Vaccines and Related Biological Products Advisory Committee Meeting

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BNT162B2

PFIZER-BIONTECH COVID-19 VACCINE

PFIZER BRIEFING MATERIALS FOR JUNE 14 - 15, 2022

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

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ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	Coronavirus Disease 2019
EUA	Emergency Use Application
FDA	(US) Food and Drug Administration
FFRNT	fluorescent focus reduction neutralization test
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IM	intramuscular
IRR	illness rate ratio
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
mITT	modified intent-to-treat
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein binding
NT50	neutralizing titer 50
PRNT	plaque-reduction neutralization test
RNA	ribonucleic acid
RVE	relative vaccine efficacy
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
US	United States
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VOC	variant of concern
VSD	Vaccine Safety Datalink

EXECUTIVE SUMMARY

Pfizer/BioNTech are seeking emergency use authorization (EUA) for individuals 6 months to <5 years (6 months through 4 years) of age to receive the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine (BNT162b2) at the 3-µg dose level. The vaccine is administered as three doses, with the initial two doses given 3 weeks apart followed by a third dose given at least 8 weeks after the second dose. This request is based on the totality of available data which include safety, immunogenicity, and supportive efficacy results in this pediatric population, which encompasses follow-up from Dose 1 to 2 months after Dose 3.

Although the peak of the Omicron wave appears to have slowed, other Omicron subvariants such as BA.2, BA.2.12.1, BA.4, and BA.5 are increasingly being reported in several states. Currently, Connecticut, Illinois, Massachusetts, New Jersey, New York, and Vermont have increasing infection rates higher than at the peak of the Delta variant wave. While rates of COVID-19 cases in children <5 years of age, who are currently ineligible for vaccination, are down from the peak of the Omicron wave, COVID-19-associated hospitalizations among US children <5 years of age are now 1.6 times higher than among children 12 to 17 years of age and 5.4 times higher than children 5 to 11 years of age.

Real-world effectiveness data indicate that in adolescents and adults, three doses of BNT162b2 are needed to provide high levels of protection against both symptomatic disease and severe illness due to Omicron. Based on the available BNT162b2 immune response and vaccine efficacy (VE) data for children 6 months to <5 years of age against symptomatic disease during a period in which the Omicron variant was predominant, it is anticipated that the protection provided by three doses of BNT162b2 in this age group will be similar to that observed in older age groups. Protection against hospitalization and severe disease does not appear to wane substantially after three doses of the vaccine in adolescents and adults and is expected to be similar in children <5 years of age after three doses.

This request meets United States (US) Food and Drug Administration (FDA) guidance for safety data expectations for follow-up of subject participants and immunobridging criteria comparing 6 months to <5 years to young adults 16 to 25 years of age. It is supported by the totality of available data including Phase 2/3 immunobridging analyses (SARS-CoV-2 wild-type) after two and three vaccine doses; supportive immune responses against wild-type, Delta, and Omicron variants; descriptive efficacy against Delta and Omicron variants after two and three vaccine doses; and safety data based on a median of at least 2 months of total follow-up after Dose 3 as of the data cutoff date of 29 April 2022. Post-Dose 3 safety, immunogenicity, and descriptive efficacy data are based on a combined population of approximately 4500 participants 6 months to <5 years of age who were randomized 2:1 to receive three doses of BNT162b2 3-µg or placebo. This included approximately 3000 BNT162b2 recipients of whom N~1000 received three doses of BNT162b2. In the 2 to <5 years of age group, this was comprised of approximately 2750 participants that included N~1800 BNT162b2 recipients of whom N~600 received three doses. In the 6 months to <2 years of age group, this was comprised of approximately 1800 participants that included N~1200 BNT162b2 recipients of whom N~380 received three doses.

Specifically, the EUA Amendment is supported by the following:

- A favorable safety profile in children 6 months to <5 years of age.

- Meeting immunobridging success criteria following three doses in children 6 months to <5 years of age – satisfying effectiveness criteria for EUA approval.

- Documented Omicron variant neutralizing antibody response at 1-month post-Dose 3.

- A descriptive efficacy analysis across the 6 months to <5 years of age population.

Overall, administration of three doses of BNT162b2 3-µg provided strong immune responses to both SARS-CoV-2 wild-type strain and variants (including Omicron) and measurable protection as evidenced by supportive VE against symptomatic illness, and with a reactogenicity profile similar to what has been observed in other age groups. A summary of the dose selection, key safety, immunogenicity and efficacy results are described below.

Dose Selection

In order to select the optimal dose level of BNT162b2 for infants and young children <5 years of age, ensuring the appropriate balance of safety and tolerability with vaccine-elicited immune responses, an age de-escalation Phase 1 dose level-finding study was conducted to evaluate dose levels of 3-µg followed by 10-µg of BNT162b2 in children 2 to <5 years of age. The 3-µg dose level was well-tolerated in this group; however, at the 10-µg dose level, higher frequencies and greater severity of reactogenicity to BNT162b2 (particularly fever, reported in approximately 19% of participants who received one or two doses) were observed, suggesting the 10-µg dose level was not sufficiently tolerated. Taken together with comparably robust neutralizing antibodies at 7 days post-Dose 2 observed at both the 3-µg and 10-µg dose levels, the 3-µg dose level of BNT162b2 was selected to proceed to Phase 2/3 for the 2 to <5 years of age group and was the only dose level tested for the younger group of children 6 months to <2 years of age, in whom it was also well-tolerated and produced a robust 7 days post-Dose 2 neutralizing antibody response. At the selected dose level, BNT162b2 3-µg demonstrated an excellent safety profile in Phase 1 participants as well as in Phase 2/3 (as summarized below), that is important to help ensure vaccination compliance in infants and toddlers.

Safety and Tolerability

Safety was evaluated from a total of 4526 children 6 months to <5 years of age who were randomized 2:1 to receive BNT162b2 3-µg or placebo, including 2750 in the 2 to <5 years of age group and 1776 in the 6 months to <2 years of age group. BNT162b2 at the 3-µg dose level was well-tolerated, based on safety data evaluated up to 1-month post-Dose 3 and AEs reported up to a data cutoff date of 29 April 2022. As of the data cutoff date, the total follow-up time for participants in both age groups who completed three doses of BNT162b2 was a median of at least 2 months post-Dose 3. The reactogenicity and AE profiles reflect a safe and tolerable vaccine profile in children 6 months to <5 years of age.

Reactogenicity to three doses of vaccine was mostly mild to moderate and short-lived, with most events occurring at similar or lower frequencies after the third dose compared with the first or second dose of BNT162b2 3-µg in children 6 months to <5 years of age and with a similar profile

as observed in other age groups. The median onset of reactogenicity events was typically 1 to 2 days after each dose and most events resolved within 1 to 2 days after onset.

The observed AE profile in this study did not suggest any new safety concerns for BNT162b2 administered as three doses at the 3-µg dose level in children 6 months to <5 years of age. Many AEs reported up to 1 month after Dose 3 were consistent with reactogenicity events, or other infections or illnesses that are expected to be observed in a pediatric general population. Few SAEs or AEs leading to

Immunobridging success criteria were met for both age groups based on the GMR and difference in seroresponse rate (as defined in Section 3.3.2), comparing neutralizing titers from children 2 to <5 years of age and children 6 months to <2 years of age who received three doses of BNT162b2 3-µg in C4591007 to those from young adults 16 to 25 years of age in C4591001 who received two doses of BNT162b2 30-µg. withdrawal, and no deaths were reported. There were few AEs of lymphadenopathy and rash reported, and there were no cases of vaccine-associated anaphylaxis or myocarditis/pericarditis observed. The observed safety profile across age groups continues to be favorable for BNT162b2.

Immune Response Data

Immunobridging success criteria were also met at 1-month post-Dose 2 in the 6 months to <2 years of age group, but only partially met in the 2 to <5 years of age group. An additional post-Dose 2 supportive noninferiority analysis (requested by FDA) compared children 2 to <5 years of age after two doses of BNT162b2 at the 3-µg dose level with older adults ≥65 years of age who received two doses of BNT162b2 at the 30-µg dose level; the data showed that noninferiority was met comparing these children to older adults who demonstrated high VE of >90% in the pivotal efficacy Study C4591001.

Three doses of BNT162b2 3-µg elicited robust neutralizing antibody responses to SARS-CoV-2 wild-type in children 2 to <5 years of age and children 6 months to <2 years of age comparable to young adults (16 to 25 years of age) who received two doses of BNT162b2 30-µg, from whom high VE have been inferred.

Compared to two doses, three doses of BNT162b2 3-µg increased neutralizing titers to the Delta variant and especially to the Omicron variant of SARS-CoV-2, in children and in adults. Immunological patterns observed for children in variant and reference strain neutralization were comparable to those of adults 18 to 55 years of age who received three doses of BNT162b2 30-µg. While adults appeared to have somewhat higher overall post-Dose 3 titers compared with pediatric groups, these differences may be explained by the fact that adults had a longer dosing interval between Dose 2 and Dose 3 (approximately 6 months) at a time when antibody levels had already waned and the effects of a booster would be more pronounced, compared to the shorter (approximately 2 to 3 months) interval between Dose 2 and Dose 3 for children.

Efficacy Data

Descriptive efficacy analyses for Phase 2/3 Study C4591007 populations of children 6 months to <5 years of age were based on symptomatic COVID-19 cases accrued from Dose 1 to a data

cutoff date of 29 April 2022. These represent available data for a still-actively enrolling study. VE was estimated across the total population of participants 6 months to <5 years of age randomized 2:1 to receive BNT162b2 3-µg vs placebo, which included 992 BNT162b2 recipients and 464 placebo recipients who received three doses of study intervention during the blinded placebo-controlled follow-up period.

As anticipated based on two-dose real-world vaccine effectiveness against Omicron seen in older age groups, the observed VE during blinded placebo-controlled follow-up including COVID-19 cases confirmed at least 7 days after Dose 2 to before Dose 3 for BNT162b2 3-µg administered to children 6 months to <5 years of age was modest at 28.3% (2-sided 95% CI: 8.0%, 43.9%), noting this was during a period when Omicron was widely circulating.

In contrast, based on COVID-19 cases confirmed from at least 7 days post-Dose 3 to the cutoff date, observed VE in children 6 months to <5 years of age after three doses increased to 80.3% (2-sided 95% CI: 13.9%, 96.7%) during a period when Omicron accounted for >98% of all COVID-19 cases globally. Relative vaccine efficacy (RVE) based on 4 cases reported at least 7 days after Dose 3 (original BNT162b2 group) vs 6 cases reported at least 7 days after Dose 2 (original placebo group unblinded to receive BNT162b2) during the same period was 76.2% (2-sided 95% CI: -0.5%, 95.1%) and is supportive of the post-Dose 3 efficacy observed in the blinded placebo-controlled period data. The reported signs and symptoms associated with confirmed COVID-19 cases reported up to the cutoff date reflected predominantly mild to moderate illness and were generally similar in the BNT162b2 and placebo groups for both age groups.

High VE has previously been observed for BNT162b2 in individuals ≥5 years of age who received the age-appropriate primary series, based on similar numbers of confirmed COVID-19 cases. After a primary series of BNT162b2 10-µg in children 5 to <12 years of age, observed VE 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 during a period of Delta variant predominance (data cutoff date: 08 October 2021). After a primary series of BNT162b2 30-µg adolescents 12 to 15 years of age, observed VE was 100% (2-sided 95% CI: 75.3%, 100.0%), based on 0 cases in the BNT162b2 group and 16 cases in the placebo group during a period of Alpha variant predominance (data cutoff date: 13 March 2021).

Benefit-Risk Assessment

Based on real-world data describing rates of COVID-19 among US children <5 years of age, vaccine effectiveness and durability of protection observed in adolescents and adults, as well as available clinical study data including descriptive efficacy against Omicron in children 6 months to <5 years of age (ie, observed VE of approximately 80%) a benefit-risk assessment assumes that vaccinating US children <5 years of age with three doses of BNT162b2 3-µg could prevent 17,448 cases per million population (range: 12,816 to 20,808 per million) based on average rates of COVID-19 seen over the entire pandemic, and in the context of the Omicron wave peak could prevent 169,108 cases per million population (range: 124,296 to 201,704 per million), over 6 months.

Myocarditis and/or pericarditis, while rare, are important identified risks associated with the Pfizer-BioNTech COVID-19 Vaccine, especially in adolescents and young adults. Although not being statistically powered to identify rare events such as myocarditis and/or pericarditis, no cases of myocarditis/pericarditis were identified in clinical study participants 6 months to <5 years of age in Study C4591007 through a median of approximately 4 months of follow-up after Dose 2 and 2.1 months of follow-up after Dose 3, and no cases were identified among clinical study participants 5 to <12 years of age in prior submissions that included at least 2 months of follow-up after Dose 2.

Conclusions

Overall, the known and potential risks and benefits of administering three doses of Pfizer-BioNTech COVID-19 Vaccine 3-μg dose to children 6 months to <5 years of age outweigh the known and potential risks, based on the available safety, immunogenicity and efficacy data. Children are individually at risk for potential serious illness, and the public health impacts of vaccinating against COVID-19 also weigh in favor of amending the current EUA to authorize the vaccine for this age range. Given that three doses of BNT162b2 3-μg to children 6 months to <5 years of age met the noninferiority criteria compared to older age groups and high level of VE against Omicron-related symptomatic disease was observed, the real-world effectiveness of BNT162b2 among children <5 years of age is reasonably expected to be similar, or higher, than that observed for older adults. Finally, BNT162b2 3-μg demonstrates an acceptable safety profile that is important to help ensure vaccination compliance in infants and toddlers.

1. BACKGROUND INFORMATION

1.1. Proposed Indication for the 3-μg Dose Level of BNT162b2

Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 6 months <5 years of age.

1.2. Product Description

The 3-μg dose level utilizes the same formulation (Tris/Sucrose drug product) as authorized for Emergency Use in children 5 to 11 years of age but diluted to a lower dose. The vaccine drug product is a preservative-free, sterile dispersion of lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer for intramuscular (IM) administration and is formulated at 0.1 mg/mL ribonucleic acid (RNA) in 10 mM Tris buffer, 300 mM sucrose, pH 7.4. To prepare the vaccine for administration, the drug product is diluted by addition of 0.9% sodium chloride to a final concentration of 0.015 mg/mL RNA, enabling a dose of 3-μg in 0.2 mL.

1.3. Dosage and Administration for the 3-μg Dose Level

The Pfizer-BioNTech COVID-19 Vaccine (3-μg Dose) supplied in multiple dose (10-dose) vials with maroon caps and labels with maroon borders requires dilution and is administered intramuscularly as three doses (0.2 mL each), with the initial two doses given 3 weeks apart followed by a third dose given at least 8 weeks after the second dose to individuals 6 months through 4 years of age. After dilution, 1 vial contains 10 doses of 0.2 mL.

The vaccine is supplied as a 10-dose multidose vial that must be diluted before use (see Table 1).

Table 1.   Pfizer-BioNTech COVID-19 Vaccine, 3-μg Dose Level, Multiple Dose Vial with Maroon Cap and Vial and Carton Label with Maroon Border

Age Range	Dilution Information	Doses Per Vial After Dilution	Dose Volume
6 months through 4 years	Dilute with 2.2 mL sterile 0.9% Sodium Chloride Injection, USP prior to use	10	0.2 mL

2. UNMET MEDICAL NEED

Although the peak of the BA.1 Omicron wave appears to have slowed, other Omicron subvariants such as BA.2, BA.4, and BA.5 are increasingly being reported in several states at the time of writing of this document. Currently, Connecticut, Illinois, Massachusetts, New Jersey, New York, and Vermont have caseloads higher than at the peak of the Delta variant wave (Figure 1).

Figure 1.   COVID-19 Case Rate in Selected United States, All Ages: 27 January 2020 Through 10 May 2022[1]
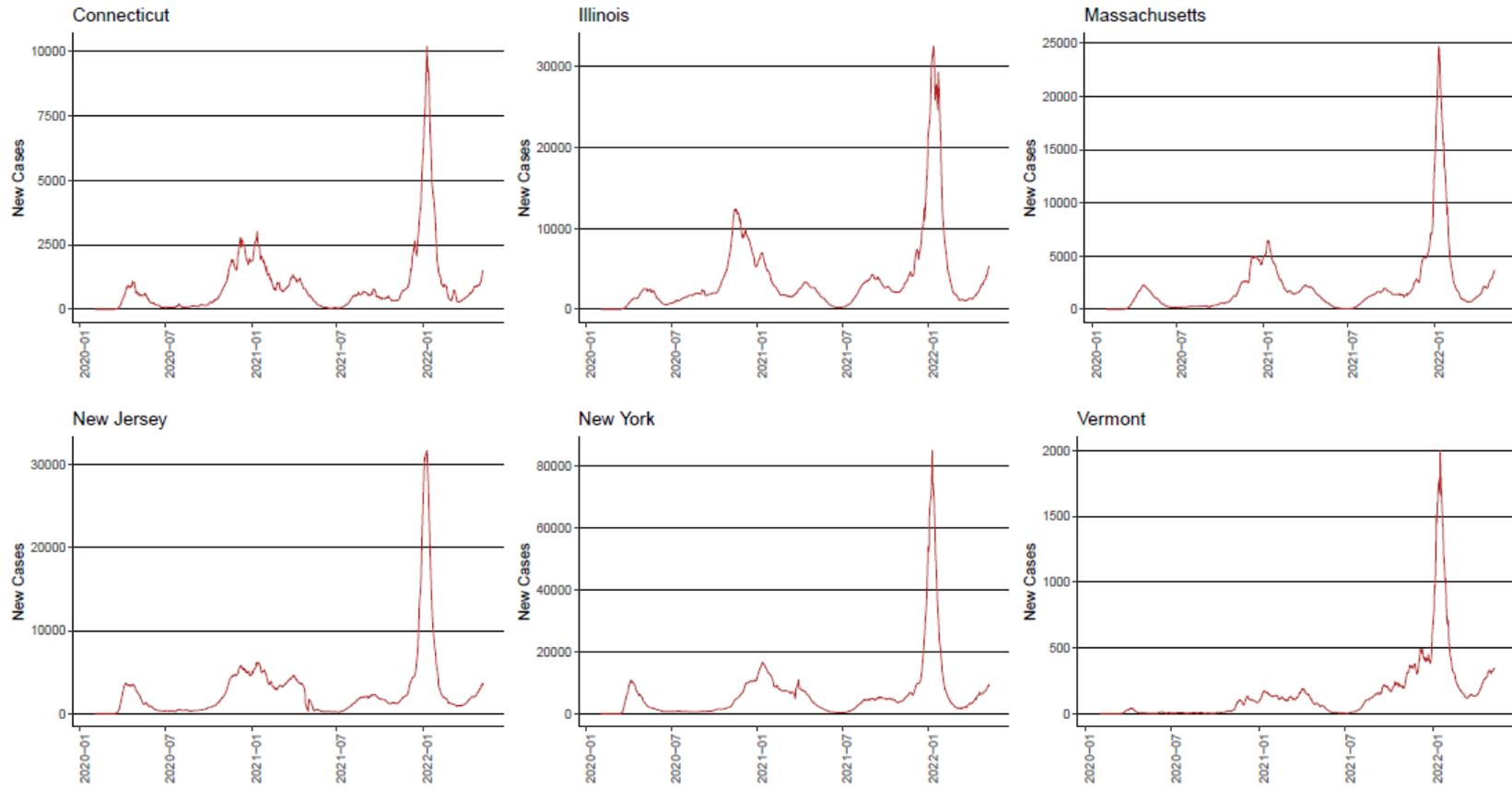
While the rates of COVID-19 cases in children <5 years of age, who are currently ineligible for vaccination, are down from the peak of the Omicron wave (Figure 2), COVID-19-associated hospitalizations among US children <5 years of age are now higher than those for older pediatric age groups for whom vaccination is available (Figure 3).[2,3]

Figure 2.   Weekly COVID-19 Rate Per 100,000 Children <5 Years of Age: 07 March 2020 Through 30 April 2022
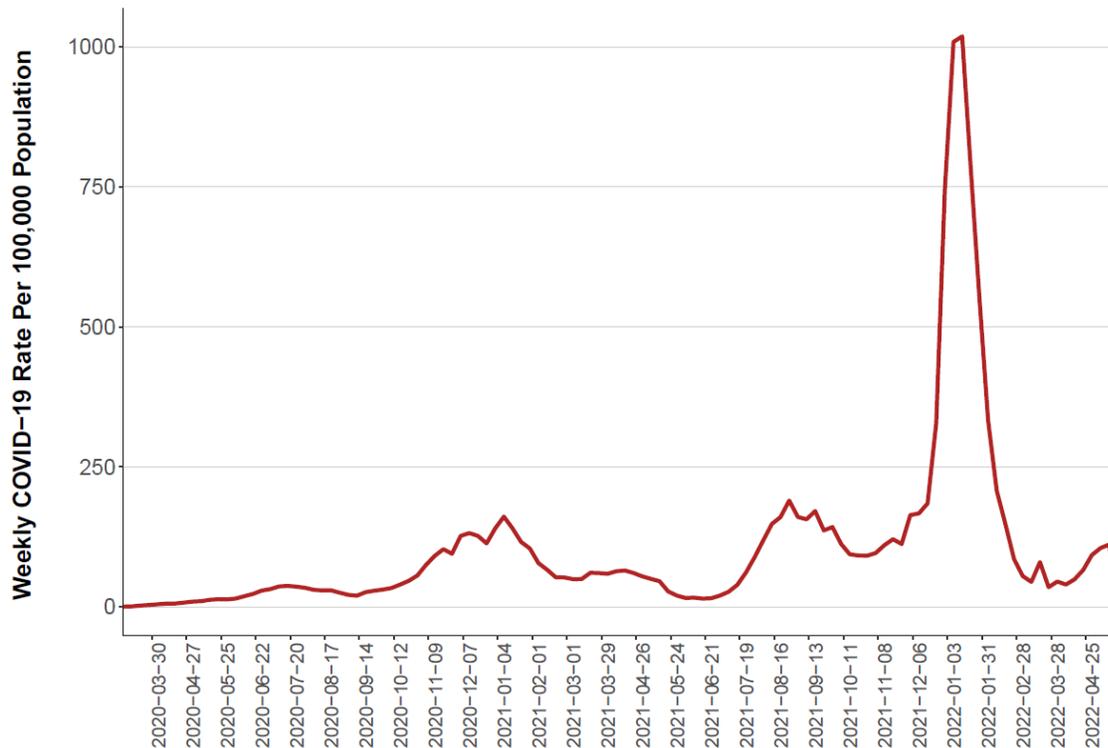
Currently, the hospitalization rate in children <5 years of age is similar to what was experienced at the peak of the Delta wave and is higher than at any other week of the pandemic, outside of the Omicron wave (Figure 3). During the Omicron wave, among vaccine ineligible children <5 years of age, COVID-19-associated hospitalization was 1.6 times higher than among children 12 to 17 years and 5.4 times higher than children 5 to 11 years of age. Given that vaccine effectiveness after three doses does not appear to wane substantially for at least several months against hospitalization and severe disease,[4,5] vaccination will be critical for helping to prevent hospitalization and severe illness in young children.

Preventing COVID-19, particularly severe forms of the disease, will also subsequently reduce acute and post-acute sequelae of COVID-19. Many persistent symptoms[6] and severe sequelae have been documented in children. Approximately 25% of the over 8,000 cases of Multisystem Inflammatory Syndrome in Children (MIS-C) have been reported in children 0 to <5 years of age. Further, the CDC documented a nearly three and a half times higher incidence of new-onset diabetes for pediatric (0 to <12 years) COVID-19 patients than patients without COVID-19.[7] Reducing the burden of infection will be critical to lessening the impact of these severe, debilitating, and sometimes life-long sequelae.

Figure 3.   Weekly COVID-19 Hospitalization Rate in Children <5 years, 5 to <12 years, and 12 to <18 years of age: 11 March 2020 Through 30 April 2022[3,4,5,6,8]
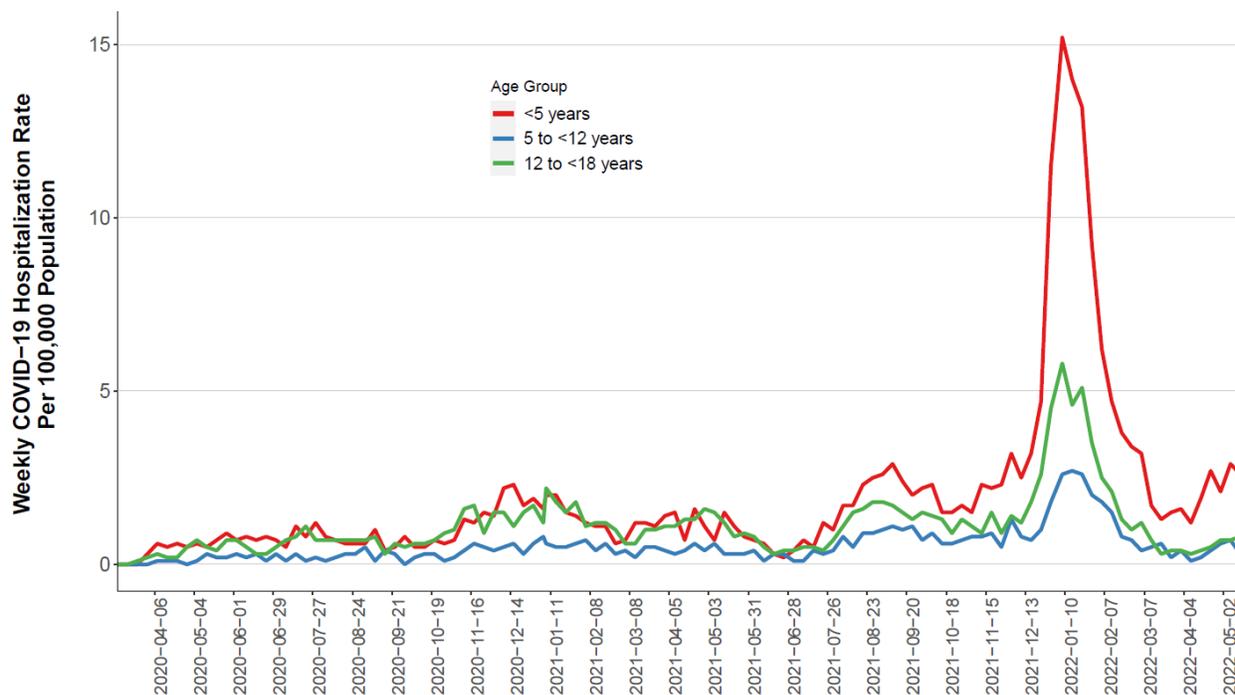
Finally, there have been nearly 500 COVID-19-associated deaths among children 0 to <5 years of age. Approximately half of these deaths have occurred over the past 8 months.

Ensuring children 6 months to <5 years of age have access to vaccine will add an important layer of direct vaccine protection to children in this age group and add another important layer of community protection against symptomatic and severe illness including hospitalization, post-acute sequelae, and death as it has in all other age groups.

3. OVERVIEW OF CLINICAL STUDIES

3.1. 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 Phase 2/3 selected dose part, in protocol defined age groups: 5 to <12 years, 2 to <5 years, and 6 months to <2 years of age. Initiation of the 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. Data from the 5 to <12 years of age group were previously submitted to the Food and Drug Administration (FDA) and supported Emergency Use Authorization (EUA) in this age group.

Phase 2/3 of Study C4591007 (which remains ongoing) commenced with the selected vaccine dose for each age group (based on review of Phase 1 dose-finding data). Participants were randomized 2:1 to receive vaccine or placebo (saline) at sites in the US, Finland, Poland, Spain, and Brazil. Eligibility in Phase 2/3 permitted enrollment of participants with medical conditions such as stable Type 1 diabetes or hypothyroidism; stable and controlled human

immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) infection; and past serological or microbiological evidence of prior (not active) SARS-CoV-2 infection. The pediatric vaccination series for children 6 months to <5 years of age was initially planned as a two-dose series given 3 weeks apart; however, based on emerging clinical and real-world data showing that three doses provide higher protection particularly against Omicron than two doses, the protocol was amended in January 2022 to add a third dose given at least 8 weeks after the second dose at the age-appropriate dose level.

At the 6-month post-Dose 2 follow-up visit, Phase 2/3 participants can be unblinded to vaccine group assignment, and those who originally received placebo may be vaccinated with BNT162b2 at the age-appropriate dose level. Unblinded participants continued to be followed in the study in an open-label manner.

3.2. Phase 1/2/3 Registrational Study C4591001

Study C4591001 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 registration study. It was started as a Phase 1/2 study in adults in the US, was then amended to expand the study to a global Phase 2/3 study 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.

Data from Phase 2/3 young adult participants 16 to 25 years of age, in which efficacy was previously demonstrated, served as an immunobridging comparator group to infer efficacy to pediatric participants in Study C4591007. Additionally, a Phase 3 booster group of adults 18 to 55 years of age contributed immunogenicity data to a descriptive analysis of SARS-CoV-2 Omicron and Delta variant neutralization at 1-month post-Dose 3, serving as a reference group to variant neutralization data in pediatric groups in Study C4591007.

3.3. Overview of Methods for Evaluation of Safety and Effectiveness

3.3.1. Study C4591007 – Safety Analysis Endpoints and Methods

Reactogenicity and antipyretic/pain medication use were recorded daily for 7 days after each dose administration using prompts from an electronic diary (e-diary). This allowed recording only within a fixed time window to provide an accurate representation of the participant's experience based on parent/caregiver assessment. Grading scales were based on FDA guidance.[9] Reactogenicity events were:

Children 2 to <5 years of age:

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

Children 6 months to <2 years of age:

- Local reactions: tenderness, redness, and swelling at the injection site
- Systemic events: fever, decreased appetite, drowsiness, and irritability

All unsolicited adverse events (AEs), as reported by parents/caregivers, are collected from Dose 1 through 1 month after Dose 2 and from Dose 3 through 1 month after Dose 3, and serious AEs (SAEs) are collected from Dose 1 through 6 months after Dose 3. Deaths are recorded to the end of study. AEs were categorized by frequency, maximum severity, seriousness, and relationship to study intervention using system organ class (SOC) and preferred term (PT) according to Medical Dictionary for Regulatory Activities (MedDRA). AEs were also categorized as Tier 1 (prespecified events of clinical importance; none designated at this time) and Tier 2 ('common' PTs, reported in ≥1% of participants in any vaccine group).

Myocarditis and pericarditis are designated in the C4591007 protocol as AEs of special interest (AESIs). For other events of specific clinical interest, Pfizer evaluates a dynamic list of MedDRA AE terms during clinical safety data review and signal detection; these include events of interest due to association with COVID-19 and vaccines in general, taking into consideration the CDC list of AESIs for COVID-19 that include events potentially indicative of severe COVID-19 and of autoimmune and neuroinflammatory disorders.

AE analyses up to 1 month after Dose 3 and to the data cutoff date which represents a median of at least 2 months of total follow-up after Dose 3 are presented in this briefing document.

Safety data were reported as descriptive summary statistics including 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. Safety data are discussed separately in children 2 to <5 years and then in children 6 months to <2 years. Safety analyses were based on blinded placebo-controlled follow-up unless otherwise indicated.

3.3.2. Study C4591007 – Immunogenicity Analysis Endpoints and Methods

3.3.2.1. Immunobridging Analyses

Immunogenicity analyses were conducted on the immunobridging subset of participants in the evaluable and all-available immunogenicity populations.

The Phase 2/3 primary immunogenicity objective was immunobridging the immune responses against SARS-CoV-2 wild-type strain from children 2 to <5 years and 6 months to <2 years of age in Study C4591007 compared to young adults 16 to 25 years of age in the Phase 3 efficacy Study C4591001. An initial analysis was conducted at 1 month after Dose 2; after adding a third dose to the pediatric regimen, immunobridging analyses were conducted to compare immune responses in children at 1 month after Dose 3 to young adults at 1 month after Dose 2.

The pediatric post-Dose 2 immunobridging subset included, approximately 300 participants in the BNT162b2 group and 150 participants in the placebo group for each pediatric age group (C4591007). Comparator data were from a randomly selected subset of participants 16 to 25 years of age from Study C4591001 and included approximately 300 participants in the BNT162b2 group and 50 participants in the placebo group. Different sets of participants from C4591001 were selected for each of the pediatric age group immunobridging analyses. Immunobridging analysis included individuals without serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2. A supportive post-Dose 2 analysis was conducted to compare SARS-CoV-2 serum neutralizing titers at 1-month post-Dose 2 from a

subset of children 2 to <5 years of age in Study C4591007 who received two doses of 3-µg BNT162b2 with those of older adults ≥65 years of age who received two doses of 30-µg BNT162b2 in Study C4591001. For this analysis, blood samples from Study C4591007 and corresponding samples from Study C4591001 that had been collected at 1-month post-Dose 2 were tested contemporaneously in the same assay.

The pediatric post-Dose 3 immunobridging subset included the first approximately 200 participants in each pediatric age group (C4591007) who received Dose 3 of BNT162b2 3-µg and 100 who received placebo, completed the 1-month post-Dose 3 visit, and had 1-month post-Dose 3 blood sample collection (note, this included a non-overlapping group of participants relative to the prior post-Dose 2 immunobridging analyses). The comparator group of young adults 16 to 25 years of age (C4591001) included a random subset of 200 participants who received Dose 2 of BNT162b2 30-µg and 50 who received placebo (note, this included a different group of young adults relative to the prior post-Dose 2 immunobridging analyses). Immunobridging analyses were based on participants without prior evidence of SARS-CoV-2 infection which was determined by serological testing (N-binding assay) at Dose 1 visit (baseline), 1-month post-Dose 2 (C4591001 only), Dose 3 (C4591007 only), and 1-month post-Dose 3 (C4591007 only); and virological testing (nucleic acid amplification test [NAAT]) on anterior nares swabs at the Dose 1 and Dose 2 visits, Dose 3 visit (C4591007 only), and any unscheduled illness visits.

A validated SARS-CoV-2 neutralization assay was used to obtain titers against the wild-type strain, with young adult group samples tested contemporaneously with pediatric group samples for comparability. Immunobridging success criteria were based on the geometric mean ratio (GMR) of 50% neutralizing geometric mean titers (GMTs) and difference in seroresponse rates.

GMR: calculated as mean of the difference of logarithmically transformed titers and exponentiating the mean. 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 confidence limits. Immunobridging success was declared if the lower bound of the CI was >0.67 and GMR point estimate was ≥0.8 (prespecified in protocol) or ≥1 (requested by FDA).

Seroresponse: defined as achieving a ≥4-fold rise in SARS-CoV-2 neutralizing titers from before Dose 1. If the baseline measurement was below lower limit of quantification (LLOQ), post-vaccination measure of ≥4 × LLOQ was considered to be seroresponse. Data were summarized as the difference in percentages of participants achieving seroresponse and associated 2-sided 95% CI calculated using the Miettinen and Nurminen method. Immunobridging success was declared if the lower limit of the CI for difference in seroresponse rate was greater than -10% and provided that the GMR success criteria had been met.

Overall, immunobridging success was declared if both the GMR and seroresponse immunobridging criteria were met (within each pediatric age group). In addition, GMTs and geometric mean fold-rises (GMFRs) were summarized with 2-sided 95% CIs obtained by taking log transforms of results, calculating CIs with reference to Student's t-distribution, then exponentiating confidence limits. Titers below LLOQ were set to 0.5 × LLOQ.

Omicron Neutralization Analysis

Descriptive analyses of SARS-CoV-2 variant neutralization were conducted on the Omicron neutralization subset. For each of the pediatric groups in Phase 2/3 Study C4591007, this included 40 BNT162b2 3-µg recipients and 5 placebo recipients randomly selected from the immunobridging subset who had received three doses of study intervention and had sufficient blood volume for testing at Dose 3 and 1-month post-Dose 3. The adult reference group from Phase 3 Study C4591001 included 40 participants 18 to 55 years of age randomly selected from the C4591001 evaluable immunogenicity population who had received a booster (third) dose of BNT162b2 30-µg at least 6 months after the second dose and were without evidence of prior SARS CoV 2 infection up to 1-month post-Dose 3. Samples from the C4591007 pediatric groups and C4591001 adult group were tested contemporaneously for comparability.

A fluorescent focus reduction neutralization test (FFRNT)[10,11] was used to determine SARS-CoV-2 serum neutralizing titers before Dose 3 vaccination and 1-month post-Dose 3. The FFRNT is a supportive assay similar to the 50% plaque-reduction neutralization test (PRNT) assay which has been used to generate confirmatory data against the reference strain and other variants.[12,13] The FFRNT assay has higher throughput and correlates well with the PRNT assay. All samples were tested at the same time to ensure comparability of results.

The 50% FFRNT titers were determined against the designated wild-type reference strain, which is a recombinant USA-WA1/2020 (clinical strain isolated in January 2020), and against recombinant Delta and Omicron (BA.1) variants, which are recombinant viruses with the Delta or Omicron variant full spike gene on the genetic background of USA-WA1/2020. Titers obtained from the FFRNT assay were reported as GMTs and GMFRs as described above.

3.3.3. Study C4591007 – Efficacy Analysis Endpoints and Methods

Descriptive efficacy analyses were conducted on the all-available efficacy (modified intent-to-treat [mITT]) population and the evaluable efficacy population for each age group. The criteria for COVID-19 case confirmation are summarized in the Appendix. Efficacy endpoints were:

- COVID-19 incidence from at least 7 days post-Dose 3 to the data cutoff date, or from Dose 1 to the data cutoff date, per 1000 person-years of blinded follow-up

- COVID-19 incidence from at least 7 days post-Dose 3 in original BNT162b2 group and at least 7 days post-Dose 2 in original placebo group unblinded to receive two doses of BNT162b2, per 1000 person-years of follow-up, for a fixed calendar time interval of interest

  - Start of interval: 07 February 2022, which corresponds to 7 days after the first administration of Dose 3 of BNT162b2 in the original BNT162b2 group

  - End of interval: 29 April 2022, which corresponds to the submission data cutoff date

- COVID-19 incidence from at least 7 days post-Dose 2 to before Dose 3 to the data cutoff date per 1000 person-years of blinded follow-up in participants in each age group (1) without or (2) with or without serological or virological evidence of past SARS-CoV-2 infection prior to 7 days post-Dose 2.

- VE was estimated overall and by variant of concern for COVID-19 cases from at least 7 days post-Dose 2 to before Dose 3 in the evaluable efficacy populations, based on strain sequence obtained as previously described;[14] for cases reported on or after 20 December 2021 with no available sequence the variant was assigned as Omicron

Efficacy Analysis Methods

VE against confirmed COVID-19 was estimated as $100 \times (1 - IRR)$, where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of blinded follow-up in the BNT162b2 group to the corresponding illness rate in the placebo group. VE is reported with a 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time.

Incidence rates (IRs) for the first reported COVID-19 illness during a fixed calendar time interval were determined using the same approach, except unblinding was not considered as the end of the surveillance period. Relative vaccine efficacy (RVE) against confirmed COVID-19 was determined using the same approach, with IRR being the calculated ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in the original active vaccine group who received three doses to the corresponding illness rate for participants in the original placebo group who were unblinded and received two doses of BNT162b2 during the same period of time. Note that participants who turned 5 years of age and were unblinded to receive the age-appropriate dose of BNT162b2 10-µg were excluded from the analysis.

Pathogen Coinfection Detection

Confirmed cases of COVID-19 were subject to BioFire® Respiratory 2.1 Panel testing for coinfection with other respiratory pathogens. BioFire® is a multiplexed nucleic acid test intended for the simultaneous qualitative detection and differentiation of nucleic acids from multiple viral and bacterial respiratory organisms (including enterovirus, rhinovirus, adenovirus, coronavirus [endemic], influenza, parainfluenza, metapneumovirus, respiratory syncytial virus [RSV], *B. pertussis*, *B. parapertussis*, *C. pneumoniae*, and *M. pneumoniae*).[15] This diagnostic test received marketing authorization from the FDA in March 2021.[16] A supplemental analysis estimated VE using the endpoints and methods described above, for confirmed COVID-19 cases excluding any participants with evidence of coinfection by other respiratory pathogens.

3.4. Study C4591007 – Dose Selection from Phase 1 Data

For children 2 to <5 years of age, higher frequencies and greater severity of reactogenicity to the BNT162b2 10-µg dose level (particularly fever, reported in approximately 19% of the Phase 1 population who received 10-µg at both Dose 1 and Dose 2) in comparison to the 3-µg dose level contributed to the decision to select a lower dose of 3-µg of BNT162b2 to proceed to Phase 2/3 for this age group. Final dose selection of BNT162b2 was based on the similarity in post-vaccination immunogenicity reflected in Day 7 post-Dose 2 GMTs across 3-µg and 10-µg dose levels, along with the most favorable reactogenicity profile observed in the 3-µg dose level. The totality of these results led to the selection of BNT162b2 at the 3-µg dose level to proceed to Phase 2/3 evaluation for this age group.

For children 6 months to <2 years of age, the single dose level of 3-µg tested in Phase 1 was informed by observed safety results from Phase 1 participants in the 2 to <5 years of age group.

For participants 6 months to <2 years of age, Phase 1 data showed a robust immune response and favorable reactogenicity profile for this dose level in this age group.

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

3.5.1. Safety Population – Phase 2/3

3.5.1.1. Children 2 to <5 Years of Age

The safety population of 2750 Phase 2/3 participants 2 to <5 years of age reflected the 2:1 randomization in the BNT162b2 (N=1835) and placebo (N=915) groups. No participants in the safety population were excluded from the study.

Duration of Follow-up

The median duration of blinded follow-up for children 2 to <5 years of age after Dose 3 (N=886) was 1.4 months (range: 0.0 to 3.2 months). Combining the blinded and open-label periods, the median duration of follow-up after Dose 3 (N=1321) was 2.1 months (range: 0.0 to 3.2 months). The median duration of blinded follow-up after Dose 2 to Dose 3 (or data cutoff) was 4.0 months (range: 0.0 to 10.4 months), similar for both the BNT162b2 and placebo groups. The median duration of follow-up including both blinded and open-label follow-up (N=2727) was 4.3 months (range: 0.0 to 10.4 months), similar for both the BNT162b2 and placebo groups.

Disposition

Most participants 2 to <5 years of age randomized to either group (>99%) received two doses, and 32.2% received the third dose of study intervention prior to unblinding, as of the data cutoff date (29 April 2022). Few participants (0.1%) discontinued from the vaccination period due to AEs. Few participants were withdrawn from the study (1.6%).

Per protocol, participants could be unblinded when they reached the 6-months post-Dose 2 study visit, or if they turned 5 years of age and were eligible for vaccination with the authorized age-appropriate dose of BNT162b2 10-µg. Endpoints were analyzed for the blinded placebo-controlled follow-up period unless otherwise indicated. Among participants originally randomized to the BNT162b2 group, unblinding occurred for 1 child (0.1%) who received open-label Dose 2 and for 435 children (51.7%) who received open-label Dose 3. Among participants originally randomized to the placebo group, unblinding during the vaccination period occurred for 370 children (87.3%) who received the first, 350 children (82.5%) who received the second dose, and for 98 children (23.1%) who received a third dose of open-label BNT162b2.

Vaccine Administration and Timing

All participants 2 to <5 years of age in the original BNT162b2 group received Dose 1 as randomized, and 99.1% and 50.1% received Dose 2 and Dose 3, respectively, as of the data cutoff date (29 April 2022). All participants in the original placebo group (initially randomized to placebo) received Dose 1 of placebo as randomized, and 99.1% and 30.6% received Dose 2 and Dose 3, respectively, during blinded follow-up.

The majority of participants received Dose 2 in the protocol defined window (19 to 23 days) after Dose 1 in the BNT162b2 (89.5%) and placebo (88.7%) groups. Dose 3 was received within 8 to 12 weeks after Dose 2 by 22.1% of BNT162b2 and 20.1% of placebo recipients, respectively. The median timing of Dose 3 administration after Dose 2 of BNT162b2 was 21.4 weeks and of placebo was 11.0 weeks.

Demographics

Most participants were White (79.6%), with 4.9% Black or African American participants and 7.4% Asian participants, 7.3% multiracial participants, and other race subgroups <1%. There were 14.0% Hispanic/Latino participants. The median age was 3.0 years and 49.9% of participants were male. A total of 6.0% of participants were reported as obese, 12.8% had baseline comorbidities and/or obesity, and 13.0% of participants had evidence at baseline of prior SARS-CoV-2 infection.

3.5.1.2. Children 6 Months to <2 Years of Age

The safety population of 1776 Phase 2/3 participants 6 months to <2 years of age reflected the 2:1 randomization in the BNT162b2 (N=1178) and placebo (N=598) groups. No participants in the safety population were excluded from the study.

Duration of Follow-up

The median duration of blinded follow-up for children 6 months to <2 years of age after Dose 3 (N=570) was 1.3 months (range: 0.0 to 3.2 months). Combining the blinded and open-label periods, the median duration of follow-up after Dose 3 (N=942) was 2.1 months (range: 0.0 to 3.2 months). The median duration of blinded follow-up after Dose 2 to Dose 3 (or data cutoff) was 6.3 months (range: 0.1 to 10.4 months), similar for both the BNT162b2 and placebo groups. The median duration of follow-up including both blinded and open-label follow-up (N=1763) was 6.3 months (range: 0.1 to 10.4 months).

Disposition

Most participants 6 months to <2 of age randomized to either group (>99%) received two doses, and 32.1% received the third dose of study intervention prior to unblinding, as of the data cutoff date (29 April 2022). Few participants (0.1%) discontinued from the vaccination period due to AEs. Few participants were withdrawn from the study (0.7%).

Endpoints were analyzed for the blinded placebo-controlled follow-up period unless otherwise indicated. Among participants originally randomized to the BNT162b2 group, unblinding (per protocol, at 6-months post-Dose 2) occurred for 1 child (0.1%) who received open-label Dose 2 and for 372 children (52.0%) who received open-label Dose 3. Among participants originally randomized to the placebo group, unblinding during the vaccination period occurred for 344 children (91.2%) who received the first dose, 296 children (78.5%) who received the second dose, and for 77 children (20.4%) who received the third dose of open-label BNT162b2.

Vaccine Administration and Timing

All participants in the original BNT162b2 group received Dose 1 as randomized, and 99.1% and 64.3% received Dose 2 and Dose 3 as randomized, respectively, as of the data cutoff date (29 April 2022). All participants in the original placebo group (initially randomized to placebo) received Dose 1 of placebo as randomized, and 99.7% and 30.8% received Dose 2 and Dose 3, respectively, during blinded follow-up.

The majority of participants received Dose 2 in the protocol defined window (19 to 23 days) after Dose 1 in most participants in the BNT162b2 (87.7%) and placebo (88.1%) groups. Dose 3 was received within 8 to 12 weeks after Dose 2 by 12.3% of BNT162b2 and 12.7% of placebo recipients, respectively. The median timing of Dose 3 administration after Dose 2 of BNT162b2 was 25.3 weeks and for placebo was 15.8 weeks.

Demographics

Most participants were White (78.9%), with 3.7% Black or African American participants and 7.4% Asian participants, 9.3% multiracial participants, and other race subgroups <1%. There were 12.7% Hispanic/Latino participants. The median age was 16.0 months and 49.5% of participants were male. A total of 4.7% had baseline comorbidities (which did not include obesity for this age group) and 7.5% had evidence at baseline of prior SARS-CoV-2 infection.

3.5.2. Reactogenicity – Phase 2/3

Local reactions and systemic events were recorded in e-diaries for 7 days after each dose and are summarized below for each pediatric age group.

Subgroup analyses by demographic characteristics (sex, race, ethnicity) and evidence of prior SARS-CoV-2 infection at baseline (positive or negative) did not show any meaningful differences in reactogenicity profile between the subgroups for either age group, noting that such data should be interpreted with caution as some subgroups include a limited number of participants.

3.5.2.1. Children 2 to <5 Years of Age

Local reactions and systemic events were assessed for Phase 2/3 participants 2 to <5 years of age for 7 days after each dose, with e-diary data from N=2734 (BNT162b2=1825, Placebo=909) after Dose 1, N=2657 (BNT162b2=1779, Placebo=878) after Dose 2, and N=814 (BNT162b2=552, placebo=262) after Dose 3 during blinded placebo-controlled period.

Local Reactions

Pain at the injection site was the most frequently reported local reaction within 7 days after each dose, with swelling and redness at the injection site reported less frequently (Figure 4). Incidences of local reactions after Dose 3 were generally similar or lower than incidences reported after Dose 1 or Dose 2. Local reactions were reported more frequently after BNT162b2 than placebo. Most local reactions were mild or moderate, with severe local reactions reported infrequently after any dose (≤0.1%). No Grade 4 local reactions were reported after any dose.

The median onset for all local reactions after any dose of BNT162b2 3-μg was 1 to 2 days, and all events resolved within a median duration of 1 day after onset.

Additional analyses of local reactions that included any e-diary data reported after a participant was unblinded did not suggest any meaningful differences in the reactogenicity profile when including post-unblinding events.

Systemic Events

Fatigue was the most frequently reported systemic event reported within 7 days after each dose, at similar frequencies in the BNT162b2 and placebo groups (Figure 5). All other events were reported at lower frequencies, that were generally similar in the BNT162b2 placebo groups. Most systemic events were mild or moderate, with severe systemic events reported infrequently after any dose (≤0.6%). No Grade 4 events were reported after any dose. The median onset for most systemic events after any dose of BNT162b2 3-μg was 2 days, and most events resolved within a median duration of 1 day after onset.

Fever 38.9 °C to 40 °C was reported by ≤1.1% of participants in the BNT162b2 group and ≤1.1% in the placebo group, after each of the three doses. The overall median onset for fevers in either group was 4 to 5 days post-dose, and fevers all resolved in a median duration of 1 to 1.5 days. One participant in the BNT162b2 group reported a fever >40.0 °C on Day 2 after Dose 1 and returning to normal body temperature on Day 6. Two participants in the BNT162b2 group reported a fever >40.0 °C on Day 4 or Day 6 after Dose 2 returning to normal body temperature by Day 7, one of whom had a clinical presentation suggestive of viral exanthem such as roseola. No participants in the placebo group reported fever >40.0 °C.

Additional analyses of systemic events that included any e-diary data reported after a participant was unblinded did not suggest any meaningful differences in the reactogenicity profile.

Figure 4. **Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Blinded-Placebo-Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population**
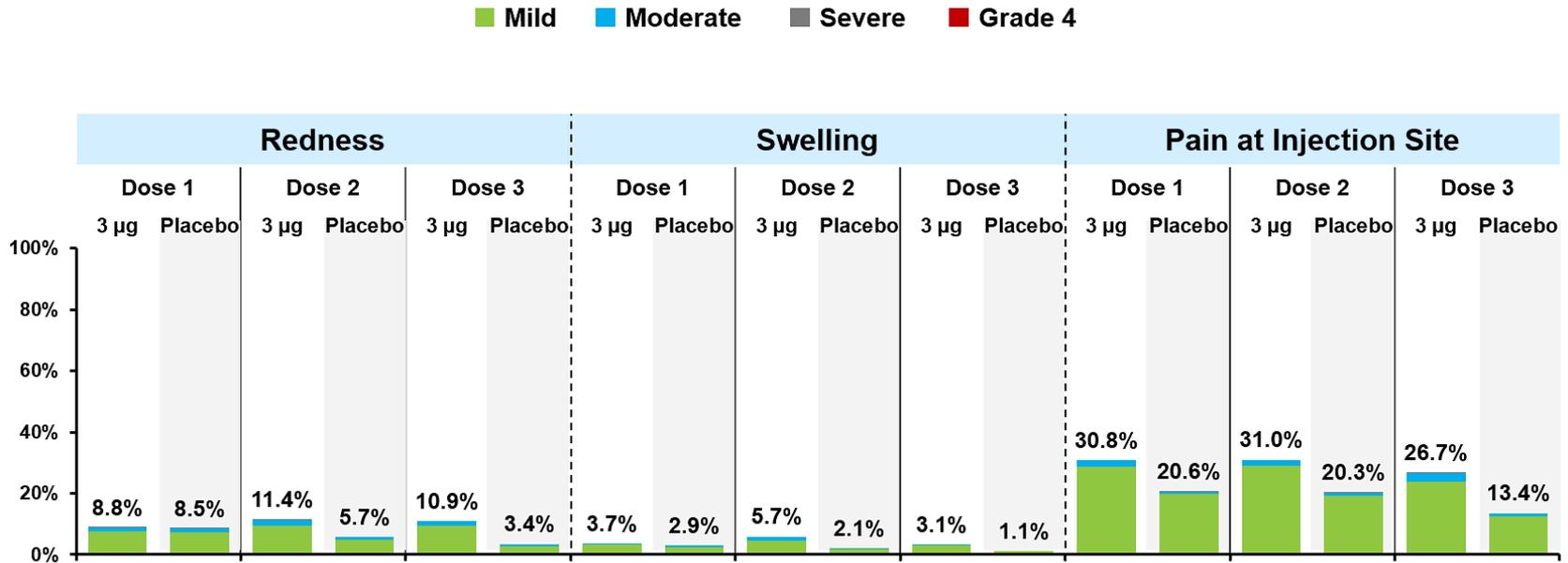
Redness and swelling severity definition: Mild= ≥0.5-2cm, Moderate= >2-7 cm; Severe= >7cm; Grade 4= necrosis
Pain at injection site severity definition: Mild=no interference; Moderate=some interference; Severe=prevents daily activity; Grade 4=ER visit or hospitalization
Dose 1: N=2734   Dose 2: N=2657 Dose 3: N=814

Figure 5. **Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population**
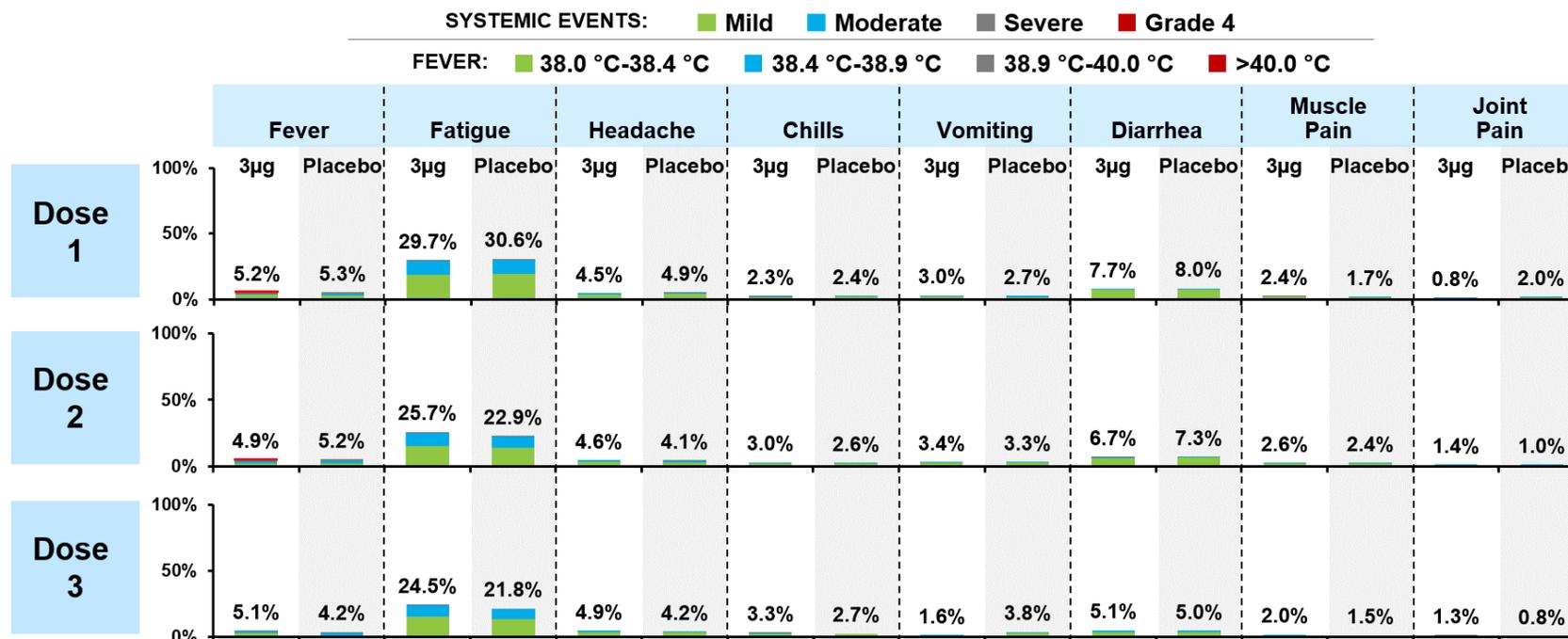
Fatigue, headache, chills, muscle pain, joint pain severity definition: Mild=no interference; Moderate=some interference; Severe=prevents daily activity; Grade 4=ER visit or hospitalization
Vomiting severity definition: Mild=1-2 time in 24h; Moderate=>2times in 24h; Severe=Requires IV hydration; Grade 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: N=2734   Dose 2: N=2657; Dose 3: N=814

3.5.2.2. Children 6 Months to <2 Years of Age

Local reactions and systemic events were assessed for Phase 2/3 participants 6 months to <2 years of age for 7 days after each dose, with e-diary data from N= 1768 (BNT162b2=1173, Placebo= 595) after Dose 1, N=1738 (BNT162b2=1147, placebo=591) after Dose 2, and N=535 (BNT162b2=365, Placebo=170) after Dose 3 of BNT162b2 3-µg.

Local Reactions

Tenderness at the injection site was the most frequently reported local reaction within 7 days after each dose, with swelling and redness at the injection site reported less frequently (Figure 6). Incidences of local reactions after Dose 3 were generally similar or lower than incidences reported after Dose 1 or Dose 2. Local reactions were reported more frequently after BNT162b2 than placebo. Most local reactions were mild or moderate, with severe local reactions reported infrequently after any dose (≤0.3%). No Grade 4 local reactions were reported after any dose. The median onset for all local reactions after any dose of BNT162b2 3-µg was 1 to 2 days, and most events resolved within a median duration of 1 day after onset.

Additional analyses of local reactions that included any e-diary data reported after a participant was unblinded did not suggest any meaningful differences in the reactogenicity profile when including post-unblinding events.

Systemic Events

Irritability was the most frequently reported systemic event reported within 7 days after each dose, followed by drowsiness and decreased appetite (Figure 7). Fever was reported at similar or lower frequencies after each dose, which were similar between the BNT162b2 and placebo groups. Systemic events (other than fever) were generally reported more frequently after BNT162b2 than placebo.

Most systemic events were mild or moderate, with severe systemic events reported infrequently after any dose (≤1.1%). No Grade 4 events were reported after any dose. The median onset for most systemic events after any dose of BNT162b2 3-µg was 2 days (noting that some events had median onset of up to 4.5 days post-dose, which was similar in BNT162b2 and placebo groups), and all events resolved within a median duration of 1 to 2 days after onset.

Fever 38.9 °C to 40 °C was reported by ≤2.0% of participants in the BNT162b2 group and ≤1.2% in the placebo group, after each of the three doses. The overall median onset for fevers in either group was 2 to 4.5 days post-dose, and all reported fevers resolved in a median duration of 1 day. Three participants in the BNT162b2 group reported a fever >40.0 °C on Day 2 after Dose 1 (n=1), Day 1 after Dose 2 (n=1), and Day 3 after Dose 3 (n=1) and returning to normal body temperature on Day 6, two of whom had a concurrent viral infection (roseola based on clinical presentation or concurrent AE of exanthema subitem due to unspecified viral infection). One participant in the placebo group reported fever >40.0 °C on Day 5 after Dose 1 returning to normal body temperature on Day 6.

Additional analyses of systemic events that included any e-diary data reported after a participant was unblinded did not suggest any meaningful differences in the reactogenicity profile.

Figure 6. **Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Blinded-Placebo-Controlled Follow-Up Period – 6 Months to <2 Years of Age – Safety Population**
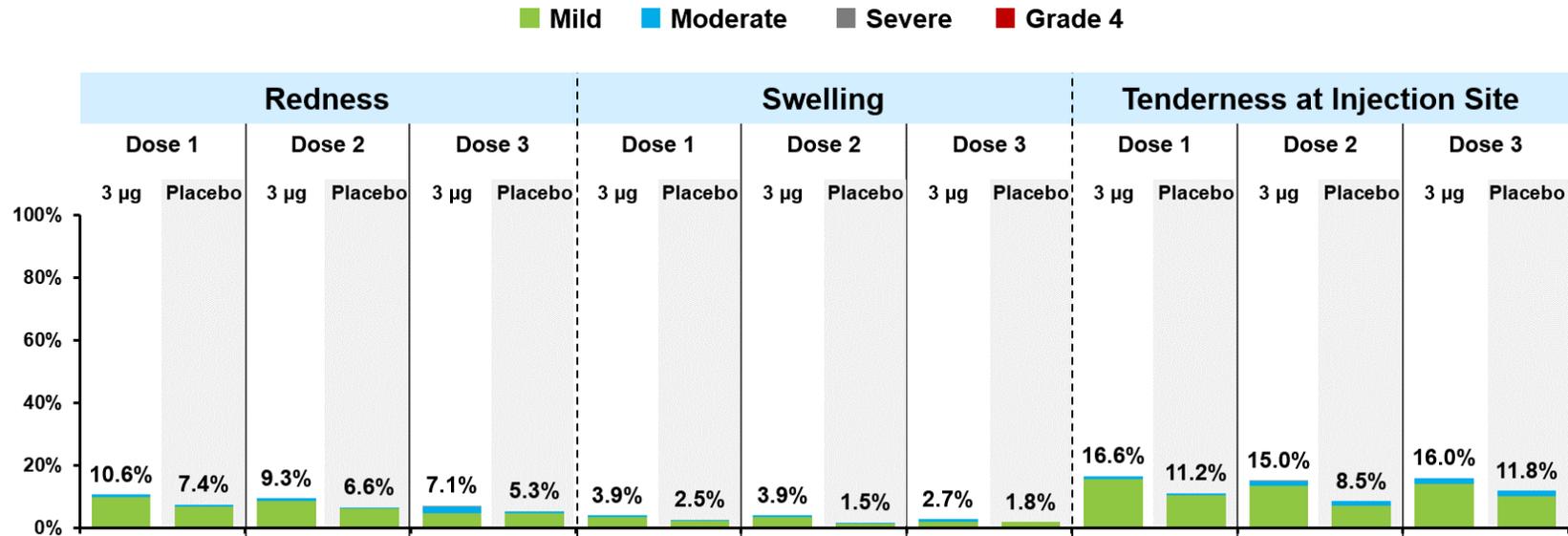
Redness and swelling severity definition: Mild= ≥0.5-2cm, Moderate= >2-7 cm; Severe= >7cm; Grade 4= necrosis
Tenderness at injection site severity definition: Mild=hurts with gentle touch; Moderate=crying with gentle touch; Severe=limitation of limb movement; Grade 4=ER visit or hospitalization
Dose 1: N=1768; Dose 2: N=1738; Dose 3: N=535

Figure 7. **Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Blinded-Placebo-Controlled Follow-Up Period – 6 Months to <2 Years of Age – Safety Population**
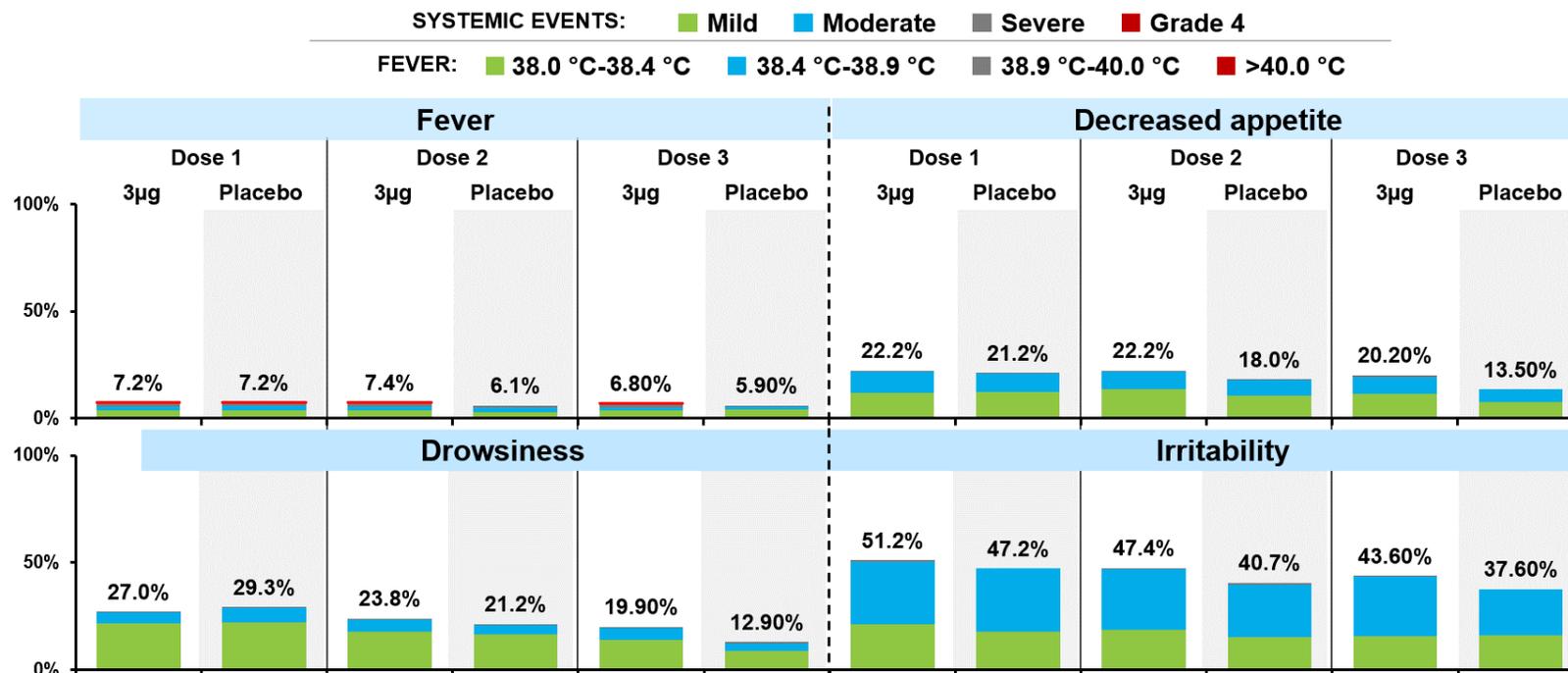
Decreased appetite severity definition: Mild=decreased interest in eating; Moderate=decreased oral intake; Severe=refusal to feed; Grade 4=ER visit or hospitalization
Drowsiness severity definition: Mild=increased/prolonged sleeping; Moderate: slightly subdued; Severe=Disabling/not interested in daily activity; Grade 4=ER visit or hospitalization
Irritability severity definition: Mild=easily consolable; Moderate=requires increased attention; Severe=inconsolable; Grade 4=ER visit or hospitalization
Dose 1: N= 1768; Dose 2: N= 1738; Dose 3: N=535

3.5.2.3. Reactogenicity Conclusions

Reactogenicity to three doses of vaccine was mostly mild to moderate and short-lived, with most events occurring at similar or lower frequencies after the third dose compared with the first or second dose of BNT162b2 3-µg in children 6 months to <5 years of age. The median onset of reactogenicity events was typically 1 to 2 days after each dose and most events resolved within 1 to 2 days after onset.

When compared with available data from 401 older children (5 to <12 years of age) in Study C4591007 and 306 adults (18 to 55 years of age) in Study C4591001 who received a third (booster) dose (from whom data were previously submitted), incidences of the most commonly observed local reactions and systemic events (collected using the same e-diary application) after vaccination with BNT162b2 were overall lower among 552 children 2 to <5 years of age and 365 children 6 months to <2 years of age who had post-Dose 3 reactogenicity data, as summarized below.

	BNT162b2 (3-µg) Children 6 months to <2 years		BNT162b2 (3-µg) Children 2 to <5 years		BNT162b2 (10-µg) Older Children 5 to <12 years		BNT162b2 (30-µg) Adults 18 to 55 years	
	Dose 2	Dose 3	Dose 2	Dose 3	Dose 2	Dose 3	Dose 2	Dose 3
• Injection site pain/tenderness:	15.0%	16.0%	31.0%	26.7%	72.2%	73.9%	78.3%	83.0%
• Irritability:	47.4%	43.6%						
• Fatigue:			25.7%	24.5%	46.6%	45.6%	61.5%	63.7%
• Headache:			4.6%	4.9%	30.1%	34.0%	54.0%	48.4%
• Muscle pain:			2.6%	2.0%	12.5%	18.3%	39.3%	39.1%
• Chills:			3.0%	3.3%	10.3%	10.5%	37.8%	29.1%
• Joint pain:			1.4%	1.3%	5.5%	6.7%	23.8%	25.3%
• Fever:	7.4%	6.8%	4.9%	5.1%	8.8%	6.7%	16.4%	8.7%
• Diarrhea:			6.7%	5.1%	6.5%	4.9%	10.0%	8.7%
• Vomiting:			3.4%	1.6%	1.8%	2.4%	2.2%	1.7%

Note: Systemic reactogenicity event of irritability solicited only in children 6 months to <2 years of age. Systemic reactogenicity events of fatigue, headache, muscle or joint pain, chills, diarrhea, and vomiting solicited only in individuals ≥2 years of age (children and adults).

3.5.3. Adverse Events – Phase 2/3

3.5.3.1. Overview of Adverse Events

AE overview for Phase 2/3 blinded and placebo-controlled follow-up of pediatric participants are reported from Dose 1 to 1 month after Dose 3 and differences in AE profile from Dose 1 until the data cutoff date (29 April 2022) are also noted in Section 3.5.3.1.1.

Subgroup analyses by demographic characteristics (sex, race, ethnicity) and evidence of prior SARS-CoV-2 infection at baseline (positive or negative) did not show any meaningful differences in AE profile between the subgroups for either age group, noting that such data should be interpreted with caution as some subgroups include a limited number of participants.

3.5.3.1.1. Adverse Events from Dose 1 to 1 Month After Dose 3

3.5.3.1.1.1. Children 2 to <5 Years of Age

The proportions of participants with any AE in the blinded placebo-controlled follow-up period were similar in the BNT162b2 (18.7%) and placebo (18.7%) groups. Any related (per investigator assessment) AEs, any severe AEs, and any SAEs were reported across the BNT162b2 and placebo groups by ≤2.0%, ≤0.7%, and ≤0.9% of participants, respectively. Few withdrawals due to AEs (including vaccine-related events of pyrexia, urticaria, and unrelated event of status epilepticus) were reported in either group (≤0.2%). No study participants died (Table 2).

Table 2.   Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 3 – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population

| | Vaccine Group (as Administered) | |
| | BNT162b2 (3 μg) (N[a]=1835) | Placebo (N[a]=915) |
Adverse Event	n[b] (%)	n[b] (%)
Any adverse event	344 (18.7)	171 (18.7)
Related[c]	37 (2.0)	18 (2.0)
Severe	9 (0.5)	6 (0.7)
Life-threatening	0	0
Any serious adverse event	12 (0.7)	8 (0.9)
Related[c]	1 (0.1)	0
Severe	5 (0.3)	3 (0.3)
Life-threatening	0	0
Any nonserious adverse event	339 (18.5)	169 (18.5)
Related[c]	37 (2.0)	18 (2.0)
Severe	4 (0.2)	3 (0.3)
Life-threatening	0	0
Any adverse event leading to withdrawal	3 (0.2)	1 (0.1)
Related[c]	2 (0.1)	1 (0.1)
Serious	1 (0.1)	0
Severe	1 (0.1)	1 (0.1)
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 the study intervention.

From Dose 1 to the data cutoff date (29 April 2022) in the blinded placebo-controlled follow-up period, the proportions of participants with any AE up to the cutoff date were similar in the BNT162b2 (18.8%) and placebo (18.9%) groups. In addition to events already reported in the blinded placebo-controlled follow-up period up to 1 month after Dose 3, a limited number of additional events were reported up to the data cutoff date. As of the data cutoff date, any related (per investigator assessment) or any severe AEs were reported across the BNT162b2 and placebo groups by 2.0% or ≤0.7% of participants, respectively. No additional SAEs or withdrawals due to AEs were reported in either group beyond 1-month post-Dose 3. No study participants died.

Additional analyses of AEs from Dose 1 to the data cutoff that included events reported after a participant was unblinded, or that were reported for the original placebo group after unblinding to receive active vaccination with BNT162b2, did not suggest any meaningful differences in the safety profile.

3.5.3.1.1.2. Children 6 Months to <2 Years of Age

The proportions of participants with any AE in the blinded placebo-controlled follow-up period were similar in the BNT162b2 (30.1%) and placebo (27.1%) groups. Any related AEs, any severe AEs, and any SAEs were reported across the BNT162b2 and placebo groups by ≤4.7%, ≤1.7%, and ≤2.3% of participants, respectively. Few withdrawals due to AEs (including vaccine-related events of pyrexia and rash) were reported in either group (≤0.3%). No study participants died (Table 3).

Table 3.   Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 3 – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 Months to <2 Years of Age – Safety Population

	Vaccine Group (as Administered)	
Adverse Event	**BNT162b2 (3 µg)** **(N[a]=1178)** **n[b] (%)**	**Placebo** **(N[a]=598)** **n[b] (%)**
Any adverse event	355 (30.1)	162 (27.1)
Related[c]	55 (4.7)	21 (3.5)
Severe	12 (1.0)	10 (1.7)
Life-threatening	0	1 (0.2)
Any serious adverse event	17 (1.4)	14 (2.3)
Related[c]	0	1 (0.2)
Severe	8 (0.7)	9 (1.5)
Life-threatening	0	1 (0.2)
Any nonserious adverse event	343 (29.1)	157 (26.3)
Related[c]	55 (4.7)	20 (3.3)
Severe	5 (0.4)	1 (0.2)
Life-threatening	0	0
Any adverse event leading to withdrawal	3 (0.3)	0
Related[c]	3 (0.3)	0

Table 3. **Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 3 – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 Months to <2 Years of Age – Safety Population**

	Vaccine Group (as Administered)	
	BNT162b2 (3 μg) (N^a=1178)	Placebo (N^a=598)
Adverse Event	n^b (%)	n^b (%)
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 the study intervention.

From Dose 1 to the data cutoff date (29 April 2022), the proportions of participants in the 6 months to <2 years of age group with any AE up to the cutoff date ere similar in the BNT162b2 (30.3%) and placebo (27.3%) groups. In addition to events already reported in the blinded placebo-controlled follow-up period up to 1 month after Dose 3, a limited number of additional events were reported up to the data cutoff date. As of the data cutoff date, any related AEs or severe AEs reported across the BNT162b2 and placebo groups by ≤4.7% or ≤1.7% of participants, respectively. No additional SAEs or withdrawals due to AEs were reported in either group beyond 1-month post-Dose 3. No study participants died.

Additional analyses of AEs from Dose 1 to the data cutoff that included events reported after a participant was unblinded, or that were reported for the original placebo group after unblinding to receive active vaccination with BNT162b2, did not suggest any meaningful differences in safety profile.

3.5.3.2. Analysis of Adverse Events – Phase 2/3

3.5.3.2.1. Adverse Events from Dose 1 to 1 Month After Dose 3: Adverse Events by System Organ Class and Preferred Term

3.5.3.2.1.1. Children 2 to <5 Years of Age

Overall, frequencies of any AEs reported after Dose 1 up to 1 month after Dose 3 during the blinded placebo-controlled follow-up period were the same in the BNT162b2 3-μg and placebo groups (18.7% vs 18.7%). Many AEs were consistent with reactogenicity events that were reported as AEs (eg, vomiting, diarrhea, and pyrexia), and there was no clinically meaningful imbalance between groups. In the general disorders and administration site conditions SOC, AEs were reported at numerically higher incidence in the BNT162b2 group than the placebo group (4.3% vs 3.9%), largely attributable to injection site reactions and fatigue.

Infections and illnesses typical of this age group were also reported with no clinically meaningful imbalance between groups. This AE profile is generally consistent with that observed for other age groups, that is, most events are either reactogenicity or age-appropriate events expected in the general population.

Few additional AEs were reported from Dose 1 to the data cutoff date (29 April 2022). Overall, frequencies of any AEs reported after Dose 1 up the data cutoff date were similar in the BNT162b2 and placebo groups (18.8% vs 18.9%) and did not suggest any meaningful differences in safety profile. Analyses of AEs from Dose 1 to the data cutoff that included events reported after a participant was unblinded, or that were reported for the original placebo group after unblinding to receive active vaccination with BNT162b2, did not suggest any meaningful differences in safety profile.

Related Adverse Events – Dose 1 to 1 Month After Dose 3

From Dose 1 to 1 month after Dose 2, AEs assessed by the investigator as related to study intervention were reported with similar frequencies in the BNT162b2 (2.0%) and placebo (2.0%) groups. Most related AEs were consistent with reactogenicity events and in the SOC of general disorders and administration site conditions, reported by 1.4% of participants in the BNT162b2 group compared with 1.2% of participants in the placebo group.

Immediate Adverse Events – After Each Dose

In the 2 to <5 years of age group, immediate AEs reported within 30 minutes of vaccination were low in frequency after any dose (≤0.3%) of BNT162b2 or placebo. No immediate events of anaphylaxis were reported after any vaccination. Most events after Dose 1 and Dose 2 were consistent with reactogenicity events, no immediate AEs were reported after Dose 3.

Severe or Life-Threatening Adverse Events – Dose 1 to 1 Month After Dose 3

In the 2 to <5 years of age group, from Dose 1 to 1 month after Dose 3, severe AEs were reported by ≤0.7% of participants in both the BNT162b2 and placebo groups. Most of the events considered severe were unrelated SAEs. No life-threatening (ie, Grade 4) AEs were reported from Dose 1 to 1 month after Dose 3. In the BNT162b2 group, severe AEs included one related event of pyrexia and unrelated events of bilateral deafness, appendicitis, viral gastroenteritis, skin laceration, epilepsy, status epilepticus, and adenoidal hypertrophy (0.1% each).

3.5.3.2.1.2. Children 6 Months to <2 Years of Age

Overall, frequencies of any AEs reported after Dose 1 up to 1 month after Dose 3 during the blinded placebo-controlled follow-up period were similar in the BNT162b2 and placebo groups (30.1% vs 27.1%). Many of the AEs were consistent with reactogenicity events that were reported as AEs (eg, vomiting, diarrhea, and pyrexia). AEs consistent with reactogenicity were reported at numerically higher incidences in the BNT162b2 group than placebo, primarily driven by a limited number of PTs (eg, injection site reactions, irritability, somnolence, headache).

Infections and illnesses typical of this age group were also reported with no clinically meaningful imbalance between groups. This AE profile is generally consistent with that observed for other

age groups, that is, most events are either reactogenicity or age-appropriate events expected in the general population.

Few additional AEs were reported from Dose 1 to the data cutoff date (29 April 2022). Overall, frequencies of any AEs reported after Dose 1 up the data cutoff date were similar in the BNT162b2 and placebo groups (30.3% vs 27.3%) and did not suggest any meaningful differences in safety profile. Analyses of AEs from Dose 1 to the data cutoff that included events reported after a participant was unblinded, or that were reported for the original placebo group after unblinding to receive active vaccination with BNT162b2, did not suggest any meaningful differences in the safety profile.

Related Adverse Events – Dose 1 to 1 Month After Dose 3

From Dose 1 to 1 month after Dose 3, AEs assessed by the investigator as related to study intervention were reported at a slightly higher frequency in the BNT162b2 group (4.7%) than in the placebo group (3.5%) among children 6 months to <2 years of age. Most related AEs were consistent with reactogenicity events, most commonly reported in both the BNT162b2 and placebo groups from the SOCs of general disorders and administration site conditions (1.6% and 0.7%) and gastrointestinal disorders (1.4% and 1.3%).

Immediate Adverse Events – After Each Dose

In the 6 months to <2 years of age group, immediate AEs reported within 30 minutes of vaccination were low in frequency after any dose (≤0.5%) of BNT162b2 or placebo. No immediate events of anaphylaxis were reported after any vaccination. Most events after Dose 1 and Dose 2 were consistent with reactogenicity events, no immediate AEs were reported after Dose 3.

Severe or Life-Threatening Adverse Events – Dose 1 to 1 Month After Dose 3

From among children 6 months to <2 years of age, severe AEs reported from Dose 1 to 1-month post-Dose 3 were reported at similar incidences in the BNT162b2 (1.0%) and placebo (1.8%) groups. Most severe AEs were gastrointestinal or respiratory infections/illnesses reported as unrelated SAEs, with no imbalance between groups. One life-threatening (ie, Grade 4) AE was reported from Dose 1 to 1 month after Dose 3, by a participant who had a thermal burn caused by a hot coffee spill that was reported as an SAE.

3.5.3.3. Deaths and Serious Adverse Events – Phase 2/3

Analysis of Deaths and SAEs From Dose 1 to Data Cutoff Date

3.5.3.3.1. Children 2 to <5 Years of Age

No deaths were reported in the Phase 2/3 pediatric population of children 2 to <5 years of age up to the data cutoff date (29 April 2022).

Few SAEs were reported among participants 2 to <5 years of age during blinded placebo-controlled follow-up in BNT162b2 3-µg (n=12, 0.7%) and placebo (n= 8, 0.9%) groups from Dose 1 to the data cutoff date (29 April 2022). Most SAEs were gastrointestinal or respiratory infections/illnesses, with no imbalance between groups (taking into account 2:1 randomization).

One participant in the BNT162b2 group reported two SAEs considered by the investigator as related to study intervention, pyrexia accompanied by viral exanthem after the second dose.

3.5.3.3.2. Children 6 Months to <2 Years of Age

No deaths were reported in the Phase 2/3 pediatric population of children 6 months to <2 years of age up to the data cutoff date (29 April 2022).

Few SAEs were reported among participants 6 months to <2 years of age during blinded follow-up in BNT162b2 3-µg (n=17, 1.4%) and placebo (n=14, 2.3%) groups from Dose 1 to the data cutoff date (29 April 2022). Most SAEs were gastrointestinal or respiratory infections/illnesses, with no imbalance between groups (taking into account 2:1 randomization). No SAEs assessed as related to BNT162b2 by the investigator were reported.

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

Analysis of AEs Leading to Withdrawal From Dose 1 to Data Cutoff Date

3.5.3.4.1. Children 2 to <5 Years of Age

Among participants 2 to <5 years of age, AEs leading to withdrawal during blinded follow-up from Dose 1 to the data cutoff date (29 April 2022) were reported by 0.2% in the BNT162b2 group and 0.1% in the placebo group. These included related nonserious events of pyrexia, urticaria, swelling face, and macular rash and an unrelated SAE of status epilepticus.

3.5.3.4.2. Children 6 Months to <2 Years of Age

Three AEs leading to withdrawal were reported among participants 6 months to <2 years of age during blinded follow-up from Dose 1 to the data cutoff date (29 April 2022), all in the BNT162b2 group; these include 2 cases of pyrexia and one case of rash, all considered by the investigator as related to study intervention.

3.5.3.5. Other Significant Adverse Events – Phase 2/3

Some AEs are of specific interest due to their autoimmune or neuroinflammatory nature, theoretical association with vaccines or known occurrence in patients with COVID-19.

There were no cases reported in the 2 to <5 years of age and 6 months to <2 years of age group as of the data cutoff date (29 April 2022) of myocarditis/pericarditis, Bell's palsy (or facial paralysis/paresis), thromboembolic events, thrombocytopenic events, MIS-C, Kawasaki disease, acute respiratory distress syndrome, meningitis, myelitis/encephalomyelitis or vaccine-related anaphylaxis. Additionally, in both age groups, no events were identified consistent with demyelination, peripheral neuropathy, or vasculitis.

3.5.3.5.1. Children 2 to <5 Years of Age

Lymphadenopathy is considered an adverse reaction to this vaccine and is noted as such in the product labeling. Based on AE analysis during blinded follow-up from Dose 1 to 1-month post-Dose 3, 1 case of lymphadenopathy was reported by 1 participant (0.1%) in the BNT162b2 group and none in the placebo group.

Hypersensitivity reactions (eg, rash, pruritus, urticaria, angioedema) are considered adverse reactions to this vaccine and are noted as such in the product labeling. Rashes were reported infrequently in children 2 to <5 years of age, but at a slightly higher incidence in the BNT162b2 group (0.4%) than placebo (0.1%). Rashes assessed as related to vaccination were typically mild to moderate in severity, occurred in anatomical locations of extremities (upper and lower), chest (upper), upper body, or abdomen, with typical onset of 1 to 7 days post-dose, and most resolved within 2 days of onset. Other notable events reported in the BNT162b2 group included 6 events of urticaria, 4 of which were considered as related to study intervention and a case of unilateral eyelid swelling, considered unrelated to study intervention by the investigator.

Convulsions were reported at the same incidence (0.2%) in the BNT162b2 and placebo groups. All events in the BNT162b2 group were considered by the investigator as not related to study intervention.

One participant in the BNT162b2 group reported a case of transient non-serious synovitis (10 days post-Dose 2) of the hip after which was assessed as not related to study intervention by the investigator and resolved.

3.5.3.5.2. Children 6 Months to <2 Years of Age

Based on AE analysis from Dose 1 to 1-month post-Dose 3 during blinded follow-up, lymphadenopathy was reported 2 participants (0.2%) in the BNT162b2 group and none in the placebo group.

Rashes were reported infrequently in children 6 months to <2 years of age and at similar incidences in the BNT162b2 (1.1%) and placebo (1.2%) groups. Rashes assessed as related to vaccination were typically mild to moderate, occurred in anatomical locations of extremities (upper and lower), torso, or face with typical onset of 1 to 5 days post-Dose, and most resolved within 6 days of onset. Other notable events reported in the BNT162b2 group included 8 events of urticaria, 1 of which was considered as related to study intervention and a case of unilateral eyelid swelling, considered unrelated to study intervention by the investigator.

Convulsions were reported at the similar incidences in the BNT162b2 (0.3%) and placebo (0.2%) groups. All were considered by the investigator as not related to study intervention.

No events consistent with arthritis were reported in this age group.

3.5.4. Safety Conclusions from Phase 2/3 Data

The observed AE profile in this study did not suggest any new safety concerns for BNT162b2 administered as three doses at the 3-µg dose level in children 6 months to <5 years of age. The reported reactogenicity appeared comparable to placebo recipients. Many AEs reported up to

1 month after Dose 3 were consistent with reactogenicity events, or other infections or illnesses that are expected to be observed in a pediatric general population. Few SAEs or AEs leading to withdrawal, and no deaths, were reported. There were few AEs of special interest reported, and no cases were observed of vaccine-associated anaphylaxis or myocarditis/pericarditis. The observed safety profile across age groups continues to demonstrate a safe and tolerable vaccine.

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

Immunogenicity was evaluated after the second dose of the vaccine regimen, including GMR and seroresponse rate comparisons at 1-month post-Dose 2 in each pediatric group in Study C4591007 with young adults 16 to 25 years of age from Study C4591001. Based on results of these analyses and emerging real-world data, the vaccine series was modified to add a third dose for children 6 months to <5 years of age. The two-dose analyses are summarized below, and the three-dose immunobridging analyses (for which all success criteria for both pediatric age groups were met) are presented for each age group in the sections that follow.

Post-Dose 2 Immunogenicity Analysis

Children 2 to <5 Years of Age

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the ratio of the SARS-CoV-2 neutralizing GMT in children 2 to <5 years of age who received the 3 µg dose level to that of young adults 16 to 25 years of age who received the 30 µg dose level was 0.61 (2-sided 95% CI: 0.53, 0.70). In this population, 96.7% of children 2 to <5 years of age and 97.6% of young adults 16 to 25 years of age achieved a seroresponse (as defined in Section 3.3.2.1) at 1 month after Dose 2 with a difference between age groups (children – young adults) of -0.9% (2 sided 95% CI: -4.3%, 2.3%).

The lower bound of the 2-sided 95% CI for GMR was <0.67 and the GMR point estimate was <0.8, indicating the prespecified success criteria (as defined in Section 3.3.2.1) for the GMR were not met; therefore, immunobridging based on GMR was not achieved for children 2 to <5 years of age. The lower limit of the 2 sided 95% CI for the difference in seroresponse rate was -4.3%, which is greater than the prespecified margin of -10%, thus the seroresponse success criterion was met. However, since success criteria for the GMR were not met; immunobridging was not declared formally for children 2 to <5 years of age.

Children 6 Months to <2 Years of Age

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the ratio of the SARS-CoV-2 neutralizing GMT in children 6 months to <2 years of age who received the 3 µg dose level to that of young adults 16 to 25 years of age who received the 30 µg dose level was 1.03 (2-sided 95% CI: 0.90, 1.19). In this population, 98.0% of children 6 months to <2 years of age and 96.2% of young adults 16 to 25 years of age achieved a seroresponse (as defined in Section 3.3.2.1) at 1 month after Dose 2 with a difference between age groups (children – young adults) of 1.7% (2 sided 95% CI: -1.4%, 5.2%).

The lower bound of the 2-sided 95% CI for GMR was >0.67 and the GMR point estimate was ≥0.8 (per protocol) and ≥1 (requested by FDA), which meets the prespecified 1.5-fold margin

and success criteria for the GMR (as defined in Section 3.3.2.1). Therefore, immunobridging based on GMR was achieved for children 6 months to <2 years of age. The lower limit of the 2 sided 95% CI for the difference in seroresponse rate was -1.4%, which is greater than the prespecified margin of -10%. Therefore, immunobridging based on seroresponse rate was achieved for children 6 months to <2 years of age.

Supportive Noninferiority Analysis Comparing Post-Dose 2 Neutralization Data from Children 2 to <5 Years of Age vs Older Adults ≥65 Years of Age

Immune responses to BNT162b2 in children in Study C4591007 and older adults in Study C4591001 have previously been compared to those for young adults in Study C4591001. In a descriptive analyses of SARS-CoV-2 neutralizing GMTs at 1 month after Dose 2 of BNT162b2, the ratio of the GMT in children 2 to <5 years of age who received 3 µg BNT162b2 to that of older adults ≥65 years of age who received 30 µg BNT162b2 was 1.92 (2-sided 95% CI: 1.56, 2.36).

At 1 month after Dose 2, SARS-CoV-2 neutralizing GMT in children 2 to <5 years of age who received 3 µg BNT162b2 was higher than the GMT among older adults ≥65 years of age who received 30 µg BNT162b2. The 1-month post-Dose 2 GMT was 830.0 in children 2 to <5 years of age and was 431.8 in adults ≥65 years of age, and the 2-sided 95% CIs were not overlapping. Neutralizing GMTs were very low after placebo for both age groups (20.5 in each group).

This analysis made a direct comparison between GMTs observed in children 2 to <5 years of age (C4591007) and in older adults ≥65 years of age (C4591001). The two-dose series of BNT162b2 at the 3-µg dose level administered to children 2 to <5 years of age elicited neutralizing antibody titers at 1 month after Dose 2 that were higher than those among older adults ≥65 years of age who received two doses of BNT162b2 at the 30 µg dose level and demonstrated observed VE of >90% in the pivotal efficacy Study C4591001.

Post-Dose 2 Immunogenicity Conclusions

Immunobridging data after Dose 2 met success criteria for the 6 months to <2 years group and did not meet GMR success criteria (but met seroresponse criteria) for the 2 to <5 years of group, compared to young adults 16 to 25 years of age; notably, a post hoc analysis demonstrated noninferiority for the 2 to <5 years of age group against an older adult population ≥65 years of age for whom efficacy was clearly demonstrated in randomized controlled studies before the Omicron wave. Given emerging real-world data in the Omicron wave that two-dose protection against symptomatic infection was only modest, a third dose was authorized for individuals 5 years and older and a third dose was evaluated for children <5 years of age.

3.6.1. Post-Dose 3 Immunogenicity Subset

3.6.1.1. Immunogenicity Populations

3.6.1.1.1. Children 2 to <5 Years of Age

The Dose 3 evaluable immunogenicity population included 204 children 2 to <5 years of age who received three doses of BNT162b2 3-µg and 92 who received placebo, of whom 143 and 59 participants, respectively, were without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 3.

The comparator group of young adults 16 to 25 years of age included 183 participants in the BNT162b2 30-µg group and 45 participants in the placebo group of Study C4591001 Dose 2 evaluable immunogenicity population, of whom 170 and 38 participants, respectively, were without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2.

Disposition

Among children 2 to <5 years of age in the immunobridging subset who received three doses of BNT162b2 3-µg or placebo, 100% completed the 1-month post-Dose 3 visit. In the comparator adult group who received two doses of BNT162b2 30-µg or placebo, most (99.5%) completed the 1-month post-Dose 2 visit.

Vaccine Administration and Timing

All children 2 to <5 years of age in the immunobridging subset received all three doses of BNT162b2 3-µg, and all comparator adults 16 to 25 years of age received two doses of BNT162b2 30-µg. Most pediatric and adult participants (>85%) received Dose 2 within the protocol defined window of 19 to 23 days after Dose 1. The median timing of Dose 3 administration after Dose 2 of BNT162b2 was 10.7 weeks (range: 8.1 to 15.6 weeks) and of placebo was 10.7 weeks (range: 8.6 to 16.0 weeks).

In the Omicron neutralization subset, median timing of Dose 3 administration to children 2 to <5 years of age was 10.6 weeks after Dose 2 (range: 8.6 to 13.7 weeks) in the BNT162b2 3-µg group. In the reference group of boosted adults, median timing of Dose 3 administration of BNT162b2 30-µg was much later compared children, at 27.1 weeks after Dose 2 (range 21.0 to 30.0 weeks) as the boosted adult comparator serum set was from a prior booster dose study.

Demographics

Most participants in the evaluable immunogenicity population were White (69.2%), with 5.6% Black or African American participants, 11.2% Asian participants, and 11.9% multiracial participants. There were 11.2% Hispanic/Latino participants. The median age was 3.0 years and 44.1% of participants were male. There were 6.3% of participants reported as obese.

3.6.1.1.2. Children 6 Months to <2 Years of Age

The Dose 3 evaluable immunogenicity population included 132 children 6 months to <2 years of age who received three doses of BNT162b2 3-µg and 67 who received placebo, of whom 82 and 49 participants, respectively, were without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 3.

The comparator group of young adults 16 to 25 years of age used for immunobridging is presented in Section 3.6.1.1.1.

Disposition

Among children 6 months to <2 years of age in the immunobridging subset who received three doses of BNT162b2 3-µg or placebo, 100% completed the 1-month post-Dose 3 visit. In the comparator adult group who received two doses of BNT162b2 30-µg or placebo, most (>99.5%) completed the 1-month post-Dose 2 visit.

Vaccine Administration and Timing

All children 6 months to <2 years of age in the immunobridging subset received all three doses of BNT162b2 3-µg, and all comparator adults 16 to 25 years of age received two doses of BNT162b2 30-µg. Most pediatric and adult participants (>88.5%) received Dose 2 within the protocol defined window of 19 to 23 days after Dose 1. The median timing of Dose 3 administration after Dose 2 of BNT162b2 was 12.9 weeks (range: 8.6 to 20.0 weeks) and of placebo was 12.2 weeks (range: 8.4 to 20.0 weeks).

In the Omicron neutralization subset, median timing of Dose 3 administration to 6 months to <2 years of age was 12.9 weeks after Dose 2 (range: 8.6 to 20.0 weeks) in the BNT162b2 3-µg group. In the reference group of boosted adults, median timing of Dose 3 administration of BNT162b2 30-µg was much later compared to children, at 27.1 weeks after Dose 2 (range 21.0 to 30.0 weeks) as the boosted adult comparator serum set was from a prior booster dose study.

Demographics

Most participants in the evaluable immunogenicity population were White (72.0%), with 1.2% Black or African American participants, 13.4% Asian participants, and 12.2% multiracial participants. There were 15.9% Hispanic/Latino participants. The median age was 16.0 months and 62.2% of participants were male.

3.6.1.2. Immunobridging Results – Phase 2/3

3.6.1.2.1. Children 2 to <5 Years of Age

GMR of Neutralizing Titers

Within the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection, the GMR of SARS-CoV-2 50% neutralizing titers in children 2 to <5 years of age (at 1-month post-Dose 3 of BNT162b2 3-µg) compared to young adults 16 to 25 years of age (at 1-month post-Dose 2 of BNT162b2 30-µg) was 1.30 (2-sided 95% CI: 1.13, 1.50).

The lower bound of the 2-sided 95% CI for GMR was >0.67 and the GMR point estimate was >0.8 (protocol specified criterion) and >1.0 (requested by FDA), indicating the prespecified immunobridging success criterion for the GMR was met.

Difference in Seroresponse Rates

Within the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection, the difference in proportions who achieved seroresponse (as defined in Section 3.3.2) among children 2 to <5 years of age (at 1-month post-Dose 3 of BNT162b2 3-µg) compared to young adults 16 to 25 years of age (at 1-month post-Dose 2 of BNT162b2 30-µg) was 1.2% (2-sided 95% CI: -1.5%, 4.2%).

The lower limit of the 2-sided 95% CI for the difference in seroresponse rate was greater than -10% and immunobridging success criterion based on the GMR was achieved, indicating the prespecified immunobridging success criterion for difference in seroresponse was met.

3.6.1.2.2. Children 6 Months to <2 of Age

GMR of Neutralizing Titers

Within the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection, the GMR of SARS-CoV-2 50% neutralizing titers in children 6 months to <2 years of age (at 1-month post-Dose 3 of BNT162b2 3-µg) compared to young adults 16 to 25 years of age (at 1-month post-Dose 2 of BNT162b2 30-µg) was 1.19 (2-sided 95% CI: 1.00, 1.42).

The lower bound of the 2-sided 95% CI for GMR was >0.67 and the GMR point estimate was >0.8 (protocol specified criterion) and >1.0 (requested by FDA), indicating the prespecified immunobridging success criterion for the GMR was met.

Difference in Seroresponse Rates

Within the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection, the difference in proportions who achieved seroresponse (as defined in Section 3.3.2) among children 6 months to <2 years of age (at 1-month post-Dose 3 of BNT162b2 3-µg) compared to young adults 16 to 25 years of age (at 1-month post-Dose 2 of BNT162b2 30-µg) was 1.2% (2-sided 95% CI: -3.4%, 4.2%).

The lower limit of the 2-sided 95% CI for the difference in seroresponse rate was greater than -10%, and immunobridging success criterion based on the GMR was achieved, indicating the prespecified immunobridging success criterion for difference in seroresponse was met.

3.6.1.3. SARS-CoV-2 Neutralizing Titers – Phase 2/3 –Wild-type Strain

3.6.1.3.1. Children 2 to <5 Years of Age

Neutralizing titers are summarized below for children 2 to <5 years of age from before Dose 1 to 1-month post-Dose 3, and for young adults from before Dose 1 to 1-month post-Dose 2.

Subgroup analyses based on demographic characteristics at baseline generally showed no meaningful differences in the immunogenicity profile. The subgroup with evidence of prior SARS-CoV-2 infection at baseline ('baseline positive') generally had higher neutralizing titers both at baseline (pre-vaccination) and post-vaccination compared with the 'baseline negative' subgroup, which is predictable in the setting of vaccinating after prior exposure. These should be interpreted with caution as some subgroups include a limited number of participants.

GMTs

Among children 2 to <5 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the observed GMT before vaccination was low (20.7) but still robust at post-Dose 2 and prior to Dose 3 (401.1), and then substantially increased at 1-month post-Dose 3 (1535.2).

In the comparator group of young adults 16 to 25 years of age, the observed GMT before vaccination was low (21.3) and substantially increased at 1-month post-Dose 2 (1180.0).

GMFRs

Among children 2 to <5 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the GMFR of SARS-CoV-2 50% serum neutralizing titers from before vaccination to 1-month post-Dose 3 was 73.3 (2-sided 95% CI: 66.3, 81.1). The GMFR from before Dose 3 to 1-month post-Dose 3 was 3.8 (2-sided 95% CI: 3.5, 4.2).

In the comparator group of young adults 16 to 25 years of age, the GMFR of SARS-CoV-2 50% serum neutralizing titers from before vaccination to 1-month post-Dose 2 was 55.3 (2-sided 95% CI: 49.6, 61.6).

Seroresponse Rates

Among children 2 to <5 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the seroresponse rate (as defined in Section 3.3.2) at 1-month post-Dose 3 was 100% (2-sided 95% CI: 97.4%, 100%).

In the comparator group of young adults 16 to 25 years of age, the seroresponse rate at 1-month post-Dose 2 was 98.8% (2-sided 95% CI: 95.8%, 99.9%).

3.6.1.3.2. Children 6 Months to <2 Years of Age

Neutralizing titers are summarized below for children 6 months to <2 years of age from before Dose 1 to 1-month post-Dose 3, and for young adults from before Dose 1 to 1-month post-Dose 2.

Subgroup analyses based on demographic characteristics at baseline generally showed no meaningful differences in the immunogenicity profile. The subgroup with evidence of prior SARS-CoV-2 infection at baseline ('baseline positive') generally had higher neutralizing titers both at baseline (pre-vaccination) and post-vaccination compared with the 'baseline negative' subgroup, which is predictable in the setting of vaccinating after prior exposure. These should be interpreted with caution as some subgroups include a limited number of participants.

GMTs

Among children 6 months to <2 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the observed GMT before vaccination was low (20.8) but still robust at post-Dose 2 and prior to Dose 3 (317.0), and then substantially increased at 1-month post-Dose 3 (1406.5).

In the comparator group of young adults 16 to 25 years of age, the observed GMT increased before vaccination was low (21.3) but was substantially increased at 1-month post-Dose 2 (1180.0).

GMFRs

Among children 6 months to <2 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the GMFR of SARS-CoV-2 50% serum neutralizing titers from before vaccination to 1-month post-Dose 3 was 68.4 (2-sided 95% CI: 58.2, 80.4). The GMFR from before Dose 3 to 1-month post-Dose 3 was 4.4 (2-sided 95% CI: 3.8, 5.2).

In the comparator group of young adults 16 to 25 years of age, the GMFR of SARS-CoV-2 50% serum neutralizing titers from before vaccination to 1-month post-Dose 2 was 55.3 (2-sided 95% CI: 49.6, 61.6).

Seroresponse Rates – Children 6 Months to <2 Years of Age

Among children 6 months to <2 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the seroresponse rate (as defined in Section 3.3.2) from before vaccination to 1-month post-Dose 3 was 100% (2-sided 95% CI: 95.5%, 100%).

In the comparator group of young adults 16 to 25 years of age, the seroresponse rate from before vaccination to 1-month post-Dose 2 was 98.8% (2-sided 95% CI: 95.8%, 99.9%).

3.6.1.4. SARS-CoV-2 Neutralizing Titers – Phase 2/3 – Omicron Variant

3.6.1.4.1. Variant Neutralizing Titers

Children 2 to <5 Years of Age

Among 34 children 2 to <5 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 3-µg, neutralizing GMTs prior to vaccination with Dose 3 against Delta (68.0) and Omicron (14.0) were increased at 1-month post-Dose 3 with respect to both Delta (471.4) and Omicron (82.5). Correspondingly, increases were also observed for the reference strain from before Dose 3 (70.1) to 1-month post-Dose 3 (471.4).

Children 6 Months to <2 Years of Age

Among 32 children 6 months to <2 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 3-µg, neutralizing GMTs prior to vaccination with Dose 3 against Delta (94.1) and Omicron (16.3) were increased at 1-month post-Dose 3 with respect to both Delta (606.3) and Omicron (127.5). Correspondingly, increases were also observed for the reference strain from before Dose 3 (103.7) to 1-month post-Dose 3 (640.0).

Adults 18 to 55 Years of Age

Similar patterns were observed for 40 adults 18 to 55 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 30-µg, for whom neutralizing GMTs prior to vaccination with Dose 3 against Delta (36.4) and Omicron (12.7) were increased at 1-month post-Dose 3 with respect to both Delta (1153.6) and Omicron (340.0) titers. Increases were also observed for the reference strain from before Dose 3 (33.9) to 1-month post-Dose 3 (1067.1).

Notably, the dosing interval between Dose 2 and Dose 3 in adults was approximately 6 months, as compared with the dosing interval between Dose 2 and Dose 3 in the pediatric age group of approximately 2 to 3 months. The longer interval, as well as potential differences in antibody waning over time, may contribute to the higher increase in GMTs observed in adults as compared to the pediatric population.

3.6.1.4.2. Fold-Rises in Variant Neutralizing Titers

Children 2 to <5 Years of Age

For children 2 to <5 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 3-µg, there was an observed 6.9-fold increase in Delta and 5.9-fold increase in Omicron neutralizing titers obtained in the FFRNT assay from before Dose 3 to 1-month post-Dose 3. The GMFR for the reference strain from before Dose 3 to 1-month post-Dose 3 was 6.7.

Children 6 Months to <2 Years of Age

For children 6 months to <2 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 3-µg, there was an observed 6.4-fold increase in Delta and

7.8-fold increase in Omicron neutralizing titers obtained in the FFRNT assay from before Dose 3 to 1-month post-Dose 3. The GMFR for the reference strain from before Dose 3 to 1-month post-Dose 3 was 6.2.

Adults 18 to 55 Years of Age

For adults 18 to 55 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 30-μg, there was an observed 31.7-fold increase in Delta and 26.7-fold increase in Omicron neutralizing titers obtained in the FFRNT assay from before Dose 3 to 1-month post-Dose 3. The GMFR for the reference strain from before Dose 3 to 1-month post-Dose 3 was 31.5.

Noting that adults had a longer dosing interval between Dose 2 and Dose 3 (approximately 6 months) at a time when antibody levels may be waning and the effects of a booster may be more pronounced, compared with children in this age group (approximately 2 to 3 months), a higher GMFR in the adults compared to the pediatric population may be expected.

3.6.2. Immunogenicity Conclusions

Analysis of immunogenicity data demonstrated a robust vaccine-elicited immune response to BNT162b2 3-μg when administered in three doses to children 6 months to <5 years of age, including successful immunobridging to young adults (16 to 25 years of age) from the original adult efficacy study based on neutralizing titers against the SARS-CoV-2 wild-type strain. Furthermore, three doses of BNT162b2 3-μg induced higher neutralizing titers against the Omicron variant compared to after two doses, with generally similar response patterns as those observed in adults. Importantly, real-world effectiveness studies during the pandemic period of Omicron predominance have consistently shown the need for a third dose of COVID-19 vaccines to achieve high levels of vaccine effectiveness against symptomatic COVID-19 caused by the Omicron variant. Note that an initial immunobridging analysis was conducted at 1-month post-Dose 2, in which the 6 months to <2 years of age group data met all success criteria but the 2 to <5 years of age group only partially fulfilled the success criteria for formal immunobridging, while a post hoc analysis comparing to an older population, for which pivotal efficacy was also demonstrated, met all success criteria. At the time of the analyses, the Omicron variant of concern (VOC) emerged and real-world data in older age groups became available to suggest a third dose would lead to higher protection, particularly against this VOC. This led to the decision to immunize children 6 months to <5 years of age with three doses of BNT162b2 3-μg to ensure enhanced immune responses and protection against COVID-19 due to Omicron.

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

3.7.1. Efficacy Population – Phase 2/3

3.7.1.1. Children 2 to <5 Years of Age

Disposition

Among randomized Phase 2/3 participants, the Dose 1 evaluable efficacy population for children 2 to <5 years of age included 1835 participants in the BNT162b2 group and 915 participants in the placebo group, which reflects the 2:1 randomization. There were 606 participants in the BNT162b2 group and 280 participants in the placebo group who received three doses of study intervention and comprised the Dose 3 all-available efficacy population. VE was analyzed for cases in blinded follow-up. RVE was analyzed for a specified calendar period for cases accrued in blinded and open-label follow-up.

Demographics

Most participants in the Dose 3 all-available efficacy population were White (76.1%), with 4.7% Black or African American participants, 10.2% Asian participants, 8.1% multiracial participants, and other race subgroups <1%. There were 12.8% Hispanic/Latino participants. The median age was 3.0 years and 46.7% of participants were male. A total of 9.9% participants in the BNT162b2 group and 12.9% in the placebo group were baseline positive with evidence of prior SARS-CoV-2 infection.

Dose 1 all-available efficacy population demographic characteristics were similar in BNT162b2 and placebo groups, and generally similar to the Dose 3 all-available efficacy population.

3.7.1.2. Children 6 Months to <2 Years of Age

Disposition

Among randomized Phase 2/3 participants, the Dose 1 all-available efficacy population for children 6 months to <2 years of age included 1178 participants in the BNT162b2 group and 598 participants in the placebo group, which reflects the 2:1 randomization. There were 386 participants in the BNT162b2 group and 184 participants in the placebo group who received three doses of study intervention and comprised the Dose 3 all-available efficacy population. VE was analyzed for cases in blinded follow-up. RVE was analyzed for a specified calendar period for cases accrued in blinded and open-label follow-up.

Demographics

Most participants in the Dose 3 all-available efficacy population were White (74.7%), with 3.7% Black or African American participants, 10.4% Asian participants, 10.9% multiracial participants, and other race subgroups <1%. There were 9.3% Hispanic/Latino participants. The median age was 16 months and 47.0% of participants were male. A total of 5.2% participants in the BNT162b2 group and 3.8% in the placebo group were baseline positive for evidence of prior SARS-CoV-2 infection. Dose 1 all-available efficacy population demographic characteristics were similar in BNT162b2 and placebo groups, and generally similar to the Dose 3 all-available efficacy population.

3.7.2. Vaccine Efficacy from Dose 1 to Cutoff Date - Dose 1 All-Available Efficacy Population

3.7.2.1. Children 2 to <5 Years of Age

The observed VE for BNT162b2 3-µg against any confirmed COVID-19 from Dose 1 onwards in the Dose 1 all-available efficacy population (ie, all randomized participants who received at least one dose of vaccination) of children 2 to <5 years of age was 32.6% (2-sided 95% CI: 10.8%, 48.8%) based on 127 cases in the BNT162b2 group and 92 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine:placebo), as of the data cutoff date (29 April 2022) (Figure 8). Note that most cases confirmed post-Dose 1 were reported in January 2022, a period when Omicron was the predominantly circulating variant.

When excluding participants who had evidence of coinfection with other respiratory pathogens the observed VE after Dose 1 for BNT162b2 3-µg administered to children 2 to <5 years of age was 36.0% (2-sided 95% CI: 12.2%, 53.2%) based on 97 cases in the BNT162b2 group and 74 cases in the placebo group, adjusted for surveillance time (noting the 2:1 randomization of vaccine:placebo). Identified coinfections that excluded participants were enterovirus, adenovirus, metapneumovirus, parainfluenza, coronavirus (endemic), RSV, and *M. pneumoniae.*

3.7.2.2. Children 6 Months to <2 Years of Age

The observed VE for BNT162b2 3-µg against any confirmed COVID-19 from Dose 1 onwards in the Dose 1 all-available efficacy population (ie, all randomized participants who received at least 1 dose of vaccination) of children 6 months to <2 years of age was 14.0% (2-sided 95% CI: -21.2%, 38.4%) based on 98 cases in the BNT162b2 group and 58 cases in the placebo group, adjusted for surveillance time (noting the 2:1 randomization of vaccine:placebo), as of the data cutoff date (29 April 2022) (Figure 9). Note that most cases confirmed post-Dose 1 were reported in January 2022, a period when Omicron was the predominantly circulating variant.

When excluding participants who had evidence of coinfection with other respiratory pathogens, the observed VE after Dose 1 for BNT162b2 3-µg administered to children 6 months to <2 years of age was 6.8% (2-sided 95% CI: -39.8%, 37.2%) based on 75 cases in the BNT162b2 group and 41 cases in the placebo group, adjusted for surveillance time (noting the 2:1 randomization of vaccine:placebo). Identified coinfections that excluded participants were adenovirus, enterovirus, parainfluenza, and coronavirus (endemic).

Figure 8. **Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Blinded Follow-Up Period – Phase 2/3 – 2 to <5 Years of Age – Dose 1 All Available Efficacy Population**

Note: "*" indicates participants with first COVID-19 occurrence from 7 days after dose 3.

Figure 9.   Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Blinded Follow-Up Period – Phase 2/3 – 6 Months to <2 Years of Age – Dose 1 All Available Efficacy Population

Note: "*" indicates participants with first COVID-19 occurrence from 7 days after dose 3.

3.7.3. Vaccine Efficacy from at Least 7 Days After Dose 2 to Before Dose 3: Dose 2 Evaluable Efficacy Population

3.7.3.1. Total Population of Children 6 Months to <5 Years of Age

The observed VE from at least 7 days after Dose 2 to before Dose 3 for BNT162b2 3-μg administered to children 6 months to <5 years of age without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was 28.3% (2-sided 95% CI: 8.0%, 43.9%) based on 163 cases in the BNT162b2 group and 113 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine:placebo) (Table 4). In this population, observed VE against Delta and Omicron was 70.2% (2-sided 95% CI: 27.2%, 88.5%) and 21.8% (2-sided 95% CI: -1.7%, 39.7%), respectively (Table 4). Note that most of the cases across this age population that were confirmed post-Dose 2 to before Dose 3 were reported in January 2022.

Similar VE was observed from at least 7 days after Dose 2 to before Dose 3 for children 6 months to <5 years of age with or without prior evidence of SARS-CoV-2 infection (Table 4).

3.7.3.2. Children 2 Years to <5 Years of Age

The observed VE from at least 7 days after Dose 2 to before Dose 3 for BNT162b2 3-μg administered to children 2 to <5 years of age without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was 35.9% (2-sided 95% CI: 11.0%, 53.7%) based on 90 cases in the BNT162b2 group and 69 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine:placebo) (Table 4). In this population, observed VE against Delta and Omicron was 56.3% (2-sided 95% CI: -27.5%, 85.3%) and 32.9% (2-sided 95% CI: 4.7%, 52.5%), respectively (Table 4). Note that most cases that were confirmed post-Dose 2 to before Dose 3 were reported in January 2022.

Similar VE was observed from at least 7 days after Dose 2 to before Dose 3 for children 2 to <5 years of age with or without prior evidence of SARS-CoV-2 infection (Table 4).

3.7.3.3. Children 6 Months to <2 Years of Age

The observed VE from at least 7 days after Dose 2 to before Dose 3 among children 6 months to <2 years of age without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was 16.1% (2-sided 95% CI: -24.9%, 43.1%) based on 73 cases in the BNT162b2 group and 44 cases in the placebo group, adjusted for surveillance time (noting the 2:1 randomization of vaccine:placebo) (Table 4). In this population, observed VE against Delta and Omicron was 91.6% (2-sided 95% CI: 30.6%, 99.8%) and 4.2% (2-sided 95% CI: -45.9%, 36.2%), respectively (Table 4). Note that most cases that were confirmed post-Dose 2 to before Dose 3 were reported in January 2022.

Similar VE was observed from at least 7 days after Dose 2 to before Dose 3 for children 6 months to <2 years of age with or without prior evidence of SARS-CoV-2 infection (Table 4).

Table 4. **Vaccine Efficacy – First COVID-19 Occurrence from 7 Days After Dose 2 to Before Dose 3 – Blinded Follow-Up Period – Phase 2/3 – Dose 2 Evaluable Efficacy Population**

	6 Months to <5 Years of Age		2 to <5 Years of Age		6 Months to <2 Years of Age	
Participants Without Prior Evidence of SARS-CoV-2 Infection						
	Case Split (BNT162b2:Placebo)	VE (2-sided 95% CI)	Case Split (BNT162b2:Placebo)	VE (2-sided 95% CI)	Case Split (BNT162b2:Placebo)	VE (2-sided 95% CI)
Overall VE	163:113	28.3% (8.0%, 43.9%)	90:69	35.9% (11.0%, 53.7%)	73:44	16.1% (-24.9%, 43.1%)
VE against Delta	9:15	70.2% (27.2%, 88.5%)	8:9	56.3% (-27.5%, 85.3%)	1:6	91.6% (30.6%, 99.8%)
VE against Omicron	154:98	21.8% (-1.7%, 39.7%)	82:60	32.9% (4.7%, 52.5%)	72:38	4.2% (-45.9%, 36.2%)
Participants With or Without Prior Evidence of SARS-CoV-2 Infection						
Overall VE	173:120	27.0% (7.1%, 42.5%)	97:73	34.3% (9.7%, 52.0%)	76:47	15.6% (-24.2%, 42.1%)
VE against Delta	10:15	66.3% (19.7%, 86.4%)	8:9	56.0% (-28.4%, 85.2%)	2:6	82.6% (2.7%, 98.3%)
VE against Omicron	163:105	21.4% (-1.4%, 38.9%)	89:64	31.2% (3.6%, 50.7%)	74:41	5.7% (-41.6%, 36.5%)

3.7.4. Vaccine Efficacy From at Least 7 Days After Dose 3 to Cutoff Date: Dose 3 All-Available Efficacy Population

3.7.4.1. Total Population of Children 6 Months to <5 Years of Age

The observed VE from at least 7 days after Dose 3 to the cutoff date (29 April 2022) across the total population of children 6 months to <5 years of age was 80.3% (2-sided 95% CI: 13.9%, 96.7%) based on 3 cases in the BNT162b2 group and 7 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine:placebo) (Figure 10). Note that all post-Dose 3 cases were reported in February through April 2022. None of these participants had reported evidence of prior SARS-CoV-2 infection at baseline.

3.7.4.2. Children 2 Years to <5 Years of Age

The observed VE from at least 7 days after Dose 3 to the cutoff date (29 April 2022) among children 2 to <5 years of age was 82.3% (2-sided 95% CI: -8.0%, 98.3%) based on 2 cases in the BNT162b2 group and 5 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine:placebo). Note that all post-Dose 3 cases were reported in March through April 2022. None of these participants had reported evidence of prior SARS-CoV-2 infection at baseline.

When excluding participants who had evidence of coinfection with other respiratory pathogens the observed VE after Dose 3 for BNT162b2 3-μg administered to children 2 to <5 years of age was 89.0% (2-sided 95% CI: -11.6%, 99.8%) based on 1 case in the BNT162b2 group and 4 cases in the placebo group, adjusted for surveillance time (noting the 2:1 randomization of vaccine:placebo). Identified coinfections that excluded participants were adenovirus, parainfluenza, and coronavirus (endemic).

3.7.4.3. Children 6 Months to <2 Years of Age

The observed VE from at least 7 days after Dose 3 to the cutoff date (29 April 2022) among children 6 months to <2 years of age was 75.5% (2-sided 95% CI: -370.1%, 99.6%) based on 1 case in the BNT162b2 group and 2 cases in the placebo group, adjusted for surveillance time (noting the 2:1 randomization of vaccine:placebo). Note that all post-Dose 3 cases were reported in February through April 2022. None of these participants had reported evidence of prior SARS-CoV-2 infection at baseline.

When excluding participants who had evidence of coinfection with other respiratory pathogens the observed VE after Dose 3 for BNT162b2 3-μg administered to children 6 months to <2 years of age was 100.0% (2-sided 95% CI: -1808.9%, 100.0%) based on no cases in the BNT162b2 group and 1 case in the placebo group, adjusted for surveillance time (noting the 2:1 randomization of vaccine:placebo). Identified coinfections that excluded participants were adenovirus and enterovirus.

Figure 10. Cumulative Incidence Curves for the First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period - Phase 2/3 – 6 Months to <5 Years of Age – Dose 3 All-Available Efficacy Population

3.7.5. Relative Vaccine Efficacy of Three vs Two Doses: Dose 1 All-Available Efficacy Population

3.7.5.1. Total Population of Children 6 Months to <5 Years of Age

The RVE of BNT162b2 3-µg against symptomatic COVID-19 based on 4 cases reported at least 7 days after Dose 3 (original BNT162b2 group who received three doses) compared with 6 cases reported at least 7 days after Dose 2 (original placebo group who were unblinded and received two doses of BNT162b2) during the period of 07 February 2022 to 29 April 2022 was 76.2% (2-sided 95% CI: -0.5%, 95.1%).

3.7.5.2. Children 2 Years to <5 Years of Age

The RVE of BNT162b2 3-µg against symptomatic COVID-19 based on 2 cases reported at least 7 days after Dose 3 (original BNT162b2 group) compared with 4 cases reported at least 7 days after Dose 2 (original placebo group who were unblinded to receive BNT162b2) during the period of 07 February 2022 to 29 April 2022 was 84.0% (2-sided 95% CI: -11.8%, 98.6%).

3.7.5.3. Children 6 Months to <2 Years of Age

The RVE of BNT162b2 3-µg against symptomatic COVID-19 based on 2 cases reported at least 7 days after Dose 3 (original BNT162b2 group) compared with 2 cases reported at least 7 days after Dose 2 (original placebo group who were unblinded to receive BNT162b2) during the period of 07 February 2022 to 29 April 2022 was 59.4% (2-sided 95% CI: -459.5%, 97.1%).

3.7.6. Characterization of COVID-19 Illness

3.7.6.1. Children 2 to <5 Years of Age

Signs and Symptoms of COVID-19

Confirmed cases occurring after Dose 1 among participants 2 to <5 years of age had signs and symptoms associated with 127 cases in the BNT162b2 group and 92 cases in the placebo group. The reported signs and symptoms were generally similar in both groups, with the most commonly reported being fever (58.0%) and new or increased cough (65.8%) from protocol defined symptoms and nasal congestion or runny nose (33.8%) from additional CDC defined symptoms. Most participants in either group reported ≤3 concurrent signs or symptoms.

Participants with Multiple Episodes of COVID-19 During the Study

Few participants in the 2 to <5 years of age group had virologically and clinically confirmed multiple episodes of COVID-19. All participants with multiple episodes had mild to moderate illness, with exception of 1 child whose initial illness met a protocol criterion for severe disease (increased heart rate), that was followed by non-severe illness in January 2022. Most children with confirmed multiple episodes had coinfections with other respiratory pathogens, and most of the illnesses were reported in January 2022 or later.

Note, several participants had multiple PCR-positive results confirming COVID-19, for which the last reported symptom of the initial case confirmation was followed within a brief period (eg, a month or less) by a subsequent PCR-positive result and new report of associated symptoms. Such instances are unlikely to represent separate illnesses. For participants meeting these criteria,

all of the reported symptoms and PCR results were in January or February 2022. All children who reported multiple episodes received three doses of assigned study intervention, except for 1 child in the BNT162b2 group who had received two doses of BNT162b2 3-μg.

Severe COVID-19 and MIS-C

Severe COVID-19 criteria (as described in the protocol, based on FDA definition and modified for children to have very high sensitivity to alert for any potential severe illness) were fulfilled for 7 cases (6 BNT162b2 and 1 placebo [taking into account 2:1 randomization]) among children 2 to <5 years of age. Of these, 5/6 cases in the BNT162b2 group fulfilled a single criterion of increased heart rate or respiratory rate and 1 case in the placebo group fulfilled a single criterion of decreased SpO_2 (88% on room air); all occurred post-Dose 2 (Table 5). Note that in 2 such cases in the BNT162b2 group, the participants reported illness after they were unblinded, which could have introduced potential bias.

All cases meeting a single protocol defined criterion were considered by the investigator as not clinically significant based on examination at the illness visit, vital signs being near normal limits, and contributing circumstances such as the child crying during examination. The remaining case in the BNT162b2 group involved a child hospitalized for decreased SpO_2 (91% on room air) and increased heart and respiratory rates who had coinfection with parainfluenza and additionally met the CDC criterion of hospitalization due to COVID-19, which was confirmed by PCR 100 days post-Dose 2. No cases of MIS-C were reported in this age group.

Table 5.   Characterization of Cases Assigned as Severe That Met FDA Criteria: Children 2 to <5 Years of Age

Group	Age	Timing[*]	Severity Criteria Met	Severity Range	Meets CDC Criteria	Coinfection
BNT162b2	4 years	32 days	HR=132	>131	No	
BNT162b2	4 years	62 days	RR=32	>29	No	
BNT162b2	3 years	183 days	RR=32	>29	No	
BNT162b2	3 years	208 days	RR-32	>29	No	
BNT162b2	2 years	44 days	HR=150	>142	No	
BNT162b2	2 years	100 days	HR=150 RR=40 SpO2=91% Hospitalization	>142 >38 ≤92%	Yes (Hospitalization)	Parainfluenza virus type 3
Placebo	2 years	162 days	SpO2=88%	≤92%	No	

* All cases occurred post-Dose 2

Highlighted row (gray) presents case information for the only participant who fulfilled >1 severity criterion per protocol pediatric-modified FDA definition and including CDC criterion of hospitalization. This participant had coinfection with parainfluenza virus type 3, and clinical assessment included reported wheezing and salbutamol administration.

HR=heart rate, RR=respiratory rate, SpO2=oxygen saturation

3.7.6.2. Children 6 Months to <2 Years of Age

Signs and Symptoms of COVID-19

Confirmed cases occurring after Dose 1 among participants 6 months to <2 years of age had signs and symptoms associated with 98 cases in the BNT162b2 group and 58 cases in the placebo group. The reported signs and symptoms were generally similar in both groups, with the most commonly reported being fever (63.5%) and new or increased cough (70.5%) from protocol defined symptoms and nasal congestion or runny nose (45.5%) from additional CDC defined symptoms. Most participants in either group reported ≤3 concurrent signs or symptoms.

Participants with Multiple Episodes of COVID-19 During the Study

Few participants in the 6 months to <2 years of age group had virologically and clinically confirmed multiple episodes of COVID-19. All participants with multiple episodes had mild to moderate illness. Most children with confirmed multiple episodes had coinfections with other respiratory pathogens, and most of the illnesses were reported in January 2022 or later. Note, several participants had multiple PCR-positive results confirming COVID-19, for which the last reported symptom of the initial case confirmation was followed within a brief period (eg, a month or less) by a subsequent PCR-positive result and new report of associated symptoms. Such instances are unlikely to represent separate illnesses. For participants meeting these criteria, the reported symptoms and PCR results were in August to September 2021, December 2021 to January 2022, or January or February 2022. All children who reported multiple episodes in the BNT162b2 group received three doses of assigned study intervention; among those in the placebo group, 1 child received two doses of placebo only and 2 children received two doses of placebo followed by three doses of open-label BNT162b2 3-µg.

Severe COVID-19 and MIS-C

As of the data cutoff date, 1 participant, in the placebo group, had confirmed COVID-19 which met a single severe case criterion from the protocol-specified and pediatric-modified version of the FDA criterion (increased heart rate [172 bpm]). This participant was diagnosed with COVID-19 34 days post-Dose 3 which did not meet the criteria for severe disease. Participant experienced febrile seizure and had heart rate of 174 bpm 10 days later (44 days post-Dose 3) that met the criteria for severe disease. The participant also had evidence of coinfection with enterovirus (Table 6). No cases in the BNT162b2 group fulfilled criteria described in the protocol for severe illness. No CDC criteria for severe illness were met. No cases of MIS-C were reported in this age group.

Table 6.   Characterization of Cases Assigned as Severe That Met FDA Criteria: Children 6 Months to <2 Years of Age

Group	Age	Timing*	Severity Criteria Met	Severity Range	Meets CDC Criteria	Coinfection
Placebo	14 months	44 days	HR=172	>156	No	Human Rhinovirus/ Enterovirus

* Case occurred post-Dose 3
HR=heart rate, RR=respiratory rate, SpO2=oxygen saturation

3.7.7. Efficacy Conclusions from Phase 2/3 Data

The totality of available data indicates vaccinating children 6 months to <5 years of age with three doses of BNT162b2 3-µg affords measurable protection against symptomatic COVID-19 based on evaluation of COVID-19 cases accrued through 29 April 2022 during a period of Omicron variant predominance, coupled with immunogenicity data demonstrating increased neutralizing titers against multiple lineages of SARS-CoV-2 including the wild-type strain and Delta and Omicron variants. Note that high VE of ≥90% has been observed against the wild-type strain and/or Delta variant of SARS-CoV-2 after two or three doses in adult and pediatric populations, before Omicron became the dominant variant. Collectively, clinical and real-world data from the period of Omicron predominance indicate that three doses of BNT162b2 are necessary to improve the protection observed after two doses against symptomatic illness particularly due to Omicron in infants and children as has been shown for adults.

4. BENEFIT/RISK ASSESSMENT

Benefits and Risks of Vaccinating Children <5 Years of Age Based on Clinical Data

Based on the observed safety and effectiveness profiles following three doses of BNT162b2 at the 3-µg dose level to children <5 years of age, it is expected that the known and potential benefits outweigh the known and potential risks at this time.

With the inclusion of the current available data from children <5 years of age who received 3-µg of BNT162b2, representing at least 2 months of follow-up after Dose 3 for most participants, the observed safety profile for BNT162b2 in both age groups continues to demonstrate a safe and tolerable vaccine. Reactogenicity was overall less frequent in children <5 years of age compared to children >5 years of age and adults, and the AE profile has reflected age-appropriate events expected to be observed in these general populations.

Administration of three doses of BNT162b2 at 3-µg elicited increased neutralizing GMTs against the wild-type strain, Delta and Omicron variant of SARS-CoV-2 in children 6 months to <5 years of age who were without evidence of SARS-CoV-2 infection up to 1 month after Dose 3. Analysis of immunogenicity data demonstrated a robust vaccine-elicited immune response to BNT162b2 3-µg when administered in three doses to children 6 months to <5 years of age, including successful immunobridging to young adults from the original adult efficacy study based on neutralizing titers against the wild-type SARS-CoV-2 strain. Furthermore, three doses of BNT162b2 3-µg induced higher neutralizing titers against the Omicron variant, with generally similar response patterns as those observed in adults. Importantly, real-world effectiveness studies during the pandemic period of Omicron predominance have consistently shown the need for a third dose of vaccine to achieve high levels of vaccine effectiveness against symptomatic COVID-19 caused by the Omicron variant.

A supportive noninferiority analysis compared children 2 to <5 years of age after two doses at the 3-µg dose level with older adults ≥65 years of age who received two doses at the 30-µg dose level; the data showed that noninferiority was met comparing these children to older adults who demonstrated high VE of >90% in the pivotal efficacy Study C4591001.

In children 6 months to <5 years of age, observed VE against symptomatic disease based on COVID-19 cases confirmed from at least 7 days post-Dose 3 to the cutoff date was 80.3% (2-sided 95% CI: 13.9%, 96.7%). Additionally, RVE based on 4 cases reported at least 7 days after Dose 3 (original BNT162b2 group) vs 6 cases reported at least 7 days after Dose 2 (original placebo group unblinded to receive BNT162b2) during the calendar interval of 07 February 2022 to 29 April 2022 was 76.2% (2-sided 95% CI: -0.5%, 95.1%). Note that this time period corresponds to when Omicron was the dominant SARS-CoV-2 variant.

Benefit-Risk Assessment for Vaccinating Children <5 Years of Age

Real-world effectiveness data indicate that in adolescents and adults, three doses of BNT162b2 are needed to provide high levels of protection both symptomatic disease and severe illness due to Omicron.[4,5,17,18,19,20,21,22,23,24] Based on the available BNT162b2 immune response data and available observed VE for children 6 months to <5 years of age against symptomatic disease during a period in which the Omicron variant was predominant, it is anticipated that the protection provided by three doses of BNT162b2 in this age group will likely be similar to that observed in older age groups.

Benefit-risk assessment was based on real-world data describing rates of COVID-19 and vaccine effectiveness and durability of protection as well as available clinical study data including descriptive efficacy against Omicron. From available evidence, we assumed VE for three doses of BNT162b2 against symptomatic COVID-19 of 80% (range: 50% to 90%) at <1 month after Dose 3, 70% (range: 50% to 85%) at 1 to <2 months after Dose 3, 65% (range: 50% to 80%) at 2 to <3 months after Dose 3, and 65% (range: 50% to 75%) at 3 to <4 months after Dose 3.

Based on observed VE of approximately 80% in children 6 months to <5 years of age and supported by real-world data[20,21] for three doses of BNT162b2 in children 12 to 17 years of age, the benefit-risk assessment assumes that vaccinating US children <5 years of age with three doses of BNT162b2 3-μg could prevent 17,448 cases per million population (range: 12,816 to 20,808 per million) based on average rates of COVID-19 seen over the entire pandemic, and in the context of variant wave peaks, could prevent 169,108 cases per million population (range: 124,296 to 201,704 per million) in a scenario resembling an Omicron wave, 31,604 cases per million population (range: 23,224 to 37,696 per million) in a scenario resembling a Delta wave, and 26,820 cases per million population (range: 19,708 to 32,000 per million) in a scenario resembling an Alpha wave (Table 7).

It is estimated that 420 per million (range: 364 to 476 per million) COVID-19 related hospitalizations would be averted based on average rates of COVID-19-related hospitalizations seen over the entire pandemic, and in the context of variant wave peaks, could prevent 3416 hospitalizations per million population (range: 2968 to 3836 per million) in a scenario resembling an Omicron wave, 644 hospitalizations per million population (range: 560 to 728 per million) in a scenario resembling a Delta wave, and 504 hospitalizations per million population (range: 448 to 588 per million) in a scenario resembling an Alpha wave in the US.

Based on pandemic averages, 20.9 MIS-C cases per million population (range: 18.3 to 23.5 per million) and 4.6 COVID-19 related deaths per million population (range: 4.0 to 5.2 per million) could be averted in the US. In the context of variant wave peaks, 28.6 COVID-19 related deaths

per million population (range: 25.0 to 32.2 per million) could be averted in a scenario resembling an Omicron wave, 13.7 COVID-19 related deaths per million population (range: 12.0 to 15.5 per million) could be averted in a scenario resembling a Delta wave, and 11.4 COVID-19 related deaths per million population (range: 10.0 to 12.9 per million) could be averted in a scenario resembling an Alpha wave.

Limited data on post-acute sequelae of SARS-CoV-2 infection, also known as long COVID, are available for the pediatric population, particularly for younger children in whom assessment of subjective long-term symptomatology may be challenging. The available evidence indicates that older children may experience long-term consequences of SARS-CoV-2 infection[25,26,27,28] and persistent symptoms such as fatigue, dyspnea, memory impairment, and sleep disturbances have been reported in 2 to 50% of pediatric COVID-19 cases.[25,28,29,30,31]

Other indirect benefits, such as vaccine pressure on SARS-CoV-2 and increased school and workforce productivity, are also included in this benefit-risk assessment. However, the impact of the vaccination program on these outcomes in the Omicron era is not well studied but assumed to be less than with previous variants. However, young children likely still play a large role in community transmission, and even a limited impact of vaccination on a significant disease wave could provide meaningful public health benefit in the weeks and months ahead. Moreover, vaccinating this age group could also allow for shorter quarantine times at daycare centers and provide more childcare stability for working parents.

Myocarditis and/or pericarditis, while rare, are important identified risks associated with the Pfizer-BioNTech COVID-19 Vaccine, especially in adolescents and young adults. Large studies reported background rates of myocarditis in children ≤5 years of age prior to the COVID-19 era, ranging from 0.9 to 5.0 per 100,000 persons per year.[32,33,34] The US CDC also estimated 1 to 10 myocarditis cases per 100,000 person years in the US population with all ages combined and an unknown study period, regardless of vaccination status.[35]

Although not being statistically powered to identify rare events such as myocarditis and/or pericarditis, no cases of myocarditis/pericarditis were identified in clinical study participants 6 months to <5 years of age in Study C4591007 through a median of approximately 4 months of follow-up after Dose 2 and 2.1 months of follow-up after Dose 3, and no cases were identified among clinical study participants 5 to <12 years of age in prior submissions that included at least 2 months of follow-up after Dose 2. Real-world surveillance of post-vaccination myocarditis and pericarditis events has observed that most cases are clinically mild, and patients tend to recover within a short time following standard treatment.[36,37,38,39,40]

Higher myocarditis risk has been reported after SARS-CoV-2 infection compared with the background rates in the pre-COVID-19 era or post-Pfizer-BioNTech COVID-19 vaccination.[41,42,43,44] A recent seroprevalence study estimated that approximately three-quarters of children in the US 0 to 11 years of age had already been infected with SARS-CoV-2, a known risk factor for myocarditis and/or pericarditis.[45] A large US hospital-based administrative database reported myocarditis among 0.133% patients <16 years of age with SARS-CoV-2 infection treated in a hospital setting from March 2020 to January 2021.[42] Using electronic health record (EHR) data from 40 US health care systems during 01 January 2021 to 31 January 2022, incidence rates of myocarditis within 7 days of SARS-CoV-2 infection were 12.6 per 100,000

persons (126 per million persons) for boys 5 to 11 years of age and 50.1 per 100,000 persons (or 501 per million persons) for boys 12 to 17 years of age.[43] The myocarditis risk within 0 to 21 days of SARS-CoV-2 infection was greater than that within 0 to 7 days for boys 5 to 11 years of age (17.6 per 100,000 persons or 176 per million persons) and 12 to 17 years of age (59 per 100,000 persons or 590 per million persons).

The US CDC has provided reporting rates of myocarditis cases per million BNT162b2 doses administered within 0 to 7 days and 8 to 21 days of vaccination using data from VAERS during 03 November 2021 to 24 April 2022.[35] Among pediatric males, myocarditis cases were highest 0 to 7 days after Dose 2 in boys 16 to 17 years of age (74.2 per million doses) followed by boys 12 to 15 years of age (48.1 per million doses) and boys 5 to 11 years of age (2.7 per million doses). Among pediatric females, the occurrence of myocarditis is less frequent, and rates were highest 0 to 7 days after Dose 2 in girls 16 to 17 years of age (7.2 per million doses) followed by girls 12 to 15 years of age (4.3 per million doses) and girls 5 to 11 years of age (0.8 per million doses). According to data from VSD and VAERS reported by the US CDC, reports of myocarditis cases per million doses following BNT162b2 Dose 3 were lower, compared with following Dose 2.[46]

Other potential risks of vaccination based in part on the observed clinical safety profile to date among approximately 4500 children 6 months to <5 years of age in Study C4591007 include mild to moderate reactogenicity and low incidence of severe or serious events. Of note, no new clinically concerning safety observations or concerns have been identified.

Overall, the known and potential benefits of administering three doses of BNT162b2 3-µg to children 6 months to <5 years of age outweigh the known and potential risks, given the large number of COVID-19 cases, hospitalizations, and medical complications that could be averted. The vaccine has demonstrated a tolerable reactogenicity and safety profile in the clinical study and the occurrence of post-vaccination myocarditis is expected to be rare (Table 7).

5. OVERALL CONCLUSIONS

Current real-world data suggest that two doses of BNT162b2 in adults provide significant protection against hospitalization and severe disease caused by the Omicron variant, and that protection is higher after three doses of BNT162b2.

Emergency use authorization of three doses of BNT162b2 3-µg for children 6 months to <5 years of age would allow protection in this pediatric population, which is an age group who remains unprotected and has experienced a recent surge in cases and hospitalizations due to Omicron. Protection against severe COVID-19 is critical, particularly in light of the unpredictability of potential new waves, including a potential autumn/winter wave and potential waves driven by the emergence of new variants of concern.

Overall, the available safety, immunogenicity, and efficacy information support a favorable benefit risk profile for the administration of three doses of BNT162b2 3-µg to children 6 months to <5 years of age. As other mitigation measures are being lifted (eg, masking, restrictions on large gatherings), authorization for this population would expand direct vaccine protection and add another important layer of community protection in the US against symptomatic and severe illness from COVID-19.

Table 7.   Benefit-Risk Assessment of Three Doses of BNT162b2 3-µg for Children 6 Months to <5 Years of Age

Benefits[a]	Risks[b]
• COVID-19 cases averted per million with three doses of vaccine over 6 months: ○ 17,448 (12,816 to 20,808) based on pandemic average ○ 169,108 (124,296 to 201,704) based on Omicron wave peak ○ 31,604 (23,224 to 37,696) based on Delta wave peak ○ 26,820 (19,708 to 32,000) based on Alpha wave peak • COVID-19-related hospitalizations averted per million with three doses of vaccine over 6 months: ○ 420 (364 to 476) based on pandemic average ○ 3416 (2968 to 3836) based on Omicron wave peak ○ 644 (560 to 728) based on Delta wave peak ○ 504 (448 to 588) based on Alpha wave peak • COVID-19-related MIS-C averted per million with three doses of vaccine over 6 months ○ 20.9 (18.3 to 23.5) based on pandemic average • COVID-19-related deaths averted per million with a three doses of vaccine over 6 months ○ 4.6 (4.0 to 5.2) based on pandemic average ○ 28.6 (25.0 to 32.2) based on Omicron wave peak ○ 13.7 (12.0 to 15.5) based on Delta wave peak ○ 11.4 (10.0 to 12.9) based on Alpha wave peak • Maintain vaccine pressure on SARS-CoV-2 rates and help prevent the emergence of future variants • Faster return to normal life • Increased school and workforce productivity, less absenteeism • Low incidence of severe or serious events (no new clinically concerning safety observations or concerns)	• Post-vaccination myocarditis (important identified risk) • Anaphylaxis (important identified risk) • Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) (important potential risk)[c] • Mild to moderate reactogenicity and other adverse events

a. Note: Based on incidence and VE assumptions.
b. No cases of myocarditis/pericarditis, anaphylaxis attributed to vaccine, or VAED/VAERD have been reported in Study C4591007 participants 6 months to <5 years of age.
c. Expected myocarditis risk was estimated based on reporting cases per million doses from the VAERS.[32] The background rate of 0.197 myocarditis cases per million doses in a 0 to 7-day window was calculated based on the reported background rate of 0.9/100,000 persons per year.[46]

6. APPENDIX

COVID-19 Case Surveillance and Criteria

Phase 2/3 Study C4591007 included continuous surveillance for potential cases of COVID-19. If a participant developed acute illness with symptoms possibly related to COVID-19, their parent/legal guardian was to contact the study site for an in-person or telehealth visit including nasal (anterior nares) swab sample collection (by site staff personnel or parent/legal guardian) for RT-PCR (Cepheid; US FDA-authorized under EUA) or equivalent NAAT to detect SARS-CoV-2. Clinical information and results from local standard-of-care tests were also assessed. The central laboratory result from a validated PCR test was used for case definition; if no central laboratory result was available, a local NAAT result could be used if obtained in the protocol specified window using a protocol approved test:

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

Evidence of SARS-CoV-2 infection was determined by serological testing for IgG to the SARS-CoV-2 N antigen (N-binding assay) at Dose 1 visit (baseline), 1-month post-Dose 2, Dose 3, and 1-month post-Dose 3; and virological testing via NAAT on anterior nares swabs at Dose 1, Dose 2, and Dose 3 visits and any unscheduled illness visits.

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

Case criteria are summarized below for protocol definition of confirmed COVID-19 (Table 8), severe illness criteria based on protocol and CDC definitions (Table 9), and MIS-C criteria based on CDC definition (Table 11). Note that the protocol definition of severe disease was modified from the FDA definition, designed to conservatively identify potential severe illnesses.

Table 8. Confirmed COVID-19 Case Criteria

Presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT positive during or within 4 days before or after the symptomatic period, from the central laboratory or local testing facility using an acceptable test, which triggered a potential COVID-19 illness visit:	
• Fever	• New loss of taste or smell
• New or increased cough	• Sore throat
• New or increased shortness of breath	• Diarrhea, as defined by ≥3 loose stools/day
• Chills	• Vomiting
• New or increased muscle pain	• Inability to eat/poor feeding

Case confirmation based on C4591007 protocol definition.

Table 9.   Severe Illness COVID-19 Case Criteria

Protocol definition of severe illness (adapted from FDA definition, modified for children)[47]
Confirmed COVID-19 and presence of <u>at least 1</u> of the following that 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[48] (see Table 10)
    - SpO_2 ≤92% on room air, >50% FiO_2 to maintain ≥92%, or PaO_2/FiO_2 <300 mm Hg

- Respiratory failure: needing high-flow oxygen including CPaP, BiPaP, noninvasive ventilation, mechanical ventilation, or ECMO

- Evidence of shock or cardiac failure:
    - SBP (mm Hg); <70 + (age in years × 2) for age up to 10 years, <90 for age ≥10 years
    - Requiring vasoactive drugs to maintain blood pressure in the normal range

- Significant acute renal failure: serum creatinine ≥2-times ULN for age or 2-fold increase in baseline creatinine

- Significant gastrointestinal/hepatic failure: total bilirubin ≥4 mg/dL or ALT 2-times ULN for age

- Significant neurological dysfunction: Glasgow Coma Scale score ≤11, or acute change in mental status with a decrease in Glasgow Coma Scale score ≥3 points from abnormal baseline[49]

- Admission to an intensive care unit (ICU)

- Death

CDC definition of severe illness[47]
Included outcomes of hospitalization, admission to the ICU, intubation or mechanical ventilation, or death

Protocol definition is modified to conservatively identify severe illness in children based on FDA definition:
https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions html
CDC definition: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions html

Table 10.   Respiratory Rate and Heart Rate Indicative of Severe Systemic Illness by Age

Participant Age	Respiratory Rate[48]	Heart Rate[48]
6 to <9 Months	>61	>168
9 Months to <12 months	>58	>161
12 to <18 Months	>53	>156
18 to <24 Months	>46	>149
2 to <3 Years	>38	>142
3 to <4 Years	>33	>136
4 to <6 Years	>29	>131
6 to <8 Years	>27	>123
8 to <12 Years	>25	>115

Based on data from: Fleming S, Thompson M, Stevens R, et al. Lancet 2011;377(9770):1011-8.

Table 11.   MIS-C Case Criteria

CDC definition of MIS-C:[50]
Met <u>all</u> of the below criteria:
• <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 including 1 or more of the following: elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, low albumin
• Evidence of clinically severe illness requiring hospitalization, 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; <u>OR</u> COVID-19 exposure within 4 weeks prior to onset of symptoms

MIS-C criteria per CDC definition: https://www.cdc.gov/mis-c/hcp/

7. REFERENCES

1   Johns Hopkins University. COVID-19 Data Repository by the Center for Systems
     Science and Engineering (CSSE) at Johns Hopkins University 2022. Available at:
     https://github.com/CSSEGISandData/COVID-19.

2   Centers for Disease Control and Prevention. COVID Data Tracker: COVID-19 Weekly
     Cases and Deaths per 100,000 Population by Age, Race/Ethnicity, and Sex 2022.
     Available at: https://covid.cdc.gov/covid-data-tracker/#demographicsovertime.

3   Wiemken TL, Niemotka SL, Clarke JA, et al. Estimating pediatric cases of COVID-19
     over time in the United States: Filling in a gap in public use data. Am J Infect Control.
     2021;50(1):4-7.

4   Ferdinands JM, Rao S, Dixon BE, et al. Waning 2-dose and 3-dose effectiveness of
     mRNA vaccines against COVID-19-associated emergency department and urgent care
     encounters and hospitalizations among adults during periods of Delta and Omicron
     variant predominance – VISION Network, 10 States, August 2021-January 2022.
     MMWR Morb Mortal Wkly Rep. 2022;71(7):255-63.

5   Tartof SY, Slezak JM, Puzniak L, et al. Immunocompromise and durability of
     BNT162b2 vaccine against severe outcomes due to omicron and delta variants. Lancet
     Respir Med. 2022;[Epub]:S2213-600(22)00170-9; doi:10.1016/S2213-2600(22)00170-
     9.

6   Osmanov IM, Spiridonova E, Bobkova P, et al. Risk factors for post-COVID-19
     condition in previously hospitalised children using the ISARIC Global follow-up
     protocol: a prospective cohort study. Eur Respir J. 2022;59(2):2101341; doi:
     10.1183/13993003.01341-2021

7   Barrett CE, Koyama AK, Alvarez P, et al. Risk for newly diagnosed diabetes >30 days
     after SARS-CoV-2 infection among persons aged <18 years – United States, March 1,
     2020-June 28, 2021. MMWR Morb Mortal Wkly Rep. 2022;71(2):59-65.

8   Centers for Disease Control and Prevention. COVID Data Tracker: COVID-NET
     Laboratory-confirmed COVID-19 hospitalizations 2022. Available at:
     https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network.

9   Food and Drug Administration (FDA). Toxicity Grading Scale for Healthy Adult and
     Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trial. Guidance for
     Industry. September 2007. Available at: https://www.fda.gov/media/73679/download.

10   Zou J, Xia H, Xie X, et al. Neutralization against Omicron SARS-CoV-2 from previous
      non-Omicron infection. Nat Commun. 2022;13:852;[ePub] doi:10.1038/s41467-022-
      28544-w.

11   Kurhade C, Zou J, Xia H, et al. Neutralization of Omicron BA.1, BA.2, and BA.3
      SARS-CoV-2 by 3 doses of BNT162b2 vaccine. bioRxiv. 2022;[ePub]
      doi:10.1101/2022.03.24.485633.

12   Liu Y, Liu J, Xia H, et al. Neutralizing activity of BNT162b2-elicited serum.
      N Engl J Med. 2021;384:1466-8.

13   Muruato AE, Fontes-Garfias CR, Ren P, et al. A high-throughput neutralizing antibody
      assay for COVID-19 diagnosis and vaccine evaluation. Nat Commun. 2020;11:4059.

14   Thomas SJ, Moreira ED, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA
      Covid-19 vaccine through 6 months. N Engl J Med. 2021;385:1761-73;
      doi:10.1056/NEJMoa2110345. Supplemental appendix available at:
      https://www.nejm.org/doi/suppl/10.1056/NEJMoa2110345/suppl_file/nejmoa2110345_
      appendix.pdf.

15   BioFire® Respiratory 2.1 (RP2.1) Panel. Available at:
      https://www.biofiredx.com/products/the-filmarray-panels/filmarrayrp/

16   US Food and Drug Administration. FDA News Release, 17 March 2021. FDA Permits
      Marketing of First SARS-CoV-2 Diagnostic Test Using Traditional Premarket Review
      Process. Available at: https://www.fda.gov/news-events/press-announcements/fda-
      permits-marketing-first-sars-cov-2-diagnostic-test-using-traditional-premarket-review-
      process.

17   Thompson MG, Natarajan K, Irving SA, et al. Effectiveness of a third dose of mRNA
      vaccines against COVID-19-associated emergency department and urgent care
      encounters and hospitalizations among adults during periods of Delta and Omicron
      variant predominance – VISION Network, 10 States, August 2021-January 2022.
      MMWR Morb Mortal Wkly Rep. 2022;71(4):139-45.

18   Kirsebom FC, Andrews N, Stowe J, et al. COVID-19 vaccine effectiveness against the
      omicron (BA.2) variant in England. Lancet Infectious Diseases. Available at:
      https://doi.org/10.1016/S1473-3099(22)00309-7.

19   UK Health Security Agency. COVID-19 vaccine surveillance report – Week 19,
      12 May 2022. Available at:
      https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment
      _data/file/1075115/COVID-
      19_vaccine_surveillance_report_12_May_2022_week_19.pdf. Accessed 17 May 2022.

20 Fleming-Dutra KE, Britton A, Shang N, et al. Association of prior BNT162b2 COVID-19 vaccination with symptomatic SARS-CoV-2 infection in children and adolescents during Omicron predominance. JAMA. 2022;[EPub]; doi: 10.1001/jama.2022.7493.

21 Klein NP, Stockwell MS, Demarco M, et al. Effectiveness of COVID-19 Pfizer-BioNTech BNT162b2 mRNA vaccination in preventing COVID-19-associated Emergency Department and Urgent Care encounters and hospitalizations among nonimmunocompromised children and adolescents aged 5-17 Years – VISION Network, 10 States, April 2021-January 2022. MMWR Morb Mortal Wkly Rep. 2022;71(9):352-8; doi:10.15585/mmwr.mm7109e3.

22 Accorsi EK, Britton A, Fleming-Dutra KE, et al. Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 Omicron and Delta variants. JAMA. 2022;327(7):639-51.

23 Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the Omicron (B.1.1.529) variant. N Engl J Med. 2022;86(16):1532-46; doi: 10.1056/NEJMoa2119451.

24 Lauring AS, Tenforde MW, Chappell JD, et al. Influenza and other viruses in the acutely Ill (IVY) network. Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. BMJ. 2022;376:e069761; doi:10.1136/bmj-2021-069761.

25 Molteni E, Sudre CH, Canas LS, et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. Lancet Child & Adolescent Health. 2021;5(10):70818;doi:10.1016/s2352-4642(21)00198-x.

26 Ashkenazi-Hoffnung L, Shmueli E, Ehrlich S, et al. Long COVID in children: observations from a designated pediatric clinic. Pediatr Infect Dis J. 2021; doi: 10.1097/INF.0000000000003285.

27 Buonsenso D, Munblit D, De Rose C, et al. Preliminary evidence on long COVID in children. Acta Paediatr. 2021;110(7):2208-11; doi:10.1111/apa.15870

28 Erol N, Alpinar A, Erol C, Sari E, Alkan K. Intriguing new faces of Covid-19: persisting clinical symptoms and cardiac effects in children. Cardiol Young. 2021:1-7; doi: 10.1017/S1047951121003693.

29 Asadi-Pooya AA, Nemati H, Shahisavandi M, et al. Long COVID in children and adolescents. World J Pediat. 2021;[ePub] doi:10.1007/s12519-021-00457-6.

30   Behnood SA, Shafran R, Bennett SD, et al. Persistent symptoms following
      SARS-CoV-2 infection among children and young people: a meta-analysis of controlled
      and uncontrolled studies. J Infection 2021:S0163-4453(21)00555-7; doi:
      10.1016/j.jinf.2021.11.011.

31   Parisi GF, Diaferio L, Brindisi G, et al. Cross-sectional survey on long term sequelae of
      pediatric COVID-19 among Italian pediatricians. Children (Basel). 2021;8(9); doi:
      10.3390/children8090769.

32   Vasudeva R, Bhatt P, Lilje C, et al. Trends in acute myocarditis related pediatric
      hospitalizations in the United States, 2007-2016. Am J Cardiol. 2021;[EPub];149:95-
      102 ;doi:10.1016/j.amjcard.2021.03.019.

33   Ozierański K, Tymińska A, Skwarek A, et al. Sex differences in incidence, clinical
      characteristics and outcomes in children and young adults hospitalized for clinically
      suspected myocarditis in the last ten years – data from the MYO-PL Nationwide
      Database. J Clin Med. 2021;10(23):5502; doi:10.3390/jcm10235502.

34   Arola A, Pikkarainen E, Sipilä JO, et al. Occurrence and features of childhood
      myocarditis: a nationwide study in Finland. J Am Heart Assoc. 2017;18;6(11):e005306;
      doi:10.1161/JAHA.116.005306.

35   Shimabukuro T. COVID-19 Vaccine Safety Updates. 19 May 2022 ACIP Meeting
      Presentation; Available at: Active safety monitoring for COVID-19 vaccines (cdc.gov).
      Accessed 25 May 2022.

36   Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA vaccine
      against Covid-19 in Israel. N Engl J Med 2021:NEJMoa2109730;[ePub] doi:
      10.1056/NEJMoa2109730.

37   Shimabukuro T. COVID-19 Vaccine Safety Updates. 21 October 2021 ACIP Meeting
      Presentation; Slide 4. Available at: CDC Awardee COVID-19 Vaccination Planning
      Meeting. Accessed 25 May 2022.

38   Oster M. mRNA COVID-19 Vaccine-Associated Myocarditis. Available at: CDC
      Awardee COVID-19 Vaccination Planning Meeting. Accessed 25 May 2022.

39   Heymans S, Cooper LT. Myocarditis after COVID-19 mRNA vaccination: clinical
      observations and potential mechanisms. Nat Rev Cardiol 2022;19(2):75-7; doi:
      10.1038/s41569-021-00662-w.

40   Shimabukuro T. Update on myocarditis following mRNA COVID-19 vaccination.
      Vaccines and Related Biologic Products Advisory Committee (VRBPAC) 07 June 2022.
      Available at: https://www.fda.gov/media/159007/download. Accessed 08 June 2022.

41   Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19
      Vaccine in a Nationwide Setting. N Engl J Med. 2021;385(12):1078-90; doi:
      10.1056/NEJMoa2110475.

42   Boehmer TK, Kompaniyets L, Lavery AM, et al. Association between COVID-19 and
      myocarditis using hospital-based administrative data – United States, March 2020-
      January 2021. MMWR Morb Mortal Wkly Rep. 2021;70(35):1228-32; doi:
      10.15585/mmwr.mm7035e5.

43   Block JP, Boehmer TK, Forrest CB, et al. Cardiac complications after SARS-CoV-2
      infection and mRNA COVID-19 vaccination – PCORnet, United States, January 2021-
      January 2022. MMWR Morb Mortal Wkly Rep. 2022;8:71(14):517-23; doi:
      10.15585/mmwr.mm7114e1.

44   Patone M, Mei XW, Handunnetthi L, et al. Risks of myocarditis, pericarditis, and
      cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection.
      Nat Med. 2021;28(2):410-422; doi:10.1038/s41591-021-01630-0.

45   Clarke KEN, Jones JM, Deng Y, et al. Seroprevalence of infection-induced
      SARS-CoV-2 antibodies – United States, September 2021-February 2022. MMWR
      Morb Mortal Wkly Rep. 2022;71(17):606-8; doi:10.15585/mmwr.mm7117e3.

46   Klein N. and Shimabukuro T. Safety update of 1st booster mRNA COVID-19
      vaccination. 20 April 2022 ACIP Meeting Presentation; Available at: Rapid Cycle
      Analysis (RCA) to Monitor the Safety of COVID-19 Vaccines in Near Real-Time
      within the Vaccine Safety Datalink (cdc.gov). Accessed 25 May 2022.

47   Centers for Disease Control and Prevention (CDC). Coronavirus Disease (COVID-19).
      Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-
      precautions/people-with-medical-conditions.html. Accessed 09 December 2020.

48   Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory
      rate in children from birth to 18 years of age: a systematic review of observational
      studies. Lancet. 2011;377(9770):1011-8.

49   Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference:
      definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med.
      2005;6(1):2-8 ;doi:10.1097/01.PCC.0000149131.72248.E6.

50   Centers for Disease Control and Prevention (CDC). Information for Healthcare
      Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). Available
      at: https://www.cdc.gov/mis-c/hcp/. Accessed 09 December 2020.