Vaccines and Related Biological Products Advisory Committee October 26, 2021 Meeting Document

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BNT162B2

[COMIRNATY (COVID-19 VACCINE, MRNA)]

VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE BRIEFING DOCUMENT

Meeting Date: 26 October 2021

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EXECUTIVE SUMMARY

The prophylactic Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) has been available in the US for prevention of Coronavirus Disease 2019 (COVID-19) as a two-dose primary series in individuals ≥16 years of age since December 2020 under an Emergency Use Authorization (EUA 27034; 11 December 2020). 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 as a two-dose primary series in individuals ≥12 years of age. Emergency Use Authorization of a single booster dose in at risk individuals[1] ≥18 of age was granted on 22 September 2021. A Biologics License Application (BLA) was approved on 23 August 2021 in the United States (US) for BNT162b2 30 µg administration as a two-dose primary series to individuals ≥16 years of age. Approximately 1.4 billion doses of BNT162b2 have been distributed globally as of 31 August 2021.

COVID-19 is a serious and potentially fatal or life-threatening infection for children. The pediatric population remains vulnerable to COVID-19, and pediatric cases have increased in the US, especially with widespread dissemination of the highly transmissible B.1.617.2 (Delta) variant. A 419% increase in COVID-19 cases among children <18 years of age was reported in the US in August and September 2021 compared to June and July 2021. Similar increases in pediatric COVID-19 cases have been documented globally.

Although the mortality rate for COVID-19 in children is substantially lower than that in adults, COVID-19 was among the top 10 leading causes of death for children 5 to 14 years of age between January and May 2021 in the US.

Based on Centers for Disease Control and Prevention (CDC) data, among children 5 to <12 years of age there have been approximately 1.8 million confirmed and reported COVID-19 cases and 143 COVID-19-related deaths in the US through 14 October 2021. In this same age group, there have been 8622 COVID-19 related hospitalizations through 18 September 2021. This translates to cumulative incidence rates of approximately 6000 and 30 per 100,000 for confirmed COVID-19 cases and COVID-19-related hospitalizations, respectively, among children 5 to <12 years of age. The pediatric burden of COVID-19 likely exceeds that of seasonal influenza. Children can also suffer from post-acute sequelae after COVID-19. Through 04 October 2021, 5217 children in the US were diagnosed with Multisystem Inflammatory Syndrome (MIS-C), half of whom were children 5 to 13 years of age.

Although comorbidities, including asthma, diabetes, and obesity, among others, increase the risk of severe COVID-19 and hospitalization among children, approximately one-third of children who are hospitalized for COVID-19 do not have any underlying comorbidities. Vaccination strategies in this group of children should not be restricted to those living with underlying comorbidities and should include the entire 5 to <12 years of age population in

[1] A single booster dose may be administered IM at least 6 months after completing the primary series in individuals ≥65 years of age or 18 through 64 years of age who have been determined to have high risk of severe COVID-19 and/or serious complications of COVID-19 due to frequent institutional or occupational exposure.

order to protect them from the unpredictable symptomatic, severe, or long sequelae of COVID-19 disease.

Children serve as important reservoirs of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission and may become a primary driver of the pandemic in the near future, particularly given the recent dramatic increases in COVID-19 cases. Even asymptomatic children have been documented to shed virus for a mean of 2 weeks, leading to substantial risk of viral exposure among contacts. Preventing COVID-19 will provide direct health benefits to children and 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.

Pfizer/BioNTech are seeking EUA of a 10-µg dose level of BNT162b2 for use in individuals 5 to <12 years of age as a two-dose primary series given 3 weeks apart. The 10-µg dose level was selected as optimal dose for the 5 to <12 years of age group based on the favorable reactogenicity profile and robust immunogenicity results from Phase 1 dose level finding evaluation (Study C4591007).

This Briefing Document (BD) contains the following supportive evidence to request EUA:

- Safety data from N~2250 participants (1518 vaccine recipients and 750 placebo recipients) 5 to <12 years of age with a follow-up time of at least 2 months after Dose 2 (Section 3.6)
- Supplemental safety data from an expansion group of an additional N~2250 participants 5 to <12 years of age recruited later than the initial enrollment group of N~2250; at the time of the most recent data cutoff date of 08 October 2021, this safety expansion group had a median follow-up time of 2.4 weeks after Dose 2 (Section 3.7).
- Effectiveness of the 10 µg dose in the 5 to <12 years of age group inferred based on the successful immunobridging analysis, which compared SARS-CoV-2 neutralizing responses in a subset of participants in this age group in Study C4591007 to responses in a group of young adult participants 16 to 25 years of age in the C4591001 efficacy study (the most clinically similar subgroup of the study population in whom vaccine efficacy (VE) had been demonstrated) (Section 3.8.1).
- Supplemental immunogenicity analyses of a subset of participants 5 to <12 years of age in Study C4591007 evaluating serum neutralizing titers against the B.1.617.2 (Delta) variant of SARS-CoV-2 (Section 3.9).
- Descriptive efficacy analysis of children 5 to <12 years of age who were in the initial enrollment group of N~2250 to evaluate confirmed COVID-19 cases accrued up to a data cutoff date of 08 October 2021. This analysis was performed for individuals without prior evidence of SARS-CoV-2 infection up to 7 days after Dose 2 and for individuals with or without prior evidence of SARS-CoV-2 infection (Section 3.10).

Although not part of the BD, the EUA is supported by a comprehensive Chemistry, Manufacturing and Controls (CMC) data package for the 10-µg dose, that describes an improved drug product formulation buffer. The modified formulation improves vaccine

stability and simplifies vaccine administration. In accordance with Centre for Biologics and Research (CBER) guidance, the modified formulation has been shown to be analytically comparable to the formulation currently authorized and approved for individuals ≥16 years of age. The exchange is not considered clinically significant.

Dose Selection

In the Phase 1 dose finding portion of the study conducted in 49 participants 5 to <12 years of age, safety and immunogenicity data demonstrated that a two-dose primary series of 10 µg BNT162b2 given 3 weeks apart had an acceptable safety profile and elicited robust immune responses against wild-type (reference strain) SARS-CoV-2, providing a balance of safety and immune responses preferable to those after immunization at the 20 and 30 µg dose levels.

Safety and Tolerability of BNT162b2 10 µg in Children 5 to <12 Years of Age

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

The reactogenicity profile in children 5 to <12 years of age was typically mild to moderate, with a majority of events arising within the first 1 to 2 days after dosing and resolving shortly thereafter. The most common local reaction was injection site pain, and the most common systemic reactions included fatigue, headache, muscle pain, and chills.

The adverse event (AE) profile after vaccination in this age group mostly reflects reactogenicity, with low incidences of related or severe events. Few serious AEs (SAEs), none of which were 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. Complete analyses of AEs were conducted up to the EUA cutoff date of 06 September 2021, and additional AE analyses were conducted up to a cutoff date of 08 October 2021, presenting new reported AEs from the time of the EUA cutoff date up to 3 months of follow-up after Dose 2. These additional analyses have revealed no meaningful difference in the vaccine safety profile.

No cases of myocarditis/pericarditis were observed during the vaccination period through approximately 3 months of follow-up post-Dose 2 in the 5 to <12 years of age group in Study C4591007.

Supplemental safety expansion group data were analyzed from approximately 1500 vaccine recipients with a median follow-up time of 2.4 weeks after Dose 2. These supplemental data demonstrate an acceptable safety profile, in alignment with safety data from the initial enrollment group for a total of 3000 vaccinated participants contributing to safety data, with no cases of myocarditis/pericarditis reported to date. Taken together with the initial enrolled group, this supplemental safety expansion group provides safety data for a total of

approximately 3000 vaccinated children 5 to <12 years of age demonstrating safety and tolerability of BNT162b2 in this age group.

Vaccine Effectiveness of BNT162b2 10 µg in Children 5 to <12 Years of Age

FDA guidance specifies that a clinical study in participants 5 to <12 years of age must be adequately powered to demonstrate that the immune responses elicited in this age group (serum neutralization of SARS-CoV-2, as analyzed with seroresponse rates and geometric mean titers) are statistically non-inferior to those elicited by the vaccine in participants 16 to 25 years of age. The FDA-specified success criteria include demonstration of a non-inferiority margin of –10% for seroresponse rates and a 1.5-fold margin for the ratio of geometric mean neutralizing titers.

In the Phase 2/3 portion of the study, immunobridging analyses using a validated SARS-CoV-2 neutralization assay were conducted in a randomly selected subset of participants (322 BNT162b2 and 163 placebo) among the initially enrolled N~2250 study participants. The results demonstrated that the two-dose primary series of BNT162b2 10 µg given to children 5 to <12 years of age elicited SARS-CoV-2 50% neutralizing titers that were non-inferior to the titers elicited by two doses of BNT162b2 30 µg in young adults 16 to 25 years of age in the C4591001 efficacy study (Section 3.8). Given the predominance of B.1.617.2 (Delta) variant, a supplemental analysis was conducted in 38 randomly selected subset of participants 5 to <12 years of age, using a non-validated plaque reduction neutralization assay. This analysis demonstrated that serum neutralizing titers at 1 month after Dose 2 against the B.1.617.2 (Delta) variant were comparable to those against the original SARS-CoV-2 wild-type strain. These results suggest that vaccine effectiveness against the wild-type strain inferred by immunobridging can also be reasonably inferred for effectiveness against the Delta variant.

Additionally, supportive descriptive VE analysis based on confirmed COVID-19 cases among the initially enrolled N~2250 study participants 5 to <12 years of age accrued up to the data cutoff date of 08 October 2021 was conducted. VE against laboratory-confirmed symptomatic COVID-19 occurring at least 7 days after Dose 2 in evaluable participants without evidence of prior SARS-CoV-2 infection was 90.7% (2-sided 95% confidence interval [CI]: 67.7%, 98.3%). There were no cases of severe COVID-19 and no cases of MIS-C reported as of the data cutoff date. It is notable that the earliest reported and confirmed COVID-19 case in this analysis was in July 2021, with most occurring in August and September 2021, therefore all confirmed cases have been reported during a time that the highly transmissible B.1.617.2 (Delta) has been the predominant SARS-CoV-2 strain in circulation in the US and globally. These data show that the two-dose primary series of BNT162b2 10 µg given to children 5 to <12 years of age confers a high degree of protective efficacy against COVID-19 during a period when the Delta variant of concern predominates in the US.

Overall Risk-Benefit Conclusions

COVID-19 continues to be a serious and potentially fatal or life-threatening infection for children and there is a significant unmet medical need in the 5 to <12 years of age population.

Two primary doses of the 10 µg BNT162b2 vaccine given 3 weeks apart in 5 to <12 years of age have shown a favorable safety and tolerability profile, robust immune responses against all variants of concern and high VE against symptomatic COVID-19 in a period where the delta variant was predominant.

The number of participants in the current clinical development program is too small to detect any potential risks of myocarditis associated with vaccination. Long-term safety of COVID-19 vaccine in participants 5 to <12 years of age will be studied in 5 post-authorization safety studies, including a 5-year follow-up study to evaluate long term sequelae of post-vaccination myocarditis/pericarditis.

Israeli safety surveillance databases suggest that incidence rates of rare post-vaccination myocarditis peaks in individuals 16 to 19 years of age males and declines in adolescents 12 to 15 years of age. In addition, the dose for children 5 to <12 years of age is 1/3 of the dose given to older vaccinees (10 µg vs. 30 µg). Based on this information, it is reasonable to predict that post-vaccine myocarditis rates are likely to be even lower in 5 to <12 years of age than those observed in adolescents 12 to 15 years of age.

Given post-authorization experience and assuming 90% efficacy as shown in the descriptive clinical study, the estimated number of COVID-19 cases and associated hospitalizations prevented over 120 days per million of fully vaccinated children 5 to <12 years of age is ~33,600 and 170, respectively. In contrast, the number of post-vaccination myocarditis cases (including myocarditis, pericarditis, and myopericarditis) expected in the same period of time per million second doses is 21 (assuming that children 5 to <12 years of age experience the same rates of post-vaccination myocarditis/pericarditis as adolescents 12 to 15 years of age in the US) (Section 4). We therefore may expect substantially fewer post-vaccination myocarditis cases among 5 to <12 of age males and females than COVID-19-associated hospitalizations given current age-specific COVID-19 cases and hospitalization rate estimates. Prevention of potential long-term sequelae of COVID-19 illness as well as other societal impacts would further increase the public health benefit of vaccination.

Given all the above, the benefits of the Pfizer-BioNTech COVID-19 Vaccine to prevent COVID-19 given as a two-dose, 10 µg dose level, primary series in children 5 to <12 years of age outweigh the known or potential risks.

1. BACKGROUND INFORMATION

1.1. Proposed Indication

Pfizer/BioNTech is requesting authorization of Pfizer-BioNTech COVID 19 Vaccine (BNT162b2) under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 5 to <12 years of age.

1.2. Product Description

Pfizer/BioNTech are requesting authorization of a modified formulation of BNT162b2 to accommodate the 10-µg dose. This modified formulation allows for an improved stability profile and greater ease of use at administration sites. The modified formulation uses a Tris buffer instead of phosphate-buffered saline (PBS) and excludes sodium chloride and potassium chloride. Authorization and future licensure of the modified formulation is based on analytical comparability to the currently authorized PBS containing formulation in accordance with CBER guidance. The change in buffer is not considered clinically significant.

The drug product is supplied as a 10-dose multi-dose vial which requires dilution with 1.3 mL 0.9% Sodium Chloride Injection, USP prior to use. The vaccine is a preservative-free, sterile dispersion of lipid nanoparticles (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.

1.3. Dosage and Administration

The Pfizer-BioNTech COVID-19 Vaccine (for 5 years to <12 years of age) is administered as a primary series of two doses of 10 µg of BNT162b2 in 0.2 mL each, given 3 weeks apart to individuals 5 to <12 years of age.

2. UNMET MEDICAL NEED

2.1. Unmet Medical Need for Safe and Effective Vaccines in the Pediatric Population 5 to <12 Years of Age

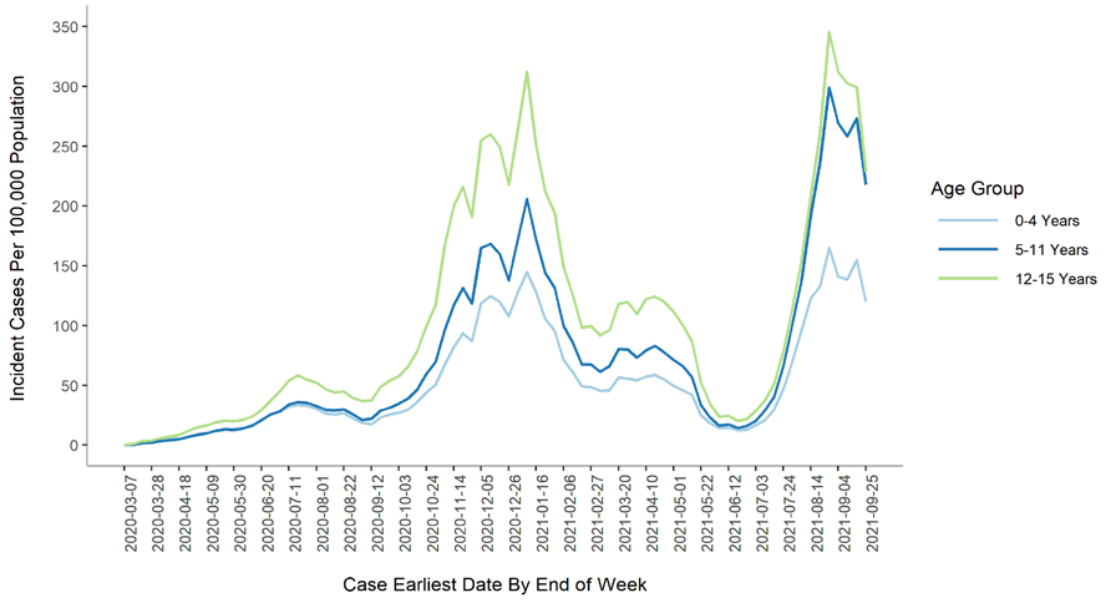
Despite an ongoing global vaccination campaign, community transmission of SARS-CoV-2 in most of the US and the world remains high [1,2] and has trended steeply upwards since July 2021, driven in part by widespread dissemination of the highly infectious B.1.617.2 (Delta) variant. [3,4] Fully vaccinated individuals remain well protected against symptomatic and serious illness for at least 6 months. However, children <12 years of age are currently ineligible for vaccination, remain at risk for COVID-19, and continue to serve as a large reservoir for community transmission. Immunization of children 5 to <12 years of age against COVID-19 could prevent harms that include, not only interruption of education, but also hospitalization, severe illness, long-term sequelae, and death. In addition, vaccinating this population will likely reduce community transmission, including transmission to older and more medically vulnerable individuals.

2.2. COVID-19 Pediatric Cases Have Recently Surged and Can Cause Severe Illness, Death, and Long-Term Sequelae

Based on CDC data, among children 5 to <12 years of age, there have been approximately 1.8 million confirmed and reported COVID-19 cases and 143 COVID-19-related deaths in the US through 14 October 2021.[5] In this age group, there have been 8622 COVID-19-related hospitalizations through 18 September 2021.[6,7] This translates to cumulative incidence rates of approximately 6000 and 30 per 100,000 for confirmed COVID-19 cases and COVID-19-related hospitalizations, respectively, among children 5 to <12 years of age. The pediatric burden of COVID-19 likely exceeds that of seasonal influenza (recently estimated at 0.8 per 100,000 influenza hospitalizations).[8]

Approximately one-quarter of all pediatric (<18 years of age) COVID-19 cases and hospitalizations have occurred since 01 August 2021, with a recent surge (Figure 1) fueled by the Delta variant.[9,10] Compared to June and July 2021, in August and September 2021, there was a 419% increase in COVID-19 cases among children <18 years of age in the US.[11] Among children 5 to <12 years of age in the US, for whom vaccines are not currently available, the increase in COVID-19 over the same period was 484%. Similar increases in pediatric COVID-19 have been documented globally.[6,12,13] Among all cases occurring since 01 August 2021 in those <18 years of age, approximately 40% were in children 5 to <12 years of age.[6,14] This underscores the role that children currently play in prolonging the pandemic, especially unvaccinated children 5 to <12 years of age. Notably, rates of COVID-19 among children 5 to <12 years of age are now as high as among adolescents 12 to 15 years of age, a group for whom BNT162b2 has been made available with rollout and uptake underway (Figure 1).

Figure 1. Estimated Reported Pediatric COVID-19 Weekly Rates in the US by Age Group, Weeks Ending 07 March 2020 – 18 September 2021



Source: Adapted from CDC COVID data tracker[14]

COVID-19 can cause severe illness in children. Among children hospitalized for COVID-19, 17–50% require respiratory support or critical care.[8,15] Although comorbidities, including asthma, diabetes, and obesity, among others, increase the risk of severe COVID-19 and hospitalization among children, approximately one-third of children who are hospitalized for COVID-19 do not have any underlying comorbidities.[16] Vaccination strategies in this group of children should not be restricted to those living with underlying comorbidities and should include the entire 5 to <12 years of age population in order to protect them from the unpredictable symptomatic, severe or long sequelae of COVID-19 disease.

The mortality rate for COVID-19 in children is substantially lower than that of adults; nevertheless, COVID-19 was among the top 10 leading causes of death for US children 5 to 14 years of age between January and May 2021.[17]

Children also suffer from post-acute COVID-19 sequelae, although the full magnitude is not yet fully characterized. Through 04 October 2021 in the US, 5217 children were diagnosed with MIS-C, half of whom were children 5 to 13 years of age.[18] Risk factors for the development of MIS-C are unclear. The unpredictable nature of the development of this syndrome was highlighted by 'The Overcoming COVID-19 Study' investigators and CDC COVID Response Team. Targeted surveillance was conducted at pediatric hospitals across the US between 15 March 2020 and 20 May 2020. During this period, 186 cases of MIS-C were identified, 73% of which occurred in children who were previously healthy, as did 2 of the 4 reported deaths.[19] In addition to the risk of MIS-C, a recent study conducted in Israel showed that approximately 2–5% of children infected with SARS-CoV-2 suffer from long-term sequelae at 6 months post infection.[20] A study conducted in the United Kingdom showed that 67% of children experienced symptoms 60 to 120 days after their initial infection and 27% still had symptoms at ≥120 days post infection.[21]

Myocarditis may occur independently from SARS-CoV-2 infection or as part of MIS-C. The risk of myocarditis for children <16 years of age was recently reported to be >30 times higher for those infected with SARS-CoV-2 than for those who have not been infected.[22] The risk of myocarditis is substantially lower after vaccination than it is after COVID-19 in populations where it has been evaluated, underscoring the benefits of vaccination despite the risk of this rare vaccine-associated adverse event.[23] US and Israeli safety surveillance databases show that incidence rates of rare myocarditis cases post-Dose 2 in vaccinated individuals 12 to 15 years of age are lower than those observed in the 16 to 19 years of age group; it is therefore reasonable to extrapolate that potential vaccine related cases of myocarditis are no higher and may be even lower in younger individuals 5 to <12 years of age than those observed in 12 to 15 years of age (Section 4).

The unpredictability and extent of COVID-19 mediated severe sequelae further highlights the need for a broad age-based vaccination strategy among children 5 to <12 years of age.

2.3. Vaccination of Children 5 to <12 Years May Play an Important Role in Reducing Overall SARS-CoV-2 Transmission

Children serve as important reservoirs of SARS-CoV-2 transmission[24] and may become a primary driver of the pandemic in the near future, particularly given the recent dramatic increases in COVID-19 cases described above.[25] Even asymptomatic children have been

documented to shed virus for a mean of 2 weeks, leading to substantial risk of viral exposure among contacts.[26] As schools opened for the 2021-2022 academic school year, exposures increased due to children being in close quarters, and many outbreaks have occurred.[27] Few studies have evaluated direct transmission to and among children, but children are documented sources of infection in the community due in part to secondary infections stemming from social interactions with household and non-household members[24,25,27,28] and appear to be readily infected by other infected individuals with whom they have close contact.[29,30] In the classroom, outbreaks from teacher to student have been reported, with infection risk correlating with proximity to the infected teacher.[30] Early evidence of reduced levels of viral mRNA and culturable virus in vaccinated people who acquire SARS-CoV-2 infection suggests that the risk of transmission is substantially reduced among the vaccinated.[31] Maximizing the proportion of the population that is vaccinated is critically important to help reduce rates of infection, decrease transmission, prevent the emergence of new variants of concern, and hasten the end of the pandemic.

Reaching herd immunity thresholds or attaining meaningful reductions in the force of infection are unlikely without vaccinating children. Children <12 years of age, who are currently ineligible for vaccination, constitute approximately 15% of the US[32] population. While actual herd immunity thresholds are unknown and may vary from region to region, generally estimates of at least 60–70% are perceived as necessary to reduce disease transmission.[33,34] These thresholds are likely higher given the predominance of the SARS-CoV-2 Delta variant, which is more transmissible and has a higher reproductive number than the wild type virus.[35,36] As of 03 October 2021, only 57% of the total US population had been fully vaccinated, and vaccine uptake had plateaued among adults.[37] Thus, ensuring COVID-19 vaccines are made available for children is an important strategy to improve overall levels of community immunity.

2.4. COVID-19 Vaccination in the 5 to <12 Years Age Group Can Restore a Safe and Effective Learning Environment

Finally, vaccination will help restore the availability of in-person learning for children by limiting community spread and school outbreaks[38] and reducing the need for student quarantine. In-person learning is critical for childhood development, adequate learning, and broader economic impact on the society due to the burden imposed on working parents/caregivers by school closures and quarantines and the impact that loss of education has on children's future economic security.[13] The impact of closures and distance learning is likely far-reaching and is only beginning to be understood fully. Decreases in reading proficiency, critical thinking skills, and test scores have been reported.[39,40,41] Recently, closures and distance learning were associated with poor educational attainment and may further increase educational disparities across racial and socioeconomic lines,[42] given that children from low-income families are disproportionately affected, potentially widening educational and health disparities.[41,43,44]

Mental health and wellbeing in children have been significantly impacted by the ongoing pandemic and rounds of school closures, associated with increased screen time and social media use, reduction in physical activity and more sedentary behavior, unhealthy dietary habits, and overall increased psychological distress in school age children. The negative

impacts of lost in-person school time are anticipated to have long-lasting effects on children's mental health and are showing negative impacts on parental/caregiver well-being and stress related behavior.[13] Results from a United Kingdom-based longitudinal study reported greater changes in parent-reported validated strengths and difficulties questionnaire among children 4 to 10 years of age than among adolescents 11 to 16 years of age. This was potentially attributed to isolation from peers and family stress during peak restrictions.[45]

3. OVERVIEW OF CLINICAL STUDIES

3.1. Phase 1/2/3 Registrational Study C4591001

Study C4591001 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 safety, immunogenicity and efficacy 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 enrolling up to approximately 46,000 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. This study served as the basis for licensure in individuals ≥16 years of age and emergency use in individuals 12 to 15 years of age. Emergency use approval in individuals 12 to 15 years of age was based primarily on inferred effectiveness by demonstration of immune non-inferiority compared to individuals 16 to 25 years of age, supported by descriptive efficacy analysis (with vaccine efficacy [VE] observed at >90% in this age group).

The immunogenicity data in young adults 16 to 25 years of age in Study C4591001 served as the comparator for immunobridging analysis of the 10-µg dose level in participants 5 to <12 years of age in Study C4591007 and, per FDA guidance, form the basis for inferring effectiveness of the 10-µg dose level in vaccine recipients 5 to <12 years of age.

3.2. Phase 1/2/3 Pediatric 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 a 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. 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. The study was conducted using a dilution of the currently authorized 30 µg PBS formulation.

Phase 1

Phase 1 of Study C4591007 was conducted in the US. Starting with the oldest age group (5 to <12 years of age), sentinel cohorts received the lowest dose level (N=16 per dose level) followed by either the progression to a subsequent higher dose level cohort or termination of a dose level based upon the safety evaluation by the Internal Review Committee (IRC). The intent was to evaluate dose levels up to 30 µg in each age cohort if the safety was acceptable for all the lower doses. Progression to a subsequent younger age cohort occurred if a dose level was judged safe in an older cohort, based upon the evaluation of the IRC.

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 until the end of study.

Phase 2/3

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

Phase 2/3 (which is ongoing) was planned to evaluate BNT162b2 at the selected dose levels for safety and tolerability, immunogenicity, and efficacy. Immunobridging and safety data from the initial enrolled group of participants 5 to <12 years of age (N~2250) are presented up to the EUA cutoff date of 06 September 2021, representing at least 2 months of follow-up after Dose 2. Supportive efficacy analyses from participants in this initial enrollment group are presented including COVID-19 cases accrued to a data cutoff date of 08 October 2021. Supportive immunogenicity analyses were conducted on the randomly selected Delta neutralization subset of approximately 40 participants 5 to <12 years of age in the evaluable immunogenicity population who had no evidence of infection up to 1-month post-Dose 2, to evaluate SARS-CoV-2 neutralization of the wild-type and Delta variants. Additionally, an updated summary of new AEs reported in the initial enrollment group is provided from the time of the EUA submission data cutoff date (06 September 2021) to the current cutoff date (08 October 2021), which represents up to approximately 3 months of follow-up post-Dose 2.

An additional safety expansion group of N~2250 participants 5 to <12 years of age, who completed enrollment after the initial enrolled group, were randomized 2:1 (1500 BNT162b2 at 10 µg and 750 placebo) in the Phase 2/3 part of C4591007 to obtain a larger safety database to support the EUA request and future licensure. Supplemental safety data for this safety expansion group are presented up to the data cutoff of 08 October 2021, which represents at least 2 weeks of follow-up after receiving Dose 2.

This briefing document reports interim C4591007 data for the 5 to <12 years of age group only, in support of authorization of the 10-µg dose level for this age group.

3.3. Overview of Methods for Evaluation of Safety, Immunogenicity, and Efficacy

3.3.1. Study C4591007 – Safety Analyses

Safety data are reported from Dose 1 to 1 month after Dose 2 for Phase 1 and Phase 2/3 participants. For Phase 2/3 participants, data are also reported through the EUA data cutoff date of 06 September 2021 (representing at least 2 months of follow-up after Dose 2) for the initial enrollment group of N~2250 participants 5 to <12 years of age. Further follow-up for this initial enrollment group is provided to a more recent data cutoff date of 08 October 2021 (representing approximately 3 months of follow-up after Dose 2). Supplemental interim Phase 2/3 safety expansion group data for an additional N~2250 who entered the study later than the initial enrollment group are reported from Dose 1 to a data cutoff date of 08 October 2021 (representing at least 2 weeks of follow-up after Dose 2).

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% confidence intervals (CIs). Missing reactogenicity e-diary data were not imputed.

Reactogenicity data are only presented from the initial enrollment group.

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. AE data are provided for initial enrollment group who had at least 2 months of follow-up after Dose 2 and further AE analysis are provided for up to 3 months of follow-up after Dose 2 as of the most recent cutoff date. Additionally, AE data from the safety expansion group who were enrolled later are provided for up to at least 2 weeks follow-up after Dose 2.

3.3.2. Study C4591007 – Immunogenicity Analyses

In Phase 1, SARS-CoV-2 50% neutralizing titers were assessed at 7 days after Dose 2 and summarized as geometric mean titers (GMTs).

In Phase 2/3, immunobridging was based on SARS-CoV-2 50% neutralizing titers at 1 month after Dose 2, comparing Phase 2/3 C4591007 participants 5 to <12 years of age to Phase 2/3 C4591001 participants 16 to 25 years of age for GMR and seroresponse assessed sequentially (ie, seroresponse was evaluated only after the prespecified geometric mean ratio (GMR) criteria for immunobridging were met). Samples for comparison from each age group/study were tested contemporaneously in the same validated SARS-CoV-2 neutralization assay using the same preparation of target virus.

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

  * 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 lower limit of quantitation (LLOQ), a postvaccination measure of ≥4 × LLOQ was considered a seroresponse. The difference in percentages and the associated 2 sided 95% CI calculated

using the Miettinen and Nurminen method were provided. Immunobridging success for seroresponse was declared if the lower limit of the 2-sided 95% CI for the difference in seroresponse rate was greater than -10%, provided that the immunobridging success criterion based on the GMR was achieved.

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

Immunobridging Subset Sample Size

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

Delta Variant Neutralization Analysis

Analyses were conducted on the Delta neutralization subset, a randomly selected subset of participants 5 to <12 years of age in the evaluable immunogenicity population who had no evidence of infection up to 1-month post-Dose 2.

A 50% plaque-reduction neutralization test (PRNT) was used to determine delta variant SARS-CoV-2 serum neutralizing titers as described previously.[46,47] The PRNT is distinct from the validated SARS-CoV-2 neutralization assay used to determine titers for immunobridging analyses that were previously submitted in the EUA amendment.

The 50% PRNT GMTs were calculated by exponentiating the mean of logarithmically transformed assay results; the associated 2-sided 95% CIs were obtained from the natural log scale of the results using the Student's t distribution and exponentiating the confidence limits.

3.3.3. Study C4591007 – Efficacy Analyses

Efficacy analyses were conducted on the evaluable efficacy population (participants who received both doses within the protocol-defined window and had no important protocol deviations prior to 7 days post-Dose 2) and on the all-available efficacy (modified intent-to-treat [mITT]) populations (all participants who received vaccination).

Efficacy endpoints are confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of follow-up in participants (1) without or (2) with or without serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection.

COVID-19 cases are summarized by vaccine group for participants 5 to <12 years of age according to the case criteria outlined in the Appendix. A validated SARS-CoV-2 PCR was used to obtain confirmed COVID-19 case data.

Descriptive VE analyses within the 5 to <12 years of age group were conducted after immunobridging success was first declared to provide available efficacy data (in addition to the completed immunogenicity and safety analyses described above) to facilitate the Vaccines and Related Biological Products Advisory Committee (VRBPAC) overall assessment of benefit-risk when the EUA for this age group is being considered. With <21 cases (protocol specified number for formal evaluation of VE) accrued by the time of this analysis, there is an increased risk of observing by chance a lower VE than the true VE compared to the same risk when ≥21 cases have been accrued. To inform VRBPAC's decision on whether to recommend approving the vaccine for this age group, Pfizer has provided the most comprehensive and up-to-date data available, despite the potential risk of a higher 'type II error' for this descriptive efficacy analysis. The hypothesis testing efficacy analysis for this age group will be performed when ≥21 cases are accrued.

VE against confirmed COVID-19 from 7 days after Dose 2 is estimated by 100 × (1 – IRR), where IRR (illness ratio rate) 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. VE estimation for confirmed COVID-19 uses the first definition (per protocol criteria).

3.4. Study C4591007 – Phase 1 – Safety Results

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 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 (Section 3.4.1), an IRC decision was made for the remaining 12/16 participants assigned to the 30 µg dose level group to receive the second dose based upon selection of the dose-level for Phase 2/3 ie, 10 µg. These subjects will not be discussed further.

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.

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.

3.4.1. Reactogenicity – Phase 1

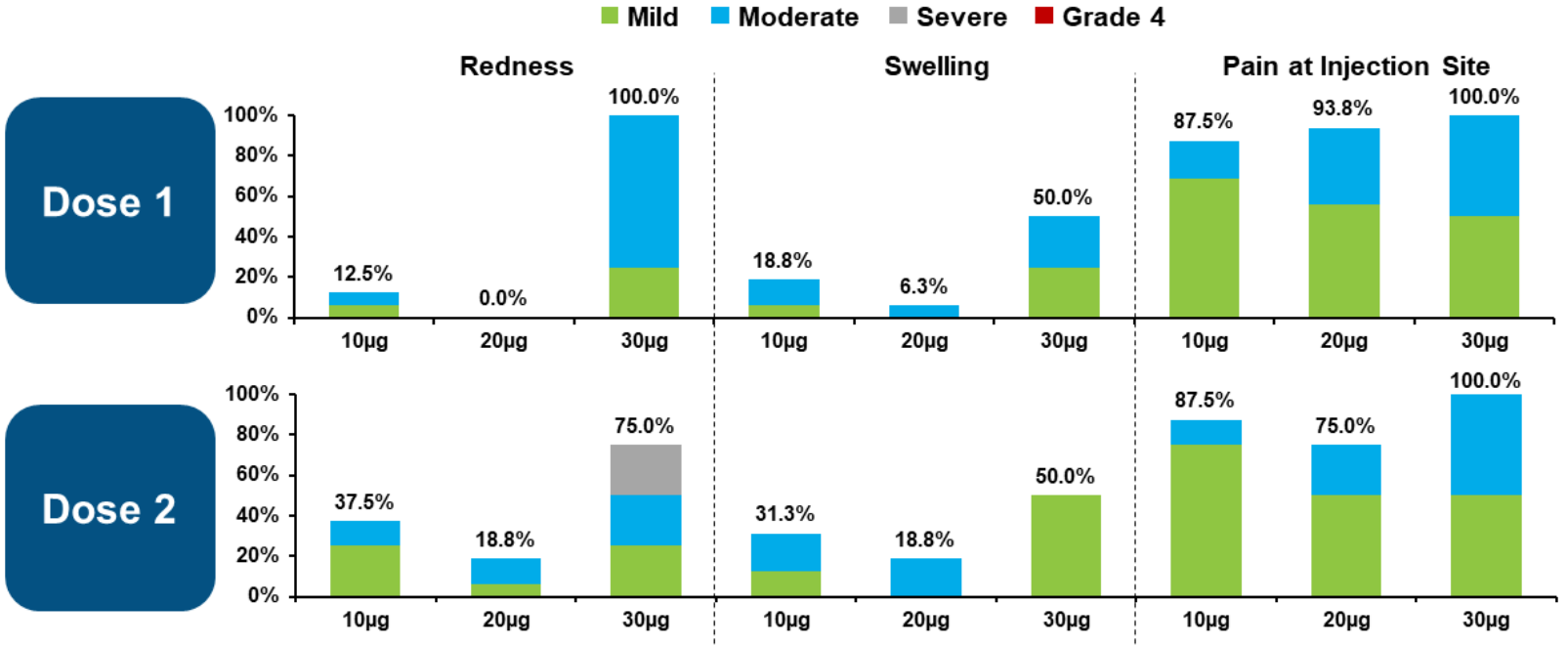
Local Reactions

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. Local reactions were mostly mild to moderate and short-lived. Local reactions at the 30-µg dose level were deemed unacceptable, leading to the discontinuation of this dose level. With regard to local reactions, the 10 and 20 µg dose levels were the best tolerated (Figure 2).

Systemic Events

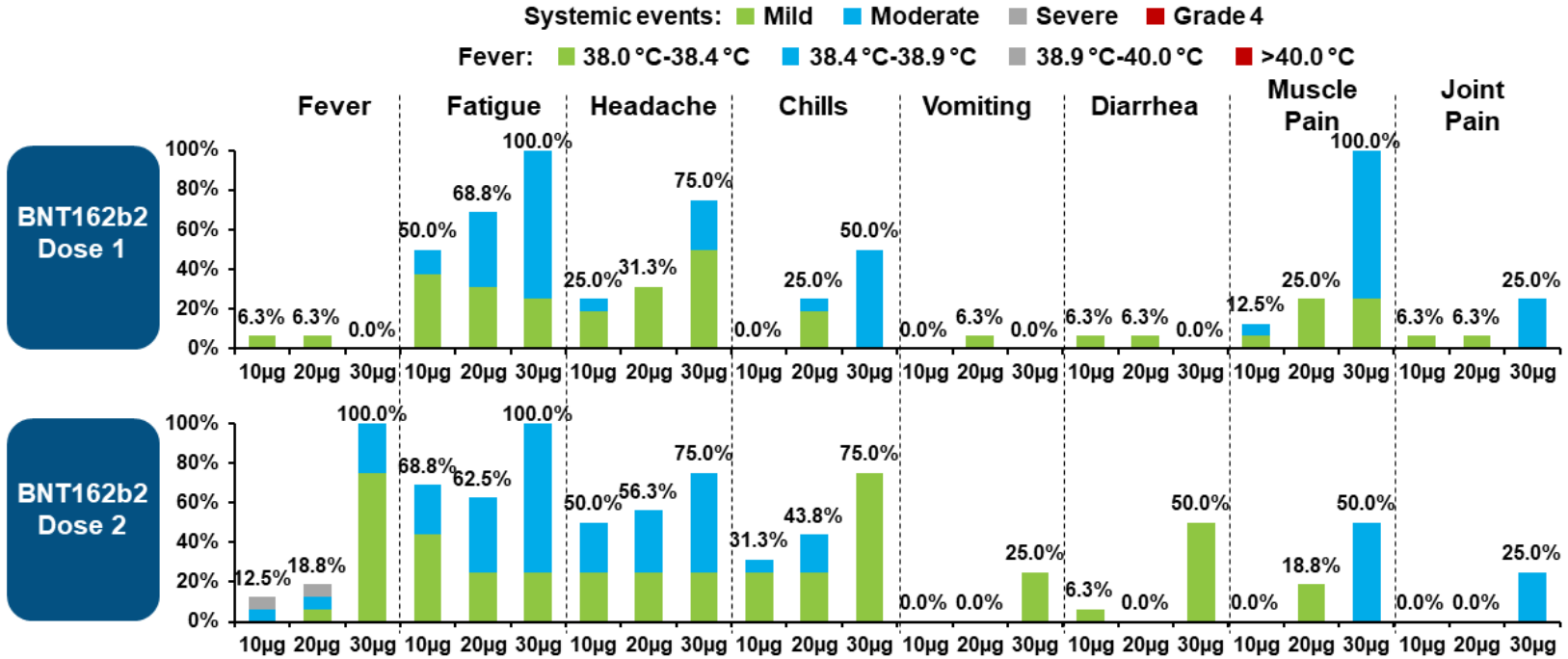
Reactogenicity generally increased in an increasing dose level- and dose number-dependent manner with regard to incidence and/or severity of systemic events at 10, 20, and 30 µg dose levels. Systemic events were mostly mild to moderate and short-lived. Systemic events at the 30-µg dose level were deemed unacceptable, leading to the discontinuation of this dose level. With regard to systemic events, the 10-µg dose level was the best tolerated (Figure 3).

Figure 2. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 – 5 to <12 Years of Age – Safety Population



Redness and swelling severity definition: Mild= >2-5 cm, Moderate= >5-10 cm; Severe= >10 cm; Grade 4= necrosis
Pain at injection site severity definition: Mild=no interference; Moderate=some interference; Severe=prevents daily activity; Grade 4=ER visit or hospitalization
10 µg = 16; 20 µg = 16; 30 µg = 4

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



Fatigue, headache, chills, muscle pain, joint pain severity definition: Mild=no interference; Moderate=some interference; Severe=prevents daily activity; Grade 4=ER visit or hospitalization
Vomiting severity definition: Mild=1-2 times in 24h; Moderate=> 2 times in 24h; Severe=Requires IV hydration; Grade 4=ER visit or hospitalization
Diarrhea severity definition: Mild=2-3 times in 24h; Moderate=4-5 times in 24h; Severe=6 or more times in 24h; Grade 4=ER visit or hospitalization
10 µg = 16; 20 µg = 16; 30 µg = 4

3.4.2. Adverse Events – Phase 1

From Dose 1 to 1 month after Dose 2, AEs were reported by 12 participants in the 10 µg and 20 µg dose level group; of these AEs were considered related to study intervention in 6 participants. Of the 4 participants who received two doses of 30 µg dose, AEs were reported by 2 participants (lymphadenopathy and arthralgia, both considered by the investigator as 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.

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 3.4.1).

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 both doses of BNT162b2 30 µg had a transient AE of Grade 2 arthralgia (right hip pain) that was judged by the investigator as related to study intervention. The event was reported as resolved the same day after administration of ibuprofen.

Two Phase 1 participants 5 to <12 years of age had cases of lymphadenopathy from Dose 1 up to the data cutoff date, occurring at the 20 and 30 µg dose levels.

3.4.3. Safety Conclusions – Phase 1

Higher 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.

3.5. Study C4591007 – Phase 1 – Immunogenicity Results

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.

Only 4 participants received a 30 ug second dose. All 16 participants assigned to the 30-µg dose level group were excluded from immunogenicity analysis. In the 10 and 20 µg dose level groups, a total of 2 participants (n=1 each per dose level) were excluded either because they did not have an assay result or did not complete both vaccinations.

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.

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

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.

3.5.2. 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.

3.5.3. 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, along with the more favorable reactogenicity profile observed in the 10-µg dose level, led to the selection of BNT162b2 at the 10-µg dose level to proceed to Phase 2/3 evaluation for participants 5 to <12 years of age.

3.6. Study C4591007 – Phase 2/3 – Safety Results

Safety Population

The safety population for Phase 2/3 pediatric participants 5 to <12 years of age initially enrolled into the study reflected the 2:1 randomization in the BNT162b2 (N=1518) and placebo (N=750) groups.

Duration of Follow-up

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 1). Almost all (95.1%) of the participants had 2 to <3 months of follow-up after Dose 2.

Table 1. 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
Mean (SD)	2.2 (0.19)	2.2 (0.22)	2.2 (0.20)
Median	2.3	2.3	2.3
Min, max	(0.0, 2.5)	(0.0, 2.5)	(0.0, 2.5)

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. Follow-up time after Dose 2 for participants who did not receive Dose 2 was counted as 0.
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.

Disposition

The disposition of Phase 2/3 pediatric participants 5 to <12 years of age is summarized in Table 2. 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.

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. None of the withdrawals from the study were reported due to an AE. Most discontinuations/withdrawals were due to parent/guardian decision.

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

	Vaccine Group (as Randomized)		
	C4591007 BNT162b2 10 µg (N[a]=1528) n[b] (%)	C4591007 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
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)

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.

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.

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.

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.

Demographics

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. 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 (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.

3.6.1. 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.

Local Reactions

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 4).

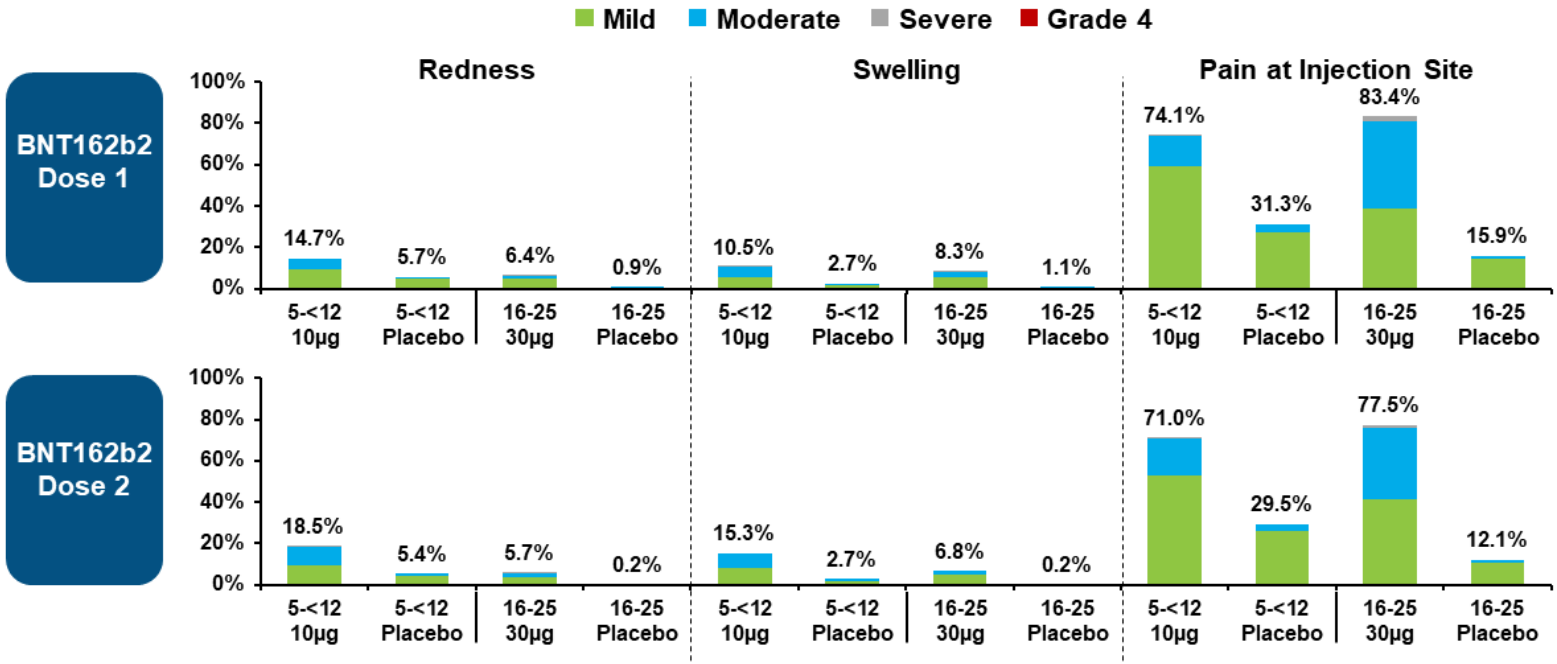
Reactogenicity patterns in children were generally similar to that previously observed in individuals ≥12 years of age in Study C4591001, with some differences. Overall, reactogenicity in children tended to appear most similar to the milder and less frequent profile previously observed in older adults >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.

Systemic Events

In the population of Phase 2/3 pediatric participants 5 to <12 years of age, systemic events showed increased frequencies 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 5, Figure 6).

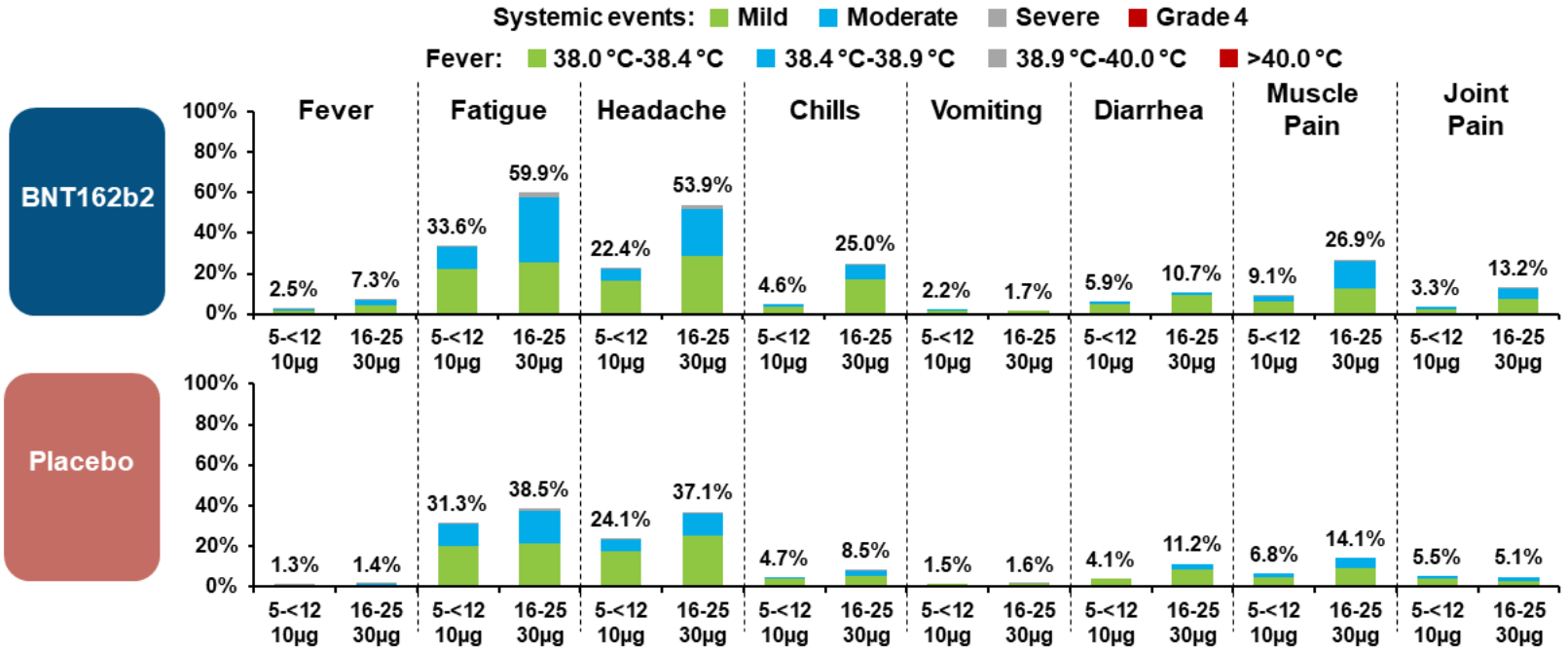
Children 5 to <12 years of age tended to have less severe systemic events (including fever and chills) after vaccine doses of 10 µg compared to those previously reported in adolescents and young adults from Study C4591001 after vaccine doses of 30 µg. Overall, reactogenicity in children tended to appear most similar to the milder and less frequent profile previously observed in older adults >55 years of age. 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.

Figure 4. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – 5 to <12 Years of Age and `16 to 25 Years of Age – Safety Population



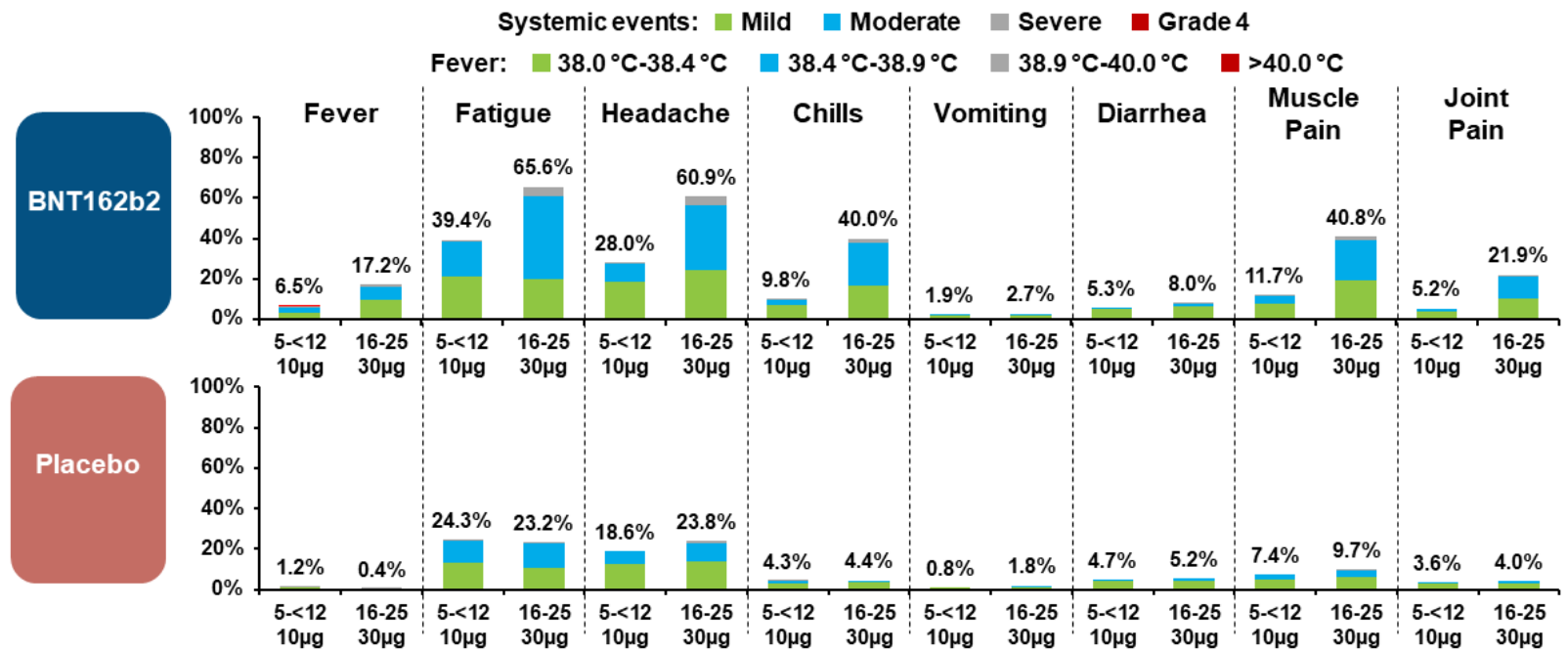
Redness and swelling severity definition: Mild= >2-5 cm, Moderate= >5-10 cm; Severe= >10 cm; Grade 4= necrosis
Pain at injection site severity definition: Mild=no interference; Moderate=some interference; Severe=prevents daily activity; Grade 4=ER visit or hospitalization
Dose 1: 5-<12 yrs N=2260; 16-25 yrs N=1064 Dose 2: 5-<12 yrs N=2242 16-25 yrs N=984

Figure 5. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Dose 1 – Phase 2/3 – 5 to <12 Years of Age and 16 to 25 Years of Age– Safety Population



Fatigue, headache, chills, muscle pain, joint pain severity definition: Mild=no interference; Moderate=some interference; Severe=prevents daily activity; Grade 4=ER visit or hospitalization
Vomiting severity definition: Mild=1-2 times in 24h; Moderate=>2 times in 24h; Severe=Requires IV hydration; Grade 4=ER visit or hospitalization
Diarrhea severity definition: Mild=2-3 times in 24h; Moderate=4-5 times in 24h; Severe=6 or more times in 24h; Grade 4=ER visit or hospitalization
Dose 1: 5-<12 yrs N=2260; 16-25 yrs N=1064

Figure 6. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Dose 2 – Phase 2/3 – 5 to <12 Years of Age and 16 to 25 Years of Age– Safety Population



Fatigue, headache, chills, muscle pain, joint pain severity definition: Mild=no interference; Moderate=some interference; Severe=prevents daily activity; Grade 4=ER visit or hospitalization
Vomiting severity definition: Mild=1-2 times in 24h; Moderate=>2 times in 24h; Severe=Requires IV hydration; Grade 4=ER visit or hospitalization
Diarrhea severity definition: Mild=2-3 times in 24h; Moderate=4-5 times in 24h; Severe=6 or more times in 24h; Grade 4=ER visit or hospitalization
Dose 2: 5-<12 yrs N=2242 16-25 yrs N=984

3.6.2. Overview of Adverse Events – Phase 2/3

3.6.2.1. Adverse Events from Dose 1 to 1 Month After Dose 2 – Phase 2/3

An overview of AEs from Dose 1 to 1 month after Dose 2 is shown in Table 3. The proportions of participants with any AE were similar in the BNT162b2 (10.9%) and placebo (9.2%) groups.

Table 3. 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

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.

3.6.2.2. Adverse Events from Dose 1 to Data Cutoff Date – Phase 2/3

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 4). Few additional AEs were reported between 1 month after Dose 2 to the data cutoff date.

Table 4. 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)	
	BNT162b2 10 µg (N[a]=1518)	Placebo (N[a]=750)
Adverse Event	n[b] (%)	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

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.

3.6.3. 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 3.6.3.1 and from Dose 1 until the data cutoff date (06 September 2021) in Section 3.6.3.2.

3.6.3.1. Adverse Events from Dose 1 to 1 Month After Dose 2 – Phase 2/3

Adverse Events by System Organ Class (SOC) and Preferred Term (PT)

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.

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.

- *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.

- *Psychiatric disorders* were reported in 0.3% of participants in the BNT162b2 group and 0.4% of participants in the placebo group.

- *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.

- *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.

- *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) and other non-drug allergies.

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.

Immediate Adverse Events

After Dose 1 and Dose 2, immediate AEs (reported within 30 minutes of vaccination) were low in frequency (≤0.4%) in the BNT162b2 and placebo groups. Immediate AEs reported after Dose 1 and Dose 2 in the BNT162b2 versus placebo groups were predominantly injection site pain. No other immediate AEs post-Dose 1 were reported in the BNT162b2 group. Other immediate AEs reported post-Dose 2 in the BNT162b2 group were injection site erythema, erythema, and nausea.

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

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

3.6.3.2. Adverse Events from Dose 1 to Data Cutoff Date – Phase 2/3

Adverse Events by System Organ Class and Preferred Term

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, 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.

3.6.3.3. Additional Adverse Event Analysis to 08 October 2021 Cutoff Date – Phase 2/3

As of the most recent cutoff date, participants in the initial enrollment group have a follow-up time of approximately 3 months after Dose 2 (median: 3.3 months). As of this more recent cutoff date, the AE profile in this group has not appreciably changed.

Cumulatively, 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. No new SAEs were after the EUA cutoff date and no withdrawals due to AEs have been reported. No study participants have had life-threatening AEs and no participants have died.

All of these newly reported AEs from after 2 months post-Dose 2 up to the present 3 months post-Dose 2 were non-serious, unrelated to study intervention, and all were mild to moderate. These newly reported AEs primarily included events consistent with mild common infections (eg, sore throat, cough, rhinitis, enterovirus, pyrexia, fatigue) and limb fractures, which would be expected and commonly reported in the general pediatric population.

No new AEs were reported that correspond to adverse events of special interest (AESIs); no cases of myocarditis were reported.

3.6.4. 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).

3.6.5. 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. Overall, 3 SAEs were reported by 2 participants: 1 participant in the BNT162b2 group had an SAE of upper limb fracture, and 1 participant in the placebo group 2 SAEs of pancreatitis and abdominal pain (reported as occurring 'post-injury') through the data cutoff date. These SAEs were all assessed by the investigator as not related to study intervention.

3.6.6. 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).

3.6.7. Other Significant Adverse Events – Phase 2/3

Adverse events of specific clinical interest, such as those in the CDC list of AESIs for COVID-19, were reviewed based on AEs reported up to the cutoff date. 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.

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.

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.

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) 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 exception of one Grade 3 event of rash 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 of the vaccine and is noted as such in the EUA Fact Sheet. 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.

Lymphadenopathy

Lymphadenopathy is considered an adverse reaction to vaccine and is noted as such in the EUA Fact Sheet. 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.

Other AEs of Clinical Interest

In addition to the FDA-requested AEs of clinical interest, as of the data cutoff date for this submission, no cases of thrombocytopenic events, thromboembolic or intravascular coagulation events, autoimmune or demyelination events, meningitis, encephalitis, neuritis, Kawasaki disease, MIS-C, or acute respiratory distress syndrome were reported.

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 events considered related by the investigator are summarized below.

Arthralgia

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

- One participant in the BNT162b2 group had a related AE of mild 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.

Paresthesia

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

- One participant in the BNT162b2 group had a related AE of moderate paresthesia (bilateral lower extremity tingling) with onset at 1 day post-Dose 2 and reported as recovered/resolved 3 days after onset.

Tic

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

One participant 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.

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 related to the CDC list of AESIs. Lymphadenopathy has been identified as related to BNT162b2 in individuals ≥12 years of age and it is also 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.

3.6.8. Other Safety Assessments – Phase 2/3

3.6.8.1. Severe COVID-19 and MIS-C Illness – Phase 2/3

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).

3.6.8.2. Pregnancy – Phase 2/3

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

3.6.9. Safety Conclusions (Initial Enrollment Group) – Phase 2/3

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 serious 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 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.

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.

Similarly, the overall AE and adverse reaction profile among approximately 22000 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 no 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.

3.7. Study C4591007 – Phase 2/3 – Additional Safety Expansion Group Results

The safety expansion group population for Phase 2/3 pediatric participants 5 to <12 years of age reflected the 2:1 randomization in the BNT162b2 (N=1591) and placebo (N=788) groups. At the time of the data cutoff date (08 October 2021), the median duration of follow-up for the Phase 2/3 pediatric safety expansion group of children 5 to <12 years of age was 2.4 weeks after Dose 2. Most participants (71.2%) had at least 2 weeks of follow-up after Dose 2. The vast majority of participants (98.5%) had at least 1 week of follow-up after Dose 2.

Disposition

One participant (0.1%) in the BNT162b2 group discontinued from the vaccination period due to an AE (details in Section 3.7.2) and two participants (0.1%) in the BNT162b2 group and 1 participant (0.1%) in the placebo group withdrew from the study before the 1-month post-Dose 2 visit. Neither of these withdrawals was reported as due to an AE.

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. The majority of participants received Dose 2 in the protocol defined window of 19 to 23 days after Dose 1 in the BNT162b2 (95.6%) and placebo (94.5%) groups.

Demographics

Demographic characteristics for the Phase 2/3 safety expansion group of pediatric participants 5 to <12 years of age were similar in BNT162b2 and placebo groups in the safety population. In total, most participants were White (76.1%), with 5.6% Black or African American participants and 10.1% Asian participants, 7.6% multiracial participants, and other racial groups <1%. There were 13.2% Hispanic/Latino participants. The median age was 8.0 years and 50.7% of participants were male.

Obese children (based on age- and sex-specific indices) made up 11.2% (BNT162b2 group) and 11.0% (placebo group) of this age group in the safety population. Comorbidities present at baseline that increase the risk of severe COVID-19 disease[48] (which include obesity) were present in similar proportions of participants in the BNT162b2 (19.7%) and placebo (20.2%) groups. The most common comorbidities reported in participants at study baseline were:

- asthma (8.4% in BNT162b2 and 9.0% in placebo)
- neurologic disorders (1.1% in BNT162b2 and 1.1% in placebo)
- congenital heart disease (0.6% in BNT162b2 and 0.4% in placebo)

3.7.1. Overview of Adverse Events – Phase 2/3 – Additional Safety Expansion Group

Proportions of participants in the safety expansion group (randomized 2:1 to receive BNT162b2 or placebo) reporting any AE from Dose 1 to the data cutoff date (08 October 2021), representing at least 2 weeks after Dose 2 for most participants, were similar in the BNT162b2 (7.2%) and placebo (6.3%) groups (Table 5).

The AEs in the safety expansion group were consistent with that observed in prior analyses of Phase 2/3 participants in the initially enrolled 5 to <12 years of age group in Study C4591007.

Table 5. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 Through Cutoff Date (08OCT2021) – Safety Expansion Group – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 10 µg (N[a]=1591)	Placebo (N[a]=788)
Adverse Event	n[b] (%)	n[b] (%)
Any adverse event	115 (7.2)	50 (6.3)
Related[c]	55 (3.5)	14 (1.8)
Severe	5 (0.3)	0
Life-threatening	0	0
Any serious adverse event	3 (0.2)	0
Related[c]	0	0
Severe	3 (0.2)	0
Life-threatening	0	0
Any nonserious adverse event	113 (7.1)	50 (6.3)
Related[c]	55 (3.5)	14 (1.8)
Severe	2 (0.1)	0
Life-threatening	0	0
Any adverse event leading to withdrawal	1 (0.1)	0
Related[c]	1 (0.1)	0
Serious	0	0
Severe	1 (0.1)	0
Life-threatening	0	0
Death	0	0

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.

3.7.2. Analysis of Adverse Events – Phase 2/3 – Additional Safety Expansion Group

Many of the AEs after Dose 1 to the data cutoff date for the safety expansion group were reflective of reactogenicity events that were reported as AEs, with little imbalance observed between BNT162b2 and placebo groups except for general disorders and administration site conditions (driven primarily by injection site pain). AE frequencies in SOCs containing the most common reactogenicity AEs (BNT162b2 vs placebo) were:

- general disorders and administration site conditions: 2.3% vs 1.8%
- gastrointestinal disorders: 0.8% vs 0.8%
- nervous system disorders: 0.6% vs 0.4%
- musculoskeletal and connective tissue disorders: 0.4% vs 0.4%

Many of the other commonly reported AEs grouped by SOC and PT are consistent with events that would be expected in healthy children in this age group and/or showed no imbalance between participants who received vaccine versus placebo.

- *Cardiac disorders* were not reported by any participants in the additional safety expansion group up to the data cutoff date.

- *Psychiatric disorders* were reported in 1 participant in the BNT162b2 group (a related event of 'irritability') and none in the placebo group.

- *Blood and lymphatic system disorders* were reported in 0.4% of participants in the BNT162b2 group and 0.4% of participants in the placebo group, which included lymphadenopathy.

- *Skin and subcutaneous disorders* were reported in 1.0% of participants in the BNT162b2 group and 0.5% of participants in the placebo group. Events reported more frequently in the BNT162b2 group included rashes, urticaria, angioedema, dermatitis, pruritis, night sweats.

- *Immune system disorders* were reported in 3 participants (0.2%) in the BNT162b2 group and none in the placebo group and included one event reported as Type IV hypersensitivity reaction and other non-drug allergies.

Related Adverse Events

From Dose 1 to the data cutoff date, AEs assessed as related by the investigator were reported at a higher frequency in the BNT162b2 group (3.5%) than in the placebo group (1.8%). Most related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions, reported by 2.0% of participants in the BNT162b2 group compared with 0.9% of participants in the placebo group.

One participant in the BNT162b2 group had a non-serious related AE reported by the investigator as moderate hematochezia 4 days after Dose 2. The participant had heme occult positive stool; was seen in the emergency department, and had no further tests done; and

went home and the event resolved the same day without sequelae. This participant had a medical history of asthma and nondrug allergy and had no other reported AEs.

Immediate Adverse Events

After Dose 1 and Dose 2, immediate AEs (reported within 30 minutes of vaccination) in the safety expansion group were low in frequency (≤0.2%) in the BNT162b2 and placebo groups. Most immediate AEs were reactogenicity events such as injection site pain. No allergic reactions to BNT162b2 were reported as immediate events after either dose.

Serious Adverse Events

A total of 3 SAEs (arthritis infective, foreign body ingestion of a penny, epiphyseal fracture; 1 each) were reported in the Phase 2/3 pediatric safety expansion group of children 5 to <12 years of age up to the data cutoff date (08 October 2021), which represents at least 2 weeks of follow-up after Dose 2 in most individuals. These SAEs were all assessed by the investigator as not related to study intervention.

Adverse Events Leading to Withdrawal

One participant withdrew due to an AE of severe pyrexia with onset of 2 days after Dose 1 considered by the investigator as related to study intervention that resolved at 1 day after onset. Participant also had severe neutropenia ('worsening from baseline') with onset of 3 days after Dose 1 considered by the investigator as related to study intervention and reported as resolving at the time of the data cutoff date. Participant had a medical history of benign transient neutropenia of unknown etiology, gingivitis, and otitis media. Prior to study enrollment, she had a full hematology work-up (including for possible leukemia) with baseline absolute neutrophil count (ANC) of 480; the hematologist indicated no concerns with study participation. After Dose 1 Day 2 she reported a temperature of 40.1 °C. Her temperature returned to normal the next day. Two days after receiving Dose 1, the participant had a planned routine hematology appointment. The participant had an ANC of 20 and platelets were normal. No other symptoms or infections were reported at that time. Subsequently on Day 19 after Dose 1, the investigator was contacted by the participant's caregiver who reported the participant had bleeding gums for 1 week prior. On Day 23, the participant attended Visit 2 to be seen by the investigator, was reported as doing well, and had a follow-up blood draw that showed the ANC had improved to 70. Dose 2 was not administered, and the participant was withdrawn from study intervention and remains in study follow-up. No other AEs were reported.

Adverse Events of Clinical Interest

No cases of myocarditis/pericarditis, anaphylaxis, or Bell's palsy/facial paralysis/facial paresis, or MIS-C were reported in the Study C4591007 5 to <12 years of age safety expansion group as of the data cutoff date (08 October 2021). No events were reported for convulsions, peripheral neuropathy, or demyelination. No pregnancies were reported up to the data cutoff date (08 October 2021).

Other AEs of clinical interest identified that relate to potential hypersensitivity are summarized below:

- One participant without a reported medical history in the BNT162b2 had a related AE Type IV hypersensitivity reaction characterized by a rash on the forehead, earlobe, and right forearm 3 days after Dose 1. A dermatologist diagnosed the rash as a Type IV hypersensitivity reaction and characterized the rash as 'plaque, erythematous and minimal crusting', and prescribed Triamcinolone and Benadryl creams. No prohibited concomitant treatments or nonstudy vaccines had been administered. The event was reported as resolving 18 days after onset without sequelae. This participant had no other reported AEs. This participant received Dose 2 without any additional AEs reported post-dose.

- One participant in the BNT162b2 group had a related AE of moderate angioedema reported as 'perioral and periorbital angioedema due to allergic reaction' and concurrent urticaria reported as 'hives of the face and back caused due to allergic reaction', both with onset of 2 days after Dose 2, and was reported as resolved 2 days after onset. Participant's medical history included past allergy (hypersensitivity with mild rash) to a vaccine, Sever's disease, contact dermatitis and seasonal allergies. This participant received no prohibited concomitant treatments or nonstudy vaccines.

An analysis of angioedema cases reported in the BNT162b2 group included angioedema (see above) and urticaria (n=3). Two of the cases of urticaria were considered by the investigator as related to study intervention; one is described above (concurrent with angioedema).

- The second case of urticaria was mild ('itchy', 'bilateral on hands and forearms') with onset at 6 days after Dose 1 and resolved within 2 days, reported shortly after an AE of mild injection site erythema at 3 days after Dose 1, in a participant with no relevant medical history and no receipt of prohibited concomitant medications or nonstudy vaccines. This participant received Dose 2 without any reported post-dose AEs.

Events of hypersensitivity reported in the BNT162b2 group (9 participants) included unrelated allergic conjunctivitis, unrelated contact dermatitis (attributed to poison ivy), Type IV hypersensitivity reaction (see above), and rashes.

Rashes were reported in 6 participants in the BNT162b2 group. Rashes considered as related to BNT162b2 were all mild or moderate included: rash maculo-papular, rash macular, rash papular and rash (n=1 each). Rash is considered an adverse reaction of the vaccine and is noted as such in the EUA Fact Sheet.

Overall, the pattern of events in the hypersensitivity analysis within the skin and subcutaneous tissue disorders SOC (including rashes) reported in children 5 to <12 years of age in the safety expansion group of Study C4591007 was consistent with that observed in prior analyses of Phase 2/3 participants in the initially enrolled 5 to <12 years of age group in Study C4591007, and higher than observed in prior analyses of Phase 2/3 participants ≥12 years of age in Study C4591001.

One participant in the BNT162b2 group had a non-serious unrelated event reported by the investigator as Henoch-Schoenlein purpura.

- One participant in the BNT162b2 group had a non-related AE of mild Henoch-Schoenlein purpura with onset of 21 days after Dose 1 and reported as ongoing at the time of the data cutoff date. The participant was treated with steroids and pain medication. Due to the initiation of steroids, the study Visit 2 appointment was delayed. This event was preceded by other non-related AEs: mild headache with onset at 10 days after Dose 1 and resolved in 2 days, and mild joint swelling of the right ankle with onset at 16 days after Dose 1 and resolved in 3 days. This participant had no reported medical history and received no prohibited concomitant treatments or nonstudy vaccines. As of the time of the data cutoff, Dose 2 was not administered.

Lymphadenopathy

There were 6 participants (0.4%) in the BNT162b2 group and 3 participants (0.4%) in the placebo group had events of lymphadenopathy.

In the BNT162b2 group, the mean time to onset after Dose 1 was 11 days (median 11 days), and after Dose 2 the mean time to onset was 1 day (median 1 day), the same day as vaccination. The mean duration of events was 3.0 days (median 3 days). All reported cases of lymphadenopathy in either group were mild.

3.7.3. Safety Conclusions – Additional Safety Expansion Group – Phase 2/3

Phase 2/3 data from approximately 2250 children 5 to <12 years of age in a safety expansion group of Study C4591007, the majority of who had follow-up of at least 2 weeks after Dose 2, support the conclusions from the initial enrolled group of N~ 2250 children, that BNT162b2 given as a two-dose primary series at 10 µg was safe and well-tolerated.

As of the data cutoff date (08 October 2021), the AE profile in this additional safety expansion group did not suggest any new safety concerns for BNT162b2 10 µg vaccination in children 5 to <12 years of age. As was observed in the initial enrollment group (who now have safety follow-up to approximately 3 months after Dose 2), further follow-up in the initial enrollment group since the time of the EUA submission to the present cutoff date has shown no meaningful change to the AE profile for this age group.

In the safety expansion group, few SAEs were reported: 3 participants (0.2%) had unrelated SAEs of arthritis infective, epiphyseal fracture, and foreign body ingestion. No deaths were reported. One withdrawal due to a non-related AEs was reported for 1 participant in the BNT162b2 group. Based on the additional follow-up for the initial enrollment group since the time of the EUA submission to approximately 3 months after Dose 2, only a limited number of non-serious, unrelated, mild to moderate AEs have been reported.

The safety and tolerability profile of BNT162b2 10 µg administered in children 5 to <12 years of age now represents a total of N~4500 participants (3000 active and 1500 placebo), with follow-up to at least 2 weeks after Dose 2 for the majority of participants in the safety expansion group, and a longer median follow-up to at least 3 months after Dose 2

for the initial enrollment group. These data collectively show no new safety concerns, including few AESIs and no reported cases of myocarditis/pericarditis, and support the safe and tolerable administration of BNT162b2 10 µg to children 5 to <12 years of age.

3.8. Study C4591007 – Phase 2/3 – Immunogenicity Results

Immunobridging Subset

The immunobridging subset included a subset of 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) and a subset of 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 from each age group/study were tested contemporaneously in the same assay.

Disposition

The disposition of participants in each age group who were included in the immunobridging subset, is summarized in Table 6. 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 6) was similar to that of all randomized participants (Table 2) 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.

Table 6. 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

Table 6. 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] (%)
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

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.

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.

Demographics

Demographic characteristics for participants in the immunogenicity population for 5 to <12 years and young adults 16 to 25 years of age were similar to the respective safety population. Comorbidities present at baseline that increase the risk of severe COVID-19 disease (which include obesity) were present in similar proportions of participants 5 to <12 years of age in the BNT162b2 group (20.5%) and placebo group (20.8%).

3.8.1. Immunobridging Analysis – Phase 2/3

Geometric Mean Ratio (GMR) of Neutralizing Titers

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the ratio of the SARS-CoV-2 50% neutralizing GMT in children 5 to <12 years of age (who received the 10-µg dose level) to that of young adults 16 to 25 years of age (who received the 30-µg dose level) was 1.04 (2-sided 95% CI: 0.93, 1.18) (Table 7).

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 (Section 3.3.2). Therefore, immunobridging based on GMR was achieved. The observed GMR point estimate also meets the requested post hoc criterion from the FDA of ≥1.

Difference in Seroresponse Rate

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, high and equal proportions (99.2% of children 5 to <12 years of age and 99.2% of young adults 16 to 25 years of age) achieved a seroresponse (as defined in Section 3.3.2) 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 8).

Since immunobridging based on GMR was achieved, the hypothesis of immunobridging based on seroresponse rate was tested subsequently (refer to analysis methods in Section 3.3.2). 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 7. 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.

Table 8. 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.

3.8.2. 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.

Geometric Mean Titers (GMTs)

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, at 1 month after Dose 2 (Day 52) of BNT162b2 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) (Table 9). 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. BNT162b2 10 µg elicited a similar level of immune response at 1 month post-Dose 2 across the age groups of 5 through 6 years, 7 through 8 years, and 9 through 11 years with neutralizing GMTs of 1164.1, 1236.1 and 1191.5, respectively.

Geometric Mean Fold-Rise (GMFR) in Titers

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the GMFRs of SARS-CoV-2 50% serum neutralizing titers from before vaccination to 1 month after Dose 2 of BNT162b2 were robust. There was a similar magnitude of rise in the pediatric 5 to <12 years of age group (118.2) compared with the young adult 16 to 25 years of age group (111.4) for BNT162b2 recipients (Table 10). GMFRs for placebo recipients in either age group were very low (1.0 to 1.1).

Seroresponse Rate

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, proportions of participants who achieved seroresponse (as defined in Section 3.3.2) in SARS-CoV-2 50% neutralizing titers 1 month after Dose 2 of BNT162b2 were the same (99.2%) in children 5 to <12 years of age and young adults 16 to 25 years of age (Table 11). Very few placebo participants in either age group had a seroresponse based on SARS-CoV-2 neutralizing titers at 1 month after Dose 2.

Table 9. 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.

Table 10. 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.

Table 11. 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.

3.8.3. Immunogenicity Conclusions – Phase 2/3

Immunobridging

Based on the SARS-CoV-2 serum neutralizing response to the 10-µg dose level of BNT162b2, among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, immunization of 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 rates 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 rates 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. The observed GMR point estimate also meets the requested post hoc criterion from the FDA of ≥1.

Substantial and comparable increases over baseline (pre-vaccination) in neutralizing GMTs, high 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.

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.

3.9. Study C4591007 – Phase 2/3 – Delta Variant Neutralization Immunogenicity Results

Disposition and Dataset Analyzed

As a supporting analysis, PRNT titers were obtained from 38 children 5 to <12 years of age randomly selected from the evaluable immunogenicity population (N=34 in the BNT162b2 group and N=4 in the placebo group).

The majority of participants were White (84.2%) with 7.9% Black or African American, 5.3% Asian, with and 2.6% multiracial participants. Hispanic/Latino participants made up 15.8% of the population. The median age of participants was 8.0 years of age, and 50.0% of participants were male. One participant, in the BNT162b2 group (2.9%), was obese.

SARS-CoV-2 Neutralizing Titers

Geometric Mean Titers (GMTs)

SARS-CoV-2 PRNT GMTs substantially increased for both the reference and Delta strains after two doses of 10 µg BNT162b2. The GMT at 1 month after Dose 2 against the reference strain was 365.3 (95% CI: 279.0, 478.4), which was approximately 36.5-times the GMT pre-vaccination.

The GMT at 1 month after Dose 2 against the Delta variant strain was 294.9 (95% CI: 214.6, 405.3), which was approximately 29.5-times the GMT pre-vaccination.

Conclusions

The two-dose primary series of BNT162b2 10 µg administered 3 weeks apart to children 5 to <12 years of age elicited high neutralizing titers to both the USA-WA1/2020 (reference) and B.1.617.2 (Delta) recombinant SARS-CoV-2 strains at 1 month after Dose 2. These data are aligned with similar results previously obtained for adults in the Phase 1 part of Study C4591001.

3.10. Study C4591007 – Phase 2/3 – Efficacy Results

A descriptive efficacy analysis was conducted in Phase 2/3 pediatric participants 5 to <12 years of age initially enrolled into the study.

Disposition and Datasets Analyzed

The Phase 2/3 evaluable efficacy population for children 5 to <12 years of age included 1450 participants in the BNT162b2 group and 736 participants in the placebo group (Table 12), which reflects the 2:1 randomization. Exclusions from the evaluable efficacy population occurred for 5.1% of the BNT162b2 group and 2.8% of the placebo group, due to receipt of Dose 2 outside the protocol defined window of 19-42 days after Dose 1 (2.0% in BNT162b2 and 2.4% in placebo) or due to other important protocol deviations on or prior to 7 days after Dose 2 (3.1% in BNT162b2 and 0.5% in placebo) primarily related to vaccine thawing, dilution, and/or administration issues that are not applicable to placebo.

Table 12. Efficacy Populations – Phase 2/3 Initial Enrollment Group – 5 to <12 Years of Age

	Vaccine Group (as Randomized)		
	BNT162b2 10 µg n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	1528 (100.0)	757 (100.0)	2285 (100.0)
Dose 1 all-available efficacy population	1517 (99.3)	751 (99.2)	2268 (99.3)
Participants without evidence of infection before Dose 1	1384 (90.6)	686 (90.6)	2070 (90.6)
Participants excluded from Dose 1 all-available efficacy population	11 (0.7)	6 (0.8)	17 (0.7)
Reason for exclusion[c]			
Did not receive at least 1 vaccination	11 (0.7)	6 (0.8)	17 (0.7)
Dose 2 all-available efficacy population	1514 (99.1)	747 (98.7)	2261 (98.9)
Participants without evidence of infection prior to 7 days after Dose 2	1362 (89.1)	671 (88.6)	2033 (89.0)
Participants excluded from Dose 2 all-available efficacy population	14 (0.9)	10 (1.3)	24 (1.1)
Reason for exclusion[c]			
Did not receive 2 vaccinations	14 (0.9)	10 (1.3)	24 (1.1)
Evaluable efficacy population	1450 (94.9)	736 (97.2)	2186 (95.7)
Participants without evidence of infection prior to 7 days after Dose 2	1305 (85.4)	663 (87.6)	1968 (86.1)
Participants excluded from evaluable efficacy population	78 (5.1)	21 (2.8)	99 (4.3)
Reason for exclusion[c]			
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	31 (2.0)	18 (2.4)	49 (2.1)
Had other important protocol deviations on or prior to 7 days after Dose 2	47 (3.1)	4 (0.5)	51 (2.2)

a. n = Number of participants with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Participants may have been excluded for more than 1 reason.

Demographics

The demographics of Phase 2/3 pediatric participants 5 to <12 years of age were similar in the evaluable efficacy population of participants without prior evidence of SARS-CoV-2 infection as in the safety population for the BNT162b2 and placebo groups. In total, 51.9% of participants were male; 77.8% were White, 6.3% were Black or African American, 6.7% were Asian, 7.5% were multiracial, and other racial groups included <1% of participants; 19.0% were Hispanic/Latino. The median age was 8.0 years. Most children (73.4%) were enrolled in the US, with 11.9% in Finland, 8.7% in Spain, and 6.0% in Poland.

Obese children (based on age- and sex-specific indices) made up 10.9% of the total evaluable efficacy population. Comorbidities present at baseline that increase the risk of severe COVID-19 disease[49] were present in 20.1% of participants.

In the evaluable efficacy population of participants with or without prior evidence of SARS CoV-2 infection prior to 7 days after Dose 2, baseline positive status for prior evidence of SARS-COV-2 infection was reported for 8.7% of the BNT162b2 group and 8.4% of the placebo group.

The overall demographics of Phase 2/3 pediatric participants 5 to <12 years of age were similar for the BNT162b2 and placebo groups in the evaluable efficacy population of participants with or without prior evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, and in the all-available (mITT) efficacy populations.

3.10.1. Efficacy Against Confirmed COVID-19 – Phase 2/3

Confirmed Cases per Protocol Criteria (First Definition)

The observed VE from at least 7 days after Dose 2 for BNT162b2 10 µg administered to children 5 to <12 years of age without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen, per protocol case criteria (refer to Section 7) was 90.7% (2-sided 95% CI: 67.7%, 98.3% based on 3 cases in the BNT162b2 group and 16 cases in the placebo group (noting the 2:1 randomization of vaccine:placebo) (Table 13).

No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection. Hence, in this case, the observed VE from at least 7 days after Dose 2 in evaluable participants in this age group with or without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen essentially the same: 90.7% (2-sided 95% CI: 67.4%, 98.3%) based on the same number of observed cases (3 cases in the BNT162b2 group and 16 cases in the placebo group).

The earliest reported and confirmed COVID-19 case in this analysis was in July 2021, with most occurring in August and September 2021.

Table 13. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 Initial Enrollment Group – 5 to <12 Years of Age – Evaluable Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 10 µg (N[a]=1305)		Placebo (N[a]=663)			
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2	3	0.322 (1273)	16	0.159 (637)	90.7	(67.7, 98.3)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1, 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 7 days after receipt of Dose 2) and had no medical history of COVID-19 were included in the analysis.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

3.10.2. Dose 1 All-Available Efficacy Population – Phase 2/3

The observed VE for BNT162b2 10 µg against any confirmed COVID-19 (per protocol case criteria) from Dose 1 onwards in the Dose 1 all-available (mITT) population (ie, all randomized participants who received at least vaccination) of children 5 to <12 years of age was 91.4% (2-sided 95% CI of 70.4% to 98.4%) based on 3 cases in the BNT162b2 group and 17 cases in the placebo group (noting the 2:1 randomization of vaccine:placebo), as of the data cutoff date (08 October 2021) (Table 14).

The Kaplan-Meier curve in Figure 7 shows that cases accrued steadily in the placebo group, starting at approximately 3 weeks after the first dose and continuing to increase up to the data cutoff date (which represents approximately 4 months since Dose 1). In contrast, the 3 cases reported in the BNT162b2 group occurred at disparate and later times, with 1 case each reported at approximately 1.5 months, 3.5 months, and 4 months after Dose 1.

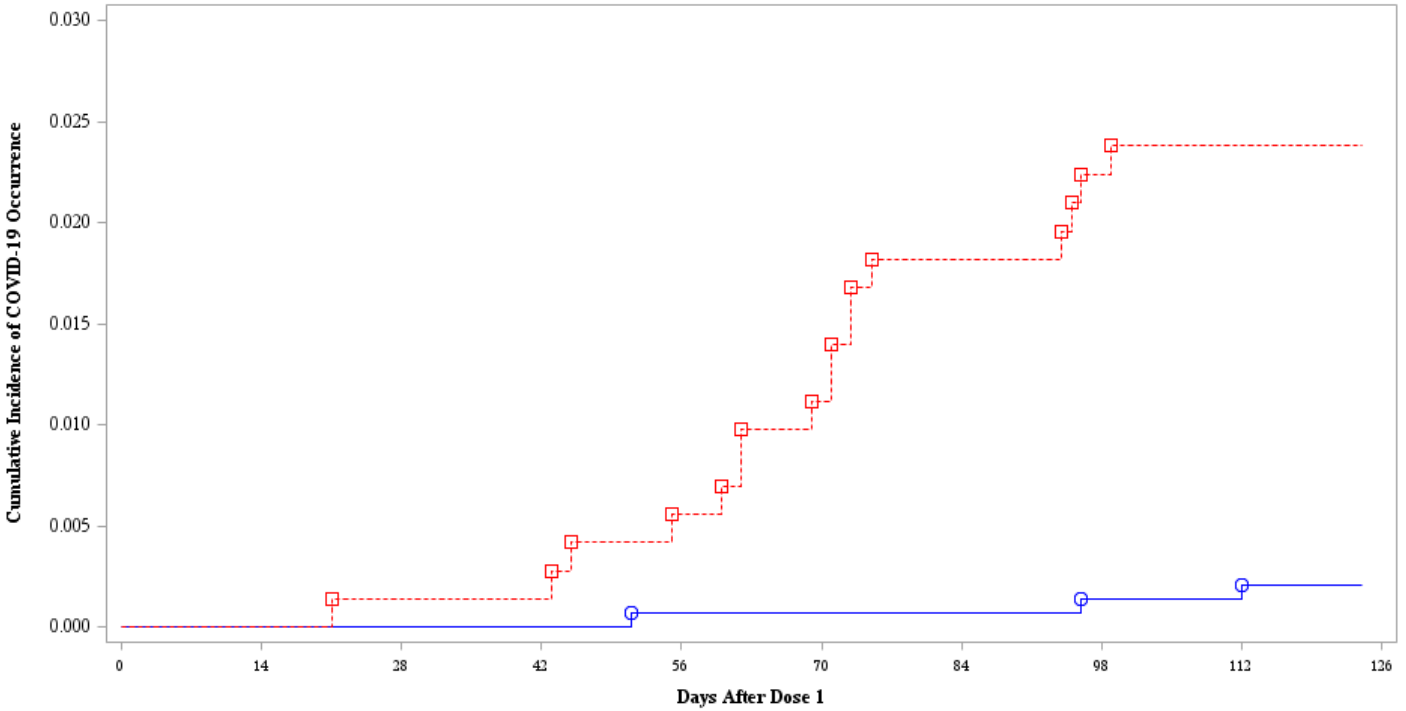
All 3 cases in the BNT162b2 group occurred ≥7 days after Dose 2, noting that 2/3 cases occurred at distant time points post-Dose 2, during a period in Fall 2021 when children in this age group were back in school and/or other related congregant settings (eg, sports teams, after school activities, etc.). As discussed in Section 3.10.3, cases in the BNT162b2 group were associated with fewer and milder signs and symptoms than cases in the placebo group reported over the same period.

Table 14. Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Phase 2/3 Initial Enrollment Group – 5 to <12 Years of Age – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 10 µg (N[a]=1517)		Placebo (N[a]=751)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	3	0.483 (1463)	17	0.235 (719)	91.4	(70.4, 98.4)
Dose 1 to before Dose 2	0	0.086 (1463)	1	0.043 (719)	100.0	(-1832.5, 100.0)
Dose 2 to <7 days after Dose 2	0	0.028 (1461)	0	0.014 (714)	NE	NE
≥7 Days after Dose 2	3	0.369 (1461)	16	0.178 (714)	90.9	(68.3, 98.3)

Abbreviations: NE = not estimable; VE = vaccine efficacy.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period for the overall row and from start to the end of range stated for each interval.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Figure 7. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Phase 2/3 Initial Enrollment Group – 5 to <12 Years of Age – Dose 1 All-Available Efficacy Population



Participants at Risk

A:	1463	1463	1462	1459	1457	1456	1455	1449	1444	0
B:	719	718	716	716	712	707	701	695	689	0

Cumulative Number of Events

A:	0	0	0	0	1	1	1	2	3	3
B:	0	0	1	1	4	8	13	16	17	17

A: BNT162b2 10 µg
B: Placebo

3.10.3. Signs and Symptoms of COVID-19 – Phase 2/3

In the evaluable efficacy population, confirmed cases occurring at least 7 days after Dose 2 among participants in the evaluable efficacy population without evidence of SARS-CoV-2 infection before or during the vaccination regimen had signs and symptoms associated with 3 cases in the BNT162b2 group and 16 cases in the placebo group (Table 15).

In the BNT162b2 group, 1 participant each (33.3%) with a confirmed COVID-19 case reported 2, 3, or 4 signs and symptoms of COVID-19. Importantly, fever was not reported in the children with confirmed COVID-19 who received BNT162b2. The reported signs and symptoms in the BNT162b2 group were:

- New or increased cough: all 3 participants (100%)
- Sore throat: all 3 participants (100%)
- Headache: 1 participant (33.3%)
- Nasal congestion or runny nose: 1 participant (33.3%)
- Nausea or abdominal pain: 1 participant (33.3%)

In the placebo group, the majority of participants (56.2%) with a confirmed COVID-19 case reported 4 or more signs and symptoms of COVID-19, including 8 participants each (50.0%) with 5 or more symptoms. The reported signs and symptoms in the placebo group order of highest to lowest frequency were:

- Fever: 10 participants (62.5%)
- Nasal congestion or runny nose: 9 participants (56.3%)
- New or increased cough: 8 participants (50.0%)
- New or increased muscle pain: 8 participants (50.0%)
- Sore throat: 8 participants (50.0%)
- Fatigue: 5 participants (31.3%)
- Chills: 4 participants (25.0%)
- New loss of taste or smell: 4 participants (25.0%)
- Headache: 4 participants (25.0%)
- Diarrhea: 3 participants (18.8%)
- Nausea of abdominal pain: 3 participants (18.8%)
- New or increased shortness of breath: 1 participant (6.3%)

Overall, COVID-9 cases reported in the placebo group reflected a higher incidence of multiple concurrent signs and symptoms for most participants. The signs and symptoms associated with cases in the BNT162b2 group were mostly limited to mild respiratory tract symptoms while signs and symptoms were more severe in the placebo group. This may be particularly important with regard to children with baseline comorbidities that increase their risk of severe COVID-19,[49] who made up approximately 20% of the evaluable efficacy population in this study. No cases in the BNT162b2 group and 3 cases in the placebo group occurred in children with reported baseline comorbidities. These data provide evidence to suggest that vaccine offers protection to individuals particularly children with comorbidities who are at risk of severe COVID-19 disease.

Table 15. Summary of Signs and Symptoms for First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 Initial Enrollment Group – 5 to <12 Years of Age – Evaluable Efficacy Population

	Vaccine Group (as Randomized)		
Signs and Symptoms	BNT162b2 10 µg (N^a=3) n^b(%)	Placebo (N^a=16) n^b(%)	Total (N^a=19) n^b(%)
Participants with specific signs and symptoms of COVID-19	3 (100.0)	16 (100.0)	19 (100.0)
Fever	0 (0.0)	10 (62.5)	10 (52.6)
New or increased cough	3 (100.0)	8 (50.0)	11 (57.9)
New or increased shortness of breath	0 (0.0)	1 (6.3)	1 (5.3)
Chills	0 (0.0)	4 (25.0)	4 (21.1)
New or increased muscle pain	0 (0.0)	8 (50.0)	8 (42.1)
New loss of taste or smell	0 (0.0)	4 (25.0)	4 (21.1)
Sore throat	3 (100.0)	8 (50.0)	11 (57.9)
Diarrhea	0 (0.0)	3 (18.8)	3 (15.8)
Additional CDC-defined symptoms			
Fatigue	0 (0.0)	5 (31.3)	5 (26.3)
Headache	1 (33.3)	4 (25.0)	5 (26.3)
Nasal congestion or runny nose	1 (33.3)	9 (56.3)	10 (52.6)
Nausea or abdominal pain	1 (33.3)	3 (18.8)	4 (21.1)
Participants with specific number of signs and symptoms			
1	0 (0.0)	2 (12.5)	2 (10.5)
2	1 (33.3)	3 (18.8)	4 (21.1)
3	1 (33.3)	2 (12.5)	3 (15.8)
4	1 (33.3)	1 (6.3)	2 (10.5)
5	0 (0.0)	4 (25.0)	4 (21.1)
>5	0 (0.0)	4 (25.0)	4 (21.1)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; CDC = Centers for Disease Control and Prevention (United States); SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1, 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 7 days after receipt of Dose 2) and had no medical history of COVID-19 were included in the analysis.
a. N = number of participants with COVID-19 occurrence from 7 days after Dose 2 in the specified group. This value is used as the denominator for the percentage calculations.
b. n = Number of participants with the specific criteria meeting the definition. A participant can have more than 1 symptom.

3.10.4. Efficacy Against Severe COVID-19 and MIS-C – Phase 2/3

No severe COVID-19 cases (per protocol definition, or per CDC definition) were reported in children 5 to <12 years of age as of the data cutoff date (08 October 2021). No cases of MIS-C were reported as of the data cutoff date.

3.10.5. Efficacy Conclusions (Initial Enrollment Group) – Phase 2/3

Based on the available number of accrued cases of confirmed COVID-19 as of the data cutoff date (08 October 2021) in the initially enrolled group, these descriptive efficacy data show BNT162b2 10 µg is protective against COVID-19 in children 5 to <12 years of age. These analyses included confirmed cases from at least 7 days after Dose 2, either without or with or without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen, as well as all cases confirmed from Dose 1 onwards.

Among participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen, the observed VE for BNT162b2 10 µg against any confirmed COVID-19 from at least 7 days after Dose 2 was 90.7% (2-sided 95% CI: 67.7%, 98.3%) which included 3 cases in the BNT162b2 group and 16 cases in the placebo group as of the data cutoff date (noting the 2:1 randomization of vaccine:placebo).

For COVID-19 cases confirmed from Dose 1 onwards in the Dose 1 all-available (mITT) population, the observed VE for BNT162b2 10 µg was 91.4% (2-sided 95% CI: 70.4, 98.4%) based on 3 cases in the BNT162b2 group and 16 cases in the placebo group as of the data cutoff date (noting the 2:1 randomization of vaccine:placebo).

No severe COVID-19 cases or MIS-C were reported in the 5 to <12 years of age group per protocol definition or per CDC definition as of the date cutoff date (08 October 2021).

It is notable that the earliest reported and confirmed COVID-19 case in this analysis was in July 2021 (first symptom observed on 05 July 2021 and PCR-confirmed on 07 July 2021), with most occurring in August and September 2021, therefore all confirmed cases have been reported during a time that the highly transmissible B.1.617.2 (Delta) has been the predominant SARS-CoV-2 strain in circulation in the US and globally.[50,51] A supportive analysis of Delta neutralizing immune responses from a subset of vaccinated and placebo recipient's sera in the 5 to <12 years of age group in Study C4591007 was conducted, which showed robust neutralizing titers against the Delta variant, and was predictive of high efficacy. Therefore, it can be inferred from these efficacy and supportive immunogenicity data that vaccination with BNT162b2 10 µg in children 5 to <12 years of age is highly effective against COVID-19 caused by the still-prevalent Delta variant of concern. Confirmatory case sequencing data for COVID-19 cases in this analysis will be reported at a later time, when the sequencing analysis is completed. The observed efficacy in children 5 to <12 years of age in this present VE analysis is in line with real-world data from individuals ≥12 years of age who received two doses of BNT162b2 30 µg and had observed efficacy of 88% against the Delta variant.[52]

4. SUPPORTIVE REAL WORLD AND POST-AUTHORIZATION DATA FROM ADOLESCENTS

While consideration is being given to authorization of BNT162b2 to vaccinate children 5 to <12 years of age, available real-world and post-authorization data have been evaluated in individuals 12 to 15 years of age in support of the benefit-risk evaluation for vaccinating children. Studies from Israel and the US have confirmed high vaccine effectiveness against SARS-CoV-2 infection and COVID-19 outcomes in children 12 to 15 years of age and in other adolescent and young-adult age groups following the introduction of BNT162b2 into these populations.[53,54]

A study from Israel, conducted as part of ongoing national surveillance and without involvement from the Sponsor, evaluated the relative risk of post-vaccination myocarditis with respect to comparator populations. This retrospective analysis of medically reviewed cases of myocarditis identified through passive and active surveillance for the period 10 December 2020 through 31 May 2021 found an overall standardized incidence ratio of 5.34 after a second dose using a 30-day risk window compared to 2017-2019 rates, driven mostly by the standardized incidence rate (SIR) in males under 30 years of age (Table 16). Elevated SIRs were not observed after Dose 1 in any age/sex category (95% CI included 1). Similar patterns were observed for rate ratios in comparison with unvaccinated matched comparators as the reference (RR for first dose not reported), although rate ratios were attenuated relative to the SIR. The clinical presentation was mild for 129 of 136 definite or probable cases of myocarditis, with resolution in most cases. One fatality occurred. Status of cases after hospital discharge and consistent measures of cardiac function were not available.[55] This study did not include information about vaccinees 12 to 15 years of age.

Table 16. Ratios Comparing Rates of Myocarditis Diagnosis of Vaccine Compared with Historical Period and Unvaccinated Individuals[55]

Age and Sex	Standardized Incidence Rate Ratio[a] (95% CI)		Rate Ratio[b] (95% CI)
	Dose 1	Dose 2	
Overall	1.42 (0.92, 2.10)	5.34 (4.48, 6.40)	2.35 (1.10, 5.02)
16-19 Year			
Male	1.62 (0.32, 4.72)	13.60 (9.30, 19.20)	8.96 (4.50, 17.83)
Female	0	6.74 (0.76, 24.35)	2.95 (1.42, 20.91)
20-24 Year			
Male	2.14 (0.69, 5.00)	8.53 (5.57, 12.50)	6.13 (3.16, 11.88)
Female	2.37 (0.03, 13.20)	10.76 (3.93, 23.43)	7.56 (1.47, 38.96)
25-29 Year			
Male	1.39 (0.28, 4.05)	6.96 (4.25, 10.75)	3.58 (1.82, 7.01)
Female	0	2.54 (0.03, 14.14)	0
≥30 Year			
Male	1.23 (0.59, 2.26)	2.90 (1.98, 4.09)	1.00 (0.61, 1.64)
Female	1.42 (0.29, 4.15)	2.44 (0.98, 4.09)	0.82 (0.33, 2.02)

a. In comparison with 2017-2019 rates
b. In comparison to matched unvaccinated comparator (11 January to 31 May 2021)

Information about myocarditis in individuals 12 to 15 years of age has been reported by the Israeli Ministry of Health as part of their overall COVID-19 Vaccine monitoring. As of 25 September 2021, 331,538 individuals 12 to 15 years of age have received a first dose of COVID-19 vaccine,[56] 255,444 have received a second dose (Table 17). A total of 18 serious post-vaccination events have been reported to the Ministry of Health including 12 cases of myocarditis. All patients received treatment and have been discharged. Among males the reporting rate of myocarditis was lower for individuals 12 to 15 years of age than for individuals 16 to 19 years of age for both Dose 1 (0.63 vs 1.21 per 100,000 doses) and Dose 2 (8.20 vs 16.47 per 100,000 doses). Among females 12 to 15 years of age, 0 cases were observed after Dose 1, and 1 case was observed after Dose 2.

Table 17. Myocarditis Rates Per Dose by Sex and Age, Israel Ministry of Health, Through 25 September 2021[56]

Sex	Age	Dose 1 (Cases Reported 21 Days Post-Dose 1)			Dose 2 (Cases Reported 0-30 Days Post-Dose 2)		
		Total doses	Cases reported	Rate per 100,000 doses	Total doses	Cases reported	Rate per 100,000 doses
Female	12-15	169,371	0	0.00	129,898	1	0.77
	16-19	244,077	0	0.00	213,483	2	0.94
	20-24	269,544	1	0.37	242,611	6	2.47
	25-29	251,240	0	0.00	228,518	1	0.44
Male	12-15	157,862	1	0.63	121,984	10	8.20
	16-19	247,611	3	1.21	212,558	35	16.47
	20-24	281,233	6	2.13	252,127	26	10.31
	25-29	261,111	3	1.15	238,608	20	8.38

No population-based studies of post-vaccination myocarditis rates among younger adolescents (eg, individuals 12 to 15 years of age) were identified in the published literature. The Sponsor engaged an external research partner to conduct a pre-specified analysis of post-vaccination myocarditis rates in the US within age strata using de-identified open insurance claims data based on unadjudicated diagnosis codes. The analyses suggest that myocarditis rates do not trend higher in individuals 12 to 15 years of age after vaccination. Among males, rates were highest in individuals 16 to 17 years of age for both Dose 1 and Dose 2 relative to other age categories. Among females, few cases were observed post-Dose 1; post-Dose 2 rates were highest in individuals 20 to 24 years of age with rates declining with by age category.

The Vaccine Adverse Event Reporting System (VAERS) has information on the number of myocarditis cases within 7 days of vaccination per million second doses from spontaneous reports in the US. A similar pattern was observed as in Israel 30 days post second dose, although rates were lower due in part to the length of the risk window. [57]

Several reports have been published describing clinical presentation, time to resolution, and long-term sequelae of post-vaccination myocarditis and pericarditis. Typically, cases present with chest pain, require minimal intervention and experience rapid resolution of symptoms.[58,59,60]

Myocarditis is an important complication of COVID-19 illness in children. CDC studied a US cohort of patients with at least one inpatient or hospital-based outpatient encounter during March 2020 to January 2021 and reported that among patients with COVID-19 the adjusted risk ratio (aRR) for myocarditis was highest in the <16 and ≥75 age groups, with more than a 30-fold greater risk of myocarditis in COVID-19 illness compared with patients without COVID-19 (aRR: <16 years = 36.8 [95% CI: 25.0 to 48.6]; 16 to 24 years = 7.4 [95% CI: 5.5 to 9.2]; 25 to 39 years = 6.7 [95% CI 5.5 to 8.0]).[22]

In India, a study following 255 children with SARS-CoV-2 infection, 100 patients (median age 5.2 years, 59% males, 70% with moderate to severe disease) were hospitalized. The incidence of myocarditis was 4% in SARS-CoV-2 infected patients, of whom 78% died in the hospital.[61]

Following the approach taken in a Morbidity and Mortality Weekly Report (MMWR), the Sponsor determined the expected number of overall and sex-specific myocarditis (including myocarditis, pericarditis, and myopericarditis) cases per 1 million fully vaccinated persons under the assumption that rates in children 5 to <12 year of age are equal to rates for adolescents 12 to 15 years of age, and compared these to the to the number of expected COVID-19 cases and hospitalizations per 1 million vaccinated persons assuming CDC rates for children 5 to <12 years of age 25 September 2021 (assuming equal rates of COVID-19 and hospitalizations for males and females).[14,62] The estimated numbers of prevented COVID-19 cases and associated hospitalizations for 1 million vaccinated children 5 to <12 years of age during the 120 days post-vaccination are ~33,600 and 170, respectively; in contrast, 21 post-vaccination myocarditis cases would be expected. Looking separately at males and females, 43 myocarditis cases would be expected per 1 million fully vaccinated males and 4 cases would be expected per 1 million fully vaccinated females.

These estimates are dependent on several assumptions. The benefit calculation assumes 90% efficacy for preventing COVID-19 and hospitalization and, further, does not take into consideration the potential for COVID-19-associated long-term sequelae as well as other societal benefits. Additionally, the risk estimate assumes that children 5 to <12 years of age will have the same rates of post-vaccination myocarditis as observed in adolescents 12 to 15 years of age in the US. The latest data from Israeli safety surveillance databases indicate that incidence rates of rare myocarditis cases post-Dose 2 in vaccinated adolescents 12 to 15 years of age are lower than those observed in individuals 16 to 19 years of age.[56] Additionally, the dose for children 5 to <12 years of age is 1/3 of the dose given to older vaccinees (10 µg vs. 30 µg dose formulation of the Pfizer-BioNTech COVID-19 Vaccine). Based on these data, it is reasonable to predict that post-vaccine myocarditis rates are likely to be even lower in 5 to <12 years of age than those observed in adolescents 12 to 15 years of age.

Overall, the existing real-world data on effectiveness, post-vaccination myocarditis rates, and risk of myocarditis in COVID-19 illness support a positive benefit-risk benefit profile in all age categories, with evidence that individuals 12 to 15 years of age do not have higher rates than older adolescents and young adult groups that demonstrate highest rates.

These real-world data in adolescents 12 to 15 years of age provide support and reassurance that younger children 5 to <12 years of age, given the available effectiveness and safety data for this latter age group, have a favorable benefit-risk benefit profile for vaccination.

5. POST-AUTHORIZATION SAFETY UPDATE

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 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. Additionally, 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 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 Pharmacovigilance 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.

5.1. Safety Update from Adolescents 12 to 15 Years of Age

Review of the cumulative available post-authorization data in individuals 12 to 15 years of age did not identify any additional or unexpected risks associated with BNT162b2 and confirms the favorable benefit-risk balance observed in the clinical study. Post-authorization surveillance activities depicted in the pharmacovigilance plan will continue.

5.2. Pharmacovigilance

Upon approval, Pfizer/BioNTech will include children 5 to <12 years of age into the ongoing pharmacovigilance activities previously agreed with the FDA for the BNT162b2.

6. BENEFIT/RISK ASSESSMENT

COVID-19 is a serious and potentially life-threatening disease for children. Based on CDC data, among children 5 to <12 years of age, the cumulative burden of COVID-19 to date is 1.8 million cases, 8622 hospitalizations, and 138 deaths. Additionally, COVID-19 causes additional long-term sequelae. More than 5200 cases of MIS-C in children have been documented, 50% in children 5 to 13 years of age.

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.

Two primary doses of the 10 µg BNT162b2 vaccine given 3 weeks apart in children 5 to <12 years of age have shown a favorable safety and tolerability profile, robust immune responses against all variants of concern including Delta, and vaccine efficacy of 90.7% against laboratory-confirmed symptomatic COVID-19 occurring at least 7 days after Dose 2 in a period where the Delta variant was predominant.

The size of the safety database is not large enough to detect any potential risks of myocarditis associated with vaccination. For this reason, long-term safety of the COVID-19 vaccine in participants 5 to <12 years of age will be studied in 5 post-authorization safety studies, including a 5-year follow-up study to evaluate long term sequelae of post-vaccination myocarditis/pericarditis.

Nevertheless, Israeli safety surveillance databases suggest that incidence rates of rare post-vaccination myocarditis peaks in individuals 16 to 19 years of age (primarily in males) and declines in adolescents 12 to 15 years of age. In addition, the dose for children 5 to <12 years of age is 1/3 of the dose given to older vaccinees (10 µg vs. 30 µg).

Based on this information, it is reasonable to predict that post vaccine myocarditis rates are likely to be even lower in 5 to <12 years of age than those observed in adolescents 12 to 15 years of age.

Considering a vaccine efficacy of 90%, the estimated number of COVID-19 cases and associated hospitalizations prevented over 120 days per million of fully vaccinated children 5 to <12 years of age is ~33,600 and 170 respectively. In contrast, the number of post-vaccination myocarditis (including myocarditis, pericarditis, and myopericarditis) cases expected in the same period of time per million second doses is 21 (assuming rates of post-vaccination myocarditis are as high in 5 to <12 years of age as in 12-17 years of age which is not likely).

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

7. APPENDIX

COVID-19 Case Criteria

Protocol Case Definition (first definition)	**CDC Case Definition (second definition)**
Presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test), which triggered 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	Protocol definition plus could include the following additional symptoms defined by the CDC,[63] but did not necessarily trigger a potential COVID-19 illness visit: • Fatigue • Headache • Nasal congestion or runny nose • Nausea or abdominal pain[64] • Lethargy

COVID-19 Severe Case Criteria

Protocol Severe Case Definition	CDC Severe Case Definition
Confirmed COVID-19 and presence of at least 1 of the following which triggered 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 normal range[65] – 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 normal range • Significant acute renal failure: defined as serum creatinine ≥2 times upper limit of normal (ULN) for age or 2-fold increase in baseline creatinine • Significant gastrointestinal/hepatic failure: defined as total bilirubin ≥4 mg/dL or ALT 2 times ULN for age • Significant neurological dysfunction: defined as Glasgow Coma Scale score ≤11, or acute change in mental status with a decrease in Glasgow Coma Scale score ≥3 points from abnormal baseline[66] • Admission to an ICU • Death	Protocol definition plus could include the following additional severe disease criteria defined by the CDC:[6] • Hospitalization • Admission to the ICU • Intubation or mechanical ventilation • Death

MIS-C Criteria

Confirmed per the CDC MIS-C case definition,[68] meeting all of the below criteria:

- An individual <21 years of age presenting with fever (≥38.0 °C for ≥24 hours or report of subjective fever lasting ≥24 hours)
- 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
- 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)
- No alternative plausible diagnoses
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test OR COVID-19 exposure within past 4 weeks of onset of symptoms

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