further, an additional 750 participants in this age group are being enrolled to collect samples for troponin I evaluation. Enrollment for this set of participants is anticipated to start in October 2021. Supportive safety data from these additional participants will be reported when available, in a future submission.

This submission reports interim C4591007 Phase 2/3 dose finding data for the 5 to <12 years of age group only, in support of authorization of the 10-µg dose for this age group.

Unblinding Considerations

Sponsor and site personnel responsible for the ongoing conduct of Study C4591007 remain blinded to individual participants' randomization. Safety evaluation for such participants by the study team remains blinded until a decision is made to unblind the entire study. A separate (from study conduct) unblinded submissions team is responsible for regulatory submissions including this submission. Serology samples are processed in a blinded manner by laboratory personnel.

A participant in the 5 to <12 years of age group of C4591007 could be unblinded to treatment assignment per protocol, if he or she turned 12 years of age and became eligible to receive a COVID-19 vaccine available under EUA or conditional marketing authorization in their country/region. Per protocol, unblinded recipients originally randomized to placebo will be offered BNT162b2 vaccination and may be thereafter followed in an open-label manner.

2.5.1.2.3.2.4. Planned Studies

Further studies (or additional groups/analyses from ongoing studies) are planned or ongoing, including pediatric populations, maternal immunization, concomitant use with adult pneumococcal and influenza vaccines, booster efficacy evaluation, and obtaining blood samples for potential evaluation for subclinical myocarditis.

2.5.1.2.4. Proposed Indication

The current indication for BNT162b2 (30 µg) is active immunization to prevent COVID-19 disease caused by SARS-CoV-2 virus in individuals ≥12 years of age, or in individuals ≥16 years of age (depending on the country/market and authorization/approval type). Refer to Section 2.5.1.3 for details of regulatory authorizations and approvals.

This submission provides data to support an indication to administer BNT162b2 (10 µg) as a two-dose primary series given 3 weeks apart to children 5 to <12 years of age.

2.5.1.2.5. Rationale for Candidate and Dose Selection

The final candidate and dose level (BNT162b2 at 30 µg) was selected following review of immunogenicity and safety data from Phase 1 of Study C4591001 and nonclinical data. The final vaccine candidate selection for clinical development in Phase 2/3 was based on:

- NHP challenge data; BNT162b2 led to earlier virus clearance, no evidence of virus in lung
- Favorable reactogenicity for BNT162b2 in both younger and older Phase 1 participants
- Robust immunogenicity in both younger and older Phase 1 participants at 30 µg dose level

BNT162b2 at 30 µg proceeded into the Phase 2/3 portion of Study C4591001 because this dose and construct provided the optimum combination of a favorable reactogenicity profile and a robust immune response, likely to afford protection against COVID-19 in younger and older age groups.

In Study C4591007, an age de-escalation strategy was used in Phase 1 to select the most appropriate dose level for pediatric age groups (5 to <12 years of age, 2 to <5 years of age, and 6 months to <2 years of age). Dose finding in C4591007 Phase 1 began in the 5 to <12 years of age group based on the safety profile and success criteria met for immunobridging of C4591001 Phase 3 adolescent participants 12 to 15 years of age compared with young adults 16 to 25 years of age.

The C4591007 Phase 1 safety (primarily reactogenicity) and immunogenicity data led to the selection of BNT162b2 at a dose level of 10 µg as it was determined to be safe, tolerable, and highly immunogenic in the 5 to <12 years of age group as well as the 2 to <5 years of age group, and a BNT162b2 dose of 3 µg was selected for the 6 months to <2 years of age group. The vaccine was administered as a two-dose primary series given approximately 3 weeks apart in all pediatric age groups (ie, same regimen as in adults).

2.5.1.3. Regulatory Status

As of August 2021, BNT162b2, 30-µg formulation, has received temporary authorization for emergency use in 46 countries and conditional marketing authorization approval in 46 countries globally. The name of the product supplied under emergency/temporary use authorization for all applicable regions is Pfizer-BioNTech COVID-19 Vaccine. The tradename of the product for all applicable regions is COMIRNATY.

European Union

A rolling Marketing Authorization Application (MAA) was initiated on 05 October 2020 with nonclinical data, followed by Module 3 documents submitted on 05 November 2020, and completed with submission of clinical modules on 07 December 2020. Conditional marketing approval was granted by the European Medicines Agency (EMA) on 21 December 2020 for individuals ≥16 years of age and was expanded to support use individuals ≥12 years of age on 28 May 2021. A Type II Variation to provide 6-month follow-up for individuals ≥16 years of age was submitted to EMA on 18 May 2021. A booster dose (third dose) of BNT162b2 30 µg administered at least 6 months after the second dose to individuals ≥18 years of age was approved in the EU on 04 October 202; on the same day, a third dose was approved in the EU to be administered at least 28 days after the second dose to individuals who are severely immunocompromised.

A Paediatric Investigational Plan (PIP) was submitted to the Paediatric Committee (PDCO) on 21 September 2020. An agreed PIP decision was received 27 November 2020. A PIP modification request was submitted to PDCO on 24 March 2021 and was agreed by PDCO on 23 April 2021.

United States

In the US, the vaccine is in clinical development under an Investigative New Drug (IND) application, BB-IND 19,736. Fast Track Designation was granted on 07 July 2020 for individuals ≥18 years of age. An EUA application was filed to the US Food and Drug Administration (FDA) on 20 November 2020 and the product was authorized for emergency use in the US on 11 December 2020 for individuals ≥16 years of age (EUA 27034). An amendment to the EUA was submitted to the FDA on 09 April 2021 and was authorized on 10 May 2021 to support emergency use in individuals ≥12 years of age. An amendment to the EUA was submitted to the FDA on 14 May 2021 to provide 6-month follow-up for individuals ≥16 years of age. Authorization for administration of a third dose of BNT162b2 30 µg for individuals ≥12 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise was granted on 13 August 2021. A single BNT162b2 30 µg booster dose was authorized on 22 September 2021 to be administered at least 6 months after completing the primary series in individuals ≥65 years of age or 18 to 64 years of age at high risk of severe COVID-19 or whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.

The initial BLA for the 30-µg formulation was submitted to US FDA on 18 May 2021 and approved on 23 August 2021 for individuals ≥16 years of age. A supplemental BLA for a single booster dose in individuals ≥16 years of age was submitted on 25 August 2021 and is current pending FDA review.

An amendment to the US EUA to allow use of the 10-µg formulation in children 5 to <12 years of age is planned for submission in early October 2021.

The initial Pediatric Study Plan (iPSP) was submitted to the FDA on 17 September 2020. FDA agreement with the final agreed PSP was issued on 23 April 2021

Rest of World

Marketing Authorization Applications were initiated beginning in October 2020 and Conditional Marketing Authorizations have been granted in many countries globally including Switzerland, Japan, Australia, New Zealand, and Brazil. Requests for temporary authorization for emergency supply have also been filed and approved in many countries globally under emergency or temporary use authorization procedures or special import procedures beginning in November 2020 (including the UK). The World Health Organization (WHO) issued a positive opinion on the Emergency Use Listing of COMIRNATY on 31 December 2021.

2.5.1.4. Ethical Considerations

All studies in the clinical development program were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council on Harmonisation (ICH) Good Clinical Practice

(GCP) Guidelines. They were designed, performed, and analyzed in accordance with all applicable regulations, laws, and guidelines in effect at the time they were conducted from the US FDA, EU Directive 2001/20/EC, and local regulatory agencies in countries where the study was conducted. The study design reflects recommendations from local review boards/committees, and other local regulatory authorities.

The pivotal Phase 1/2/3 Study C4591001 was conducted at sites in the US, Brazil, Argentina, Turkey, South Africa, and Germany; the majority of participants were enrolled at sites in the US. The supporting Phase 1/2 Study BNT162-01 was conducted at sites in Germany. Pediatric Study C4591007 was conducted at sites in the US, Finland, Poland, and Spain.

2.5.2. Overview of Biopharmaceutics

2.5.2.1. Formulation Development

In the present submission, data are submitted in support of a new presentation for use in children 5 to <12 years of age: the BNT162b2 (10 µg) Tris/Sucrose vaccine is provided in a 10-dose multi-dose vial (MDV) that contains a frozen concentrate solution and must be thawed and diluted prior to administration. The BNT162b2 concentrate must be diluted in its original vial using 0.9% Sodium Chloride Injection resulting in an off-white suspension. The BNT162b2 Tris/Sucrose solution is a preservative-free, sterile concentrate for dispersion of LNPs in aqueous cryoprotectant buffer for IM administration.

To provide a vaccine with an improved stability profile and greater ease of use at administration sites, Pfizer/BioNTech have developed a new drug product formulation using tromethamine (Tris) buffer instead of phosphate-buffered saline (PBS) and exclusion of sodium chloride and potassium chloride. Additionally, due to the lower concentration of mRNA, this formulation enables administration of smaller doses necessary for pediatric patients.

This new drug product formulation is referred to as the 'Tris/Sucrose formulation' to emphasize the change in formulation buffer. The current registered, concentrated formulation is referred to as the 'PBS/Sucrose formulation'.

The Tris/Sucrose drug product is a preservative-free, sterile dispersion of LNPs in aqueous cryoprotectant buffer for IM administration and is formulated at 0.1 mg/mL RNA in 10 mM Tris buffer, 300 mM sucrose, pH 7.4. The presentations of the vaccine are anticipated as:

- 30 µg RNA dose for individuals ≥12 years of age, same as current PBS/Sucrose formulation
- 10 µg RNA dose for individuals 5 to <12 years of age

The 30 µg and 10 µg RNA doses are prepared by filling the identically formulated drug product with different volumes: either 2.25 mL or 1.3 mL, respectively. The Tris/Sucrose formulation is currently manufactured at the Pfizer Puurs site using facilities already authorized for manufacture of the PBS/Sucrose formulation.

For the 30-µg RNA dose, a multi-dose vial (MDV) format (6 doses) using 2.25 mL is planned to maintain supply capacity. A single-dose vial (SDV) with a 0.48 mL for single-dose vials is possible for a future time where demand may be diminished and preventing waste of extra doses in a vial may become more important. All vials are filed into a 2-mL glass vials. The vaccine is administered without dilution for the 30-µg presentation.

For the 10-µg RNA dose, dilution of the vaccine with 0.9% sodium chloride for injection is required, as follows: dilute the 1.3-mL filled vial with 1.3 mL 0.9% sodium chloride for injection to provide 10 doses at 10 µg RNA / 0.2 mL Injection volume.

Only the Tris/Sucrose formulation can be used to deliver the 10-µg dose of the vaccine. Therefore, this change in formulation is critical to support an extension enabling dosing individuals 5 to <12 years of age.

Details of formulation development and storage conditions are provided in Module 3.

2.5.2.2. Biopharmaceutical Studies

Bioavailability and bioequivalence assessments are not relevant to vaccine antigenicity and have not been measured. The major pharmacodynamic effect of a vaccine, unlike a drug, is to elicit an immune response to the antigens included in the vaccine. Vaccine induced activation of antigen-presenting cells takes place at the site of injection (ie, muscle) which is rapidly followed by antigen-presenting cell migration via lymphatic vessels towards the draining lymph node where vaccine antigens activate specific B and T cells. There is no specific vaccine antigen blood level required to elicit the immune response.

2.5.2.3. Bioanalytical and Analytical Methods Used in Human Studies

Information on assays used to assess SARS-CoV-2 infection and immune response is in Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods.

2.5.3. Overview of Clinical Pharmacology

Pharmacokinetic studies are not usually required for vaccines. Measurement of the plasma concentration of the vaccine over time is not feasible.

2.5.4. Overview of Efficacy (Including Immunogenicity)

Efficacy was previously evaluated in Phase 2/3 of pivotal Study C4591001. Immunogenicity data were previously evaluated in Phase 1 and Phase 2 of Study C4591001. These modules were previously submitted in a Type II Variation (refer to Section 2.5.1.3).

The basis of BNT162b2 effectiveness in children is immunobridging: demonstration that the immune response to BNT162b2 10 µg at 1 month after Dose 2 in children 5 to <12 years of age is within the prespecified margin of that observed at 1 month after Dose 2 of BNT162b2 30 µg in young adults 16 to 25 years of age, based on SARS-CoV-2 50% neutralizing titers in participants without prior evidence of SARS-CoV-2 infection. Immunogenicity endpoints are summarized in Section 2.5.4.1.1 and analysis methods are summarized in Section 2.5.4.1.2.

Efficacy analyses for 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 only if immunobridging success criteria had first been met.

No efficacy analyses are included in this submission.

The event-driven efficacy analysis was not conducted as an insufficient number of confirmed COVID-19 cases accrued by the submission cutoff date of 06 September 2021. Efficacy endpoints and case criteria are summarized in Section 2.5.4.2.1 and planned analysis methods are summarized in Section 2.5.4.2.2, for reference.

Only validated (SARS-CoV-2 neutralization immunoassay and PCR) methods are used to obtain these data. Assay validation information is provided in Module 2.7.1.

2.5.4.1. Immunogenicity Endpoints and Analysis Methods in Study C4591007

The statistical analyses of immunogenicity data from Study C4591007 were based on the evaluable immunogenicity populations and all-available immunogenicity populations (described in the C4591007 Protocol and SAP).

2.5.4.1.1. 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 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

2.5.4.1.2. 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 (GMTs) 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. Immunobridging based on seroresponse was evaluated only after the pre-specified criteria for immunobridging based on the GMR were met.

- GMR was calculated as the mean of the difference of logarithmically transformed titers and exponentiating the mean. The associated 2-sided 95% confidence intervals (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 also 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.

Note that an additional, ongoing immunogenicity analysis of a subset of participants 5 to <12 years of age in Study C4591007 is evaluating neutralizing sera titers against both the wild-type and highly transmissible B.1.617.2 (Delta) variants of SARS-CoV-2, and data are expected to be available by end of October 2021.

Immunogenicity Subset Sample Size

The immunogenicity subset for the Phase 2/3 primary immunobridging assessment was comprised of a sample size of 225 evaluable participants in Study C4591007 (5 to <12 years of age) and in and the corresponding randomly selected comparator group in Study C4591001 (16 to 25 years of age), providing a power of 90.4% and 92.6% to declare immunobridging success based on GMR and seroresponse difference, respectively. Assuming a 25% nonevaluable rate with a 2:1 randomization ratio, this would require approximately 450 participants (300 in the active vaccine group and 150 in the placebo group) with 1-month post-Dose 2 blood sample collection to achieve 225 evaluable participants in the active vaccine group.

Subgroup Analyses

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

2.5.4.2. Efficacy Endpoints and Analysis Methods

As of the data cutoff date for this submission (06 September 2021), an insufficient number of confirmed cases of COVID-19 had accrued to conduct the event-drive, supportive efficacy analysis. Efficacy analyses are planned to be conducted with the statistical methods described in the study statistical analysis plan, based on the evaluable efficacy populations and all-available (modified intent-to-treat [mITT]) efficacy populations (described in the C4591007 Protocol and SAP). Case criteria and summary of efficacy analysis methods are provided below for reference. These data are not considered required for licensure or marketing authorization and will be submitted in a future variation when available.

2.5.4.2.1. Efficacy Endpoints

COVID-19 cases including those considered as severe or MIS-C are planned to be summarized by vaccine group for participants 5 to <12 years of age according to the case criteria below.

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, and 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-approved 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 then 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 <u>at least 1</u> of the following symptoms <u>and</u> 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[18], 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[19], 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[20]
  - SpO_2 ≤92% on room air, >50% FiO_2 to maintain ≥92%, or PaO_2/FiO_2 <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:
  - SBP (mm Hg); <70 + (age in years × 2) for age up to 10 years, <90 for age ≥10 years
  - requiring vasoactive drugs to maintain blood pressure 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[21]

- Admission to an intensive care unit

- Death

Confirmed MIS-C definition:[22] 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)
  - gastrointestinal/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

2.5.4.2.2. Efficacy Analysis Methods

Efficacy against confirmed COVID-19 is planned to be evaluated if at least 22 cases accrued in the 5 to <12 years of age group in participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen and immunobridging success criteria were first met (refer to Section 2.5.4.1).

Vaccine efficacy (VE) against confirmed COVID-19 from 7 days after Dose 2 is estimated by 100 × (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 only for all cases per FDA definition adopted in the protocol), 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), and for all cases (regardless of severity) and severe COVID-19 cases as defined by CDC.[23]

2.5.4.3. Immunogenicity Results

Immunogenicity data from Study C4591007 Phase 1 dosing groups are presented in Section 2.5.4.3.1, and immunogenicity data from the Phase 2/3 population are presented in Section 2.5.4.3.2.

Immunogenicity data from Study C4591007 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).

This section of the CO presents the following data for C4591007 participants 5 to <12 years of age:

- Phase 1 immunogenicity across dose levels, up to 7 days after Dose 2 (Section 2.5.4.3.1).
- Phase 2/3 immunobridging analysis comparing Phase 2/3 C4591007 participants 5 to <12 years of age to Phase 2/3 C4591001 participants 16 to 25 years of age, at 1 month after Dose 2 (Section 2.5.4.3.2).

2.5.4.3.1. C4591007 Immunogenicity Results – 5 to <12 Years of Age – Phase 1

Robust immune responses were previously demonstrated in Study C4591001 based on 1-month post-Dose 2 serum samples from participants ≥16 years of age. After BNT162b2 efficacy against COVID-19 was demonstrated in Study C4591001, immunobridging for adolescents to young adults was established by comparing SARS-CoV-2 neutralizing titers for C4591001 participants 12 to 15 years of age to neutralizing titers for C4591001 participants 16 to 25 years of age.

Phase 1 of Study C4591007 was designed to establish the neutralizing immune response at pediatric dose levels, to inform the preferred dose level selection for Phase 2/3 immunobridging.

Since the 30-µg dose level was discontinued per IRC decision following review of reactogenicity for this group (see details in Section 2.5.5.2.1.2), immunogenicity analyses were limited to the 10-µg and 20-µg dose levels. Phase 1 participants were without serological or virological evidence of SARS-CoV-2 infection up to 7 days post-Dose 2.

2.5.4.3.1.1. Immunogenicity Population – Phase 1

Disposition and Data Sets Analyzed

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

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.

The demographic make-up of the evaluable immunogenicity population was similar to the all-available immunogenicity population, and to the safety population (refer to Section 2.5.5.2.1.1).

2.5.4.3.1.2. SARS-CoV-2 Neutralizing Titers – Phase 1

Geometric Mean Titers (GMTs)

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.

2.5.4.3.1.3. Immunogenicity Conclusions – 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.

Immunogenicity results from Phase 1 dose level groups supported the Phase 2/3 dose level selection (refer to Section 2.5.5.2.1.5).

2.5.4.3.2. C4591007 Immunogenicity Results – 5 to <12 Years of Age – Phase 2/3

2.5.4.3.2.1. Immunobridging Subset – Phase 2/3

2.5.4.3.2.1.1. Disposition and Datasets Analyzed – 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).

The evaluable immunogenicity population for children 5 to <12 years of age included 294 participants in the BNT162b2 group and 147 participants in the placebo group, and for young adults 16 to 25 years of age included 273 participants in the BNT162b2 group and 47 participants in the placebo group. 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 (Table 1).

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.

Disposition

Disposition of participants in each age group who were included in the immunobridging subset, is summarized in Table 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 (Table 2) was similar to that of all randomized participants (Table 14) 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%).

Table 1. 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) n[a] (%)	30 µg 16-25 Years (C4591001) n[a] (%)	5 to <12 Years (C4591007) n[a] (%)	16-25 Years (C4591001) 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 1. 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.

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Table 2. Disposition of All Randomized Participants Through 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

	Vaccine Group (as Randomized)			
	BNT162b2		Placebo	
	10 µg 5 to <12 Years (C4591007) (N[a]=322) n[b] (%)	30 µg 16-25 Years (C4591001) (N[a]=300) n[b] (%)	5 to <12 Years (C4591007) (N[a]=163) n[b] (%)	16-25 Years (C4591001) (N[a]=50) n[b] (%)
Randomized	322 (100.0)	300 (100.0)	163 (100.0)	50 (100.0)
Not vaccinated	0	0	0	0
Vaccinated	322 (100.0)	300 (100.0)	163 (100.0)	50 (100.0)
Dose 1	322 (100.0)	300 (100.0)	163 (100.0)	50 (100.0)
Dose 2	319 (99.1)	300 (100.0)	162 (99.4)	50 (100.0)
Completed 1-month post–Dose 2 visit (vaccination period)	319 (99.1)	293 (97.7)	161 (98.8)	50 (100.0)
Discontinued from vaccination period but continued in the study up to 1-month post–Dose 2 visit	2 (0.6)	0	1 (0.6)	0
Discontinued after Dose 1 and before Dose 2	2 (0.6)	0	1 (0.6)	0
Discontinued after Dose 2 and before 1-month post–Dose 2 visit	0	0	0	0
Reason for discontinuation from vaccination period				
Withdrawal by participant	1 (0.3)	0	1 (0.6)	0
Withdrawal by parent/guardian	1 (0.3)	0	0	0
Withdrawn from the study before 1-month post-Dose 2 visit	1 (0.3)	6 (2.0)	1 (0.6)	0
Withdrawn after Dose 1 and before Dose 2	1 (0.3)	0	0	0
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	0	6 (2.0)	1 (0.6)	0
Reason for withdrawal from the study				
Lost to follow-up	0	3 (1.0)	0	0
Withdrawal by participant	0	2 (0.7)	0	0
Withdrawal by parent/guardian	1 (0.3)	1 (0.3)	1 (0.6)	0

Table 2. Disposition of All Randomized Participants Through 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

	Vaccine Group (as Randomized)			
	BNT162b2		Placebo	
	10 µg 5 to <12 Years (C4591007) (N[a]=322) n[b] (%)	30 µg 16-25 Years (C4591001) (N[a]=300) n[b] (%)	5 to <12 Years (C4591007) (N[a]=163) n[b] (%)	16-25 Years (C4591001) (N[a]=50) n[b] (%)

a. N = number of randomized participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
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Vaccine Administration and Timing

Among C4591007 Phase 2/3 participants 5 to <12 years of age in the immunobridging subset, almost all (>99%) participants were administered study intervention as randomized. Altogether, 100% received Dose 1 of either BNT162b2 or placebo, and 99.1% and 99.4% received Dose 2 of BNT162b2 and placebo, respectively.

Among C4591001 Phase 2/3 participants in the 16 to 25 years of age group in the immunobridging subset, all participants were administered study intervention (Dose 1 and Dose 2) as randomized.

The majority of C4591007 participants in the immunobridging subset (N=322 randomized to BNT162b2 and N=163 randomized to placebo) received Dose 2 in the protocol defined window of 19 to 23 days after Dose 1 in the BNT162b2 (94.7%) and placebo (95.7%) groups. Second doses administered outside of the protocol specified window included 0.9% and 1.2% of the BNT162b2 and placebo groups, respectively, who received Dose 2 at <19 days after Dose 1 and 3.4% and 2.5% of the BNT162b2 and placebo groups, respectively, who received Dose 2 at >23 days after Dose 1.

Longer time intervals reported for Dose 2 administration after Dose 1, in C4591007 participants in the BNT162b2 and placebo groups of the immunobridging subset, were:

- 28 to 34 days: 1.6% vs 0.6%
- 35 to 41 days: 0.9% vs 1.8%

The majority of C4591001 participants in the immunobridging subset (N=300 randomized to BNT162b2 and N=50 randomized to placebo) received Dose 2 in the protocol defined window of 19 to 23 days after Dose 1 in the BNT162b2 (94.7%) and placebo (86.0%) groups. Second doses administered outside of the protocol specified window included 0.3% and none of the BNT162b2 and placebo groups, respectively, who received Dose 2 at <19 days after Dose 1 and 5.0% and 14.0% of the BNT162b2 and placebo groups, respectively, who received Dose 2 at >23 days after Dose 1.

Longer time intervals reported for Dose 2 administration after Dose 1, in C4591001 participants in the BNT162b2 and placebo groups of the immunobridging subset, were:

- 28 to 34 days: 2.3% vs 2.0%
- 35 to 41 days: 0.7% vs 2.0%
- 49 to 55 days: none vs 2.0%
- >55 days: 0.7% vs none

The total range for timing of Dose 2 administration after Dose 1 of BNT162b2 or placebo for pediatric participants in C4591007 was 14 to 41 days. For young adult participants in C4591001, the total range for timing of Dose 2 administration after Dose 1 was 14 day to >55 days.

2.5.4.3.2.1.2. Demographics – Phase 2/3

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 3). Baseline SARS-CoV-2 status was positive for 7.1% and 8.8% of participants in the BNT162b2 and placebo groups, respectively. Obese children (based on age- and sex-specific indices) made up 8.0% and 11.5% of participants in the BNT162b2 and placebo groups, respectively.

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 3). Baseline SARS-CoV-2 status was positive for 4.8% and 2.1% of participants in the BNT162b2 and placebo groups, respectively. Obese adults made up 15.8% and 31.1% of participants in the BNT162b2 and placebo groups, respectively.

Demographics of participants without evidence of infection up to 1 month after Dose 2 in the evaluable immunogenicity population were similar to those for all participants in the evaluable immunogenicity population and all-available immunogenicity population. Likewise, the immunogenicity population demographics were generally similar to those in the safety population (Section 2.5.5.2.2.1.3).

Table 3. 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)

Table 3. 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 (%)
Native Hawaiian or other Pacific Islander	1 (0.4)	0	0	0
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/m² 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

2.5.4.3.2.2. Immunobridging Analysis – Phase 2/3

2.5.4.3.2.2.1. Geometric Mean Ratio (GMR) in Neutralization Titers – Phase 2/3

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 4).

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 2.5.4.1.2). Therefore, immunobridging based on GMR was achieved. Note that the observed GMR point estimate meets the requested criterion from the FDA of ≥1 (which was considered in a post hoc manner, as the database release was in progress at the time of the FDA request).

Table 4. 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

2.5.4.3.2.2.2. Seroresponse – Phase 2/3

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 2.5.4.1.2) from before vaccination to 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the two age groups (children – young adults) was 0.0% (2-sided 95% CI: -2.0%, 2.2%) (Table 5).

Since immunobridging based on GMR was achieved, hypothesis of immunobridging based on seroresponse rate was tested subsequently (refer to analysis methods in Section 2.5.4.1.2). 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 5. 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

2.5.4.3.2.3. SARS-CoV-2 Neutralizing Titers – Phase 2/3

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.

2.5.4.3.2.3.1. Geometric Mean Titers (GMTs) – Phase 2/3

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 the 10-µg dose level) and young adults 16 to 25 years of age (who received the 30-µg dose level) (Figure 1, Figure 2, and Table 6).

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. Neutralizing GMTs were very 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 with regard to the BNT162b2 and placebo groups when evaluated by sex, race, and ethnicity (Table 7). 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) (Table 7).

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) (Table 7). 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) (Table 7).

Baseline SARS-CoV-2 Status

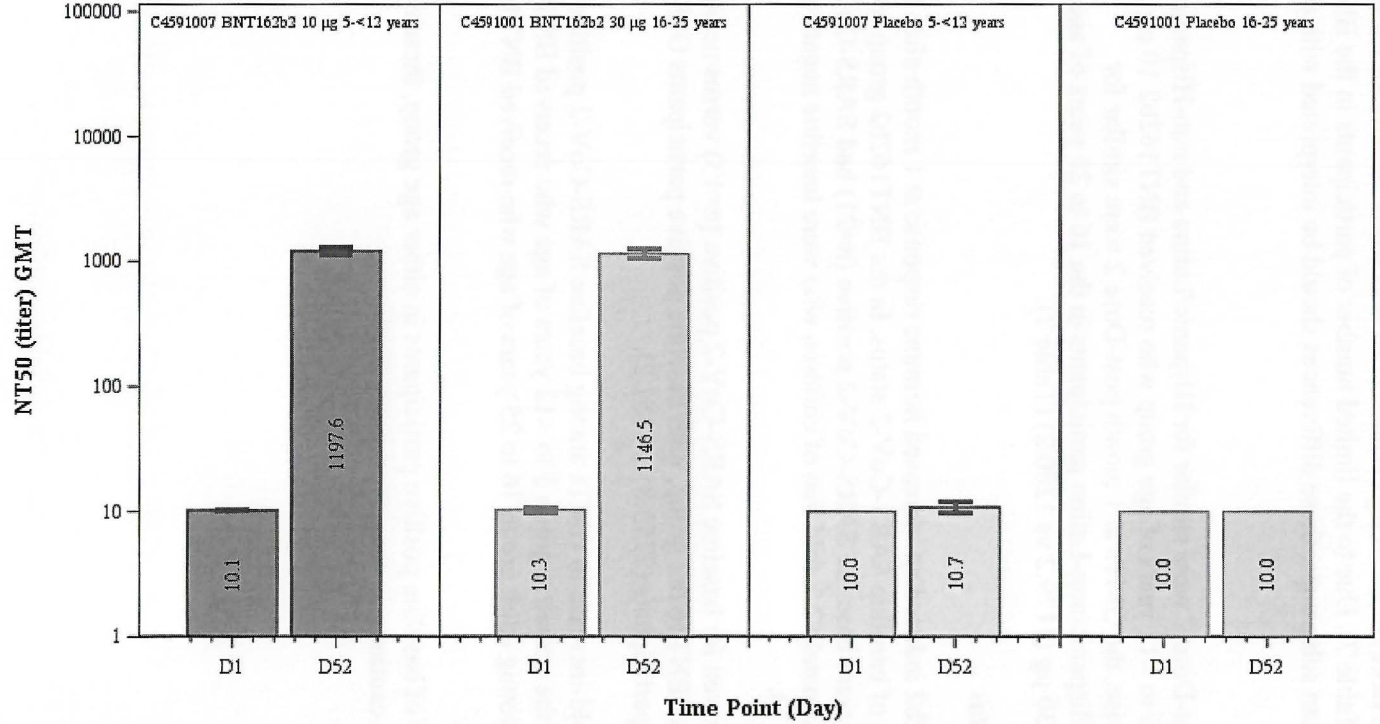
Vaccination with BNT162b2 induced an increased immune response at 1 month after Dose 2 for all participants, regardless of baseline SARS-CoV-2 status. In the BNT162b2 group, children 5 to <12 years of age who were baseline SARS-CoV-2 positive (n=21) had SARS-CoV-2 50% neutralizing GMTs approximately 2.7-fold that of children who were baseline negative (n=273) (3270.0 vs 1211.3) (Table 7).

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% Confidence Intervals: 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.

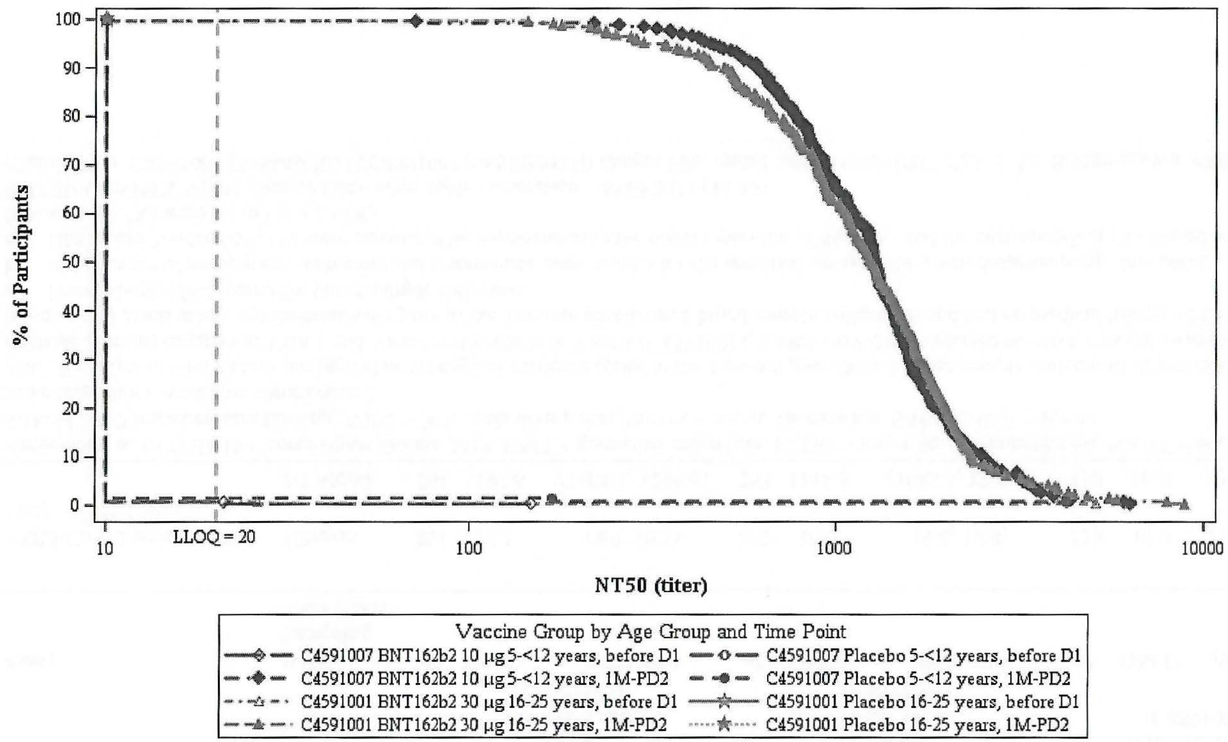
Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 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 6. 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

Table 7. 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)
		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)

Table 7. 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	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)
	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								

Table 7. 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])
		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)
		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]								

Table 7. 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])**
		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)

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

2.5.4.3.2.3.2. Geometric Mean Fold-Rise (GMFR) in Titers – Phase 2/3

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 9). 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 9).

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

Table 9. 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

2.5.4.3.2.3.3. Seroresponse Rate – Phase 2/3

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 2.5.4.1.2) 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 10). 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 with regard to the BNT162b2 and placebo groups when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status (Table 11). 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%) (Table 11).

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%) (Table 11).

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%) (Table 11).

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 11).

Table 10. 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.

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(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File: ./nda2 ubped/C4591007 P23 5 12 Bridging/adva s003 fr4 p2 12 wout evl

Table 11. 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)
		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)

Table 11. 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

Assay	Dose/ Sampling Time Point[a]	Subgroup	BNT162b2: 10 µg 5 to <12 Years (C4591007) N[c]	BNT162b2: 10 µg 5 to <12 Years (C4591007) n[d] (%) (95% CI[e])	BNT162b2: 30 µg 16-25 Years (C4591001) N[c]	BNT162b2: 30 µg 16-25 Years (C4591001) n[d] (%) (95% CI[e])	Placebo: 5 to <12 Years (C4591007) N[c]	Placebo: 5 to <12 Years (C4591007) n[d] (%) (95% CI[e])	Placebo: 16-25 Years (C4591001) N[c]	Placebo: 16-25 Years (C4591001) n[d] (%) (95% CI[e])
		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 11. 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.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 17SEP2021 (07:55)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File: ./nda2_ubped/C4591007_P23_5_12_Bridging/adva_s003_fr4_p2_12_sub_evl

2.5.4.3.2.4. Immunogenicity Conclusions – Phase 2/3

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 post hoc criterion requested by 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

2.5.4.4. Efficacy Results

Efficacy analyses for the 5 to <12 years of age group in Study C4591007 are planned to be conducted only when at least 22 confirmed cases of COVID-19 have accrued in participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen and if success criteria for immunobridging were first met (see results in Section 2.5.4.3.2). 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 2.5.4.2), 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.

2.5.5. Overview of Safety

Safety endpoints are summarized in Section 2.5.5.1.1, safety analyses methods are summarized in Section 2.5.5.1.2, and safety data are presented in Section 2.5.5.2.

2.5.5.1. Safety Endpoints and Analysis Methods in Study C4591007

Details of safety methods and analyses in Study C4591007 are located in the C4591007 Protocol and SAP and summarized below.

2.5.5.1.1. Safety Endpoints

Reactogenicity

Phase 1 and Phase 2/3 participants or their parent/legal guardian were to monitor and record reactogenicity for 7 days after each dose; in the 5 to <12 years of age group, events included:[24]

- Local reactions: pain, redness, swelling at the injection site
- Systemic events: fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, new or worsened joint pain

Antipyretic/pain medication usage was also to be recorded for 7 days after each dose. Reactogenicity and antipyretic use was to be recorded each evening for 7 days after each dose administration using prompts from an electronic diary (e-diary). This allowed recording only within a fixed time window to provide an accurate representation of the participant's experience.

Adverse Events

For Phase 1 and Phase 2/3, adverse events (AEs) were collected from the Dose 1 to 1 month after Dose 2 and serious AEs (SAEs) were collected from Dose 1 to 6 months after Dose 2. AEs were categorized by frequency, maximum severity, seriousness, and relationship to study intervention using system organ class (SOC) and preferred term (PT) according to MedDRA. Deaths are recorded to the end of study.

Myocarditis and pericarditis were designated in the C4591007 protocol as AEs of special interest (AESIs). For other events of specific clinical interest that were not designated as AESIs, Pfizer utilizes a list of Targeted Medical Events (TMEs) of clinical interest that are highlighted during clinical safety data review and signal detection. TMEs are a dynamic list of MedDRA AE terms that are reviewed on an ongoing basis throughout the clinical study; the TMEs are based on review of known pharmacology, toxicology findings, possible class effects, published literature, and potential signals arising from safety data assessments. The list of TMEs includes events of interest due to their association with COVID-19 and terms of interest for vaccines in general; it takes into consideration the CDC list of AESIs for COVID-19 that include events potentially indicative of severe COVID-19 or autoimmune and neuroinflammatory disorders.

Other Assessments

Prior SARS-CoV-2 infection was determined by virological testing via nucleic acid amplification test (NAAT) on anterior nares swab and serological testing for IgG to the

SARS-CoV-2 N-antigen at baseline, and via NAAT at Dose 2. Participants were surveilled for potential COVID-19 illness from Visit 1 onwards.

Narratives

Narratives for safety events are located in Module 5.3.5.1 C4591007 Interim CSR (5 to <12 Years) Section 14 Subject Narratives, and were prepared for participants if they had the following events:

- deaths, vaccine-related SAEs, safety-related withdrawals
- COVID-19 cases for participants with severe and/or multiple episodes
- AEs of interest including those requested by FDA* (anaphylaxis, Bell's palsy, appendicitis, pregnancy exposures and outcomes, myocarditis/pericarditis, MIS-C cases)

* In lieu of individual narratives on lymphadenopathy, which typically are related AEs with little additional information, these cases are presented in tables summarizing incidence, timing relative to Dose 1 or 2, anatomical location, duration, severity, and event resolution.

Phase 1 Stopping Rules

Stopping rules were based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the last dose of study intervention in Phase 1 in each age group, whichever was later. These data were monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

1. If any participant vaccinated with the BNT162b2 candidate at any dose level developed an SAE that is assessed by the investigator as possibly related, or for which there was no alternative, plausible, attributable cause.

2. If any participant vaccinated with the BNT162b2 candidate at any dose level developed a Grade 4 local reaction or systemic event after vaccination that was assessed as possibly related by the investigator, or for which there was no alternative, plausible, attributable cause.

3. If any participant vaccinated with the BNT162b2 candidate at any dose level developed a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination that was assessed as possibly related by the investigator, or for which there was no alternative, plausible, attributable cause.

4. If any 2 participants vaccinated with the BNT162b2 candidate at any dose level within the same age group reported the same or similar severe (Grade 3) AE after vaccination, assessed as possibly related by the investigator, or for which there was no alternative, plausible, attributable cause.

5. If any participant died or required ICU admission due to SARS-CoV-2 infection; if this stopping rule was met, all available clinical and preclinical safety and immunogenicity data would be reviewed to evaluate for enhanced COVID-19.

Refer to the C4591007 Protocol for details on Phase 1 stopping rules.

2.5.5.1.2. Safety Analysis Methods

Safety data were analyzed and reported using descriptive summary statistics for the safety population. Phase 1 and Phase 2/3 safety were assessed from Dose 1 to 1 month after Dose 2. Data are also provided through the relevant data cutoff date: 16 July 2021 for Phase 1 and 06 September 2021 for Phase 2/3.

Reactogenicity

Descriptive statistics were provided for each reactogenicity endpoint after each dose for participants who completed an e-diary. Local reactions and systemic events from Day 1 through Day 7 after vaccination are presented by severity and cumulatively across severity levels. Descriptive summary statistics included counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. Missing reactogenicity e-diary data were not imputed.

Adverse Events

AE data were summarized descriptively for the safety population. Descriptive summary statistics including counts, percentages, and associated Clopper-Pearson 2-sided 95% CIs were provided for AEs reported from Dose 1 through 1 month after Dose 2.

Subgroup Analyses

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

2.5.5.2. Safety Results

Safety data from Study C4591007 Phase 1 dosing groups are presented in Section 2.5.5.2.1, and safety data from the Phase 2/3 population are presented in Section 2.5.5.2.2.

Safety data from Study C4591007 are detailed in Module 5.3.5.1 C4591007 (5 to <12 Years) Interim CSR Section 10 (study populations) and Section 12 (safety analysis results).

This section of the CO presents the following data for C4591007 participants 5 to <12 years of age:

- Phase 1 safety and tolerability across dose levels, up to 1 month after Dose 2 and to data cutoff date of 16 July 2021 which represents follow-up of 3 months after Dose 2 (Section 2.5.5.2.1)
- Phase 2/3 safety and tolerability for BNT162b2 10 µg vs placebo, up to 1 month after Dose 2 and to data cutoff date of 06 September 2021, which represents at least 2 months of follow-up after Dose 2 (Section 2.5.5.2.2)

2.5.5.2.1. C4591007 Safety Results – 5 to <12 Years of Age – Phase 1

2.5.5.2.1.1. Safety Population Characteristics – Phase 1

Disposition and Data Sets Analyzed

In Phase 1, a total of 49 participants in the 5 to <12 years of age group were assigned into dose level groups (in a 1:1:1 ratio) to receive 10, 20, or 30 µg BNT162b2. Of these, 48/49 were vaccinated and received both doses of BNT162b2 (N=16 per dose level) and were in the safety population. No participants were withdrawn from the Phase 1 part of the study.

Due to reactogenicity observed in the initial 4/16 participants assigned to the 30-µg dose level group after they received both doses of BNT162b2 (see Section 2.5.5.2.1.2), an IRC decision was made for the remaining 12/16 participants assigned to the 30-µg dose level group to receive a lower dose of 10 µg for the second dose. All participants originally assigned to the 30-µg group received 30 µg for Dose 1. With regard to participants in the 30-µg dose level group, note the following:

- Phase 1 immunogenicity results in this submission are not presented for the 30-µg dose level group; results are presented only for 10 and 20 µg groups of whom all participants received both BNT162b2 doses as assigned.
- Phase 1 participants assigned to the 30-µg dose level are all included in safety analyses, but safety results are reported separately for those who received different dose levels at Dose 1 and Dose 2 (ie, those who received 30/30 µg and those who received 30/10 µg).

Protocol Deviations

No important protocol deviations occurred in Phase 1 participants.

Vaccine Administration and Timing

For Phase 1 pediatric participants 5 to <12 years of age, almost all participants were administered study intervention as assigned. Except for 1 participant assigned to the 20-µg dose level group who did not receive BNT162b2, 48 (98.0%) of participants received Dose 1 and Dose 2. Due to observed reactogenicity in the initial 4/16 participants who received 30 µg for both doses as assigned (see Section 2.5.5.2.1.2), 12/16 participants who received a 30 µg dose at Dose 1 received the 10-µg dose level at Dose 2 (based on 10-µg dose being selected for Phase 2/3 progression in this age group).

The majority of participants received Dose 2 between 19 to 23 days after Dose 1 in the 10-µg and 20-µg dose level groups (100.0% and 82.4%, respectively). In the 30-µg dose level group, the 4 (25.0%) participants who received 30/30 µg dosing received Dose 2 between 19 to 23 days after Dose 1; the 12 (75.0%) participants who received a 30/10 µg dosing received Dose 2 at >23 days after Dose 1.

Demographics

Overall, most Phase 1 participants 5 to <12 years of age in the safety population were White (79.2%), with 6.3% Black or African American participants and 10.4% Asian participants, and other racial groups were <5%. There were 8.3% Hispanic/Latino participants. The median age was 8.0 years and 50.0% of participants were male.

Medical History and Concomitant Vaccines

Participants in the Phase 1 safety population had a medical history profile consistent with that of individuals in the general population in the same age group. Psychiatric disorders (8 [16.7%]) immune system disorders (6 [12.5%]), and infections and infestations (4 [8.3%]) were the 3 most frequently reported SOCs. The psychiatric disorders included attention deficit hyperactive disorder (n=5), anxiety (n=2), and insomnia (n=1). There were no participants with a history of any cardiac disorder.

No Phase 1 participants 5 to <12 years of age received concomitant vaccines after Dose 1.

2.5.5.2.1.2. Reactogenicity – Phase 1

Local Reactions

Reactogenicity in the 5 to <12 years of age group tended to increase in a dose level- and dose number-dependent manner with regard to incidence and/or severity of local reactions at 10, 20, and 30 µg dose levels (Figure 3). Local reactions were mostly mild to moderate and short-lived.

For 10 and 20 µg groups, pain at the injection site was the most commonly reported local reaction within 7 days after any dose (range: 87.5% to 93.8%) with the highest frequency in the 20 µg dose level after Dose 1 (Figure 3). Redness and swelling were reported in the 10 and 20 µg dose level groups without a clear dose level or dose number effect on incidence or severity.

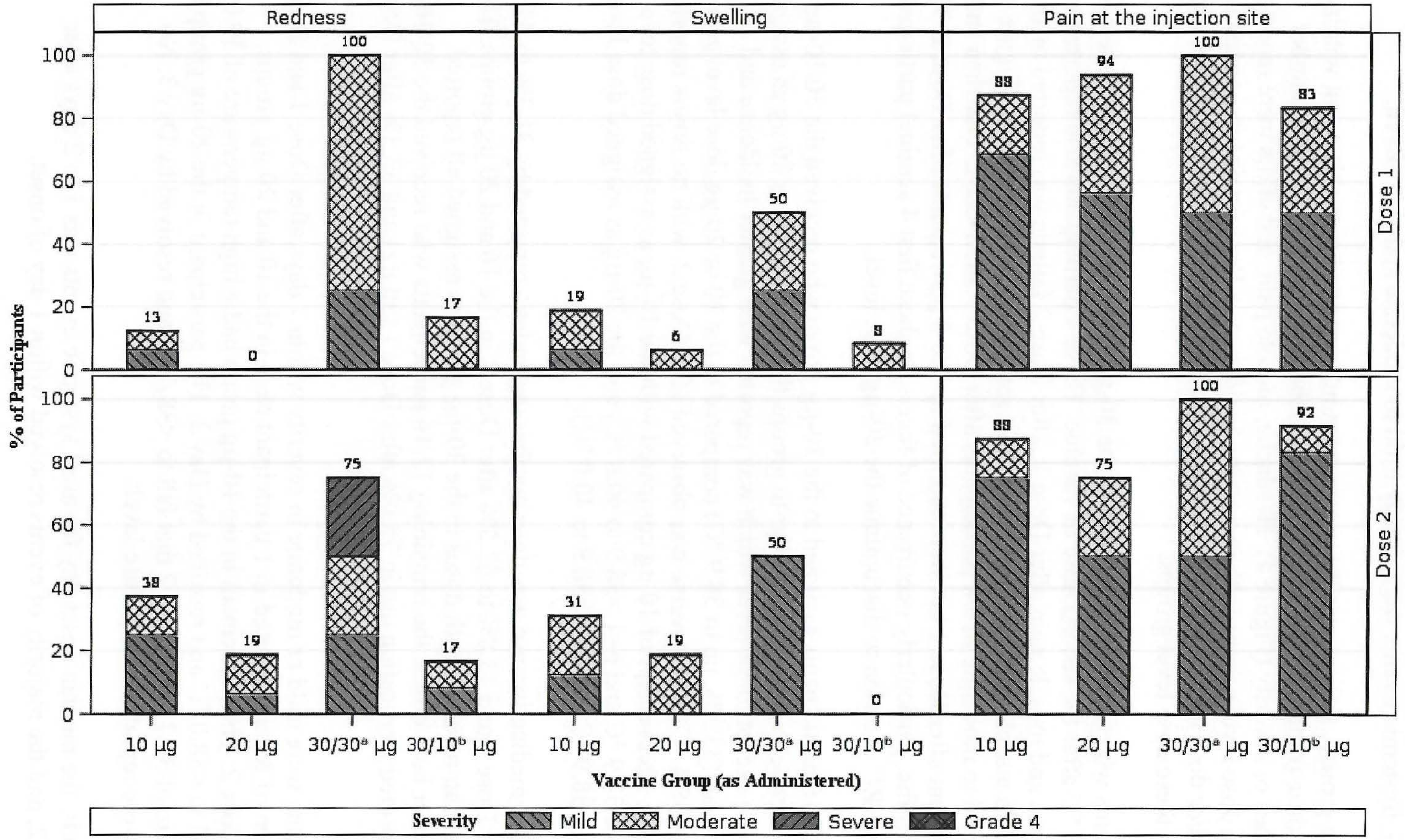
In the 4/16 participants who received both doses in the 30-µg dose level group as assigned, pain at the injection site was reported in all 4 participants after Doses 1 and 2. Redness was reported in all 4 participants after Dose 1 and 3/4 participants after Dose 2 with 1 participant reporting severe redness. Swelling was reported in 2/4 participants after each dose and was mild to moderate. The high frequency of local reactions for these first 4 sentinel participants at Dose 2 contributed to the IRC decision to discontinue the 30-µg dose level for Dose 2 in the remaining of the 30-µg group.

The remaining 12/16 participants assigned to the 30-µg group who received 10 µg for Dose 2 (the 30/10-µg dose regimen) had a local reaction profile similar to groups that received 10 or 20 µg as assigned (Figure 3).

All local reactions were mild or moderate in severity, except for 1 severe event of redness within 7 days after Dose 2 in the 30/30-µg dose regimen.

Across dose levels, the median onset day for most local reactions was within 1 to 2 days after Dose 1 or Dose 2, and the majority of events resolved within 1 or 2 days of onset.

Figure 3. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 – 5 to <12 Years of Age Group – Safety Population



Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.

a. Of the 16 participants who received 30 µg at Dose 1, 4 participants received 30 µg at Dose 2.

b. Of the 16 participants who received 30 µg at Dose 1, 12 participants received 10 µg at Dose 2.

PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: adfacevd Table Generation: 17AUG2021 (06:18)
(Cutoff Date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: ./nda3/C4591007_Phase1_EUA/adce_f001_lr_p1_12

Systemic Events

Reactogenicity generally increased in an increasing dose level- and dose number-dependent manner with regard to incidence and/or severity of systemic events at 10, 20, and 30 µg dose levels (Figure 4). Systemic events were mostly mild to moderate and short-lived.

For 10 and 20 µg groups, fatigue was the most commonly reported systemic event within 7 days after either dose (range: 50.0% to 68.8%) which did not show a clear dose number effect for incidence or severity (Figure 4). Headache, muscle pain, and chills were reported in the 10 and 20 µg dose level groups with increasing incidence and/or severity associated with dose number and/or dose level. Vomiting, diarrhea, and joint pain were uncommon or absent after any dose in these dose level groups.

In the 4 participants who received both doses in the 30-µg group as assigned, 4/4 developed fevers up to 38.9 °C after the second dose of vaccine. These 4 participants also reported mild to moderate fatigue and muscle pain after Dose 1; after Dose 2 fatigue was reported in all 4 participants while muscle pain became moderate in severity in 2/4 participants (Figure 4). Headache was mild to moderate in 3/4 participants after Dose 1 and Dose 2. Diarrhea and vomiting were absent after Dose 1 but were reported in 1 to 2 participants after Dose 2. This systemic event profile, particularly occurrence of fevers, in these first 4 sentinel participants contributed to the IRC decision to discontinue the 30-µg dose level.

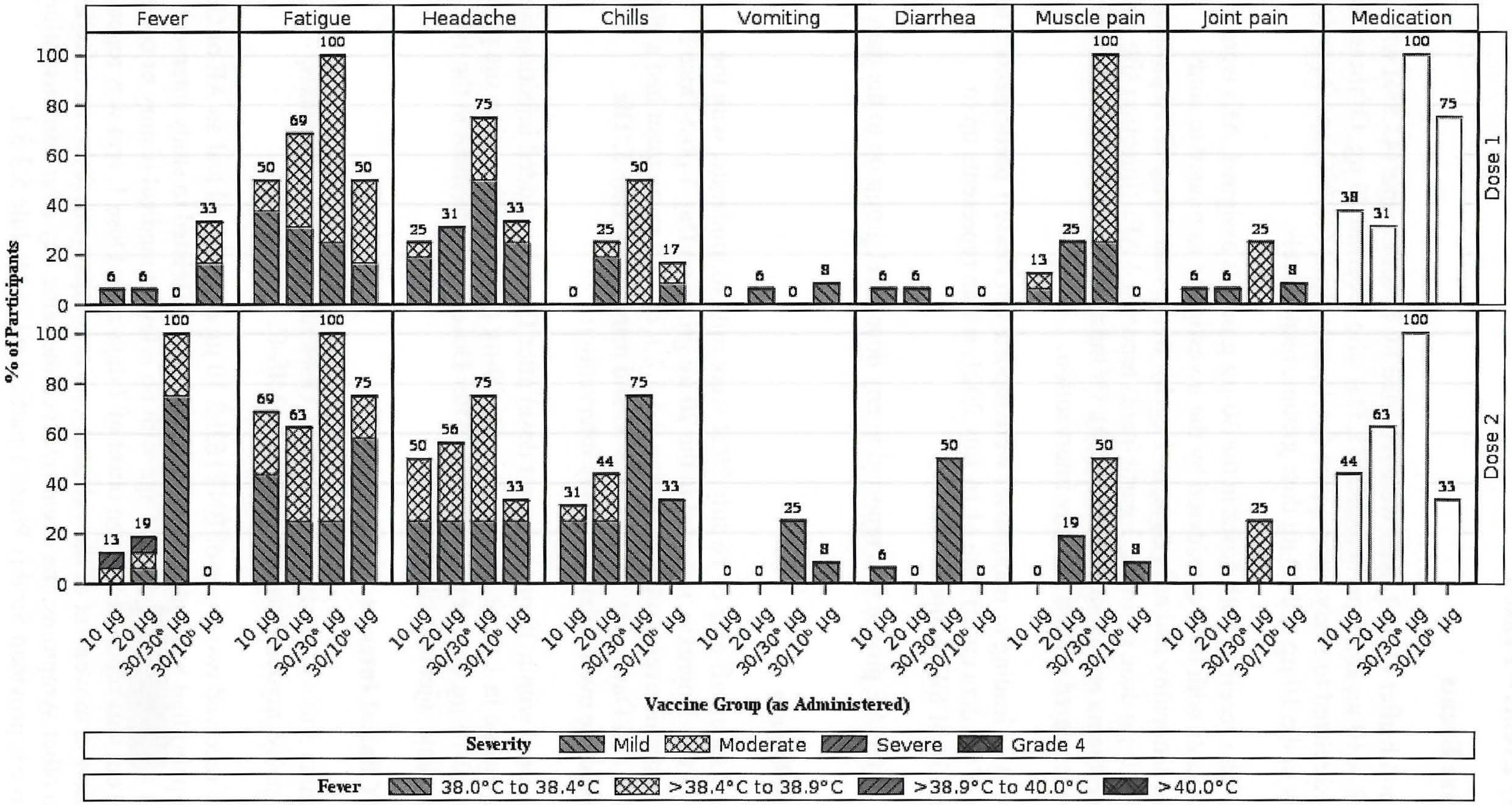
The remaining 12/16 participants assigned to the 30-µg group who received the 30/10-µg dose regimen had a systemic event profile similar to groups that received 10 or 20 µg as assigned (Figure 4), with the exception of fever which was reported with greater incidence and severity after Dose 1 of 30 µg (33.3%, up to 38.9 °C) compared to the 10 or 20 µg dose level groups (6.3% each, up to 38.4 °C). The reverse was observed after Dose 2, with no fevers reported in the 30/10-µg group after receipt of 10 µg compared with the 10-µg as assigned dose level (12.5%; n=1 up to 38.9 °C and n=1 >38.9 to 40.0 °C) and the 20-µg as assigned dose level (18.8%; n=2 up to 38.9 °C and n=1 >38.9 to 40.0 °C).

Antipyretic or pain medication use was dose number dependent, reported by 31.3% to 37.5% participants after Dose 1 and 43.8% to 62.5% after Dose 2 in the 10 and 20 µg groups. The 4/16 participants who received both doses in the 30-µg group as assigned all reported medication use after both doses; the remaining 12/16 participants who received the 30/10-µg dose regimen reported medication use in 75.0% after Dose 1 (30 µg) and 33.3% after Dose 2 (10 µg).

All systemic events were mild or moderate in severity within 7 days after Dose 1 and Dose 2, with the exception of fevers reported in 1 participant each in the 10 and 20 µg groups, occurring after Dose 2. The participant in the 10-µg group had a high temperature of 39.0 °C on Day 2 that fell to <38.0 °C and resolved by Day 3. The participant in the 20-µg group had a high temperature of 39.7 °C on Day 2 that fell to <38.0 °C and resolved by Day 3. No Grade 4 events were reported at any dose levels.

Across dose levels, the median onset day for most systemic events was 1 to 2 days after Dose 1 or Dose 2, and the majority of events resolved within 1 day of onset.

Figure 4. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 – 5 to <12 Years of Age Group – Safety Population



Note: Severity was not collected for use of antipyretic or pain medication.
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
a. Of the 16 participants who received 30 µg at Dose 1, 4 participants received 30 µg at Dose 2.
b. Of the 16 participants who received 30 µg at Dose 1, 12 participants received 10 µg at Dose 2.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: adfacevd Table Generation: 17AUG2021 (06:18)
(Cutoff Date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: ./nda3/C4591007_Phase1_EUA/adce_f001_se_p1_12

2.5.5.2.1.3. Adverse Events – Phase 1

Overview of Adverse Events

From Dose 1 to 1 month after Dose 2, AEs were reported by 7 participants (43.8%) who received BNT162b2 at 10 µg and 5 participants (31.3%) who received 20 µg. Of these, the AEs were considered related to study intervention for 4 participants (25.0%) and 2 participants (12.5%) participants in the 10 µg and 20 µg dose groups, respectively.

In 4/16 participants who received both doses in the 30-µg group as assigned, AEs were reported by 2 participants with both considered by the investigator as related to study intervention (lymphadenopathy and arthralgia, n=1 each). In the remaining 12/16 participants who received the 30/10-µg dose regimen, 3 participants reported 4 AEs (injection site pain, n=2; injection site erythema and vomiting, n=1 each). Of these, the 3 AEs localized to the injection site were considered related to study intervention.

No SAEs, deaths, or AEs leading to withdrawal were reported in Phase 1 participants 5 to <12 years of age as of the data cutoff date of 16 July 2021, which represents up to approximately 3 months of follow-up.

Overall, no change in the AE profile was reported in any dose level group up to the data cutoff date.

Analysis of Adverse Events

All AEs through the data cutoff date of 16 July 2021 were mild to moderate, with the exception of AE of Grade 3 pyrexia, reported in the 20 µg group on Day 1 post-Dose 2 (also recorded as a systemic event; refer to Section 2.5.5.2.1.2). This participant had a high temperature of 39.7 °C on Day 2 that fell to <38.0 °C and resolved by Day 3. The investigator considered the event related to study intervention.

Immediate AEs (reported within 30 minutes post dose) after Dose 1 included injection site discomfort and presyncope in 1 participant each in the 10-µg group and injection site pain in 2 participants in the 30/10-µg dose regimen group. After Dose 2, 1 participant in the 10-µg group reported immediate injection site pain.

Adverse Events of Clinical Interest

No Phase 1 participants 5 to <12 years of age had any cases reported of anaphylaxis, appendicitis, Bell's palsy, myocarditis/pericarditis, or MIS-C.

One participant who received two doses of BNT162b2 30 µg as assigned had an AE of Grade 2 arthralgia (right hip pain) that was judged by the investigator as related to study intervention. This participant was a [redacted] years of age with no relevant medical history or concomitant vaccinations. The event was reported with an onset of 7 days after Dose 1, and was reported as involving no limitation in movement of the extremity, no accompanying fever, no injection site abnormality, and no other symptoms; the event resolved the same day after administration of ibuprofen. A narrative is provided for this Phase 1 participant in Module 5.3.5.1.

Lymphadenopathy

Two participants 5 to <12 years of age had cases of lymphadenopathy up to the data cutoff date.

- 1 [redacted] participant [redacted] years of age in the 20-µg group had Grade 1 bilateral cervical and inguinal lymphadenopathy with onset at 21 days post-Dose 2 and reported as ongoing at the time of the data cutoff. This event was considered by the investigator as not related to study intervention.

- 1 [redacted] participant [redacted] years of age in the 30-µg group as assigned (ie, received both doses of 30 µg), had Grade 1 left axillary lymphadenopathy with onset at 3 days post-Dose 2 and reported as resolved 17 days after onset. This event was considered by the investigator to be related to study intervention.

2.5.5.2.1.4. Safety Conclusions – Phase 1

High frequencies of reactogenicity to the 20 and 30 µg dose levels in participants 5 to <12 years of age contributed to the decision to select a lower dose of 10 µg as the final dose level of BNT162b2 to proceed to Phase 2/3 for this age group. The dose level selection decision for this age group was based on Phase 1 safety and immunogenicity results. BNT162b2 at 10 µg was well tolerated in participants 5 to <12 years of age based on available Phase 1 safety results representing follow-up to approximately 3 months after Dose 2.

Safety results from Phase 1 dose level groups supported the Phase 2/3 dose level selection (refer to Section 2.5.5.2.1.5).

2.5.5.2.1.5. Dose Selection from Phase 1 Data

The similarity in post-vaccination immunogenicity as reflected in Day 7 post-Dose 2 GMTs across 10 µg and 20 µg dose levels (see Section 2.5.4.3.1.2), along with the most favorable reactogenicity profile observed in the 10 µg dose level (see Section 2.5.5.2.1.2), 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.

2.5.5.2.2. C4591007 Safety Results – 5 to <12 Years of Age – Phase 2/3

2.5.5.2.2.1. Safety Population – Phase 2/3

The safety population for Phase 2/3 pediatric participants 5 to <12 years of age reflected the 2:1 randomization in the BNT162b2 (N=1518) and placebo (N=750) groups (Table 12). The only exclusions from the safety population were due to 17 participants (0.7%) not receiving study vaccine. No participants 5 to <12 years of age included in the safety population were HIV+.

Table 12. Safety Population – Phase 2/3 – 5 to <12 Years of Age

	Vaccine Group (as Administered)		
	BNT162b2 10 µg n[a]	Placebo n[a]	Total n[a] (%)
Randomized[b]			2285
Vaccinated	1518	750	2268 (99.3)
Safety population	1518	750	2268 (99.3)
HIV-positive	0	0	0
Excluded from safety population			17 (0.7)
Reason for exclusion			
Participant did not receive study vaccine			17 (0.7)

Abbreviation: HIV = human immunodeficiency virus.
a. n = Number of participants with the specified characteristic, or the total sample.
b. This value is the denominator for the percentage calculations.
PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (23:25) Source Data: adsl Table Generation: 16SEP2021 (06:12)
(Cutoff Date: 06SEP2021, Snapshot Date: 13SEP2021) Output File:
./nda2_ubped/C4591007_P23_EUA/adsl_s008_saf_pop_p2_12

2.5.5.2.2.1.1. Duration of Follow-Up – Phase 2/3

The duration of follow-up for Phase 2/3 pediatric participants 5 to <12 years of age was at least 2 months after Dose 2 for most participants (Table 13). Almost all (95.1%) of the participants had 2 to <3 months of follow-up after Dose 2.

Table 13. Follow-up Time After Dose 2 - Phase 2/3 - 5 to <12 Years of Age - Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 10 µg (N[a]=1518) n[b] (%)	Placebo (N[a]=750) n[b] (%)	Total (N[a]=2268) n[b] (%)
Time from Dose 2 to cutoff date			
<1 Month	7 (0.5)	4 (0.5)	11 (0.5)
≥1 Month to <2 months	67 (4.4)	32 (4.3)	99 (4.4)
≥2 Months to <3 months	1444 (95.1)	714 (95.2)	2158 (95.1)
≥3 Months	0	0	0

Note: Follow-up time was calculated from Dose 2 to the cutoff date or withdrawal date or the date of unblinding (per protocol), whichever date was earlier.
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.
PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (23:25) Source Data: adsl Table Generation: 15SEP2021 (11:51)
(Cutoff Date: 06SEP2021, Snapshot Date: 13SEP2021) Output File:
./nda2_ubped/C4591007_P23_EUA/adsl_s005_fup_time_12

2.5.5.2.2.1.2. Disposition – Phase 2/3

The disposition of Phase 2/3 pediatric participants 5 to <12 years of age is summarized in Table 14. In total, 1528 participants were randomized to receive BNT162b2 10 µg and 757 participants were randomized to placebo, reflecting the 2:1 randomization ratio. Most participants randomized to either group (≥98.7%) received Dose 1 and Dose 2.

Two participants (0.1%) in the BNT162b2 group and 2 participants (0.3%) in the placebo group discontinued from the vaccination period and are continuing in the study for safety follow-up. Most participants across both groups completed the visit at 1 month after Dose 2 (≥98.5%). Among participants who discontinued from the vaccination period but continued in the study up to the 1-month post-Dose 2 visit, none of the discontinuations were reported as due to an AE.

Two participants (0.1%) in the BNT162b2 group and 2 participants (0.3%) in the placebo group withdrew from the study before the 1-month post-Dose 2 visit. None of these withdrawals were reported as due to an AE.

Table 14. Disposition of All Randomized Participants – Phase 2/3 – 5 to <12 Years of Age

	Vaccine Group (as Randomized)		
	BNT162b2 10 µg (N[a]=1528) n[b] (%)	Placebo (N[a]=757) n[b] (%)	Total (N[a]=2285) n[b] (%)
Randomized	1528 (100.0)	757 (100.0)	2285 (100.0)
Not vaccinated	11 (0.7)	6 (0.8)	17 (0.7)
Vaccinated	1517 (99.3)	751 (99.2)	2268 (99.3)
Dose 1	1517 (99.3)	751 (99.2)	2268 (99.3)
Dose 2	1514 (99.1)	747 (98.7)	2261 (98.9)
Completed 1-month post–Dose 2 visit (vaccination period)	1510 (98.8)	746 (98.5)	2256 (98.7)
Discontinued from vaccination period but continued in the study	2 (0.1)	2 (0.3)	4 (0.2)
Discontinued after Dose 1 and before Dose 2	2 (0.1)	2 (0.3)	4 (0.2)
Discontinued after Dose 2 and before 1-month post–Dose 2 visit	0	0	0
Reason for discontinuation from vaccination period			
Withdrawal by participant	1 (0.1)	2 (0.3)	3 (0.1)
Withdrawal by parent/guardian	1 (0.1)	0	1 (0.0)
Withdrawn from the study	5 (0.3)	6 (0.8)	11 (0.5)
Withdrawn after Dose 1 and before Dose 2	1 (0.1)	2 (0.3)	3 (0.1)
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	2 (0.1)	2 (0.3)	4 (0.2)
Withdrawn after 1-month post–Dose 2 visit	2 (0.1)	2 (0.3)	4 (0.2)
Reason for withdrawal from the study			
Other	1 (0.1)	0	1 (0.0)
Withdrawal by participant	0	2 (0.3)	2 (0.1)
Withdrawal by parent/guardian	4 (0.3)	4 (0.5)	8 (0.4)

a. N = number of randomized participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
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During the course of the study, 3 participants in the 5 to <12 years of age group turned 12 years of age and became eligible to receive a COVID-19 vaccine outside of the study. These participants were unblinded to their treatment assignment per protocol to seek vaccination with a COVID-19 vaccine (eg, BNT162b2 30 µg) that is authorized for individuals ≥12 years of age under EUA or conditional approval. Of these, 2 participants received both doses of BNT162b2 10 µg prior to being unblinded and 1 participant received both doses of placebo before being unblinded and withdrew to receive a COVID-19 vaccine outside of the study. Data from these participants are included in endpoint analyses up to the point at which they were unblinded.

Protocol Deviations

Important protocol deviations were reported in 48 participants (3.1%) in the BNT162b2 group and 4 participants (0.5%) in the placebo group. Nearly all protocol deviations in the BNT162b2 group (47 [3.1%]) were related to investigational product, most (38 [2.5%]) due to being unsuitable for use (as BNT162b2 requires thawing/dilution prior to administration, whereas saline placebo does not).

Vaccine Administration and Timing

Among all randomized Phase 2/3 pediatric participants 5 to <12 years of age, almost all (>99%) participants were administered study intervention as randomized. Altogether, 99.3% and 99.2% received Dose 1 of BNT162b2 and placebo, respectively, and 99.1% and 98.7% received Dose 2 of BNT162b2 and placebo, respectively. One participant, who was randomized to the placebo group, received vaccination not as randomized (ie, received two doses of BNT162b2 10 µg).

The majority of participants received Dose 2 in the protocol defined window of 19 to 23 days after Dose 1 in the BNT162b2 (94.4%) and placebo (94.5%) groups. Second doses administered outside of the protocol specified window included 0.7% and 0.4% of the BNT162b2 and placebo groups, respectively, who received Dose 2 at <19 days after Dose 1 and 4.0% and 3.8% of the BNT162b2 and placebo groups, respectively, who received Dose 2 at >23 days after Dose 1.

Longer time intervals reported for Dose 2 administration after Dose 1, in the BNT162b2 and placebo groups within the safety population, were:

- 28 to 34 days: 1.7% vs 1.6%
- 35 to 41 days: 0.5% vs 0.7%
- 42 to 48 days: 0.1% vs 0.1%
- 49 to 55 days: 0.2% vs 0.4%
- >55 days: 0.1% vs none

The total range for timing of Dose 2 administration after Dose 1 of BNT162b2 was 14 days to >55 days. For placebo, the total range for timing of Dose 2 administration after Dose 1 was 14 to 55 days.

2.5.5.2.2.1.3. Demographics – Phase 2/3

Demographic characteristics for Phase 2/3 pediatric participants 5 to <12 years of age were similar in BNT162b2 and placebo groups in the safety population (Table 15). In total, most participants were White (78.9%), with 6.5% Black or African American participants and 6.0% Asian participants, 7.0% multiracial participants, and other racial groups <1%. There were 21.1% Hispanic/Latino participants. The median age was 8.0 years and 52.1% of participants were male.

Obese children (based on age- and sex-specific indices) made up 11.5% (BNT162b2 group) to 12.3% (placebo group) of this age group in the safety population. Comorbidities present at baseline that increase the risk of severe COVID-19 disease[25] (which include obesity) were present in similar proportions of participants in the BNT162b2 group (20.6%) and placebo group (20.3%). The most common comorbidities reported in participants at study baseline were:

- asthma (7.8% in BNT162b2 and 8.3% in placebo)
- neurologic disorders (1.3% in BNT162b2 and 0.4% in placebo)
- congenital heart disease (1.0% in BNT162b2 and 0.7% in placebo)

One participant, who was in the BNT162b2 group, had an immunocompromised condition reported at baseline (acute lymphocytic leukemia).

In the safety population, similar proportions of participants in the BNT162b2 group (8.8%) and placebo group (8.7%) had baseline SARS-CoV-2 positive status.

Table 15. Demographic Characteristics – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 10 µg (N[a]=1518) n[b] (%)	**Placebo (N[a]=750) n[b] (%)**	**Total (N[a]=2268) n[b] (%)**
Sex			
Male	799 (52.6)	383 (51.1)	1182 (52.1)
Female	719 (47.4)	367 (48.9)	1086 (47.9)
Race			
White	1204 (79.3)	586 (78.1)	1790 (78.9)
Black or African American	89 (5.9)	58 (7.7)	147 (6.5)
American Indian or Alaska Native	12 (0.8)	3 (0.4)	15 (0.7)
Asian	90 (5.9)	47 (6.3)	137 (6.0)
Native Hawaiian or other Pacific Islander	5 (0.3)	0	5 (0.2)
Multiracial	109 (7.2)	49 (6.5)	158 (7.0)
Not reported	9 (0.6)	7 (0.9)	16 (0.7)
Ethnicity			
Hispanic/Latino	319 (21.0)	159 (21.2)	478 (21.1)
Non-Hispanic/Non-Latino	1196 (78.8)	591 (78.8)	1787 (78.8)
Not reported	3 (0.2)	0	3 (0.1)
Age at vaccination (years)			
Mean (SD)	8.2 (1.93)	8.1 (1.97)	8.2 (1.94)
Median	8.0	8.0	8.0
Min, max	(5, 11)	(5, 11)	(5, 11)
Obese[c]			
Yes	174 (11.5)	92 (12.3)	266 (11.7)
No	1343 (88.5)	658 (87.7)	2001 (88.2)
Missing	1 (0.1)	0	1 (0.0)

Table 15. Demographic Characteristics – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 10 µg (N[a]=1518) n[b] (%)	Placebo (N[a]=750) n[b] (%)	Total (N[a]=2268) n[b] (%)
Baseline SARS-CoV-2 status			
Positive[d]	133 (8.8)	65 (8.7)	198 (8.7)
Negative[e]	1385 (91.2)	685 (91.3)	2070 (91.3)
Comorbidities[f]			
Yes	312 (20.6)	152 (20.3)	464 (20.5)
No	1206 (79.4)	598 (79.7)	1804 (79.5)

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; MMWR = Morbidity and Mortality Weekly Report; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
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. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html charts/bmiagerev htm.
d. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
e. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
f. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥ 95th percentile).
PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (23:25) Source Data: adsl Table Generation: 15SEP2021 (11:51) (Cutoff Date: 06SEP2021, Snapshot Date: 13SEP2021) Output File: ./nda2 ubped/C4591007 P23 EUA/adsl s005 demo p2 12

Medical History

The safety population included children with a medical history profile consistent with the general population. The most frequently reported SOCs in either group were:

- *immune system disorders* (22.8% in BNT162b2 and 22.7% in placebo) mostly consisting of a variety of non-drug allergies, also including drug hypersensitivity (2.8% in BNT162b2 and 3.2% in placebo) and anaphylactic reaction (0.2% in BNT162b2 and 0.1% in placebo)
- *respiratory, thoracic, and mediastinal disorders* (11.7% in BNT162b2 and 13.2% in placebo) mostly consisting of asthma and respiratory illnesses commonly seen in this age group
- *psychiatric disorders* (10.3% in BNT162b2 and 10.1% in placebo) including attention deficit hyperactivity disorder (6.7% in BNT162b2 and 6.5% in placebo) and a variety of behavioral disorders commonly seen in this age group

- *infections and infestations* (6.9% in BNT162b2 and 9.5% in placebo) including a variety of ear, nose, and throat infections commonly seen in this age group
- *nervous system disorders* (3.6% in BNT162b2 and 2.8% in placebo) including various types of epilepsy, headaches, and sensory disorders commonly seen in this age group
- *cardiac disorders* in 9 participants (0.6%), all in the BNT162b2 group, that included arrhythmias, congestive cardiomyopathy, and Wolff-Parkinson-White syndrome. Additionally, congenital cardiac conditions were reported in both the BNT162b2 and placebo groups including atrial septal defect (0.3% in BNT162b2 and 0.1% in placebo), ventricular septal defect (0.2% in BNT162b2 and 0.3% in placebo), bicuspid aortic valve (0.2% in BNT162b2 and 0.1% in placebo), and coarctation of the aorta (0.1% in BNT162b2 and none in placebo). Cardiac murmurs were reported for 11 participants (0.7%) in the BNT162b2 group and 4 participants (0.5%) in the placebo group.

Concomitant Vaccines

A small percentage of participants in either group (≤0.8%) received any concomitant vaccine after Dose 1, and most concomitant vaccines received were routine pediatric immunizations (ie, diphtheria, pertussis, tetanus vaccine; human papilloma virus vaccine; and meningococcal vaccine).

2.5.5.2.2.2. Reactogenicity – Phase 2/3

Reactogenicity (local reactions and systemic events) was assessed via e-diary in all Phase 2/3 pediatric participants 5 to <12 years of age for 7 days after each dose. Participants with e-diary data included N=1511 in the BNT162b2 group and N=749 in the placebo group post-Dose 1, and N=1501 in the BNT162b2 group and N=741 in the placebo group post-Dose 2.

2.5.5.2.2.2.1. Local Reactions – Phase 2/ 3

In the BNT162b2 group, pain at the injection site was most frequently reported in pediatric participants 5 to <12 years of age, and frequency was similar after Dose 1 and after Dose 2 of BNT162b2 (74.1% vs 71.0%), shown in Figure 5. In the placebo group, pain at the injection site after Doses 1 and 2 was less frequently reported compared to the BNT162b2 group and was similar after each dose (31.3% vs 29.5%).

In the BNT162b2 group, frequencies of redness and swelling were similar after Doses 1 and 2 (Figure 5). Frequencies of redness showed a modest increase from after Dose 1 compared to after Dose 2 of BNT162b2 (14.7% vs 18.5%). Frequencies of swelling also showed a modest increase after Dose 1 compared with Dose 2 of BNT162b2 (10.5% vs 15.3%). In the placebo group, redness was less frequently reported compared to the BNT162b2 group and was similar after each dose (5.7% vs 5.4%), and swelling was infrequent (2.7%) after both Dose 1 and Dose 2.

After the first and second dose, most local reactions were mild or moderate in severity. Severe local reactions were reported infrequently (≤0.3%) across the BNT162b2 and placebo groups after either dose. No Grade 4 local reactions were reported in either group.

Across groups, median onset for all local reactions after receiving BNT162b2 was 1 to 2 days after Dose 1 or Dose 2, and all events resolved with a median duration of 1 to 2 days.

Overall, the pattern of local reactions reported in children 5 to <12 years of age after each dose was generally similar to that observed in prior analyses of Phase 2/3 participants ≥12 years of age in Study C4591001 with regard to pain at the injection site, but children had slightly higher frequencies of swelling and redness at the injection site (still within tolerable limits). Further details are provided in the risk discussion (Section 2.5.6.2).

Subgroup Analyses

Subgroups of Phase 2/3 pediatric participants 5 to <12 years of age had similar reactogenicity, with regard to local reactions, across the BNT162b2 and placebo groups when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status. Subgroups of race (Black or African American), ethnicity (Hispanic/Latino), and baseline SARS-CoV-2 status (positive) included a limited number of participants, and their results should be interpreted with caution. There were no meaningful differences in the overall patterns of local reactions across these subgroups. Subgroup data are summarized below.

Sex

The frequencies of redness, swelling, and pain at the injection site after any dose of BNT162b2 was 26.5%, 20.3%, and 82.0% compared with 26.3%, 20.5%, and 86.9% for male and female participants, respectively. There were no clinically meaningful differences between the two groups.

Race

The frequency of redness, swelling, and pain at the injection site after any dose of BNT162b2 was similar across race subgroups. Lower proportions of Black or African American participants experienced redness and swelling compared to White and 'All Other' (ie, American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories) groups. Frequencies of pain at injection site was similar across the groups. Local reaction frequencies in the BNT162b2 group by race subgroup included:

- redness: White: 27.7%, Black or African American: 12.5%, All Others: 25.3%
- swelling: White: 20.5%, Black or African American: 13.6%, All Others: 22.2%
- pain at injection site: White: 85.0%, Black or African American: 78.4%, All Others: 82.7%

While the frequencies of local reactions were numerically different between subgroups, these differences are not clinically meaningful.

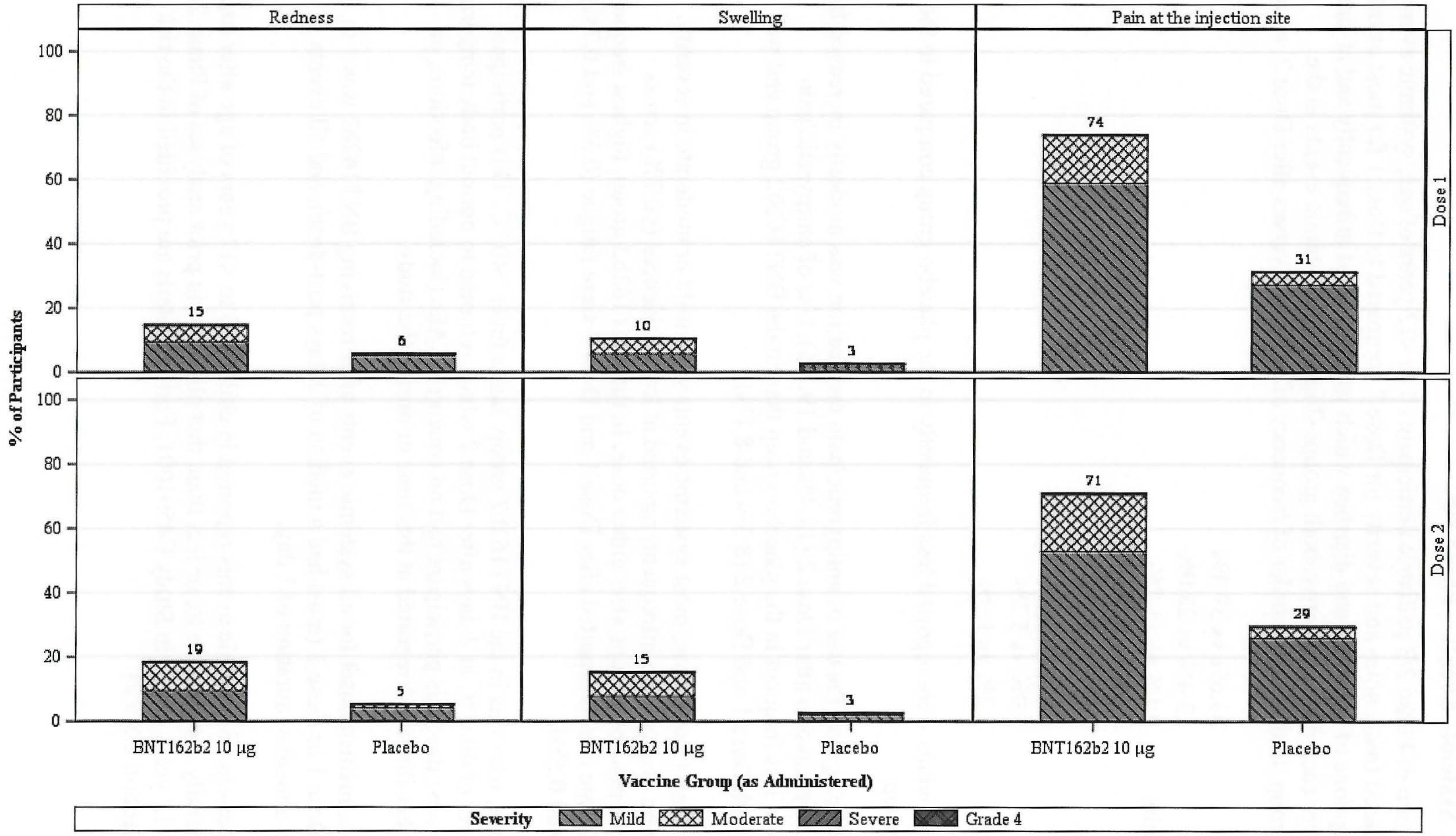
Ethnicity

The frequencies of redness, swelling, and pain at the injection site after any dose of BNT162b2 were 21.7%, 20.4%, and 84.0% compared with 27.7%, 20.4%, and 84.4% for Hispanic/Latino and non-Hispanic/non-Latino participants, respectively. While there were numerical differences in the frequencies of redness between the two groups, these differences are not clinically meaningful.

SARS-CoV-2 Baseline Status

There were 133 BNT162b2 and 65 placebo participants with baseline positive SARS-CoV-2 status, and 1378 BNT162b2 and 684 placebo participants with baseline negative SARS-CoV-2 status). The frequencies of redness, swelling, and pain at the injection site after any dose of BNT162b2 was 20.3%, 12.8%, and 82.7% compared with 27.0%, 21.1%, and 84.5% for those positive and negative at baseline, respectively. The frequencies between individuals positive or negative at baseline were similar although numerically lower in those positive at baseline. Note that the baseline SARS-CoV-2 positive subgroup included far fewer participants than the negative subgroup, so their results should be interpreted with caution.

Figure 5. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – 5 to <12 Years of Age – Safety Population



Note: The number above each bar denotes the percentage of participants reporting the reaction with any severity.
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Table Generation: 15SEP2021 (23:02) (Cutoff Date: 06SEP2021, Snapshot Date: 13SEP2021) Output File: ./nda2_ubped/C4591007_P23_EUA/adce_f001_lr_p2_12

2.5.5.2.2.2.2. Systemic Events – Phase 2/3

In the population of Phase 2/3 pediatric participants 5 to <12 years of age, systemic events showed increased frequencies and severity for Dose 2 compared to Dose 1 for most events, with the exceptions of vomiting and diarrhea which were reported infrequently and at similar incidences after each dose and across both groups (Figure 6). Systemic events in the BNT162b2 group, in decreasing order of frequency after Dose 1 versus after Dose 2, were:

- fatigue: 33.6% vs 39.4%
- headache: 22.4% vs 28.0%
- muscle pain: 9.1% vs 11.7%
- chills: 4.6% vs 9.8%
- joint pain: 3.3% vs 5.2%
- fever: 2.5% vs 6.5%
- diarrhea: 5.9% vs 5.3%
- vomiting: 2.2% vs 1.9%

Most systemic events were reported less frequently in the placebo group compared to the BNT162b2 group.

In the BNT162b2 group the use of antipyretic/pain medication was modestly increased from after Dose 1 compared to after Dose 2 (14.4% and 19.7%). Use of antipyretic/pain medication was less frequent in the placebo group than in the BNT162b2 group and was similar after both Dose 1 and Dose 2 (8.3% and 8.1%).

After the first and second dose, most systemic events were mild or moderate in severity. Severe systemic events were infrequent, reported at low incidences (≤0.7%) across BNT162b2 and placebo groups after either dose. In the BNT162b2 group, highest frequencies of severe systemic events reported after Dose 1 and Dose 2 were fatigue (0.3% and 0.7%) and fever (0.2% and 0.5%).

One participant, who was in the BNT162b2 group, had a fever >40 °C. This participant reported a fever of 40.0 °C at 2 days after Dose 2 which returned to normal body temperature (36.7 °C) the next day; this participant had no concurrent AEs (including infections, or injuries, or other illnesses) reported at this time or during the study.

Across groups, median onset for all systemic events after receiving BNT162b2 was 1 to 4 days after Dose 1 or Dose 2 (most had a median of 2 days post-dose), and all events resolved with a median duration of 1 day.

Overall, the pattern of systemic events reported in children 5 to <12 years of age after each dose was generally comparable to, or less than, that observed in prior analyses of Phase 2/3 participants ≥12 years of age in Study C4591001. Further details are provided in the risk discussion (Section 2.5.6.2).

Subgroup Analyses

Subgroups of Phase 2/3 pediatric participants 5 to <12 years of age had similar reactogenicity, with regard to systemic events, across the BNT162b2 and placebo groups when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status. Subgroups of race (Black or African American), ethnicity (Hispanic/Latino), and baseline SARS-CoV-2 status (positive) included a limited number of participants, and their results should be interpreted with caution. There were no meaningful differences in the overall patterns of systemic events across these subgroups.

Sex

The frequencies of the most commonly reported systemic events of fatigue, headache, and muscle pain after any dose of BNT162b2 were 51.6%, 36.7%, and 16.4% compared with 51.9%, 39.8%, and 18.8% for male and female participants, respectively. Fevers after any dose of BNT162b2 were reported at similar frequencies in male and female participants (7.0% vs 9.7%). There were no clinically meaningful differences between the sex subgroups.

Race

The frequencies of the most commonly reported systemic events of fatigue, headache, and muscle pain after any dose of BNT162b2 were similar across race subgroups. There were no clinically meaningful differences between the groups. Frequencies of these systemic events and of fever after any dose of BNT162b2 by race subgroups of White, Black or African American, or 'All Others' (ie, American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories) were:

- fatigue: White: 51.7%, Black or African American: 46.6%, All Others: 53.8%
- headache: White: 38.6%, Black or African American: 37.5%, All Others: 36.0%
- muscle pain: White: 17.9%, Black or African American: 19.3%, All Others: 15.1%
- fever: White: 8.2%, Black or African American: 10.2%, All Others: 8.0%

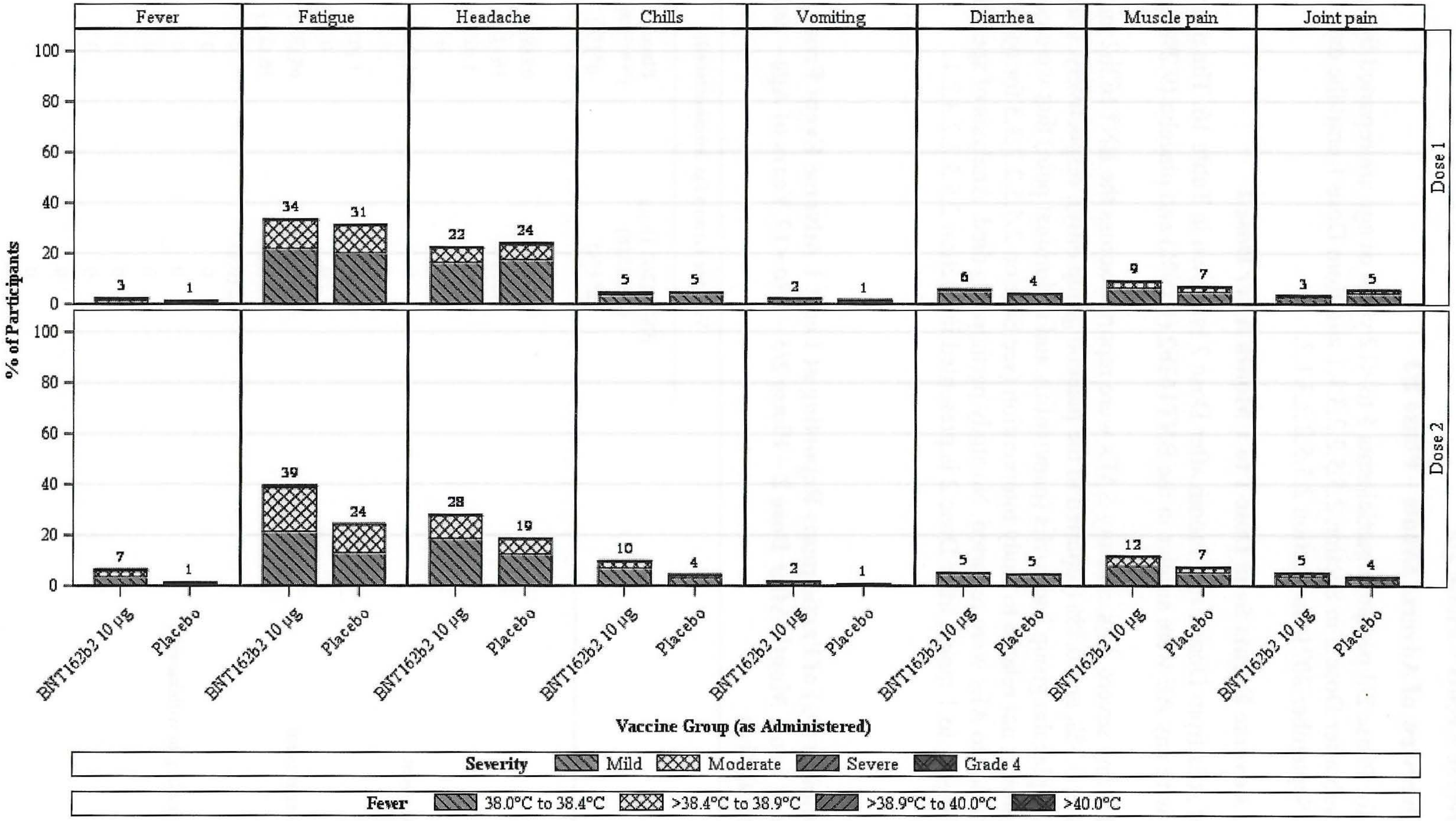
Ethnicity

The frequencies of the most commonly reported systemic events of fatigue, headache, and muscle pain after any dose of BNT162b2 were 50.0%, 37.7%, and 19.5% compared with 52.3%, 38.4%, and 17.1% for Hispanic/Latino and non-Hispanic/non-Latino participants, respectively. Fevers after any dose of BNT162b2 were reported at similar frequencies in Hispanic/Latino and non-Hispanic/non-Latino participants (8.2% vs 8.4%). There were no clinically meaningful differences between the ethnicity subgroups.

SARS-CoV-2 Baseline Status

There were 133 BNT162b2 and 65 placebo participants with baseline positive SARS-CoV-2 status, and 1384 BNT162b2 and 685 placebo participants with baseline negative SARS-CoV-2 status. The frequencies of the most commonly reported systemic events of fatigue, headache, and muscle pain after any dose of BNT162b2 was generally similar, or numerically lower among those positive at baseline: fatigue, headache and muscle pain frequencies were 40.6%, 39.1% and 15.8% compared with 52.8%, 38.1%, and 17.7% for those positive and negative for SARS-CoV-2 at baseline, respectively. Fevers after any dose of BNT162b2 were reported at a slightly lower frequency in baseline positive compared to baseline negative participants (6.0% vs 8.5%). Note that the baseline SARS-CoV-2 positive subgroup included far fewer participants the negative subgroup, so their results should be interpreted with caution.

Figure 6. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – 5 to <12 Years of Age – Safety Population



Note: Severity was not collected for use of antipyretic or pain medication.
Note: The number above each bar denotes the percentage of participants reporting the event with any severity.
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Table Generation: 15SEP2021 (23:02) (Cutoff Date: 06SEP2021, Snapshot Date: 13SEP2021) Output File: ./nda2_ubped/C4591007_P23_EUA/adce_f001_se_p2_12

2.5.5.2.2.3. Adverse Events – Phase 2/3

2.5.5.2.2.3.1. Overview of Adverse Events – Phase 2/3

AE overviews for Phase 2/3 pediatric participants 5 to <12 years of age are reported from Dose 1 to 1 month after Dose 2 in Section 2.5.5.2.2.3.1.1 and from Dose 1 until the data cutoff date (06 September 2021) in Section 2.5.5.2.2.3.1.2.

2.5.5.2.2.3.1.1. Adverse Events from Dose 1 to 1 Month After Dose 2

An overview of AEs from Dose 1 to 1 month after Dose 2 is shown in Table 16. The proportions of participants with any AE were similar in the BNT162b2 (10.9%) and placebo (9.2%) groups.

Any related AEs, any severe AEs, and any SAEs were reported across the BNT162b2 and placebo groups by ≤3.0%, 0.1%, and 0.1% (reported in the placebo group only), respectively. One participant in the placebo group had SAEs (pancreatitis and abdominal pain) that were considered by the investigator as not related to study intervention (see Section 2.5.5.2.2.3.3 for details). No withdrawals due to AEs were reported. No study participants died. Analysis of specific AEs reported from Dose 1 to 1 month after Dose 2 is presented in Section 2.5.5.2.2.3.2.1.

Table 16. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)	
Adverse Event	BNT162b2 10 µg (N[a]=1518) n[b] (%)	Placebo (N[a]=750) n[b] (%)
Any adverse event	166 (10.9)	69 (9.2)
Related[c]	46 (3.0)	16 (2.1)
Severe	2 (0.1)	1 (0.1)
Life-threatening	0	0
Any serious adverse event	0	1 (0.1)
Related[c]	0	0
Severe	0	1 (0.1)
Life-threatening	0	0
Any nonserious adverse event	166 (10.9)	68 (9.1)
Related[c]	46 (3.0)	16 (2.1)
Severe	2 (0.1)	0
Life-threatening	0	0
Any adverse event leading to withdrawal	0	0
Related[c]	0	0
Serious	0	0
Severe	0	0
Life-threatening	0	0
Death	0	0

Table 16. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 10 µg (N[a]=1518)	Placebo (N[a]=750)
Adverse Event	n[b] (%)	n[b] (%)

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any adverse event," n = the number of participants reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (17:16) Source Data: adae Table Generation: 15SEP2021 (17:46)
(Cutoff Date: 06SEP2021, Snapshot Date: 13SEP2021) Output File:
./nda2 ubped/C4591007 P23 EUA/adae s130 1md2 p2 12

Subgroup Analyses

Subgroups of Phase 2/3 pediatric participants 5 to <12 years of age had similar AE profiles from Dose 1 to 1 month after Dose 2, overall and categorically (ie, related or severe events) across the BNT162b2 and placebo groups when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status. Subgroups of race (Black or African American), ethnicity (Hispanic/Latino) and baseline SARS-CoV-2 status (positive) included a limited number of participants, and their results should be interpreted with caution. No life-threatening AEs or any AEs leading to withdrawal were reported in the study. There were no meaningful differences in the overall patterns of AEs by category across these subgroups.
These subgroups are summarized below.

Sex

In the BNT162b2 group, overall incidences of participants reporting at least 1 AE were 11.1% for male participants and 10.7% for female participants. Any related AEs were reported in 3.3% of male participants and 2.8% of female participants. Any severe AEs were reported by 0.3% of male participants and no female participants. Two SAEs were reported for 1 participant within 1 month after Dose 2 (details provided in Section 2.5.5.2.2.3.3):

- 1 female participant in the placebo group reported SAEs of pancreatitis and abdominal pain (reported as occurring 'post-injury') that occurred up to 1 month after Dose 2, considered by the investigator as not related to study intervention

There were no clinically meaningful differences between the two sex subgroups.

Race

In the BNT162b2 group, overall incidences of participants reporting at least 1 AE were similar (range: 9.0% to 12.0%) across race subgroups of White, Black or African American, and 'All Others' (ie, American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories). Any related AEs were reported in 2.8% to 4.0% of participants across race subgroups. Any severe AEs were reported by 0.2% of participants across race subgroups. The participant who had SAEs (refer to Section 2.5.5.2.2.3.3), that were both considered as not related to study intervention, was White. While the frequency of AEs was numerically different, these differences between race subgroups are not clinically meaningful.

Ethnicity

In the BNT162b2 group, overall incidences of participants reporting at least 1 AE were 11.3% for Hispanic/Latino participants and 10.9% for non-Hispanic/non-Latino participants. Any related AEs were reported in 2.8% of Hispanic/Latino participants and 3.1% of non-Hispanic/non-Latino participants. Any severe AEs were reported by 0% of Hispanic/Latino participants and 0.2% of non-Hispanic/non-Latino participants. The participant who had SAEs (refer to Section 2.5.5.2.2.3.3), that were both considered as not related to study intervention, was non-Hispanic/non-Latino. There were no clinically meaningful differences between the two ethnicity groups.

SARS-CoV-2 Baseline Status

There were 133 BNT162b2 and 65 placebo participants with baseline positive SARS-CoV-2 status, and 1385 BNT162b2 and 685 placebo participants with baseline negative SARS-CoV-2 status. In the BNT162b2 group, overall incidences of participants reporting at least 1 AE were 8.3% for baseline positive participants and 11.2% for baseline negative participants. Any related AEs were reported in 1.5% of baseline positive participants and 3.2% of baseline negative participants. Any severe AEs were reported by none of the baseline positive participants and 0.1% of baseline negative participants. The participant who had reported SAEs (refer to Section 2.5.5.2.2.3.3), both considered as not related to study intervention, did not have a determinant baseline status. While the frequencies of AEs were numerically different, these differences are not clinically meaningful. Note that the baseline SARS-CoV-2 positive subgroup included far fewer participants the negative subgroup, so their results should be interpreted with caution.

2.5.5.2.2.3.1.2. Adverse Events from Dose 1 to Data Cutoff Date

From Dose 1 to the data cutoff date (06 September 2021), which represents at least 2 months of follow-up after Dose 2, the proportions of Phase 2/3 pediatric participants 5 to <12 years of age with any event was similar in the BNT162b2 (11.6%) and placebo (9.6%) groups (Table 17).

Few additional AEs were reported between 1 month after Dose 2 (Table 16) to the data cutoff date (Table 17). Any related AEs, any severe AEs, and any SAEs were reported across the BNT162b2 and placebo groups by ≤3.0%, ≤0.2%, and 0.1%, respectively, up to the data cutoff date. From 1 month after Dose 2 up to the data cutoff date, 1 SAE (limb fracture) was reported in a participant in the BNT162b2 group that was considered by the investigator as not related to study intervention (see Section 2.5.5.2.2.3.3 for details). No withdrawals due to AEs were reported. As of the data cutoff date, no study participants died. Analysis of specific AEs reported from Dose 1 to the data cutoff date is presented in Section 2.5.5.2.2.3.2.2.

Table 17. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 Through Cutoff Date (06SEP2021) – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)	
Adverse Event	**BNT162b2 10 µg (N[a]=1518) n[b] (%)**	**Placebo (N[a]=750) n[b] (%)**
Any adverse event	176 (11.6)	72 (9.6)
Related[c]	46 (3.0)	16 (2.1)
Severe	3 (0.2)	1 (0.1)
Life-threatening	0	0
Any serious adverse event	1 (0.1)	1 (0.1)
Related[c]	0	0
Severe	1 (0.1)	1 (0.1)
Life-threatening	0	0
Any nonserious adverse event	176 (11.6)	71 (9.5)
Related[c]	46 (3.0)	16 (2.1)
Severe	3 (0.2)	0
Life-threatening	0	0
Any adverse event leading to withdrawal	0	0
Related[c]	0	0
Serious	0	0
Severe	0	0
Life-threatening	0	0
Death	0	0

Table 17. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 Through Cutoff Date (06SEP2021) – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)	
Adverse Event	BNT162b2 10 µg (N[a]=1518) n[b] (%)	Placebo (N[a]=750) n[b] (%)

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any adverse event," n = the number of participants reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (17:16) Source Data: adae Table Generation: 15SEP2021 (17:46)
(Cutoff Date: 06SEP2021, Snapshot Date: 13SEP2021) Output File:
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2.5.5.2.2.3.2. Analysis of Adverse Events – Phase 2/3

AE analyses for Phase 2/3 pediatric participants 5 to <12 years of age were reported from Dose 1 to 1 month after Dose 2 in Section 2.5.5.2.2.3.2.1 and from Dose 1 until the data cutoff date (06 September 2021) in Section 2.5.5.2.2.3.2.2.

2.5.5.2.2.3.2.1. Adverse Events from Dose 1 to 1 Month After Dose 2

Adverse Events by System Organ Class and Preferred Term

AEs reported from Dose 1 to 1 month after Dose 2 for Phase 2/3 participants 5 to <12 years of age who were randomized 2:1 to receive BNT162b2 10 µg or placebo are presented in Table 18. Overall, frequencies of any AEs reported after Dose 1 up to 1 month after Dose 2 were similar in the BNT162b2 and placebo groups (10.9% vs 9.2%). Many of the AEs were reflective of reactogenicity events that were reported as AEs (ie, headache, vomiting, and injection site pain). AE frequencies in these reactogenicity SOCs (BNT162b2 vs placebo) were:

- general disorders and administration site conditions: 1.6% vs 1.7%
- gastrointestinal disorders: 1.6% vs 1.7%
- nervous system disorders: 0.7% vs 0.5%
- musculoskeletal and connective tissue disorders: 0.5% vs 0.7%

Overall, many AEs reported up to 1 month after Dose 2 were attributable to vaccine reactogenicity events. This observation provides a reasonable explanation for the greater rates of some AEs observed in the BNT162b2 group compared with the placebo group. In this regard, the pattern of AEs reported in children 5 to <12 years of age was generally consistent with that observed in prior analyses of Phase 2/3 participants ≥12 years of age in Study C4591001. Of note, the frequencies of some of these events were not differentiated between the BNT162b2 and placebo group in children 5 to <12 years of age, which may be a function of the similarity of overall AE frequencies reported between the groups up to 1 month post-Dose 2. Further details are provided in the risk discussion (Section 2.5.6.2).

Aside from SOCs that reflect events consistent with reactogenicity, other categories of events are discussed below by SOC and PT. Many of the other commonly reported AEs are consistent with events that would be expected in a general population of healthy children in this age group and/or showed no imbalance between the vaccine and placebo groups.

- *Infections and infestations* were reported in 1.9% of participants in the BNT162b2 group and 2.0% of participants in the placebo group. The events reported in this SOC are typical for this age group, including ear infections, conjunctivitis, and terms consistent with common colds and infections. There was no imbalance in reported infections between the BNT162b2 and placebo groups.

- *Injury, poisoning and procedural complications* were reported in 1.7% of participants in the BNT162b2 group and 0.7% of participants in the placebo group. The events reported in this SOC are typical for this age group, such as fractures and sprains, sunburns, and insect bites. The overall numerical difference between BNT162b2 and placebo groups is primarily due to unrelated events of insect bites, sunburns, and a variety of concurrent events (ie, fall and contusion) reported in a limited number of participants in the BNT162b2 group, which is a larger group of participants due to the 2:1 randomization of BNT162b2: placebo.

- *Psychiatric disorders* were reported in 0.3% of participants in the BNT162b2 group and 0.4% of participants in the placebo group. The events reported in this SOC include several terms typical for this age group, such as attention deficit hyperactivity disorder, as well as several that may be part of the constellation of reactogenicity such as irritability and poor quality sleep. One participant in the BNT162b2 group had a Grade 3 event of tic that was considered by the investigator as related to study intervention (later determined by neurology consultation to be unrelated); this event is discussed further in AEs of clinical interest in Section 2.5.5.2.2.3.6. There was no imbalance in reported psychiatric disorders between the BNT162b2 and placebo groups.

- *Blood and lymphatic system disorders* were reported in 0.9% of participants in the BNT162b2 group and 0.1% of participants in the placebo group, which included lymphadenopathy and lymph node pain. Lymphadenopathy is discussed as an AE of clinical interest in Section 2.5.5.2.2.3.6. Note that this incidence of lymphadenopathy in children 5 to <12 years of age is slightly higher than that previously reported in Phase 2/3 participants ≥12 years of age after receiving the two-dose primary series of BNT162b2 30 µg in Study C4591001. Further details are provided in the risk discussion (Section 2.5.6.2).

- *Skin and subcutaneous disorders* were reported in 1.4% of participants in the BNT162b2 group and 0.8% of participants in the placebo group, and included rashes, urticaria, eczema, and pruritis that were overall reported more frequently in the BNT162b2 group than in the placebo group. Events in this SOC including rash and urticaria are discussed further with AEs of clinical interest and in Section 2.5.5.2.2.3.6.

- *Immune system disorders* were reported in 0.1% of participants in the BNT162b2 group and 0.1% of participants in the placebo group and included hypersensitivity (n=1 in the placebo group) and other non-drug allergies. Hypersensitivity is an AE of clinical interest and is discussed in Section 2.5.5.2.2.3.6. There was no imbalance in reported immune system disorders between the BNT162b2 and placebo groups.

- *Cardiac disorders* were reported in 1 participant in the BNT162b2 group. One non-serious Grade 1 event of angina pectoris was considered by the investigator as related to study intervention; the episode was characterized as mild, transient chest pain that lasted 1 minute and was reported 2 days after receiving Dose 2, then resolved with no sequalae. No additional investigations were warranted as determined by the investigator. This event is discussed further in AEs of clinical interest in Section 2.5.5.2.2.3.6.

Table 18. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 10 µg (N^a=1518)		Placebo (N^a=750)	
System Organ Class Preferred Term	n^b (%)	(95% CI^c)	n^b (%)	(95% CI^c)
Any adverse event	166 (10.9)	(9.4, 12.6)	69 (9.2)	(7.2, 11.5)
Blood and lymphatic system disorders	14 (0.9)	(0.5, 1.5)	1 (0.1)	(0.0, 0.7)
Lymphadenopathy	13 (0.9)	(0.5, 1.5)	1 (0.1)	(0.0, 0.7)
Lymph node pain	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Cardiac disorders	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Angina pectoris	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Congenital, familial and genetic disorders	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Phimosis	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Ear and labyrinth disorders	4 (0.3)	(0.1, 0.7)	2 (0.3)	(0.0, 1.0)
Ear pain	2 (0.1)	(0.0, 0.5)	2 (0.3)	(0.0, 1.0)
Cerumen impaction	1 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.7)
Otorrhoea	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Eye disorders	3 (0.2)	(0.0, 0.6)	2 (0.3)	(0.0, 1.0)
Conjunctivitis allergic	1 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.7)
Dry eye	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Hypermetropia	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Periorbital oedema	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Vision blurred	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Gastrointestinal disorders	25 (1.6)	(1.1, 2.4)	13 (1.7)	(0.9, 2.9)
Nausea	6 (0.4)	(0.1, 0.9)	2 (0.3)	(0.0, 1.0)
Vomiting	6 (0.4)	(0.1, 0.9)	2 (0.3)	(0.0, 1.0)
Abdominal pain	4 (0.3)	(0.1, 0.7)	2 (0.3)	(0.0, 1.0)

Table 18. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 10 µg (N[a]=1518)		Placebo (N[a]=750)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Diarrhoea	5 (0.3)	(0.1, 0.8)	1 (0.1)	(0.0, 0.7)
Abdominal pain upper	0	(0.0, 0.2)	2 (0.3)	(0.0, 1.0)
Toothache	0	(0.0, 0.2)	2 (0.3)	(0.0, 1.0)
Aphthous ulcer	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Flatulence	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Gastrooesophageal reflux disease	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Odynophagia	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Oral pain	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Pancreatitis	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Rectal haemorrhage	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
General disorders and administration site conditions	25 (1.6)	(1.1, 2.4)	13 (1.7)	(0.9, 2.9)
Injection site pain	11 (0.7)	(0.4, 1.3)	3 (0.4)	(0.1, 1.2)
Pyrexia	3 (0.2)	(0.0, 0.6)	6 (0.8)	(0.3, 1.7)
Fatigue	1 (0.1)	(0.0, 0.4)	3 (0.4)	(0.1, 1.2)
Injection site erythema	3 (0.2)	(0.0, 0.6)	0	(0.0, 0.5)
Axillary pain	2 (0.1)	(0.0, 0.5)	0	(0.0, 0.5)
Malaise	2 (0.1)	(0.0, 0.5)	0	(0.0, 0.5)
Non-cardiac chest pain	1 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.7)
Injection site haemorrhage	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Injection site induration	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Injection site rash	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Peripheral swelling	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Swelling	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Swelling face	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Thirst	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Immune system disorders	2 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.7)
Seasonal allergy	2 (0.1)	(0.0, 0.5)	0	(0.0, 0.5)
Allergy to animal	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Hypersensitivity	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Mite allergy	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Infections and infestations	29 (1.9)	(1.3, 2.7)	15 (2.0)	(1.1, 3.3)
Otitis externa	7 (0.5)	(0.2, 0.9)	6 (0.8)	(0.3, 1.7)
Nasopharyngitis	3 (0.2)	(0.0, 0.6)	1 (0.1)	(0.0, 0.7)
Hordeolum	3 (0.2)	(0.0, 0.6)	0	(0.0, 0.5)
Cellulitis	1 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.7)
Impetigo	1 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.7)
Upper respiratory tract infection	1 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.7)
Conjunctivitis	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)

Table 18. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 10 µg (N[a]=1518)		Placebo (N[a]=750)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Ear infection	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
External ear cellulitis	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Folliculitis	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Gastroenteritis viral	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Herpes zoster	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Molluscum contagiosum	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Onychomycosis	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Oral candidiasis	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Otitis media	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Paronychia	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Parotitis	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Pharyngitis	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Rhinitis	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Tonsillitis	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Tooth abscess	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Urinary tract infection	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Viral infection	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Vulvovaginal mycotic infection	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Injury, poisoning and procedural complications	26 (1.7)	(1.1, 2.5)	5 (0.7)	(0.2, 1.5)
Fall	5 (0.3)	(0.1, 0.8)	1 (0.1)	(0.0, 0.7)
Arthropod bite	5 (0.3)	(0.1, 0.8)	0	(0.0, 0.5)
Contusion	3 (0.2)	(0.0, 0.6)	0	(0.0, 0.5)
Skin laceration	3 (0.2)	(0.0, 0.6)	0	(0.0, 0.5)
Sunburn	2 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.7)
Ligament sprain	1 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.7)
Upper limb fracture	2 (0.1)	(0.0, 0.5)	0	(0.0, 0.5)
Accident	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Arthropod sting	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Back injury	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Burns first degree	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Concussion	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Foreign body	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Hand fracture	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Head injury	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Heavy exposure to ultraviolet light	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Joint dislocation	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Joint injury	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Limb fracture	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Limb injury	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)

Table 18. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 10 µg (N[a]=1518)		Placebo (N[a]=750)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Muscle strain	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Radius fracture	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Investigations	1 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.7)
Body temperature increased	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Serum ferritin decreased	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Metabolism and nutrition disorders	1 (0.1)	(0.0, 0.4)	2 (0.3)	(0.0, 1.0)
Decreased appetite	1 (0.1)	(0.0, 0.4)	2 (0.3)	(0.0, 1.0)
Musculoskeletal and connective tissue disorders	7 (0.5)	(0.2, 0.9)	5 (0.7)	(0.2, 1.5)
Pain in extremity	3 (0.2)	(0.0, 0.6)	2 (0.3)	(0.0, 1.0)
Musculoskeletal chest pain	1 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.7)
Arthralgia	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Muscle mass	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Myalgia	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Osteitis	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Synovitis	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Pyogenic granuloma	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Nervous system disorders	10 (0.7)	(0.3, 1.2)	4 (0.5)	(0.1, 1.4)
Headache	6 (0.4)	(0.1, 0.9)	2 (0.3)	(0.0, 1.0)
Disturbance in attention	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Dizziness	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Dyslexia	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Migraine	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Paraesthesia	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Somnolence	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Psychiatric disorders	4 (0.3)	(0.1, 0.7)	3 (0.4)	(0.1, 1.2)
Attention deficit hyperactivity disorder	1 (0.1)	(0.0, 0.4)	2 (0.3)	(0.0, 1.0)
Irritability	1 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.7)
Poor quality sleep	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Tic	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Renal and urinary disorders	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Dysuria	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Reproductive system and breast disorders	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Balanoposthitis	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Respiratory, thoracic and mediastinal disorders	22 (1.4)	(0.9, 2.2)	9 (1.2)	(0.6, 2.3)
Nasal congestion	5 (0.3)	(0.1, 0.8)	4 (0.5)	(0.1, 1.4)

Table 18. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 10 µg (N[a]=1518)		Placebo (N[a]=750)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Cough	5 (0.3)	(0.1, 0.8)	2 (0.3)	(0.0, 1.0)
Oropharyngeal pain	5 (0.3)	(0.1, 0.8)	1 (0.1)	(0.0, 0.7)
Epistaxis	3 (0.2)	(0.0, 0.6)	0	(0.0, 0.5)
Rhinorrhoea	2 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.7)
Asthma	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Sneezing	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Throat irritation	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Tonsillolith	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Skin and subcutaneous tissue disorders	22 (1.4)	(0.9, 2.2)	6 (0.8)	(0.3, 1.7)
Urticaria	3 (0.2)	(0.0, 0.6)	3 (0.4)	(0.1, 1.2)
Rash	5 (0.3)	(0.1, 0.8)	0	(0.0, 0.5)
Dermatitis contact	3 (0.2)	(0.0, 0.6)	0	(0.0, 0.5)
Erythema	2 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.7)
Rash papular	3 (0.2)	(0.0, 0.6)	0	(0.0, 0.5)
Eczema	1 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.7)
Cold sweat	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Dermatitis	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Dermatitis allergic	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Macule	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Mechanical urticaria	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Pruritus	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Rash erythematous	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Rash macular	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Rash pruritic	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Surgical and medical procedures	1 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.7)
Suture insertion	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Tooth extraction	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)

Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (17:16) Source Data: adae Table Generation: 15SEP2021 (12:20)
(Cutoff Date: 06SEP2021, Snapshot Date: 13SEP2021) Output File:
./nda2 ubped/C4591007 P23 EUA/adae s150 1md2 soc p2 12

Related Adverse Events

From Dose 1 to 1 month after Dose 2, AEs assessed as related by the investigator were reported at a slightly higher frequency in the BNT162b2 group (3.0%) than in the placebo group (2.1%). Most related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions, reported by 1.1% of participants in the BNT162b2 group compared with 0.9% of participants in the placebo group. Other notable related events reported from Dose 1 to 1 month after Dose 2 are summarized below.

- Non-serious, non-severe, related events of lymphadenopathy were reported in 0.7% of participants in the BNT162b2 group and none in the placebo group. All cases were considered mild. Refer to AEs of clinical interest in Section 2.5.5.2.2.3.6 for details.
- Non-serious related events of rash, urticaria, and other skin and subcutaneous tissue disorders were reported in 0.4% participants in the BNT162b2 group and 0.5% of participants in the placebo group. Refer to analysis of rashes as AEs of clinical interest in Section 2.5.5.2.2.3.6 for details.
- One non-serious, non-severe event of angina pectoris considered by the investigator as related to study intervention was reported by a participant in the BNT162b2 group. This event lasted 1 minute in duration, with onset at 2 days after Dose 2, and resolved with no sequalae or further investigation deemed warranted by the investigator. Refer to AEs of clinical interest in Section 2.5.5.2.2.3.6 for details.
- One related non-serious, Grade 3 event of tic was reported in a participant in the BNT162b2 group (later determined by neurology consultation to be unrelated). Refer to AEs of clinical interest in Section 2.5.5.2.2.3.6 for details.
- One non-serious, immediate (post-Dose 1) event of Grade 1 periorbital edema considered by the investigator as related to study intervention was reported in a participant in the placebo group. This same participant reported other non-serious, Grade 1 AEs of hypersensitivity, erythema, and urticaria considered by the investigator as related to study intervention; all of these events occurred on the same day the participant received the first dose of placebo, all were reported as resolved the same day, and the participant later received the second dose of placebo without any AEs reported post-Dose 2. Refer to analysis of hypersensitivity as an AE of clinical interest in Section 2.5.5.2.2.3.6 for details.

Immediate Adverse Events

After Dose 1, immediate AEs (reported within 30 minutes of the first vaccination) were low in frequency (≤0.4%) in the BNT162b2 and placebo groups. Immediate AEs reported after Dose 1 in the BNT162b2 versus placebo groups were predominantly injection site pain, reported in 3 participants (0.2%) in the BNT162b2 group and 2 participants (0.3%) in the placebo group. No other immediate AEs post-Dose 1 were reported in the BNT162b2 group. Immediate AEs post-Dose 1 reported in the placebo group (n=1 each) were fatigue, hypersensitivity, erythema, urticaria, and periorbital edema.

After Dose 2, immediate AEs (reported within 30 minutes of the second vaccination) were low in frequency (0.3%) in the BNT162b2 and placebo groups. Immediate AEs reported after Dose 2 in the BNT162b2 versus placebo groups were predominantly injection site pain, reported in 1 participant (0.1%) in the BNT162b2 group and 2 participants (0.3%) in the placebo group. Other immediate AEs reported post-Dose 2 in the BNT162b2 group (n=1 each) were injection site erythema, erythema, and nausea.

Refer to AEs of clinical interest in Section 2.5.5.2.2.3.6 for details on hypersensitivity and rashes.

No allergic AEs were reported after either dose of BNT162b2 within 30 minutes after vaccination.

Severe or Life-Threatening Events

From Dose 1 to 1 month after Dose 2, severe AEs were low in frequency (0.1%) in both the BNT162b2 and placebo groups. Severe events reported included Grade 3 events of abdominal pain and pancreatitis (noted as occurring 'post-injury') both reported in 1 participant in the placebo group that were reported as SAEs considered not related to study intervention (refer to Section 2.5.5.2.2.3.3).

A non-serious Grade 3 AE of tic considered by the investigator as related to study intervention (later determined by neurology consultation to be unrelated) was reported in 1 participant in the BNT162b2 group; refer to AEs of clinical interest in Section 2.5.5.2.2.3.6 for details. A Grade 3 rash (bilateral pleomorphic light eruption on arms) was reported by a participant in the BNT162b2 group, considered by the investigator as not related to study intervention and noted as possibly due to a reaction to sunscreen, and this same participant had an unrelated Grade 2 AE of leg (flank, hip, thigh) folliculitis after Dose 2 due to 'exposure in hot tub' at 24 days post-Dose 2 that resolved after 7 days of onset. Refer to AEs of clinical interest in Section 2.5.5.2.2.3.6 for details on rashes.

No life-threatening (ie, Grade 4) AEs were reported from Dose 1 to 1 month after Dose 2.

Subgroup Analyses

Subgroups of Phase 2/3 pediatric participants 5 to <12 years of age had similar AE profiles from Dose 1 to 1 month after Dose 2 with regard to most frequently reported events by SOC and PT across the BNT162b2 and placebo groups when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status. Subgroups of race (Black or African American), ethnicity (Hispanic/Latino) and baseline SARS-CoV-2 status (positive) included a limited number of participants, and their results should be interpreted with caution. There were no meaningful differences in the AEs profiles across these subgroups. These subgroups are summarized below.

Sex

In the BNT162b2 group, overall incidences of participants reporting at least 1 AE were 11.1% for male participants and 10.7% for female participants. Consistent with the overall safety population, most commonly reported AEs were in the reactogenicity SOCs (male vs female):

- general disorders and administration site conditions: 1.8% vs 1.5%
- gastrointestinal disorders: 1.9% vs 1.4%
- nervous system disorders: 0.4% vs 1.0%
- musculoskeletal and connective tissue disorders: 0.6% vs 0.3%

Notably, in the BNT162b2 group, lymphadenopathy and/or lymph node pain were reported by more male participants (10 [1.3%]) than in female participants (4 [0.6%]). Skin and subcutaneous tissue disorders were reported at a higher frequency in male participants (18 [2.3%]) than in female participants (4 [0.6%]), mostly due to more events of rash reported in males (refer to Section 2.5.5.2.2.3.6 for additional detail on rashes analyzed as of AEs of clinical interest).

The few observed numerical differences in AE frequencies were not associated with clinically meaningful differences between the sex subgroups.

Race

In the BNT162b2 group, overall incidences of participants reporting at least 1 AE were similar (range: 9.0% to 12.0%) across race subgroups. The frequencies of the most commonly reported AEs were similar across race subgroups. Frequencies of the most commonly reported AEs in the reactogenicity SOCs in the BNT162b2 group by race subgroups for White versus Black or African American versus 'All Others' (ie, American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories) were:

- general disorders and administration site conditions: 1.7% vs 1.1% vs 1.8%
- gastrointestinal disorders: 1.5% vs 2.2% vs 2.2%
- nervous system disorders: 0.7% vs 0% vs 0.9%
- musculoskeletal and connective tissue disorders: 0.4% vs 0% vs 0.9%

Lymphadenopathy and/or lymph node pain were reported by more White or Black or African American participants (1.0% and 1.1%) than in the 'All Other' race subgroup (0.4%). Skin and subcutaneous tissue disorders were reported in 1.3%, 0%, and 2.7% of White, Black or African American, and All Other race subgroups, respectively.

The few observed numerical differences in AE frequencies were not associated with clinically meaningful differences between the race subgroups. Due to limited number of participants in the Black or African American subgroup, these results should be interpreted with caution.

Ethnicity

In the BNT162b2 group, overall incidences of participants reporting at least 1 AE were 11.3% for Hispanic/Latino participants and 10.9% for non-Hispanic/non-Latino participants. The frequencies of the most commonly reported AEs were similar across ethnic subgroups. Frequencies of the most commonly reported AEs in the reactogenicity SOCs in the BNT162b2 group by ethnic subgroups were (Hispanic/Latino vs Non-Hispanic/Non-Latino):

- general disorders and administration site conditions: 1.3% vs 1.8%
- gastrointestinal disorders: 2.5% vs 1.4%
- nervous system disorders: 1.3% vs 0.5%
- musculoskeletal and connective tissue disorders: 0.6% vs 0.4%

The frequency of lymphadenopathy and/or lymph node pain was similar (0.9% each) in the Hispanic/Latino and Non-Hispanic/Non-Latino subgroups. Skin and subcutaneous tissue disorders were similar between the Hispanic/Latino and non-Hispanic/non-Latino subgroups (1.9% vs 1.3%).

While the frequency of AEs was generally numerically higher in the Hispanic/Latino subgroup, due to limited number of participants, these results should be interpreted with caution.

SARS-CoV-2 Baseline Status

There were 133 BNT162b2 and 65 placebo participants with baseline positive SARS-CoV-2 status, and 1385 BNT162b2 and 685 placebo participants with baseline negative SARS-CoV-2 status. In the BNT162b2 group, overall incidences of participants reporting at least 1 AE were 8.3% for baseline positive participants and 11.2% for baseline negative participants. The most commonly reported AEs in the reactogenicity SOCs in the BNT162b2 group by baseline SARS-CoV-2 status (positive vs negative) were:

- general disorders and administration site conditions: 0.8% vs 1.7%
- gastrointestinal disorders: 3.0% vs 1.5%
- nervous system disorders: 0.8% vs 0.6%
- musculoskeletal and connective tissue disorders: 0.8% vs 0.4%

The frequency of lymphadenopathy and/or lymph node pain was similar (0.8% vs 0.9%) in the baseline positive and negative subgroups. Skin and subcutaneous tissue disorders were reported at a lower incidence in the SARS-CoV-2 baseline positive subgroup compared to the baseline negative subgroup (0.8% vs 1.5%).

While there were numerical differences in the frequencies of AEs between the SARS-CoV-2 baseline subgroups, due to limited number of participants in the baseline positive subgroup, these results should be interpreted with caution.

2.5.5.2.2.3.2.2. Adverse Events from Dose 1 to Data Cutoff Date

AEs reported in Phase 2/3 pediatric participants 5 to <12 years of age through the data cutoff date (06 September 2021), which represented at least 2 months of follow-up after Dose 2, were reported at similar frequencies in the BNT162b2 group (11.6%) and placebo group (9.6%). In addition to the AEs reported up to 1 month after Dose 2 (Table 18), the most frequently reported AEs in the BNT162b2 group through the data cutoff date were reactogenicity events. Overall, few additional AEs were reported from after 1-month post-Dose 2 to the cutoff date, and no additional AEs of clinical interest were identified.

2.5.5.2.2.3.3. Serious Adverse Events – Phase 2/3

SAEs were reported from Dose 1 through the data cutoff date (06 September 2021), which represents at least 2 months of follow-up after Dose 2 (Table 19). Overall, 1 participant (0.1%) in each group reported any SAE after receiving BNT162b2 or placebo through the data cutoff date. These SAEs were all assessed by the investigator as not related to study intervention.

As of the data cutoff date, a total of 3 SAEs were reported by 2 participants (n=1 each in the BNT162b2 and placebo groups) as of the data cutoff date, as summarized below.

- The participant in the BNT162b2 group was a [redacted] years of age who had a non-serious Grade 3 AE of fall reported 45 days after receiving Dose 2; this was concurrent with a reported Grade 3 SAE of upper limb fracture (elbow) identified the same day (45 days post-Dose 2) as being due to a ‘[redacted]. The fracture was reported as recovering/resolving at the time of the data cutoff. The SAE was considered by the investigator as not related to study intervention.
- The participant in the placebo group was a [redacted] years of age who reported an SAE of Grade 3 pancreatitis (noted as occurring ‘post-injury’) with onset at 4 days post-Dose 2 and reported as resolved within 7 days of onset with concomitant drug treatment. This same participant reported a second Grade 3 SAE of abdominal pain with onset at 11 days post-Dose 2 and reported as resolved within 6 days after onset. Both SAEs were considered by the investigator as not related to study intervention. This participant had no reported medical history and received no prohibited concomitant treatments or nonstudy vaccines.

Table 19. Number (%) of Participants Reporting at Least 1 Serious Adverse Event From Dose 1 Through Cutoff Date (06SEP2021), by System Organ Class and Preferred Term – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 10 µg (N^a=1518)		Placebo (N^a=750)	
System Organ Class Preferred Term	n^b (%)	(95% CI^c)	n^b (%)	(95% CI^c)
Any adverse event	1 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.7)
Gastrointestinal disorders	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Abdominal pain	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Pancreatitis	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.7)
Injury, poisoning and procedural complications	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)
Upper limb fracture	1 (0.1)	(0.0, 0.4)	0	(0.0, 0.5)

Table 19. Number (%) of Participants Reporting at Least 1 Serious Adverse Event From Dose 1 Through Cutoff Date (06SEP2021), by System Organ Class and Preferred Term – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 10 µg (N^a=1518)		Placebo (N^a=750)	
System Organ Class Preferred Term	n^b (%)	(95% CI[c])	n^b (%)	(95% CI[c])

Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (17:16) Source Data: adae Table Generation: 15SEP2021 (12:21)
(Cutoff Date: 06SEP2021, Snapshot Date: 13SEP2021) Output File:
./nda2_ubped/C4591007_P23_EUA/adae_s150_1md2_sae_p2_12

2.5.5.2.2.3.4. Deaths – Phase 2/3

No deaths were reported in the Phase 2/3 pediatric population of children 5 to <12 years of age up to the data cutoff date (06 September 2021).

2.5.5.2.2.3.5. Adverse Events Leading to Withdrawal – Phase 2/3

No AEs leading to withdrawal were reported in the Phase 2/3 pediatric population of children 5 to <12 years of age up to the data cutoff date (06 September 2021).

2.5.5.2.2.3.6. Adverse Events of Clinical Interest – Phase 2/3

Adverse events of specific clinical interest, such as those in the CDC list of AESIs for COVID-19, were reviewed and are summarized below. Narratives were prepared for a defined set of events as described in Section 2.5.5.1.1. Information on events of clinical interest included terms requested by the FDA included: anaphylaxis, appendicitis, Bell's palsy, and lymphadenopathy. The protocol defined AESI of myocarditis/pericarditis was also considered in the safety review. These cases are summarized below for reported events up to the data cutoff date (06 September 2021), which represents at least 2 months of follow-up after Dose 2.

AEs of Clinical Interest Requested by FDA

Among the FDA-requested AEs of clinical interest, no cases were reported in the 5 to <12 years of age group up to the data cutoff date, representing at least 2 months of follow-up after Dose 2, of anaphylaxis, myocarditis/pericarditis, Bell's palsy (or facial paralysis/paresis), or appendicitis. Other events of potential clinical interest that were reported in the study safety database are summarized below.

Anaphylaxis/Hypersensitivity

No cases of anaphylaxis or anaphylactic/anaphylactoid reaction were reported in the study.

No cases of hypersensitivity were reported in the BNT162b2 group. One participant in the placebo group reported hypersensitivity and several additional AEs considered by the investigator as related to study intervention following the first dose of placebo, as summarized below.

- 1 [redacted] years of age in the placebo group had concurrent AEs of Grade 1 hypersensitivity, erythema, urticaria ([redacted]), and periorbital edema (which was reported as an immediate AE, occurring within 30 minutes after the first dose) all occurring on the day of receiving Dose 1 of placebo, all considered by the investigator as related to study intervention, and all reported as resolved on the same day as onset. This participant received the second dose of placebo without any AEs reported post-Dose 2. This participant had a reported medical history including past [redacted] reported no other AEs or any severe reactogenicity events, and received no prohibited concomitant treatments or nonstudy vaccines.

A further safety review was conducted using standardized MedDRA queries (SMQs) of angioedema/hypersensitivity reported from Dose 1 to 1 month after Dose 2. Among approximately 2250 participants 5 to <12 years of age randomized 2:1 to receive BNT162b2 or placebo, 18 participants (1.2%) in the BNT162b2 group and 6 participants (0.8%) in the placebo group had events in angioedema/hypersensitivity SMQs.

Events in the SMQ of angioedema reported in the BNT162b2 group included face swelling (caused by an insect bite and considered by the investigator as not related to study intervention) (n=1) and urticaria (n=3). Urticaria was also reported in the placebo group in the same number of participants (n=3), therefore there was no imbalance between the groups.

Events in the SMQ of hypersensitivity more commonly reported in the BNT162b2 group than the placebo group were dermatitis (including contact and allergic dermatitis, n=5 in the BNT162b2 group vs none in the placebo group) of which all cases were deemed as not related to vaccine; and rash (including pruritic, macular, injection site rash, n=8 in the BNT162b2 group vs n=1 in the placebo group). Of the rashes in the BNT162b2 group, 4 were considered by the investigator as related to study intervention: all of these were Grade 1, typically had an onset 7 days or more post-vaccination; only 1 injection site rash was reported with earlier onset at 3 days post-Dose 2. All but 1 event (rash on torso with onset at 11 days post-Dose 2) were reported as resolved. These related rashes were observed on the arm, torso, face and/or body with no clear pattern, and two participants had other skin reactions in the same anatomical location a short time before or after the reported SMQ event (ie, prior erythema reaction to Tegaderm patch on arm, or subsequent rash on face due to bee sting).

Allergic conjunctivitis and eczema were also reported, at the same frequencies in BNT162b2 and placebo groups (n=1 each).

All angioedema/hypersensitivity SMQ events were mild or moderate, with the exception of 1 participant in the BNT162b2 group who had a Grade 3 rash (bilateral pleomorphic light eruption on arms) with onset at 3 days post-Dose 1 and reported as resolved 6 days later, not related to study intervention, and noted as possibly due to a reaction to sunscreen.

Rash is considered an adverse reaction to vaccine and is noted as such in the product labeling. Overall, the pattern of events in the hypersensitivity SMQ within the skin and subcutaneous tissue disorders SOC (including rashes) reported in children 5 to <12 years of age in Study C4591007 was consistent with that observed in prior analyses of Phase 2/3 participants ≥12 years of age in Study C4591001. Further details are provided in the risk discussion (Section 2.5.6.2).

Lymphadenopathy

Lymphadenopathy is considered an adverse reaction to vaccine and is noted as such in the product labeling. Among approximately 2250 children 5 to <12 years of age randomized 2:1 to receive BNT162b2 or placebo, as of the data cutoff date (06 September 2021), 13 participants (0.9%) in the BNT162b2 group and 1 participant (0.1%) in the placebo group had events of lymphadenopathy.

In the BNT162b2 group, the mean time to onset after Dose 1 was 6.2 days (median 3 days), and after Dose 2 was 2.6 days (median 2 days). The mean duration of the events was 4.7 days (median 3.5 days, range 1 to 14 days). The single event in the placebo group had an onset at 22 days post-Dose 1 with a duration of 2 days. All reported cases of lymphadenopathy in either group were mild.

Overall, the pattern of lymphadenopathy cases reported in children 5 to <12 years of age was generally similar to that observed in prior analyses of Phase 2/3 participants ≥12 years of age in Study C4591001. Further details are provided in the risk discussion (Section 2.5.6.2).

Other AEs of Clinical Interest

In addition to the FDA-requested AEs of clinical interest, notable pertinent negatives (ie, no cases reported in this population as of the data cutoff for this submission) with regard to the CDC list of AESIs included (but were not limited to): thrombocytopenic events, thromboembolic or intravascular coagulation events, autoimmune or demyelination events, meningitis, encephalitis, neuritis, Kawasaki disease, MIS-C, or acute respiratory distress syndrome.

Additional AEs of clinical interest, regardless of inclusion on the CDC AESI list, were evaluated based on sponsor safety data review. These AEs were identified from the C4591007 study database as of the data cutoff date (06 September 2021) and are summarized below.

Arthralgia

In the BNT162b2 group, an event of arthralgia was reported in 1 participant:

- 1 [redacted] years of age in the BNT162b2 group had an AE of Grade 1 arthralgia (right elbow joint pain) with an onset the same day as Dose 2 (administered in the left deltoid muscle), that was reported as resolved the next day. The AE was considered by the investigator as related to study intervention. This participant had a medical history including [redacted] ([redacted]), reported one other unrelated AE of vomiting (attributed to 'car sickness'), and reported no severe reactogenicity events. He received no prohibited concomitant treatments or nonstudy vaccines. A narrative is provided for this Phase 2/3 participant in Module 5.3.5.1.

Paresthesia

In the BNT162b2 group, an event of paresthesia was reported in 1 participant:

- 1 [redacted] years of age in the BNT162b2 group had an AE of Grade 2 paresthesia (bilateral lower extremity tingling) with onset at 1 day post-Dose 2 and reported as recovered/resolved 3 days after onset. The AE was considered by the investigator as related to study intervention. This participant had a medical history including [redacted] reported no other AEs or any severe reactogenicity events, and received no prohibited concomitant treatments or nonstudy vaccines.

Tic

In the BNT162b2 group, a psychiatric disorder event of tic was reported in 1 participant:

- 1 [redacted] years of age in the BNT162b2 group had an AE of Grade 3 tic with onset at 7 days post-Dose 2 and reported as recovering/resolving at the time of the data cutoff. The AE was considered by the investigator as related to study intervention. This participant reported no medical history, no other AEs or any severe reactogenicity events, and received no prohibited concomitant treatments or nonstudy vaccines. Within approximately 1 week after onset of the tic, the participant was evaluated by [redacted] primary care physician; approximately 1 week later [redacted] had an MRI which showed no pathology. A pediatric neurologist was consulted, which did not result in a specific diagnosis and included a recommendation of lifestyle change, and the neurologist assessed the event as not related to the vaccine. As of the cutoff date, the child was reported as continuing in [redacted] regular daily routine.

Chest Pain

In the BNT162b2 group, an event of angina pectoris was reported in 1 participant, and in the placebo group, an event of non-cardiac chest pain was reported in 1 participant:

- 1 [redacted] years of age in the BNT162b2 group had an AE of Grade 1 angina pectoris with onset at 2 days post-Dose 2; the episode was characterized as mild, transient chest pain lasting 1 minute in duration, and reported as resolved with no sequalae. Further investigation into the chest pain was not clinically indicated per the investigator. The AE was considered by the investigator as related to study intervention. This participant had a medical history of [redacted] This participant reported no other AEs or any severe reactogenicity events and received no prohibited concomitant treatments or nonstudy vaccines. Other mild to moderate reactogenicity events reported by this participant during the time period when the AE was reported after Dose 2 were pain at injection site (Day 2 post-Dose 2) and fatigue and headache (Days 2-4 post-Dose 2).

- 1 [redacted] years of age in the placebo group had an AE of Grade 1 non-cardiac chest pain with onset at 6 days post-Dose 2 and resolved 3 days after onset. The event was characterized as transient in nature, with no cardiac involvement. Further investigation into the non-cardiac chest pain was not clinically indicated per the investigator. [redacted] previously had reported an AE of Grade 1 pain in extremity ('[redacted]') with onset at 2 days post-Dose 2 that resolved 8 days after onset. Both events were considered by the investigator as related to study intervention. This participant had a medical history of [redacted] This participant reported no other AEs or any severe reactogenicity events and received no prohibited concomitant treatments or nonstudy vaccines. Other mild or moderate reactogenicity events reported by this participant during the time period when the AE of non-cardiac chest pain was reported after Dose 2 included pain at injection site (Days 2-7 post-Dose 2), headache (Days 2-3 post-Dose 2), fatigue (Days 2-4 and Days 6-7 post-Dose 2), and new or worsened muscle pain (Days 4-5 post-Dose 2).

Conclusions from Review of Adverse Events of Clinical Interest

Following review of all reported AEs and SAEs for participants 5 to <12 years of age in Study C4591007, as of the data cutoff date (06 September 2021), there were very few AEs of clinical interest corresponding to those requested by the FDA or per the CDC list of AESIs. Lymphadenopathy has been identified as related to BNT162b2 in individuals ≥12 years of age and it is clearly observed in the pediatric 5 to <12 years of age group. No cases of anaphylaxis or hypersensitivity to vaccine were reported, no serious or severe related rashes were reported after BNT162b2 vaccination, and no cases of myocarditis/pericarditis were reported over the course of at least 2 months of follow-up after Dose 2 in children 5 to <12 years of age. AEs of clinical interest continue to be monitored in all participants in ongoing Study C4591007.

2.5.5.2.3. Other Safety Assessments

2.5.5.2.3.1. Severe COVID-19 and MIS-C Illness

As of the data cutoff date (06 September 2021), no severe COVID-19 or MIS-C were reported in pediatric participants 5 to <12 years of age in Study C4591007 in the safety database.

Prior analyses of efficacy for all C4591001 Phase 2/3 participants ≥12 years of age, previously submitted to support the current EUA, showed confinement of severe cases predominantly to the placebo group. Together, these data continue to suggest no evidence for vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD).

2.5.5.2.3.2. Pregnancies

No pregnancies were reported in Study C4591007 as of the data cutoff date (06 September 2021).

2.5.5.2.3.3. Adverse Drug Reactions

ADRs, defined as AEs for which there is reason to conclude that the vaccine caused the event, have been identified from clinical study safety data and are specified in the current product labeling. No new ADRs were identified from safety data associated with administration of BNT162b2 10 µg to children 5 to <12 years of age in Study C4591007.

2.5.5.3. Safety in Special Groups and Situations

Details of safety in special groups and situations are summarized below.

2.5.5.3.1. Geriatric Use

Clinical studies of BNT162b2 (30 µg) include participants ≥65 years of age whose data contribute to overall assessment of safety and efficacy. The clinical data have demonstrated a predominantly mild reactogenicity profile in older adults, overall and compared with younger adults. This is coupled with evidence of robust immune response following the two-dose vaccination regimen, and overwhelming efficacy comparable to younger adults (>90%).

2.5.5.3.2. Pediatric Use

Further study of pediatric use of the vaccine and/or immunobridging study will be undertaken to characterize the vaccine response in children <5 years of age.

2.5.5.3.3. Use During Pregnancy and Lactation

Individuals who were pregnant or breastfeeding were not eligible to participate in Study C4591007 or Study C4591001.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In a DART study, no vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for vaccination with BNT162b2 and any potential adverse effects on the breastfed child from BNT162b2 or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

2.5.5.3.4. Use in Immunocompromised Individuals

Individuals who are immunocompromised or taking immunosuppressive therapy at the time of vaccine administration may have diminished response to immunization. Study C4591001 included enrollment of individuals with medical history of immunocompromised condition or immunosuppressive therapy. There are limited data on the safety and effectiveness of the vaccine in this patient population at the time of this submission.

A third dose of BNT162b2 30 µg may be given to individuals ≥12 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

2.5.5.3.5. Other Safety Considerations

Overdose

In Study C4591007, any dose of study intervention exceeding one dose of study intervention within a 24-hour time period was considered an overdose. No overdoses of BNT162b2 were reported in participants 5 to <12 years of age in Study C4591007.

Drug Abuse or Withdrawal and Rebound

Not applicable.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

BNT162b2 has no or negligible influence on the ability to drive and use machines.

2.5.5.4. Post-Authorization Safety Summary

Post-authorization safety data are continually monitored by Pfizer and BioNTech for pharmacovigilance and risk management purposes, including weekly reviews of the safety database. Pfizer's safety database contains AEs reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of SAEs reported from clinical studies regardless of causality assessment.

Post-authorization safety data are communicated in the following contexts:

- The first Periodic Safety Update Report covering the period of 19 December 2020 through 18 June 2021 that evaluated safety data and signal detection, and concluded: "Risks have been evaluated in the context of the benefits of the vaccine. Based on the available safety and efficacy/effectiveness data from the reporting interval for BNT162b2, the benefit-risk profile of BNT162b2 remains favourable."

- Post-authorization Summary Monthly Safety Reports (SMSRs) that include safety events reported from countries in which BNT162b2 is authorized or conditionally approved and are submitted monthly to regulatory authorities. These monthly reports provide information on safety signals and risks determined from signal detection activity.

Myocarditis/pericarditis is considered an important identified risk of the vaccine in the US Pharmacovigilance Plan and the EU Risk Management Plan; however, the very low incidence and favorable prognosis of these events compared to the known risks of COVID-19, including COVID-19 associated myocarditis, support a positive benefit/risk profile for this vaccine in the 5 to <12 years of age group.

Overall, review of the post-authorization safety data has continued to confirm the overall favorable risk-benefit assessment of the vaccine for individuals ≥12 years of age.

2.5.5.5. Safety Conclusions

Phase 1 dose-finding safety data (in conjunction with Phase 1 immunogenicity data) led to the selection of BNT162b2 at the 10-µg dose level for children 5 to <12 years of age.

Phase 2/3 data from approximately 2250 children 5 to <12 years of age with a follow-up time of at least 2 months after Dose 2 showed BNT162b2 at 10 µg was safe and well-tolerated.

Reactogenicity in children 5 to <12 years of age was mostly mild to moderate and short-lived, with median onset of 1 to 4 days after dosing (most within a median of 2 days post-dose), and resolution within 1 to 2 days after onset. Local reactions presented predominantly as injection site pain with no effect of dose number, which was similar to what was previously reported in Study C4591001 participants ≥12 years of age; however mild to moderate redness and swelling occurred at higher frequencies in children than previously reported in C4591001. Systemic events most commonly included fatigue, headache, and muscle pain, and generally increased in frequency and/or severity with increasing dose number; these were typically milder and less frequent than previously reported in Study C4591001.

The observed AE profile in this study did not suggest any new safety concerns for BNT162b2 vaccination in children 5 to <12 years of age. Most reported AEs occurred from Dose 1 to 1 month after Dose 2 and reflected reactogenicity events occurring post-vaccination with BNT162b2, or other unrelated infections or injuries that are expected to be observed in a pediatric general population with similar frequencies in the BNT162b2 and placebo groups.

A total of 3 unrelated SAEs were reported in 2 participants (1 participant in the BNT162b2 group had an unrelated SAE of limb fracture, and 1 participant in the placebo group had 2 unrelated SAEs of pancreatitis and abdominal pain noted as occurring 'post-injury'), and no deaths or withdrawals due to AEs were reported as of the data cutoff date (06 September 2021), which represents at least 2 months of follow-up after Dose 2.

As of the data cutoff date, there were very few AEs of clinical interest reported in children 5 to <12 years of age, and no cases of myocarditis/pericarditis were reported. Lymphadenopathy has been identified as related to BNT162b2 in study participants ≥12 years of age and is also observed in children 5 to <12 years of age, with all events reported as mild. Rashes were more frequent in the BNT162b2 group than the placebo group, but very few (n=4) were considered as related to vaccination and these were characterized as mild and self-limited.

Overall, the safety and tolerability profile of BNT162b2 10 µg when administered as a two-dose primary series 3 weeks apart to approximately 1500 children 5 to <12 years of age, who had at least 2 months of follow-up since receiving their second dose, reflects age-appropriate events that are consistent with a pediatric general population and the known reactogenicity profile of BNT162b2. Subgroup analyses of safety endpoints suggested no meaningful differences in safety profile based on participant demographics or baseline SARS-CoV-2 status.

Additionally, review of the post-authorization safety data has continued to confirm the overall favorable risk-benefit assessment of the vaccine.

2.5.6. Benefits and Risks Conclusions

2.5.6.1. Benefits

COVID-19 is a serious and potentially fatal or life-threatening disease, and can lead to hospitalization and serious illness in children including MIS-C. Based on the available clinical data, it is expected that the 10-µg formulation of BNT162b2 elicits an immune response that will confer protection against COVID-19.

Immunogenicity and Immunobridging

Administration of BNT162b2 at 10 µg elicited robust neutralizing GMTs in children 5 to <12 years of age who had completed the two-dose primary series who were without evidence of SARS-CoV-2 infection up to 1 month after Dose 2. Success criteria for immunobridging were based on GMR and seroresponse and both met prespecified margins of difference at 1 month after Dose 2 compared with the response at 1 month after Dose 2 in young adults 16 to 25 years of age.

A robust BNT162b2-induced immune response has been observed after the two-dose primary series of BNT162b2 30 µg in Study C4591001 across age groups of 12 to 15, 16 to 55, and ≥56 years of age. For adolescents 12 to 15 years of age, successful immunobridging criteria for GMR and seroresponse were met in an analysis comparing immune responses with young adults 16 to 25 years of age at 1 month after Dose 2, with adolescents showing greater immune responses than young adults. The present data from participants 5 to <12 years of age in Study C4591007 demonstrate that children who received a lower dose of BNT162b2 10 µg had comparable immune responses to older participants who received a higher dose of BNT162b2 30 µg.

Planned Efficacy Analyses

Efficacy analyses are planned to be conducted when at least 22 confirmed COVID-19 cases accrue among participants 5 to <12 years of age without serological or virological evidence of past SARS-CoV-2 infection prior to 7 days after receipt of Dose 2, and will be reported at that time. At the time of submission data cutoff date, 13 confirmed cases of COVID-19 meeting evaluability criteria had accrued in this age group. No severe COVID-19 cases or MIS-C were reported in the safety database for the 5 to <12 years of age group as of the data cutoff date (06 September 2021), representing at least 2 months of follow-up after Dose 2.

High VE was observed in the pivotal efficacy Study C4591001 of >95% across age groups for individuals ≥12 years of age. The present available data from primary immunogenicity analyses in Study C4591007 show successful immunobridging of children 5 to <12 years of age who received BNT162b2 10 µg to young adults 16 to 25 years of age who received BNT162b2 30 µg in Study C4591001. Supportive efficacy analyses from Study C4591007 will be submitted when available.

2.5.6.2. Risks

This submission includes an evaluation of safety data for Study C4591007 participants 5 to <12 years of age who received the two-dose primary series of vaccine: 48 participants in Phase 1 were assigned to receive BNT162b2 at dose levels of 10, 20, or 30 µg (N=16 per dose level), and approximately 2250 participants in Phase 2/3 were randomized 2:1 to receive BNT162b2 10 µg or placebo. Phase 1 participants had approximately 3 months of follow-up time after Dose 2, and Phase 2/3 participants had at least 2 months of follow-up time after Dose 2.

In comparison, available safety data from participants ≥12 years of age in Study C4591001 (who received two doses of BNT162b2 30 µg) have been consistent across age groups and over time, which includes up to 2 months of follow-up after Dose 2 for adolescents 12 to 15 years of age and up to 6 months of follow-up after Dose 2 for participants ≥16 years of age. The safety profile for children 5 to <12 years of age in Study C4591007 who received two doses of BNT162b2 10 µg and have at least 2 months of follow-up is overall very similar, with no new or unexpected safety findings, in line with the established safety profile for BNT162b2.

Reactogenicity Profile

The reactogenicity profile after BNT162b2 10 µg administration in children 5 to <12 years of age was typically mild to moderate, with the majority of events arising within the first 1 to 2 days after dosing, with reactions or events that were short-lived. The most common prompted local reaction after any dose administration was injection site pain, which was similar after either dose. The most common prompted systemic events included fatigue, headache, muscle pain, and chills, which were slightly higher in frequency after Dose 2 than after Dose 1. The frequency of any severe systemic event after any dose was low. Subgroup analyses of reactogenicity suggested no meaningful differences based on participant demographics or baseline SARS-CoV-2 status.

Reactogenicity patterns in children were generally similar to that previously observed in individuals ≥12 years of age in Study C4591001, with some differences. Children 5 to <12 years of age tended to have less severe systemic events (including fever and chills) after vaccine doses of 10 µg compared to those previously reported in adolescents 12 to 15 years of age and young adults 16 to 55 years of age from Study C4591001 after vaccine doses of 30 µg. Overall, reactogenicity in children tended to appear most similar to the milder and less frequent profile previously observed in older adults >55 years of age. Local reactions of redness and swelling were reported at higher frequencies in children compared to adolescents and adults, noting that severe reactions were rarely reported. Conversely, systemic events of fatigue and headache were reported at lower frequencies in children compared to adolescents and adults, and joint pain more common to older participants was infrequent in children.

Adverse Event Profile

The AE profile after vaccination of children 5 to <12 years of age mostly reflects reactogenicity, with low incidences of related or severe events. Most reported AEs occurred from Dose 1 to 1 month after Dose 2 and were predominantly reactogenicity events occurring after BNT162b2 vaccination, or unrelated infections or injuries typically observed in a pediatric general population with similar frequencies in the BNT162b2 and placebo groups. Few serious AEs (none related to vaccine) and no AEs leading to withdrawal were reported. Review of AEs, SAEs, and AEs of clinical interest suggest no short-term safety concerns after administration of BNT162b2 10 µg. Subgroup analyses of AEs suggested no meaningful differences based on participant demographics or baseline SARS-CoV-2 status.

There were very few AEs of clinical interest corresponding to those requested by the FDA or per the CDC list of AESIs, and no cases of myocarditis/pericarditis were reported up through at least 2 months of follow-up post-Dose 2. No events of anaphylaxis or hypersensitivity were reported after BNT162b2 vaccination. Rashes considered by the investigator as related to vaccine were reported in 4 participants in the BNT162b2 group, all of which were mild, typically had an onset of 7 days post-vaccination or later and most reported as resolved. Several of these participants had other skin reactions attributable to unrelated causes in the same anatomical location a short time before or after the related rash.

The pattern of rashes reported in children 5 to <12 years of age was generally similar to that observed in prior analyses of Phase 2/3 participants ≥12 years of age in Study C4591001, with rashes usually more common in the vaccine group than placebo. Rashes were reported more frequently in children than in adolescents or adults. In Study C4591007, 1.4% of children 5 to <12 years of age reported AEs in the skin and subcutaneous tissue disorders SOC up to 1 month after Dose 2, and 0.8% of children reported events in the skin and subcutaneous tissue disorders SOC in the hypersensitivity SMQ analysis. In comparison, in Study C4591001, AEs in the skin and subcutaneous tissue disorders SOC were reported by 0.5% of adolescents 12 to 15 years of age and 0.9% of young adults 16 to 25 years of age. The CDC notes that rashes may be common from a few days to >1 week after COVID-19 vaccination, most commonly occurring after the first dose, can be treated with over-the-counter-medications, and should not interfere with receiving the second dose.[26]

Similarly, the overall AE and adverse reaction profile among approximately 22,000 participants ≥16 years of age and 1100 adolescents 12 to 15 years of age enrolled and vaccinated with BNT162b2 in double-blinded placebo follow-up, as of the most recent safety cutoff date (13 March 2021), was mostly reflective of reactogenicity events with low incidences of severe and/or related events. The incidence of SAEs was low and few participants withdrew from the study due to AEs. Few deaths occurred overall in participants ≥16 years of age, and no deaths were reported in adolescents. Review of AEs of clinical interest have suggested no clear patterns or safety concerns across these studies.

The incidence of lymphadenopathy in children 5 to <12 years of age (0.9%) was similar, albeit slightly higher, than that previously observed in Phase 2/3 AE analyses for adolescents 12 to 15 years of age (0.8%) and participants ≥16 years of age (0.4%). These analyses to date suggest a potential association of lower age with higher incidence of lymphadenopathy, noting that the numerical differences remain incremental and small. Lymphadenopathy has been identified as an adverse reaction causally associated with the vaccine and has been observed during the two-dose primary series across age groups in these studies. These events are typically mild and self-limited.

Overall, the safety and tolerability profile of BNT162b2 10 µg when administered as a two-dose primary series 3 weeks apart to approximately 1500 children 5 to <12 years of age, who had at least 2 months of follow-up after their second dose, reflects age-appropriate events that are consistent with a pediatric general population and the known reactogenicity profile of BNT162b2.

Study participants continue to be followed for 2 years or end of study. Study protocol C4591007 has been amended to add enhanced monitoring for myocardial events including blood sampling from a subset of study participants for troponin evaluation, and these data will be submitted when available.

2.5.6.3. Benefit-Risk Conclusions

The totality of available clinical evidence for the 30-µg and the 10-µg formulations of BNT162b2 effectiveness includes induction of strong immune responses and high vaccine efficacy, with a satisfactory safety profile, suggesting that the vaccine confers safe and effective protection against COVID-19 in individuals ≥12 years of age (Study C4591001) and in individuals 5 to <12 years of age (Study C4591007).

Risk-Benefit Assessment Summary

Preventing COVID-19 will not only provide direct health benefits to children 5 to <12 years of age, but indirect educational and social development benefits can be anticipated based on alleviating the disruption to in-person education caused by COVID-19 outbreaks in school settings. Facilitating the return to school may also have associated economic and social benefits for children's families.[15,16] Although this study was not designed to demonstrate prevention of transmission, increasing the proportion of the overall population with immunity to SARS-CoV-2 by immunizing children 5 to <12 years of age could also contribute to containment of the pandemic. Expanding COVID-19 vaccination eligibility to include school-age children 5 to <12 years of age would help protect individuals and communities in terms of both public health and the critical need for children to remain in-person learning at school.

Available safety data and immunobridging for the group of children 5 to <12 years of age in Study C4591007 support the effectiveness and satisfactory safety profile of the two-dose primary series of BNT162b2 at 10 µg in this age group. Clinical study efficacy data have suggested highly effective protection against COVID-19 in a broad population of individuals across demographic characteristics in Studies C4591001. Clinical study immunogenicity data have shown strong immune responses across age groups in these studies. Additionally, ongoing immunogenicity analyses of a subset of participants 5 to <12 years of age in Study C4591007 are evaluating neutralizing sera titers against both the wild-type and highly transmissible B.1.617.2 (Delta) variants of SARS-CoV-2; prior analyses from adult sera have shown high titers against both variants.

The potential risks are based in part on the observed clinical study safety profile to date, which shows mostly mild to moderate reactogenicity, low incidence of severe or serious events, and no new clinically concerning safety observations or concerns.

No cases of myocarditis/pericarditis were identified in participants 5 to <12 years of age in Study C4591007 through at least 2 months of follow-up after Dose 2, among approximately 1500 participants who received BNT162b2. The study includes ongoing monitoring for potential cases, including in an expanded safety group of an additional 1500 vaccine recipients, and will also conduct troponin testing on a subset of participants for subclinical safety signal detection. The vaccine has been shown to be safe and well-tolerated in Studies C4591001 and C4591007, across age groups and demographic subgroup characteristics.

Overall Risk-Benefit Conclusions

Overall, the potential risks and benefits, as assessed by the safety profile and immunogenicity of BNT162b2, are balanced in favor of the potential benefits to prevent COVID-19 including administration of BNT162b2 at 10 µg to children 5 to <12 years of age.

The available efficacy and immunobridging data strongly support a positive risk-benefit assessment for BNT162b2 across age groups including adults ≥16 years of age, adolescents 12 to 15 years of age, and now also children 5 to <12 years of age. BNT162b2 has been shown to be safe and well tolerated across age groups in the studies.

Children 5 to <12 years of age are individually at risk for potential serious illness, and the public health impacts of vaccinating school-age children against COVID-19 also weigh in favor of extending the current conditional approval to include vaccination of this age group.

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