Vaccines and Related Biological Products Advisory Committee Meeting
June 15, 2022

FDA Briefing Document

EUA amendment request for Pfizer-BioNTech COVID-19 Vaccine for use in children 6 months through 4 years of age

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1. Executive summary

On May 27, 2022, Pfizer submitted a request to FDA to amend the Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) for prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The amendment would expand use of BNT162b2 to include a 3-dose primary series (3 µg each dose) for use in infants and children 6 months through 4 years of age. In its request, Pfizer submitted safety, immunogenicity, and preliminary descriptive efficacy data from an ongoing randomized, double-blinded, placebo-controlled trial, C4591007. Study participants 6 months through 4 years of age were randomized 2:1 to receive 2 doses of either BNT162b2 at 3 µg mRNA per dose or saline placebo, administered 3 weeks apart. Following analysis of the post-Dose 2 safety and effectiveness data, the protocol was amended to administer a third primary series dose to participants 6 months through 4 years of age at least 8 weeks after Dose 2.

The EUA request included Phase 2/3 safety data from 1,178 BNT162b2 recipients and 598 placebo recipients 6 months through 23 months (hereafter 6-23 months) of age; and 1,835 BNT162b2 recipients and 915 placebo recipients 2 years through 4 years (hereafter 2-4 years) of age who received at least one dose of the investigational product. Among participants 6 months through 4 years of age, the median follow up was 2.1 months after Dose 3 (inclusive of both blinded and open-label follow up) at the time of the April 29, 2022, data cutoff.

In study C4591007, vaccine effectiveness was inferred by immunobridging based on SARS-CoV-2 50% neutralizing antibody titers (NT50, SARS-CoV-2 mNG microneutralization assay). In each of two further divided age groups (6-23 months and 2-4 years), neutralizing antibody titers at 1 month post-Dose 3 were compared to titers at 1 month post-Dose 2 from a randomly selected subset of 16-25-year-old participants who had received two doses of 30 µg BNT162b2 in the Phase 2/3 efficacy study, C4591001. A preliminary descriptive analysis of vaccine efficacy (VE) among participants who received 3 study vaccinations (following accrual of 10 total confirmed COVID-19 cases occurring at least 7 days post-Dose 3) was also provided.

The primary immunogenicity endpoints evaluated neutralizing antibody titers against the USA_WA1/2020 reference strain, a Wuhan-like strain, as assessed by microneutralization assay, among study participants with no evidence of prior SARS-CoV-2 infection up to 1 month post-Dose 3. Immunobridging endpoints and statistical success criteria were tested sequentially in the following order for each of the age groups 6-23 months and 2-4 years:

- SARS-CoV-2 neutralizing antibody geometric mean titers (GMTs) measured 1 month after Dose 3 in study C4591007 Phase 2/3 participants 6-23 months of age versus GMTs 1 month after Dose 2 in a randomly selected subset of 16-25-year-old participants from study C4591001, with immunobridging success criteria of >0.67 for the lower bound of the 95% confidence interval (CI) around the GMT ratio (pediatric age group / 16-25 years of age), and a point estimate of the GMT ratio ≥1.0.
- Seroresponse rates (percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing antibody titer from pre-Dose 1 baseline), with immunobridging success criterion of >−10% for the lower bound of the 95% CI around the difference in seroresponse rates (pediatric age group minus 16-25 years of age).

Immunobridging statistical success criteria, as described above, were met for both age groups. Post-Dose 3 neutralizing antibody GMTs were numerically higher among participants in both age groups with evidence of prior SARS-CoV-2 infection at baseline as compared to those

without evidence of prior SARS-CoV-2 infection at baseline. Otherwise, subgroup analyses of immunogenicity by age, gender, race and ethnicity showed no notable differences as compared with the overall study population, although some subgroups were too small to draw meaningful conclusions. Additional descriptive immunogenicity analyses, based on a non-validated SARS-CoV-2 fluorescent focus reduction neutralization test (FFRNT), showed lower post-Dose 3 GMTs against the Omicron variant, as compared to the ancestral strain and Delta variant, in both age groups.

Preliminary descriptive efficacy analyses of COVID-19 cases occurring at least 7 days post-Dose 3 included 376 BNT162b2 recipients and 179 placebo recipients 6-23 months of age and 589 BNT162 recipients and 271 placebo recipients 2-4 years of age. In these analyses, three COVID-19 cases occurred in participants 6-23 months of age, with 1 COVID-19 case in the BNT162b2 group compared to 2 in the placebo group, corresponding to an estimated VE of 75.6% (95% CI: −369.1%, 99.6%), and 7 COVID-19 cases occurred in participants 2-4 years of age, with 2 cases in the BNT162b2 group and 5 in the placebo group, corresponding to an estimated VE of 82.4% (95% CI: −7.6%, 98.3%). In a combined analysis of both age groups, VE was 80.4% (95% CI: 14.1%, 96.7%) with 3 cases in the BNT162b2 group and 7 cases in the placebo group. Cases were accrued during February 2022 through April 2022, when the Omicron variant was prevalent in the United States. Among all COVID-19 cases accrued from Dose 1 through the data cutoff of April 29, 2022, 1 placebo recipient 6-23 months of age and 7 participants 2-4 years of age (6 BNT162b2 recipients and 1 placebo recipient) met the protocol-specified criteria for severe COVID-19 during both blinded and open-label follow-up. Only one of these severe COVID-19 cases (in a BNT162b2 recipient 99 days post-Dose 2) resulted in hospitalization, and the remainder met criteria for severe COVID-19 based on vital sign findings that were not clinically significant in the opinion of the investigator and FDA.

Solicited local adverse reactions (ARs) generally occurred at similar frequencies after any dose and solicited systemic ARs occurred at slightly decreasing frequencies with each successive dose. The most commonly reported solicited ARs after any dose for participants 6-23 months of age were irritability (68.4%), drowsiness (41.3%), decreased appetite (38.6%), and tenderness at the injection site (26.4%). The most commonly reported solicited ARs after any dose for participants 2-4 years of age were pain at the injection site (47.0%), fatigue (44.8%), and injection site redness (18.9%). Most local and systemic reactions were mild to moderate in severity, with median onset 1-2 days post vaccination, and a median duration of 1-2 days after onset. Subgroup safety analyses of reactogenicity by baseline SARS-CoV-2 status showed no notable differences as compared with the overall study population.

The frequencies of unsolicited non-serious adverse events (AEs) reported were similar in the BNT162b2 and placebo groups for participants 6-23 months of age (29.1% versus 26.3%) and for participants 2-4 years of age (18.7% versus 18.7%). The most commonly observed unsolicited AEs were consistent with those reported as solicited adverse events (local and systemic reactogenicity) and/or were consistent with events frequently reported in this age group, including infections and injuries. Lymphadenopathy was observed following vaccination in two BNT162b2 recipients 6-23 months of age and one BNT162b2 recipient 2-4 years of age; no cases were reported in the placebo groups. From the combined safety database of 3,013 BNT162b2 recipients 6 months through 4 years of age, 1% of participants (N=29) reported serious adverse events (SAEs), as compared to 1.5% of participants (N=22) in the combined safety database of 1,513 placebo recipients 6 months through 4 years of age. Two SAEs (pyrexia [>40°C] and pain in extremity) which occurred in the same BNT162b2 recipient were considered by the study investigator as possibly related to vaccination; FDA considered that viral myositis could be an alternative etiology. Three participants in the BNT162b2 group

withdrew from the study due to pyrexia (>40°C); these AEs were classified as non-serious. There were no reports of myocarditis/pericarditis, no cases of anaphylaxis considered caused by vaccination, and no deaths.

This June 15, 2022 meeting of Vaccines and Related Biological Products Advisory Committee (VRBPAC) is being held to discuss whether, based on the totality of scientific evidence available, the benefits of the Pfizer-BioNTech COVID-19 Vaccine, when administered as a three-dose primary series, outweigh its risks for use in infants and children 6 months through 4 years of age.

2. Background

2.1. SARS-COV-2 virus and COVID-19 disease

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome, leading to multiorgan failure and death. Symptoms associated with SARS-CoV-2 infection in individuals less than 18 years of age are similar to those in adults, but are generally milder, with fever and cough most commonly reported.[1,2] Other symptoms in children include nausea and vomiting, diarrhea, dyspnea, nasal symptoms, rashes, fatigue and abdominal pain.[3] Most children with COVID-19 recover within 1 to 2 weeks. Estimates of asymptomatic infection in children vary from 15% to 50% of infections.[4,5] However, COVID-19-associated hospitalizations and deaths have occurred in children (see below), and for some children, COVID-19 symptoms may continue for weeks to months after their initial illness.[6]

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of June 8, 2022, has caused over 533 million cases of COVID-19, including 6.3 million deaths worldwide.[7] In the US, approximately 84 million cases and 1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC).[8,9] Following EUA of the first COVID-19 vaccines in December 2020, COVID-19 cases and deaths in the US declined sharply during the first half of 2021. The emergence of the Delta variant, variable implementation of public health measures designed to control spread, and continued transmission among unvaccinated individuals were major factors in the resurgence of COVID-19 in the US, leading to the Delta variant-associated peak in September of 2021 and the more recent surges in cases attributed to the Omicron variant. As of the week ending March 26, 2022, the Omicron variant (B.1.1.529, also called BA.1) comprised all of the tested strains in the US, and sublineages of the Omicron variant (previously BA.2, which replaced BA.1 as the dominant strain, and currently BA.4, and BA.5) are increasingly identified among tested strains.[10]

Of the total COVID-19 cases reported in the US to date, 3.3% occurred among children 0-4 years of age.[11] According to death certificate data, 202 deaths have been attributed to COVID-19 among children 6 months to 4 years of age through May 11, 2022.[12] During the week ending May 21, 2022, there were 40 COVID-19-associated hospitalizations of children 0-4 years of age.[13] During December 19, 2021 to May 7, 2022, when the Omicron variant was predominant, children 6 months to 4 years accounted for 24% of COVID-19 associated intensive care unit (ICU) admissions (n=535) among children 6 months to 17 years.[14] Of children 6 months to 4 years of age with COVID-19 associated hospitalization, 49% had one or more underlying health conditions.[15] The most common underlying medical conditions among

hospitalized children (≤18 years) were obesity (31.9%), neurologic disorders (14.8%), and asthma (14.5%). Obesity was associated with increased risk of severe disease. Available evidence suggests that highest risk groups include children with special healthcare needs, including genetic, neurologic, metabolic conditions, or with congenital heart disease.[16] However, a majority of children hospitalized for COVID-19 have no underlying medical conditions. As in the adult population, COVID-19 in children disproportionally affects underrepresented racial and ethnic groups, with hospitalizations and deaths more frequent among Native American/Alaskan, Hispanic or Latin American, and non-Hispanic Black children than among White children.[17,18] Data on the prevalence of long COVID in children is sparse; however, a national survey in the United Kingdom found that among children ages 2-11 years who tested positive for COVID-19, 7.2% reported continued symptoms at 12 weeks.[19]

Following observation of an increased incidence of myocarditis in 2020 compared with 2019, several studies have suggested an association between COVID-19 and myocarditis.[20,21] While the overall incidence of myocarditis following COVID-19 is low, persons with COVID-19 have a nearly 16-fold increase in risk for myocarditis, compared to individuals without COVID-19. Myocarditis may also present as part of the multisystem inflammatory syndrome in children (MIS-C), usually 3 to 5 weeks after a SARS-CoV-2 infection. MIS-C is a rare but serious COVID-19-associated condition that occurs in less than 1% of children with confirmed SARS-CoV-2 infection.[22] MIS-C presents with persistent fever, laboratory evidence of inflammation, and at least two affected organs. In severe cases, hypotension and shock can occur. Approximately 60-70% of patients are admitted to intensive care, and 1-2% die.[23,24,25] Between May 2020 and May 2022, the CDC received reports of 8,210 cases and 68 deaths that met the definition for MIS-C; the median age of participants was 9 years with 24% of cases occurring in children 0-4 years. Males comprised 61% of cases, and 57% were reported in children who were reported as Hispanic or Black.[26] Up to 66.7% of patients with MIS-C had cardiac involvement, [27] including left ventricular dysfunction, mitral or tricuspid regurgitation, coronary artery aneurysms, and/or arrhythmias.[28] One study of outcomes in children with MIS-C followed up to 9 months found that while 76% children with MIS-C required ICU admission and therapy with inotropes or pressors; most symptoms, including cardiovascular manifestations, resolved within 1 to 4 weeks.[29] Limited data are available on long-term outcomes in MIS-C.

2.2. Authorized and approved vaccines and therapies for COVID-19

2.2.1. Comirnaty and Pfizer-BioNTech COVID-19 Vaccine

Comirnaty (COVID-19 Vaccine, mRNA) made by BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.) is approved for active immunization to prevent COVID-19 in individuals 16 years of age and older. Comirnaty contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 that is formulated in lipid particles. The primary immunization series consists of 2 intramuscular doses administered 21 days apart, with each 0.3 mL dose of the approved formulation containing 30 µg mRNA. During clinical development it was called BNT162b2.

Under EUA, the vaccine is called the Pfizer-BioNTech COVID-19 Vaccine and is authorized for use as: a two-dose primary series for individuals 12 years of age and older; a third primary series dose for individuals 12 years of age and older with certain immunocompromising conditions; a homologous first booster dose administered at least 5 months after completion of primary vaccination to individuals 12 years of age and older; a heterologous first booster dose administered after completion of primary vaccination to individuals 18 years of age and older (the dosing interval is the same as that authorized for a booster dose of the vaccine used for

primary vaccination); and a second booster dose administered at least 4 months after a first booster dose with any FDA authorized or approved COVID-19 vaccine to individuals 50 years of age and older and individuals 12 years of age and older with certain immunocompromising conditions. A different formulation of Pfizer-BioNTech COVID-19 Vaccine containing 10 µg mRNA per 0.2 mL dose is authorized under EUA for use in children 5-11 years of age as: a two-dose primary series; a third primary series dose in individuals with certain kinds of immunocompromise; and a single homologous booster dose administered at least 5 months after completion of a primary series. Safety and effectiveness data supporting approval of Comirnaty and emergency use authorization of Pfizer-BioNTech COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

2.2.2. Spikevax and Moderna COVID-19 Vaccine

Spikevax (COVID-19 Vaccine, mRNA), manufactured by Moderna, is approved for active immunization to prevent COVID-19 in individuals 18 years of age and older. Under EUA, the vaccine is called the Moderna COVID-19 Vaccine. The vaccine is authorized for use under EUA as: a two-dose primary series for individuals 18 years of age and older; a third primary series dose for individuals 18 years of age and older with certain immunocompromising conditions; a homologous or heterologous first booster dose administered after completion of primary vaccination to individuals 18 years of age and older (the authorized dosing interval for a homologous booster is at least 5 months after completion of a primary series, and the authorized interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination); and a homologous or heterologous second booster dose administered at least 4 months after the first booster dose to individuals 50 years of age and older and individuals 18 years of age and older with certain immunocompromising conditions.

Safety and effectiveness data supporting approval of Spikevax and authorization of Moderna COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

2.2.3. Janssen COVID-19 Vaccine

The Janssen COVID-19 Vaccine is authorized for use in individuals 18 years of age and older for whom other FDA-authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, or who elect to receive the Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine. The vaccine is authorized for use in these individuals as a single primary vaccination dose and as a single homologous or heterologous booster dose (the dosing interval for a homologous booster is at least 2 months after the single primary vaccination dose, and the dosing interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination). Safety and effectiveness data supporting emergency use authorization of the Janssen COVID-19 Vaccine are detailed in the decision memorandum on the FDA website.

2.2.4. Therapies for COVID-19

The antiviral remdesivir is currently approved by the FDA for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 testing who are hospitalized, or who are not hospitalized and have mild-to-moderate COVID-19 and are at high risk for severe COVID-19. Additionally, the immune modulator baricitinib is approved by the FDA for the treatment of COVID-19 in hospitalized

adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Other pharmacological products for pre-exposure prophylaxis of COVID-19, post-exposure prophylaxis and/or treatment of COVID-19 that have received emergency use authorization are as follows:

Antivirals: Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Molnupiravir is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.

SARS-CoV-2-targeting monoclonal antibodies: Bebtelovimab is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years of age and older weighing at least 40 kg with positive results of direct SARS-CoV-2 testing, who are at high risk for progression to severe COVID-19 and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. Tixagevimab co-packaged with cilgavimab is authorized under EUA as pre-exposure prophylaxis for prevention of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg).

Immune modulators: Baricitinib is authorized for the treatment of COVID-19 in hospitalized patients 2 to less than 18 years of age who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Tocilizumab is authorized for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

COVID-19 convalescent plasma with high antibody titer is authorized for emergency use as a treatment for patients with COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings.

2.3. Post-licensure/post-authorization experience with Comirnaty and Pfizer-BioNTech COVID-19 Vaccine

2.3.1. Vaccine effectiveness against SARS-CoV-2 variants of concern

The emergence of the highly transmissible Omicron variant of SARS-CoV-2 in December 2021 resulted in several waves of COVID-19 cases in many parts of the world and, in the US, coincided with a rapid increase in COVID-19-associated hospitalizations among all age groups, including children 6 months through 4 years of age.[30] Observational studies have indicated waning effectiveness of mRNA COVID-19 vaccine primary series against symptomatic infection over time for all age groups for which they are authorized, as well as reduced and more rapidly waning effectiveness against symptomatic infection caused by the Omicron variant. Observed estimates of vaccine effectiveness against symptomatic disease due to the Omicron variant

include the following: 8.8% (95% CI, 7.0 to 10.5) at 25 or more weeks since primary vaccination in adults; 59.5% among adolescents 12 to 15 years of age 2 to 4 weeks after dose 2, 16.6% during month 2 after the second dose, and 9.6% during month 3 after the second dose.; and 60.1% for children 5 to 11 years of age 2 to 4 weeks after dose 2, and 28.9% during month 2 after dose 2.[31,32,33,34]

Recent estimates of primary series vaccine effectiveness against serious outcomes have been lower for during the Omicron predominant period as compared to the Delta predominant period across pediatric and adult age groups evaluated. Observed estimates of primary series mRNA vaccine effectiveness against hospitalizations due to the Omicron variant in adults have been reported at 41%-57% at 6-9 months or longer after the second dose.[35,36] In one observational study among adolescents 12 to 18 years of age (median interval since vaccination, 162 days) during the Omicron-predominant period, primary series vaccine effectiveness was 40% (95% CI, 9 to 60) against hospitalization for COVID-19, 79% (95% CI, 51 to 91) against critical COVID-19, and 20% (95% CI, −25 to 49) against noncritical COVID-19. Among children 5 to 11 years of age (median interval since vaccination, 34 days), vaccine effectiveness against hospitalization was 68% (95% CI, 42 to 82).[37] Observed estimates of primary series mRNA vaccine effectiveness against emergency department/urgent care visits due to the Omicron variant in adults have been reported between 31%-38% at 6-9 months or longer after the second dose.[38,39] Data from observational studies have also indicated higher estimates of vaccine effectiveness against COVID-19 and serious outcomes in adults and adolescents among those who have received a booster dose than among those who have received only a primary series.[40] Additional updated data on vaccine effectiveness will be presented by CDC during the VRBPAC meeting.

2.3.2. Post-EUA and post-licensure safety surveillance

As of May 18, 2022, more than 343 million doses of the Pfizer-BioNTech COVID-19 Vaccine have been administered in the US.[41] The Vaccine Adverse Event Reporting System (VAERS) was queried for AE reports following the Pfizer-BioNTech COVID-19 Vaccine, and the results are summarized below. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, stimulated reporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported event was actually due to the vaccine.

As of May 19, 2022, VAERS received 749,249 reports (including 385,218 US reports) following vaccination with Pfizer-BioNTech COVID-19 Vaccine; 245 US reports were in children 6 months through 4 years of age, 10,740 US reports were in children ages 5-11 years, 15,160 US reports were in children ages 12-15 years, and 8,119 US reports were in children ages 16-17 years. The top ten most frequently reported MedDRA Preferred Terms (PTs; US and foreign reports) included:

- All ages: SARS-CoV-2 test, headache, fatigue, COVID-19, pyrexia, dizziness, pain, nausea, pain in extremity, chills.
- Persons ≤17 years of age: dizziness, pyrexia, headache, syncope, product storage error, nausea, product administered to patient of inappropriate age, fatigue, chest pain, vomiting.
- Persons 6 months through 4 years of age: product administered to patient of inappropriate age, exposure via breastmilk, pyrexia, SARS-CoV-2 test, body temperature, off-label use, cough, headache, rash, diarrhea.

Note that a report may have one or more PTs. Among US VAERS reports for individuals aged 6 months through 4 years, which may reflect unauthorized use of the vaccine or may reflect a reporting error, the majority (96.3%) were non-serious.

Safety concerns identified from post-authorization safety surveillance data in VAERS are summarized below. Anaphylaxis, myocarditis, and pericarditis are existing safety concerns that have been added to the product Fact Sheets. Review of passive surveillance adverse event reports and the Sponsor's periodic safety reports does not indicate new safety concerns. Most adverse events are labeled events and consistent with the safety profile for this vaccine. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

Anaphylaxis
Post-authorization surveillance has identified a risk of anaphylaxis, occurring at a rate similar to reported rates of anaphylaxis following licensed preventive vaccines, primarily in individuals with history of prior severe allergic reactions to other medications or foods.[42,43] Anaphylaxis is an important identified risk in the pharmacovigilance plan and included in the Warnings sections of the vaccine Fact Sheets and Prescribing Information. The estimated crude reporting rate for anaphylaxis following Pfizer-BioNTech COVID-19 Vaccine for all ages in the US is 4.7 cases per million doses administered based on VAERS data as of May 20, 2022, which is similar to estimated rates for other vaccines.[44]

Myocarditis and pericarditis
Post-EUA safety surveillance reports received by FDA and CDC identified increased risks of myocarditis and pericarditis, particularly within 7-days following administration of the second dose of the 2-dose primary series. Reporting rates for medical chart-confirmed myocarditis and pericarditis in VAERS have been higher among males under 40 years of age than among females and older males. The highest reporting rates have been in males 12 through 17 years of age (rates of verified cases per million doses within 7-days following dose 2 administration were 74.2 cases among males ages 16-17 years, 48.1 cases among males ages 12-15 years, and 2.7 cases among males ages 5-11 years: data per CDC presentation to the Advisory Committee on Immunization Practices [ACIP] on May 19, 2022). VAERS monitoring has also shown that reporting rates of myocarditis among individuals ages 12-29 years following a first booster dose exceeded background rates but were lower compared to post-Dose 2 rates for the primary series (data per CDC presentation to the ACIP on April 20, 2022).

Although some cases of vaccine-associated myocarditis/pericarditis have required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae and outcomes in affected individuals, or whether the vaccine might be associated initially with subclinical myocarditis (and if so, what are the long-term sequelae). CDC is conducting enhanced surveillance for VAERS case reports using patient and healthcare provider surveys to assess functional status and clinical outcomes among individuals reported to have developed myocarditis after mRNA COVID-19 vaccination. A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established. Myocarditis and pericarditis were added as important identified risks in the pharmacovigilance plan and included in the Warnings sections of the vaccine Fact Sheets and Prescribing Information. The Sponsor is conducting additional post-authorization/post-marketing studies to assess known serious risks of myocarditis and pericarditis as well as to identify an unexpected serious risk of subclinical myocarditis.

2.4. EUA amendment request for the Pfizer-BioNTech COVID-19 Vaccine for use in children 6 months through 4 years of age

On May 27, 2022, Pfizer and BioNTech submitted a request to amend this EUA for use of the Pfizer-BioNTech COVID-19 Vaccine in individuals 6 months through 4 years of age for active immunization to prevent COVID-19 caused by SARS-CoV-2. The proposed regimen is a 3-dose primary series (3 µg each dose), with a 3-week interval between the first two doses, followed by a third dose at least 8 weeks after Dose 2.

The EUA amendment request contains data from participants in Phase 2/3 of ongoing study C4591007, with a data cutoff date of April 29, 2022, by the following pre-specified age groups:

- Participants 6-23 months of age: Safety data from 1,178 BNT162b2 (3 µg) recipients and 598 placebo recipients, of whom 461 (60.8%) and 68 (37.0%), respectively, had at least 2 months (blinded and open-label) safety follow-up after completing a three-dose primary series. Vaccine effectiveness was inferred by immunobridging based on a comparison of immunogenicity endpoints (SARS-CoV-2 neutralizing antibody geometric mean concentrations (GMTs) and seroresponse rates 1 month after Dose 3) between participants 6-23 months of age from study C4591007 (n=146) and participants 16 through 25 years of age from study C4591001. Efficacy against COVID-19 was also assessed descriptively.
- Participants 2-4 years of age: Safety data from 1,835 BNT162b2 (3 µg) recipients and 915 placebo recipients, of whom 596 (57.3%) and 104 (37.1%), respectively, had at least 2 months (blinded and open-label) safety follow-up after completing a three-dose primary series. Vaccine effectiveness was inferred by immunobridging based on a comparison of immunogenicity endpoints (SARS-CoV-2 neutralizing antibody GMTs and seroresponse rates 1 month after Dose 3) between participants 2-4 years of age from study C4591007 (n=217) and participants 16 through 25 years of age from study C4591001. Efficacy against COVID-19 was also assessed descriptively.

Vaccine Formulation for children 6 months through 4 years of age
Each 0.2 mL dose of the Pfizer-BioNTech COVID-19 tris/sucrose formulation contains 3 µg of mRNA encoding the S glycoprotein of SARS-CoV-2 that is formulated in lipid particles. The vaccine is supplied as a concentrated multi-dose frozen suspension in a 2-mL vial (0.4 mL volume). The frozen multiple dose vial needs to be thawed, then diluted with 2.2 mL of 0.9% sodium chloride for injection prior to administration. After dilution, each vial contains 10 doses.

3. EUA requirements, guidance and considerations pertaining to COVID-19 vaccines

3.1. US requirements to support issuance of an EUA for a biological product

Based on the declaration by the Secretary of the United States Department of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).

- The chemical, biological, radiological, or nuclear agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency.

3.2. FDA guidance for industry related to COVID-19 vaccines

An EUA allowing for rapid and widespread deployment of the vaccine to millions of individuals, including healthy people, would need to be supported by clear and compelling evidence of effectiveness and adequate safety follow-up to make a determination of favorable benefit/risk (see guidance for industry "Emergency Use Authorization for Vaccines to Prevent COVID-19" March 2022, originally issued October 2020).[45] These expectations would apply to age-group specific data to support an EUA amendment for use of an unapproved COVID-19 vaccine in children 6 months through 4 years of age. The timing, design, and appropriate endpoints for pediatric studies are discussed in the context of specific vaccine development programs as described in the guidance for industry "Development and Licensure of Vaccines to Prevent COVID-19" from June 2020.[46]

3.3. Regulatory considerations for clinical development of COVID-19 vaccines in children

The VRBPAC convened on June 10, 2021, to discuss, in general, the data needed to support authorization and/or licensure of COVID-19 vaccines for use in pediatric populations.

Effectiveness
Regulatory precedent with other preventive vaccines provides a basis for inference of vaccine effectiveness in pediatric populations based on immunobridging to an adult population in which clinical disease endpoint VE has been demonstrated for the same prototype vaccine. The immune marker(s) used for immunobridging do not need to be scientifically established to predict protection but should be clinically relevant to the disease. Based on available data in humans and animal models, FDA considers neutralizing antibody titers (a functional measure of the vaccine immune response against SARS-CoV-2) to be clinically relevant for immunobridging to infer effectiveness of COVID-19 vaccines in pediatric age groups. Because no specific

neutralizing antibody titer has been established to predict protection against COVID-19, two immunogenicity endpoints (GMT and seroresponse rate) are considered appropriate for comparing the range of neutralizing antibody responses elicited by the vaccine in pediatric versus young adult populations.

Safety
The size of the safety database sufficient to assess risks of COVID-19 vaccines for EUA in pediatric age groups would generally be the same as for other preventive vaccines for infectious diseases, provided that no specific safety concern is identified that could reasonably be evaluated in pre-authorization clinical trials. These safety data would include characterization of common ARs (reactogenicity, including injection site and systemic ARs), and less common but medically important ARs. Depending on prior experience with the vaccine in adults, and prior experience with licensed vaccines based on the same or similar platforms, FDA has accepted an overall pediatric safety database in the range of ~500 to ~3,000 trial participants exposed to the age-appropriate dose and regimen intended for licensure and have at least 6 months of follow-up evaluations after completion of the vaccination regimen. Since COVID-19 vaccines represent a new class of vaccines, with many of the lead candidates based on new platform technologies, an appropriate overall pediatric safety database would approach the upper end of this range, with adequate representation across all pediatric age groups, in particular younger age groups (e.g., <12 years) that are less physiologically similar to adults. A control group (ideally placebo control) would be important to inform interpretation of safety data and to comply with the expectation for adequate and well- controlled studies to support licensure. If another COVID-19 vaccine is licensed or authorized for use in the age group(s) enrolled in the trial, recommended by public health authorities, and widely available such that it is unethical to use a placebo control, the licensed or authorized COVID-19 vaccine could serve as a control.

Within the overall pre-licensure safety database, solicited reactogenicity could be adequately characterized among several hundred trial participants in each relevant age group. Additionally, safety evaluation in all trial participants would include collection of all AEs through at least 1 month after each study vaccination and collection of serious and other medically attended AEs for the duration of the trial. Although longer-term follow-up (through 1 year or longer post-vaccination) of trial participants would be important to ongoing assessment of both benefits and risks, completion of such longer-term follow-up would not be a prerequisite to licensure unless warranted by a specific safety concern. Post-licensure/post-authorization safety surveillance and observational studies in pediatric populations would be needed to evaluate for ARs that occur too rarely to be detected in clinical trials.

4. FDA review of clinical safety and effectiveness data

4.1. Overview of study C4591007

The EUA amendment request contains safety, immunogenicity, and efficacy data from participants 6 months through 4 years of age enrolled in study C4591007, an ongoing Phase 1/2/3, randomized, placebo-controlled study (Table 1). Details of the study design and a summary of data from the Phase 1 dose-ranging portion of the study that informed dose selection for Phase 2/3 are provided in Appendix A.

The comparator groups for the Phase 2/3 immunobridging analyses to support vaccine effectiveness in the pre-specified age groups (6-23 months, 2-4 years) were randomly selected subsets of Phase 2/3 participants 16-25 years of age enrolled in study C4591001, the study in which VE against COVID-19 was established in individuals 16 years of age or older.

Table 1. Study C4591007 in Participants 6 Months Through 4 Years of Age

Study Number/ Countries	Description	BNT162b2 3 µg N	Placebo (Saline) N	Study Status
C4591007 United States, Brazil, Finland, Poland, and Spain	Phase 1/2/3 randomized, placebo- controlled; to evaluate safety, immunogenicity and efficacy of COVID- 19 vaccine	Phase 1: 32 Phase 2/3*: 3013	Phase 1:0 Phase 2/3: 1513	Ongoing

Abbreviation: N=number of randomized participants as of data cutoff dates July 16, 2021 (Phase 1 participants) and April 29, 2022 (Phase 2/3 participants). Phase 1 was conducted only in the United States.
* First participant was randomized on June 21, 2021.

4.2. Phase 2/3

4.2.1. Phase 2/3 study design

In Phase 2/3, a total of 4,526 participants 6 months through 4 years of age were randomized 2:1 to receive two doses of 3 µg BNT162b2 or placebo, 3 weeks apart. The Phase 2/3 portion of the study did not exclude participants with a history of prior SARS-CoV-2 infection or clinical symptoms/signs of COVID-19, participants with known HIV, hepatitis B or hepatitis C, or stable pre-existing disease (defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment). Based on analyses of post-Dose 2 safety and effectiveness data, the protocol was amended to add a third primary series dose at least 8 weeks after Dose 2 (C4591007 protocol amendment 6). Participants enrolled prior to implementation of protocol amendment 6 (N=3,883; February 1, 2022), were able to be unblinded at their 6-month post-Dose 2 visit, and those originally randomized to placebo were offered BNT162b2 vaccination at the age-appropriate dose level. Participants enrolled after implementation of protocol amendment 6 will be unblinded at their 6-month post-Dose 3 visit, and those originally randomized to placebo will be offered BNT162b2 vaccination.

Parent/guardians of participants who turned 5 years of age during the study were offered the option for their child to be unblinded to the treatment assignment and to receive the 10-µg dose level of the Pfizer-BioNTech COVID-19 Vaccine under EUA if they originally received placebo. Participants in the placebo crossover group who were unblinded and had not received any BNT162b2 doses, but were age 5 years or older at the time of crossover vaccination, would then receive two BNT162b2 doses 3 weeks apart and BNT162b2 Dose 3 at least 6 months after Dose 2.

4.2.1.1. Phase 2/3 immunogenicity evaluation

Immunobridging was based on SARS-CoV-2 neutralizing antibody responses at 1 month post Dose 2 or Dose 3 among participants in two separate age groups (6-23 months; 2-4 years) compared to neutralizing antibody responses in a random subset of participants 16-25 years of age at 1 month post Dose 2 (study C4591001, Phase 2/3), as measured by 50% neutralizing antibody titers (NT50, SARS-CoV-2 mNG microneutralization assay) against the reference strain (USA_WA1/2020).

Immunogenicity analyses of GMTs and seroresponse rates at 1 month after Dose 2 were evaluated for both age groups, and the pre-specified immunobridging success criteria (below) were not met for participants 2-4 years of age. Therefore, a third primary series dose was added for both age groups with protocol amendment 6.

The primary analysis for the 3-dose primary series is based on the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after

Dose 2 (comparator group 16-25 years of age) or Dose 3 (participants 6-23 months and 2-4 years of age).

Primary endpoints and statistical success criteria were evaluated sequentially in the following order:

- Immunobridging success based on GMT was declared if the lower limit (LL) of the 95% CI for the GMT ratio (pediatric age group / 16-25-year-olds) was >0.67, and the point estimate of the GMT ratio was ≥1.0.
- Immunobridging success based on the seroresponse rate was declared if the LL of the 95% CI for the difference in seroresponse rates (pediatric age group minus 16-25-year-olds) was >−10%. Seroresponse was defined as a ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination (pre-Dose 1) to 1 month after Dose 2 or Dose 3.

4.2.1.2. Phase 2/3 efficacy evaluation

A secondary objective is to evaluate efficacy of BNT162b2 against laboratory-confirmed symptomatic COVID-19 occurring at least 7 days after Dose 3 in participants without evidence of prior SARS-CoV-2 infection and in participants with or without evidence of prior SARS-CoV-2 infection. A secondary analysis to evaluate VE against a null hypothesis of H0: VE ≤30% was planned once 21 confirmed cases had accrued across both each age groups, conditional on successful immunobridging. See Appendix B for case definitions of COVID-19 and severe COVID-19.

4.2.1.3. Phase 2/3 safety evaluation

Reactogenicity (solicited local and systemic ARs)

Parents/guardians of participants recorded local and systemic reactions and antipyretic/pain medication use daily for 7 days (Day 1 through Day 7) after each vaccination in an e-diary. Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling), which were the same for both age groups, and systemic AEs, which differed in each age group (6-23 months of age: fever, irritability, drowsiness, decreased appetite and 2-4 years of age: fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain).

Unsolicited adverse events

Other safety assessments included: AEs occurring within 30 minutes after each dose, non-serious unsolicited AEs from Dose 1 through 1 month after Dose 3, and SAEs from Day 1 to 6 months after Dose 3 or the data cutoff date (April 29, 2021). AEs were categorized by frequency and maximum severity according to MedDRA System Organ Class (SOC) and PT, and relationship to the study intervention. Deaths will be recorded to the end of the study.

Adverse events of clinical interest

Specified events of interest including myocarditis/pericarditis were assessed as part of the safety review, as well as additional AEs of clinical interest requested by FDA (including angioedema, arthritis, convulsions, demyelination, hypersensitivity, peripheral neuropathy, vasculitis, lymphadenopathy, and MIS-C cases).

4.2.2. Phase 2/3 analysis populations

- Safety: All participants who receive at least 1 dose of the study intervention.

- All-available immunogenicity: All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after vaccination.
- Dose 3 evaluable immunogenicity: All eligible randomized participants who receive three doses of the vaccine to which they are randomized, with Dose 2 received within the predefined window (19-42 days after Dose 1), and Dose 3 received at least 60 days after Dose 2, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window (28-35 days after the specified dose), and have no other important protocol deviations as determined by the clinician.
- All-available efficacy: All randomized participants who complete 1, 2 or 3 doses of the study intervention.
- Evaluable efficacy: All randomized participants who receive all vaccinations as randomized, with Doses 2 and 3 received within the predefined windows and have no other important protocol deviations as determined by the clinician.

Data analysis cutoff dates:
- Phase 1: July 16, 2021
- Phase 2/3 Three-Dose Primary Series: April 29, 2022

4.2.3. Phase 2/3 disposition

Overall study disposition for each age group, prior to and following unblinding, are provided in Table 2 through Table 9. More than 99% of participants received at least 2 doses of study intervention, and approximately 33% received 3 doses as of the April 29, 2022 data cutoff date.

Immunogenicity population
Participants 6-23 months of age
The Dose 3 all-available immunogenicity population for Phase 2/3 participants 6-23 months of age consisted of 146 BNT162b2 recipients and 73 placebo recipients. A total of 16 (10.8%) subjects were excluded from the Dose 3 evaluable immunogenicity analysis population from the BNT162b2 group, most commonly due to invalid or indeterminant immunogenicity results after vaccination or because blood was drawn outside of the window. The analysis population for the primary immunogenicity endpoint was the evaluable immunogenicity population, without evidence of SARS CoV-2 infection up to 1 month after Dose 3 (n=82).

Comparator group for immunobridging analyses: The comparator group for both age groups (6-23 months, 2-4 years) consisted of 200 randomly selected participants 16-25 years of age who received both doses of BNT162b2 30 µg in study C4591001 Phase 2/3. A total of 17 (8.5%) subjects were excluded from the evaluable immunogenicity analysis population, most commonly due to invalid or indeterminant immunogenicity results after vaccination or because Dose 2 was not administered within the prespecified window (Table 2). The analysis population for the primary immunogenicity endpoint was the evaluable immunogenicity population, without evidence of SARS CoV-2 infection up to 1 month after Dose 2 (n=170).

Table 2. Disposition of Participants Ages 6-23 Months and 16-25 Years, Phase 2/3 Three-Dose Primary Series Immunogenicity Populations, Studies C4591007 and C4591001

Disposition, n (%)	C4591007 6-23 Months BNT162b2 3µg N=148	C4591001 16-25 Years BNT162b2 30µg N=200
All-available immunogenicity populations*	146 (98.6)	192 (96.0)
Participants excluded from all-available immunogenicity population	2 (1.4)	8 (4.0)
Did not have at least 1 valid and determinate immunogenicity result after vaccination	2 (1.4)	8 (4.0)
Evaluable immunogenicity populations*	132 (89.2)	183 (91.5)
Without evidence of infection up to 1 month after Dose 2 or 3[a]	82 (55.4)	170 (85.0)
Participants excluded from evaluable immunogenicity population[b]	16 (10.8)	17 (8.5)
Did not receive Dose 2 within 19-42 day window after Dose 1	4 (2.7)	1 (0.5)
Did not receive Dose 3 within window (at least 60 days after Dose 2)	0	N/A
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after Dose 2 or 3	11 (7.4)	14 (7.0)
Did not have blood draw at 1 month after Dose 2 visit	N/A	2 (1.0)
1 Month after Dose 2 or 3 blood draw outside of window (28-42 days after Dose 2 or 3)	10 (6.8)	7 (3.5)
Had blood draw within the window but no valid and determinate immunogenicity result obtained in lab	1 (0.7)	5 (2.5)
Had important protocol deviation(s) as determined by the clinician	4 (2.7)	2 (1.0)

Source: EUA 27034.556, C4591007-dose3-tables-ns-listings-6mo-4yr-immuno.pdf, Pages 51-53.
Abbreviations: NAAT=nucleic acid amplification test; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
N=number of randomized participants in the specified group (the denominator for the percentage calculations); n=number of participants with the specified characteristic.
* Dose 2 populations applicable to adults 16-25 years of age from Study C4591001 and Dose 3 populations applicable to participants 6-23 months of age from Study C4591007.
a. Participants who had no serological or virological evidence (prior to the blood sample collection 1 month post-Dose 2 or 3) of past SARS-CoV-2 infection (i.e., N-binding ant body [serum] negative at Dose 1 and 1 month post-Dose 2 or 3 visits, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 or 3 visits, and negative NAAT [nasal swab] result at any unscheduled visit prior to the blood sample collection 1 month post-Dose 2 or 3) and had no medical history of COVID-19 were included in the analysis.
b. Participants may have been excluded for more than one reason.

Vaccine administration timing: BNT162b2 recipients 6-23 months of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection up to 1 month post Dose 3 received Dose 3 of BNT162b2 at least 8 weeks after Dose 2, most commonly between 8 and <13 weeks post-Dose 2. The median timing of Dose 3 administration was 11.0 weeks (range: 8.6 to 20.0 weeks) after Dose 2 of BNT162b2.

Participants 2-4 years of age

The Dose 3 all-available immunogenicity population for Phase 2/3 participants 2-4 years of age consisted of 217 BNT162b2 recipients and 98 placebo recipients. A total of 14 (6.4%) subjects were excluded from the Dose 3 evaluable immunogenicity analysis population from the BNT162b2 group, most commonly due to invalid or indeterminant immunogenicity results after vaccination or because blood was drawn outside of the pre-specified window. The analysis population for the primary endpoint was the evaluable immunogenicity population, without evidence of SARS CoV-2 infection up to 1 month after Dose 3 (n=143).

Table 3. Disposition of Participants Ages 2-4 Years and 16-25 Years, Phase 2/3 Three-Dose Primary Series Immunogenicity Populations, Studies C4591007 and C4591001

Disposition, n (%)	C4591007 2-4 Years BNT162b2 3µg N=218	C4591001 16-25 Years BNT162b2 30µg N=200
All-available immunogenicity population*	217 (99.5)	192 (96.0)
Participants excluded from all-available immunogenicity population	1 (0.5)	8 (4.0)
Did not have at least 1 valid and determinate immunogenicity result after vaccination	1 (0.5)	8 (4.0)
Evaluable immunogenicity populations*	204 (93.6)	183 (91.5)
Without evidence of infection up to 1 month after Dose 2 or 3[a]	143 (65.6)	170 (85.0)
Participants excluded[b] from evaluable immunogenicity populations*	14 (6.4)	17 (8.5)
Did not receive Dose 2 within 19-42 day window after Dose 1	0	1 (0.5)
Did not receive Dose 3 within window (at least 60 days after Dose 2)	3 (1.4)	N/A
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after Dose 2 or 3	10 (4.6)	14 (7.0)
Did not have blood draw at 1 month after Dose 2 visit	N/A	2 (1.0)
1 month after Dose 2 or 3 blood draw outside of window (28-42 days after Dose 2)	10 (4.6)	7 (3.5)
Had blood draw within the window but no valid and determinate immunogenicity result obtained in lab	0	5 (2.5)
Had important protocol deviation(s) as determined by the clinician	1 (0.5)	2 (1.0)

Source: IND 19736.800, C4591007-dose3-tables-ns-listings-6mo-4yr-immuno.pdf, Pages 54-56.
Abbreviations: NAAT=nucleic acid amplification test; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
* Dose 2 populations applicable to adults 16-25 years of age from Study C4591001 and Dose 3 populations applicable to participants 2-4 years of age from Study C4591007.
N=number of randomized participants in the specified group (the denominator for the percentage calculations).
n=number of participants with the specified characteristic.
a. Participants who had no serological or virological evidence (prior to the blood sample collection 1 month post-Dose 2 or 3) of past SARS-CoV-2 infection (i.e., N-binding ant body [serum] negative at Dose 1 and 1 month post-Dose 2 or 3 visits, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 or 3 visits, and negative NAAT [nasal swab] result at any unscheduled visit prior to the blood sample collection 1 month post-Dose 2 or 3) and had no medical history of COVID-19 were included in the analysis.
b. Participants may have been excluded for more than one reason.

Vaccine administration timing: BNT162b2 recipients 2-4 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection up to 1 month post Dose 3 received Dose 3 of BNT162b2 at least 8 weeks after Dose 2, most commonly between 8 and <13 weeks post-Dose 2. The median timing of Dose 3 administration after Dose 2 of BNT162b2 was 10.7 weeks (range: 8.6 to 15.6 weeks).

Efficacy population

Participants 6-23 months of age

The Phase 2/3 Dose 3 evaluable efficacy population for participants 6-23 months of age included 376 BNT162b2 recipients and 179 placebo recipients. The treatment groups appear imbalanced with respect to receipt of 3 vaccination and unblinding on or before 7 days post Dose 3 because the Sponsor tabulated placebo recipients who did not receive 3 vaccinations due to unblinding as “did not receive 3 vaccinations.” However, taking both reasons for exclusion into account together, the treatment groups are balanced. As shown in Table 4, a total of 802 (68.1%) and 419 (69.2%) participants were excluded from the BNT162b2 and placebo

groups, respectively, primarily due to not receiving Dose 3 or unblinding on or before 7 days post-Dose 3. Approximately 32.7% of participants 6-23 months of age had ≥2 months of blinded follow up time after Dose 3.

Table 4. Disposition of Participants 6-23 Months, Phase 2/3 Efficacy Population, Study C4591007

Disposition, n (%)	C4591007 BNT162b2 3 µg N=1178	C4591007 Placebo N=598	Total N=1776
Dose 1 all-available efficacy population	1178 (100.0)	598 (100.0)	1776 (100.0)
Dose 2 all-available efficacy population	1166 (99.0)	596 (99.7)	1762 (99.2)
Participants excluded[a] from Dose 2 all-available efficacy population	12 (1.0)	2 (0.3)	14 (0.8)
Did not receive 2 vaccinations	11 (09)	2 (0.3)	13 (0.7)
Unblinded on or before 7 days post Dose 2	1 (0.1)	0	1 (0.1)
Dose 3 all-available efficacy population	386 (32.8)	184 (30.8)	570 (32.1)
Participants excluded[a] from Dose 3 all-available efficacy population	792 (67.2)	414 (69.2)	1206 (67.9)
Did not receive 3 vaccinations	420 (35.7)	414 (69.2)	843 (47.0)
Unblinded on or before 7 days post Dose 3	372 (31.6)	0	372 (20.9)
Dose 2 Evaluable efficacy population	1132 (96.1)	588 (98.3)	1720 (96.8)
Participants without evidence of infection prior to 7 days after Dose 2	1012 (85.9)	514 (86.0)	1526 (85.9)
Participants excluded[a] from Dose 2 evaluable efficacy population	46 (3.9)	10 (1.7)	56 (3.2)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	31 (2.6)	9 (1.5)	40 (2.3)
Had other important protocol deviations on or prior to 7 days after Dose 2	18 (1.5)	1 (0.2)	19 (1.1)
Unblinded on or before 7 days post Dose 2	1 (0.1)	0	1 (<0.1)
Dose 3 Evaluable efficacy population	376 (31.9)	179 (29.9)	555 (31.3)
Participants without evidence of infection prior to 7 days after Dose 3	256 (21.7)	130 (21.7)	386 (21.7)
Participants excluded[a] from Dose 3 evaluable efficacy population	802 (68.1)	419 (69.2)	834 (47.0)
Did not receive all vaccinations as randomized	420 (35.7)	414 (69.2)	834 (47.0)
Did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	31 (2.6)	9 (1.5)	40 (2.3)
Did not receive Dose 3 within the predefined window[b]	0	2 (0.3)	2 (0.1)
Had other important protocol deviations on or prior to 7 days after Dose 3	11 (0.9)	2 (0.3)	13 (0.7)
Unblinded on or before 7 Days post Dose 3	372 (31.6)	0	372 (20.9)

Source: IND 19736.803, C4591007-dose-tables-figures-6mo-4yr-efficacy.pdf, Page 23 and 27034.567. Response to FDA 5 June IR, Table 5, Page 17.
N=number of randomized participants in the specified group (the denominator for the percentage calculations).
n=number of participants with the specified characteristic.
a. Participants may have been excluded for more than one reason.
b. At least 60 days after Dose 2 for participants enrolled before Protocol Amendment 6 and 54-70 days for participants enrolled after Protocol Amendment 6.

Vaccine administration timing: In the Dose 3 evaluable efficacy population, the median interval between Dose 2 and Dose 3 among participants 6-23 months of age was 16.0 weeks (range:

8.0 to 31.9 weeks) for BNT162b2 recipients and 15.9 weeks (range: 8.0 to 35.0 weeks) for placebo recipients.

Participants 2-4 years of age

The Phase 2/3 Dose 3 evaluable efficacy population for participants 2-4 years of age included 589 BNT162b2 recipients and 271 placebo recipients. The treatment groups appear imbalanced with respect to receipt of 3 vaccination and unblinding on or before 7 days post Dose 3 because the Sponsor tabulated placebo recipients who did not receive 3 vaccinations due to unblinding as "did not receive 3 vaccinations." However, taking both reasons for exclusion into account together, the treatment groups are balanced: As shown in Table 5, a total of 1,246 (67.9%) and 635 (69.4%) participants were excluded from the BNT162b2 and placebo groups, respectively, primarily due to not receiving Dose 3 or unblinding on or before 7 days post Dose 3. 34.8% of participants 2-4 years of age had ≥2 months of blinded follow up time after Dose 3.

Table 5. Disposition of Participants 2-4 Years, Phase 2/3 Efficacy Population, Study C4591007

Disposition, n (%)	C4591007 BNT162b2 3 µg N=1835	C4591007 Placebo N=915	Total N=2750
Dose 1 all-available efficacy population	1835 (100.0)	915 (100.0)	2750 (100.0)
Dose 2 all-available efficacy population	1819 (99.1)	907 (99.1)	2726 (99.1)
Participants excluded[a] from Dose 2 all-available efficacy population	16 (0.9)	8 (0.9)	24 (0.9)
Did not receive 2 vaccinations	15 (0.9)	8 (0.9)	13 (0.7)
Unblinded on or before 7 days post Dose 2	1 (0.1)	0	1 (<0.1)
Dose 3 all-available efficacy population	606 (33.0)	280 (30.6)	886 (32.2)
Participants excluded[a] from Dose 3 all-available efficacy population	1229 (67.0)	635 (69.4)	1864 (67.8)
Did not receive 3 vaccinations	794 (43.3)	635 (69.4)	1429 (52.0)
Unblinded on or before 7 days post Dose 3	435 (23.7)	0	435 (15.8)
Dose 2 Evaluable efficacy population	1778 (96.9)	893 (97.6)	2671 (97.1)
Participants without evidence of infection prior to 7 days after Dose 2	1495 (81.5)	745 (81.4)	2240 (81.5)
Participants excluded[a] from Dose 2 evaluable efficacy population	57 (3.1)	22 (2.4)	79 (2.9)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	38 (2.1)	20 (2.2)	58 (2.1)
Had other important protocol deviations on or prior to 7 days after Dose 2	21 (1.1)	6 (0.7)	27 (101)
Unblinded on or before 7 days post Dose 2	1 (0.1)	0	1 (<0.1)
Dose 3 Evaluable efficacy population	589 (32.1)	271 (29.6)	860 (31.3)
Participants without evidence of infection prior to 7 days after Dose 3	412 (22.5)	166 (18.1)	572 (21.0)
Participants excluded[a] from Dose 3 evaluable efficacy population	1246 (67.9)	644 (70.4)	1890 (68.7)

Disposition, n (%)	C4591007 BNT162b2 3 µg N=1835	C4591007 Placebo N=915	Total N=2750
Did not receive all vaccinations as randomized	915 (49.9)	635 (69.4)	1550 (56.4)
Did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	37 (2.0)	20 (2.2)	57 (2.1)
Did not receive Dose 3 within the predefined window[b]	10 (0.5)	5 (0.5)	15 (0.5)
Had other important protocol deviations on or prior to 7 days after Dose 2	6 (0.3)	2 (0.2)	8 (0.3)
Unblinded on or before 7 Days post Dose 3	435 (23.7)	0	435 (15.8)

Source: IND 19736.803, C4591007-dose-tables-figures-6mo-4yr-efficacy.pdf, Page 24 and 27034.567. Response to FDA 5 June IR, Table 7, Page 21.
N=number of randomized participants in the specified group (the denominator for the percentage calculations).
n=number of participants with the specified characteristic.
a. Participants may have been excluded for more than one reason.
b. At least 60 days after Dose 2 for participants enrolled before Protocol Amendment 6 and 54-70 days for participants enrolled after Protocol Amendment 6.

Vaccine administration timing: In the Dose 3 evaluable efficacy population, the median interval between Dose 2 and Dose 3 among participants 2-4 years of age was 11.0 weeks (range: 8.0 to 34.1 weeks) for BNT162b2 recipients and 11.0 weeks (range: 8.0 to 31.1 weeks) for placebo recipients.

Safety population:
The overall Phase 2/3 safety population included 1,776 (1,178 BNT162b2, 598 placebo) participants 6-23 months of age and 2,750 (1,835 BNT162b2, 915 placebo) participants 2-4 years of age. Of the 1,178 BNT162b2 recipients 6-23 months of age, 386 (32.8%) received 3 vaccine doses. Of the 1,835 BNT162b2 recipients 2-4 years of age, 606 (33.0%) received 3 vaccine doses.

Per protocol, the first participant unblinding occurred on September 28, 2021, the first placebo crossover occurred on November 3, 2021, and the first Dose 3 was administered on January 31, 2022. Protocol amendment 6, which added the third primary series dose for participants 6 months through 4 years of age, was implemented on February 1, 2022.

The median duration of blinded follow-up for participants 6-23 months of age after Dose 3 was 1.3 months (range: 0-3.2 months). The median duration of blinded follow-up for participants 2-4 years of age after Dose 3 was 1.4 months (range: 1-3.2 months). The median duration of combined blinded and unblinded follow-up after Dose 3 was 2.1 months for each age group.

Participants 6-23 months of age
The safety population for Phase 2/3 participants ages 6-23 months consisted of 1,178 BNT162b2 recipients and 598 placebo recipients. A total of 13 participants withdrew from the study (9 BNT162b2 recipients and 4 placebo recipients).

Table 6. Disposition of Participants 6-23 Months of Age, Prior to Unblinding, Phase 2/3 Study C4591007

Disposition, n (%)	C4591007 BNT162b2 3 µg N=1178	C4591007 Placebo N=598	Total N=1776
Vaccinated: Dose 1	1178 (100.0)	598 (100.0)	1776 (100.0)
Vaccinated: Dose 2	1166 (99.0)	596 (99.7)	1762 (99.2)
Vaccinated: Dose 3	386 (32.8)	184 (30.8)	570 (32.1)
Completed 1 month post-Dose 2 visit (vaccination period)	1165 (98.9)	596 (99.7)	1761 (99.2)
Completed 1 month post-Dose 3 visit (vaccination period)	262 (22.2)	179 (29.9)	441 (24.8)
Discontinued from vaccination period but continued in the study	1 (0.1)	0	1 (0.1)
Discontinued after Dose 1 and before Dose 2	1 (0.1)	0	1 (0.1)
Reason for discontinuation: Adverse event	1 (0.1)	0	1 (0.1)
Withdrawn from study	9 (0.8)	4 (0.7)	13 (0.7)
Withdrawn after Dose 1 and before Dose 2	5 (0.4)	0	5 (0.3)
Withdrawn on or after 1-month post-Dose 2 visit and before Dose 3	3 (0.3)	3 (0.5)	6 (0.3)
Withdrawn on or after 1-month post-Dose 3 visit	1 (0.1)	1 (0.2)	2 (0.1)
Reason for withdrawal: Adverse event	1 (0.1)	0	1 (0.1)
Reason for withdrawal: Lost to follow-up	1 (0.1)	0	1 (0.1)
Reason for withdrawal: Withdrawal by participant	2 (0.2)	0	2 (0.1)
Reason for withdrawal: Withdrawal by parent/guardian	5 (0.4)	4 (0.7)	9 (0.5)

Source: EUA 27034.556. eua-amendment-6m-4y-safety-immuno.pdf. Table 12.

A total of 715 (60.7%) original BNT162b2 and 377 (63.0%) original placebo recipients 6-23 months of age were unblinded. For participants 6-23 months of age originally randomized to the BNT162b2 group prior to the implementation of protocol amendment 6, unblinding occurred for 1 (0.1%) participant who received Dose 2 open-label and 372 (52.0%) participants who received Dose 3 open-label. For participants ages 6-23 months originally randomized to the placebo group prior to the protocol revision which added the third primary series dose, unblinding occurred for 344 participants (91.2%) who received BNT162b2 Dose 1 open-label, 296 (78.5%) participants who received BNT162b2 Dose 2 open-label and 77 (20.4%) participants who received Dose 3 open-label. Only 3 (4%) of original placebo recipients had follow-up through at least 1 month post Dose 3 after unblinding and receiving BNT162b2.

Table 7. Disposition of Participants 6-23 Months of Age, After Unblinding, Phase 2/3 Study C4591007

Disposition, n (%)	C4591007 BNT162b2 3 µg N[a]=715	C4591007 Placebo N[a]=377
Originally received BNT162b2	715 (100.0)	--
Completed 3 doses before unblinding	174 (24.3)	--
Vaccinated: Dose 2	1 (0.1)	--
Vaccinated: Dose 3	372 (52.0)	--
Awaiting next vaccination	158 (22.1)	--
Completed 1-month post-Dose 2 visit (vaccination period)	2 (0.3)	--

Disposition, n (%)	C4591007 BNT162b2 3 µg N[a]=715	C4591007 Placebo N[a]=377
Completed 1-month post-Dose 3 visit (vaccination period)	499 (69.8)	--
Discontinued from vaccination period but continued in the study	4 (0.6)	--
Discontinued after Dose 1 and before Dose 2	0	--
Discontinued after Dose 2 and before 1-month post-Dose 2 visit	1 (0.1)	--
Discontinued after Dose 3 and before 1-month post-Dose 3 visit	3 (0.4)	--
Reason for discontinuation: Adverse event	1 (0.1)	--
Reason for discontinuation: Withdrawal by participant	1 (0.1)	--
Reason for discontinuation: Other	2 (0.3)	--
Withdrawn from study*	9 (1.3)	--
Withdrawn after Dose 1 and before Dose 2	0	--
Withdrawn after Dose 2 and before 1-month post-Dose 2 visit	0	--
Withdrawn on or after 1-month post-dose 2 visit and before Dose 3	8 (1.1)	--
Withdrawn after Dose 3 and before 1-month post-Dose 3 visit	1 (<0.1)	--
Withdrawn on or after 1-month post-Dose 3 visit	3 (0.4)	--
Reason for withdrawal: Lost to follow-up	1 (0.1)	--
Reason for withdrawal: Withdrawal by parent/guardian	5 (0.7)	--
Reason for withdrawal: Refused further study procedures	2 (0.3)	--
Reason for withdrawal: Other	1 (0.1)	--
Originally received Placebo	--	377 (100.0)
Did not receive BNT162b2 after unblinding	--	33 (8.8)
Received First dose of BNT162b2	--	344 (91.2)
Received Second dose of BNT162b2	--	296 (78.5)
Received Third dose of BNT162b2	--	77 (20.4)
Awaiting next vaccination	--	23 (6.1)
Completed 1-month post-Dose 2 (BNT162b2) visit (vaccination period)	--	127 (33.7)
Completed 1-month post-Dose 3 (BNT162b2) visit (vaccination period)	--	15 (4.0)
Discontinued from vaccination period but continued in the study	--	0
Withdrawn from vaccination and/or study	--	10 (2.7)
Reason for withdrawal: Lost to follow-up	--	1 (0.3)
Reason for withdrawal: Withdrawal by parent/guardian	--	8 (2.1)
Reason for withdrawal: Refused further study procedures	--	1 (0.3)

Source: EUA 27034.556. c4591007-dose3-tables-ns-listings-6m-4y-safety-pdf. Pages 21-23. And EUA 27034.561 Response to Information Request-31May22-safe-immuno-6m-4y.pdf. Table 1, Page 4.
a. N=number of participants unblinded.
*One participant was unblinded after withdrawal from the study and is not included.

Vaccine administration timing*:* In the safety population of participants 6-23 months of age, the median timing of Dose 3 administration after Dose 2 was 25.3 weeks (range: 8.0 to 41.0 weeks) for BNT162b2 recipients and 15.8 weeks (range: 8.0 to 35.0 weeks) for placebo recipients.

Participants 2-4 years of age

The safety population for Phase 2/3 participants 2-4 years of age included 1,835 BNT162b2 recipients and 915 placebo recipients. A total of 45 participants withdrew from the study (24 BNT162b2 recipients and 21 placebo recipients).

Table 8. Disposition of Participants 2-4 Years of Age, Prior to Unblinding, Phase 2/3 Study C4591007

Disposition, n (%)	C4591007 BNT162b2 3 µg N=1835	C4591007 Placebo N=915	Total N=2750
Vaccinated: Dose 1	1835 (100.0)	915 (100.0)	2750 (100.0)
Vaccinated: Dose 2	1819 (99.1)	907 (99.1)	2726 (99.1)
Vaccinated: Dose 3	606 (33.0)	280 (30.6)	886 (32.2)
Completed 1-month post-Dose 2 visit (vaccination period)	1814 (98.9)	907 (99.1)	2721 (98.9)
Completed 1-month post-Dose 3 visit (vaccination period)	503 (27.4)	274 (29.9)	777 (28.3)
Discontinued from vaccination period but continued in the study	0	3 (0.3)	3 (0.1)
Discontinued after Dose 1 and before Dose 2	0	2 (0.2)	2 (0.1)
Discontinued after Dose 2 and before 1-month post-dose 2 visit	0	1 (0.1)	1 (<0.1)
Reason for discontinuation: Adverse event	0	1 (0.1)	1 (<0.1)
Reason for discontinuation: Withdrawal by participant	0	1 (0.1)	1 (<0.1)
Reason for discontinuation: Other	0	1 (0.1)	1 (<0.1)
Withdrawn from study	24 (1.3)	21 (2.3)	45 (1.6)
Withdrawn after Dose 1 and before Dose 2	6 (0.3)	4 (0.4)	10 (0.4)
Withdrawn on or after 1-month post-dose 2 visit and before Dose 3	14 (0.8)	16 (1.7)	30 (1.1)
Withdrawn after Dose 3 and before 1-month post-dose 3 visit	2 (0.1)	1 (0.1)	3 (0.1)
Withdrawn on or after 1-month post-dose 3 visit	2 (0.1)	0	2 (0.1)
Reason for withdrawal: Adverse event	1 (0.1)	0	1 (0.0)
Reason for withdrawal: Lost to follow-up	4 (0.2)	3 (0.3)	7 (0.3)
Reason for withdrawal: Protocol deviation	2 (0.1)	3 (0.3)	5 (0.2)
Reason for withdrawal: Withdrawal by participant	4 (0.2)	2 (0.2)	6 (0.2)
Reason for withdrawal: Withdrawal by parent/guardian	13 (0.7)	13 (1.4)	26 (0.9)

Source: EUA 27034.556. eua-amendment-6m-4y-safety-immuno.pdf. Table 3, Page 21.

A total of 842 (45.9%) original BNT162b2 and 424 (46.3%) original placebo recipients 2-4 years of age were unblinded. For participants 2-4 years of age originally randomized to the BNT162b2 group prior to implementation of protocol amendment 6, unblinding occurred for 1 (0.1%) participant who received Dose 2 open-label and 435 (51.7%) participants who received Dose 3 in an open-label manner.

For participants 2-4 years of age originally randomized to the placebo group prior to the protocol revision which added the third primary series dose, unblinding occurred for 370 participants (87.3%) who received BNT162b2 Dose 1 open-label, 350 (82.5%) participants who received BNT162b2 Dose 2 open-label and 98 (23.1%) participants who received Dose 3 open-label. Only 5% of original placebo recipients had follow-up through at least 1 month post Dose 3 after unblinding and receiving BNT162b2.

Participants who turned 5 years of age during the study were voluntarily unblinded to receive the age-appropriate dose (10 µg BNT162b2) authorized for emergency use; One participant (0.1%) received the 10 µg dose level for Dose 2 and 121 participants (6.6%) received the 10 µg dose level for Dose 3.

Table 9. Disposition of Participants 2-4 Years of Age, After Unblinding, Phase 2/3 Study C4591007

Disposition, n (%)	C4591007 BNT162b2 3 µg N=842	C4591007 Placebo N=424
Originally received BNT162b2	842 (100.0)	--
Completed 3 doses before unblinding	118 (14.0)	--
Vaccinated: Dose 2	1 (0.1)	--
Vaccinated: Dose 3	435 (51.7)	--
Awaiting next vaccination	236 (28.0)	--
Completed 1-month post-dose 2 visit (vaccination period)	9 (1.1)	--
Completed 1-month post-dose 3 visit (vaccination period)	553 (65.7)	--
Discontinued from vaccination period but continued in the study	2 (0.2)	--
Discontinued after Dose 1 and before Dose 2	0	--
Discontinued after Dose 2 and before 1-month post-dose 2 visit	1 (0.1)	--
Discontinued after 1-month post-dose 2 visit and before Dose 3	1 (0.1)	--
Discontinued after Dose 3 and before 1-month post-dose 3 visit	0	--
Reason for discontinuation: Withdrawal by parent/guardian	2 (0.2)	--
Withdrawn from vaccination or study study*	52 (6.2)	--
Withdrawn after Dose 1 and before Dose 2	3 (0.4)	--
Withdrawn after Dose 2 and before 1-month post-dose 2 visit	0	--
Withdrawn on or after 1-month post-dose 2 visit and before Dose 3	47 (5.6)	--
Withdrawn after Dose 3 and before 1-month post-dose 3 visit	1 (0.1)	--
Withdrawn on or after 1-month post-dose 3 visit	2 (0.2)	--
Reason for withdrawal: Adverse event	1 (0.1)	--
Reason for withdrawal: Protocol deviation	13 (1.5)	--
Reason for withdrawal: Withdrawal by participant	5 (0.6)	--
Reason for withdrawal: Withdrawal by parent/guardian	30 (3.6)	--
Reason for withdrawal: Refused further procedures	3 (0.4)	--
Originally received Placebo	--	424 (100.0)
Did not receive BNT162b2 after unblinding	--	54 (12.7)
Received Dose 1 of BNT162b2	--	370 (87.3)
Received Dose 2 of BNT162b2	--	350 (82.5)
Received Dose 3 of BNT162b2	--	98 (23.1)
Awaiting next vaccination	--	21 (5.0)
Completed 1-month post-dose 2 (BNT162b2) visit (vaccination period)	--	212 (50.0)
Completed 1-month post-dose 3 (BNT162b2) visit (vaccination period)	--	21 (5.0)
Discontinued from vaccination period but continued in the study	--	0
Withdrawn from vaccination and/or study	--	33 (7.8)
Reason for withdrawal: Adverse event	--	1 (0.2)
Reason for withdrawal: Protocol deviation	--	3 (0.7)
Reason for withdrawal: Withdrawal by participant	--	2 (0.5)
Reason for withdrawal: Withdrawal by parent/guardian	--	27 (6.4)
Reason for withdrawal: Other	--	1 (0.2)

Source: EUA 27034.556. c4591007-dose3-tables-ns-listings-6m-4y-safety-pdf. Pages 24-25. and EUA 27034.561 Response to Information Request-31May22-safe-immuno-6m-4y.pdf. Table 2, Page 5.
*One participant was unblinded after withdrawal from the study and is not included.

Vaccine administration timing: In the safety populations of participants 2-4 years of age, the median timing of Dose 3 administration after Dose 2 was 21.4 weeks (range: 8.0 to 41.3 weeks) for BNT162b2 recipients and was 11.0 weeks (range: 6.3 to 31.1 weeks) for placebo recipients.

4.2.4. Phase 2/3 comorbidities at baseline

Comorbidities were defined as one of the pre-specified comorbidities that increase the risk of severe COVID-19 disease, as defined in Kim et al 2020,[47] and/or obesity (body mass index [BMI] >95% percentile). Obesity was not evaluated in participants <2 years of age, since BMI-for-age percentiles are based on CDC growth charts for children and teenagers 2 through 19 years of age.[48]

Participants 6-23 months of age
Among participants 6-23 months of age, 4.2% of BNT162b2 recipients and 5.7% of placebo recipients had a comorbidity at baseline (pre-Dose 1). In the BNT162b2 group, the most common comorbidity (comorbidity category/PT) at baseline was prematurity (1.6%), followed by asthma and congenital heart disease (each 0.8%), cardiovascular disease (0.4%), neurologic disorder (0.3%), chronic lung disease (0.2%). Congenital heart disease was more frequent in the placebo group (1.8%) than the BNT162b2 group (0.8%).

Participants 2-4 years of age
Among participants 2-4 years of age, 12.1% of BNT162b2 recipients and 14.2% of placebo recipients had a comorbidity (including obesity) at baseline. Obesity was reported in 6.5% of BNT162b2 and 4.9% of placebo recipients. Comorbidities at baseline that increase the risk of severe COVID-19 disease were reported in 6.4% of the BNT162b2 group and 9.7% of the placebo group. Other than obesity, the most common comorbidities at baseline in BNT162b2 group included asthma (2.8%), prematurity (1.1%), congenital heart disease (0.7%) and neurologic disorders (0.6%). One BNT162b2 participant had a baseline comorbidity of immunocompromised condition (neutropenia).

4.2.5. Phase 2/3 demographic and baseline characteristics

Safety populations
Participants 6-23 months of age
Demographic characteristics for the safety population of participants 6-23 months of age who received 3 µg BNT162b2 are summarized in Table 10. Participants were predominately White, with a mean age of 15.2 months. In the BNT162b2 group, 7.6% had evidence of prior SARS-CoV-2 infection. Overall, 81.2% of participants in this age group were enrolled in the United States. The percentage of participants 6-23 months of age who received other vaccines (e.g., influenza and other routine pediatric immunizations) after Dose 1 were similar between treatment groups (27.2% BNT162b2, 28.8% in placebo).

Table 10. Demographic and Baseline Characteristics of Participants 6-23 Months, Phase 2/3 Safety Population, Study C4591007

Characteristic	BNT162b2 N=1178	Placebo N=598
Sex, n (%)	--	--
Female	589 (50.0)	307 (51.3)
Male	589 (50.0)	291 (48.7)

Characteristic	BNT162b2 N=1178	Placebo N=598
Race, n (%)	--	--
White	922 (78.3)	480 (80.3)
Black or African American	42 (3.6)	24 (4.0)
American Indian or Alaska Native	3 (0.3)	1 (0.2)
Asian	91 (7.7)	40 (6.7)
Multiracial	117 (9.9)	49 (8.2)
Not reported	3 (0.3)	4 (0.7)
Ethnicity, n (%)	--	--
Hispanic or Latino	161 (13.7)	64 (10.7)
Not Hispanic or Latino	1014 (86.1)	530 (88.6)
Not reported	3 (0.3)	4 (0.7)
Age	--	--
Mean, months (SD)	15.2 (4.97)	15.4 (5.06)
Median, months	16.0	16.0
Comorbidities[a], n (%)	--	--
Yes	50 (4.2)	34 (5.7)
No	1128 (95.8)	564 (94.3)
Baseline evidence of prior SARS-CoV-2 infection, n (%)	--	--
Negative[b]	1078 (91.5)	541 (90.5)
Positive[c]	89 (7.6)	44 (7.4)
Missing	11 (0.9)	13 (2.2)
Country, n (%)	--	--
Brazil	0	2 (0.3)
Finland	54 (4.6)	26 (4.3)
Poland	125 (10.6)	63 (10.5)
Spain	42 (3.6)	22 (3.7)
United States	9577 (81.2)	485 (81.1)

Source: IND 19736.800, C4591007-dose3-tables-ns-listings-6mo-4yr-safety.pdf, Pages 7-8.
Abbreviations: NAAT=nucleic acid amplification test; N-binding=SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SD=standard deviation
N=number of randomized participants in the specified group (the denominator for the percentage calculations).
n=number of participants with the specified characteristic.
a. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the prespecified comorbidities based on MMWR 69(32);1081-1088.
b. Negative N-binding antibody result and negative NAAT result at Visit 1 and no medical history of COVID-19.
c. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.

Participants 2-4 years of age

Demographic characteristics for the safety population of participants 2-4 years of age who received 3 µg BNT162b2 are summarized in Table 11. Participants were predominately White, with a mean age of 3 years of age. In the BNT162b2 group, 12.7% had evidence of prior SARS-CoV-2 infection. Overall, 81.4% of participants in this age group were enrolled in the United States. The percentage of 2-4-year-olds who received other vaccines (e.g., influenza and other routine pediatric immunizations) after Dose 1 were similar between treatment groups (13.1% BNT182b2, 11.6% in placebo).

Table 11. Demographic and Baseline Characteristics of Participants 2-4 Years, Phase 2/3 Safety Population, Study C4591007

Characteristic	BNT162b2 N=1835	Placebo N=915
Sex, n (%)	--	--
Female	934 (50.9)	444 (48.5)
Male	901 (49.1)	471 (51.5)
Race, n (%)	--	--
White	1469 (80.1)	720 (78.7)
Black or African American	94 (5.1)	41 (4.5)
American Indian or Alaska Native	3 (0.2)	4 (0.4)
Asian	127 (6.9)	76 (8.3)
Native Hawaiian or other Pacific Islander	2 (0.1)	1 (0.1)
Multiracial	131 (7.1)	69 (7.5)
Not reported	9 (0.5)	4 (0.4)
Ethnicity, n (%)	--	--
Hispanic or Latino	261 (14.4)	120 (13.1)
Not Hispanic or Latino	1568 (85.4)	795 (86.9)
Not reported	3 (0.2)	0
Age	--	--
Mean, years (SD)	3.1 (0.79)	3.0 (0.79)
Median, years	3.0	3.0
Obese[a], n (%)	--	--
Yes	120 (6.5)	16 (3.9)
No	1712 (93.3)	870 (95.1)
Missing	3 (0.2)	0
Comorbidities[b], n (%)	--	--
Yes	222 (12.1)	130 (14.2)
No	1613 (87.9)	785 (85.8)
Baseline evidence of prior SARS-CoV-2 infection, n (%)	--	--
Negative[c]	1597 (87.0)	783 (85.6)
Positive[d]	233 (12.7)	125 (13.7)
Missing	5 (0.3)	7 (0.8)
Country, n (%)	--	--
Finland	63 (3.4)	30 (3.3)
Poland	205 (11.2)	103 (11.3)
Spain	73 (4.0)	35 (3.8)
United States	1494 (81.4)	747 (81.6)

Source: IND 19736.800, C4591007-dose3-tables-ns-listings-6mo-4yr-safety.pdf, Pages 9-11.
Abbreviations BMI, body mass index; MMWR=Morbidity and Mortality Weekly Report; NAAT=nucleic acid amplification test; N-binding=SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SD=standard deviation.
N=number of randomized participants in the specified group (the denominator for the percentage calculations).
n=number of participants with the specified characteristic.
a. Obese is defined as a BMI at or above the 95th percentile according to the Centers for Disease Control and Prevention growth charts (https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm).
b. Number of participants who have one or more comorbidities that increase the risk of severe COVID-19: defined as participants who had at least one of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥95th percentile).
c. Negative N-binding antibody result and negative NAAT result at Visit 1 and no medical history of COVID-19.
d. Positive N-binding ant body result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.

Immunogenicity and efficacy populations

Demographic and other baseline characteristics for the immunogenicity and efficacy populations for each age group were generally similar to those described above for the safety populations, with the exception that the immunogenicity subsets were derived only from participants in the United States.

Comparator groups for immunogenicity
Phase 2/3 C4591001 participants, the study group for immunobridging comparisons, included 170 participants 16-25 years of age from sites in the United States (74.1%), Argentina (14.1%), Brazil (7.6%), and South Africa/Turkey (4.1% combined total).

4.2.6. Phase 2/3 vaccine effectiveness results

4.2.6.1. Primary immunogenicity objectives

For each age group, SARS-CoV-2 neutralizing GMTs and seroresponse rates were assessed against the reference strain (USA_WA1/2020) upon which the vaccine was based in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection.

Participants 6-23 months of age

GMTs of neutralizing antibodies to the reference strain: Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2 (comparator group 16-25 years of age) or Dose 3 (participants 6-23 months of age), the ratio of SARS-CoV-2 50% neutralizing GMTs was 1.19 (95% CI: 1.00, 1.42). The lower bound of the 2-sided 95% CI for GMT ratio was >0.67, and the point estimate was ≥1, which met the prespecified immunobridging success criteria (Table 12).

Table 12. SARS-CoV-2 Neutralizing GMTs (NT50)[a] After Three Primary Series Doses in BNT162b2 (3 µg) Recipients 6-23 Months of Age (1 Month After Dose 3) and BNT162b2 (30 µg) Recipients 16-25 Years of Age (1 Month After Dose 2) Without Evidence of SARS-CoV-2 Infection, Phase 2/3 Evaluable Immunogenicity Populations[b], Studies C4591007 and C4591001

6-23 Months of Age Study C4591007 N=82 GMT (95% CI)	16-25 Years of Age Study C4591001 N=170 GMT (95% CI)	GMT Ratio (6-23 Months of Age / 16-25 Years of Age)[c] (95% CI)
1406.5 (1211.3, 1633.1)	1180.0 (1066.6, 1305.4)	1.19 (1.00, 1.42)

Source: EUA 27034.556 eua-amendment-6m-4y-safety-immuno.pdf. Table 32, Page 139.
Abbreviations: CI=confidence interval; GMT=geometric mean titer; N=number of Phase 2/3 participants with valid and determinate assay results for the specified assay at the given dose/sampling time point within specified window; NT50=50% neutralizing titer; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)] of past SARS-CoV-2 infection [(i.e., N-binding antibody [serum] negative at Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (Study 3) study visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection)] and had no medical history of COVID-19 were included in the analysis.
a. SARS-CoV-2 mNeonGreen virus microneutralization assay (SARS-CoV-2 mNG NT), reference strain: recombinant USA_WA1/2020.
b. Evaluable immunogenicity population pertaining to Phase 2/3 BNT162b2 participants 6-23 months of age (study C4591007) and Phase 2/3 BNT162b2 participants 16-25 years of age (study C4591001).
c. Immunobridging statistical success is declared if the lower limit of the 2-sided 95% CI for the GMT ratio is greater than 0.67 and the point estimate of the GMT ratio is ≥1.0.

Rates of neutralizing antibody seroresponse to the reference strain: Seroresponse rates among participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 2 (comparator group 16-25 years of age) or Dose 3 (participants 6-23 months of age) are presented in Table 13. Participants 6-23 months of age had a similar seroresponse rate (as

measured from pre-Dose 1 to 1 month after Dose 3) as in the comparator group 16-25 years of age (as measured from pre-Dose 1 to 1 month after Dose 2). The difference in seroresponse rates between the two age groups was 1.2% (95% CI: -3.4, 4.2). The immunobridging criterion based on seroresponse rate was met, since the LL of the 95% CI for the difference in seroresponse rate was −3.4%, which was greater than the prespecified margin of −10%.

Table 13. Seroresponse Rates[a,b,c] After Three Primary Series Doses in BNT162b2 (3 µg) Recipients 6-23 Months of Age (1 Month After Dose 3) and BNT162b2 (30 µg) Recipients 16-25 Years of Age (1 Month After Dose 2) Without Evidence of SARS-CoV-2 Infection, Phase 2/3 Evaluable Immunogenicity Populations[d], Studies C4591007 and C4591001

6-23 Months of Age Study C4591007 N=80 Seroresponse Rate (%[e]) (95% CI)	6-25 Years of Age Study C4591001 N=170 Seroresponse Rate (%[e]) (95% CI)	% Difference in Seroresponse Rate (Age Group 6-23 Months Minus Age Group 16-25 Years)[f] (95% CI)
100 (95.5, 100.0)	98.8 (95.8, 99.9)	1.2 (-3.4, 4.2)

Source: EUA 27034.556 eua-amendment-6m-4y-safety-immuno.pdf. Table 33, Page 140.
Abbreviations: CI=confidence interval; LLOQ=lower limit of quantitation; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2
N=number of subjects with valid and determinate assay results for the specified assay within the specified window for blood samples collected at baseline (pre-Dose 1) and 1 month after primary series.
n=number of participants with seroresponse for the given assay at the given dose/sampling time point.
Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)] of past SARS-CoV-2 infection [(i.e., N-binding antibody [serum] negative at Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (Study 3) study visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection)] and had no medical history of COVID-19 were included in the analysis.
a. SARS-CoV-2 mNeonGreen virus microneutralization assay (SARS-CoV-2 mNG NT), reference strain: recombinant USA_WA1/2020.
b. Seroresponse defined as at least 4-fold rise relative to pre-Dose 1; if the baseline measurement was below LLOQ
c. Postvaccination titer of ≥4 × LLOQ was considered a seroresponse.
d. Evaluable immunogenicity population pertaining to Phase 2/3 BNT162b2 participants 6-23 months of age (study C4591007) and Phase 2/3 BNT162b2 participants 16-25 years of age (study C4591001).
f. Immunobridging statistical success is declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%.

Participants 2-4 years of age

GMTs of neutralizing antibody titers to the reference strain: Among participants in the evaluable immunogenicity population without prior evidence of SARS- CoV-2 infection up to 1 month after Dose 2 (comparator group 16-25 years of age) or Dose 3 (participants 2-4 years of age), the ratio of SARS-CoV-2 50% neutralizing GMTs was 1.30 (95% CI: 1.13, 1.50). The lower bound of the 2-sided 95% CI for GMT ratio was >0.67 and the point estimate was ≥1, which met the prespecified immunobridging success criteria; see Table 14.

Table 14. SARS-CoV-2 Neutralizing GMTs (NT50)[a] After Three Primary Series Doses in BNT162b2 (3 µg) Recipients 2-4 Years of Age (1 Month After Dose 3) and BNT162b2 (30 µg) Recipients 16-25 Years of Age (1 Month After Dose 2) Without Evidence of SARS-CoV-2 Infection, Phase 2/3 Evaluable Immunogenicity Population[b], Studies C4591007 and C4591001

2-4 Years of Age Study C4591007 N=143 GMT (95% CI)	16-25 Years of Age Study C4591001 N=170 GMT (95% CI)	GMT Ratio (2-4 Years / 16-25 Years)[c] (95% CI)
1535.2 (1388.2, 1697.8)	1180.0 (1066.6, 1305.4)	1.30 (1.13, 1.50)

Source: EUA 27034.556 eua-amendment-6m-4y-safety-immuno.pdf. Table 22, Page 113.
Abbreviations: CI=confidence interval; GMT=geometric mean titer; NT50=50% neutralizing titer; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2
N=number of Phase 2/3 participants with valid and determinate assay results for the specified assay at the given dose/sampling time point within specified window.
Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)] of past SARS-CoV-2 infection [(i.e., N-binding antibody [serum] negative at Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (Study 3) study visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection)] and had no medical history of COVID-19 were included in the analysis.
a. SARS-CoV-2 mNeonGreen virus microneutralization assay (SARS-CoV-2 mNG NT), reference strain: recombinant USA_WA1/2020
b. Evaluable immunogenicity population pertaining to Phase 2/3 BNT162b2 participants 2-4 years of age (study C4591007) and Phase 2/3 BNT162b2 participants 16-25 years of age (study C4591001)
c. Immunobridging statistical success is declared if the lower limit of the 2-sided 95% CI for the GMT ratio is greater than 0.67 and the point estimate of the GMT ratio is ≥1.0

Rates of neutralizing antibody seroresponse to the reference strain: Seroresponse rates among participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 2 (comparator group 16-25 years of age) or Dose 3 (2-4 years of age) are displayed in Table 15. Participants 2-4 years of age had a similar seroresponse rate (as measured from before vaccination to 1 month after Dose 3) as in the comparator group 16-25 years of age (as measured from before vaccination to 1 month after Dose 2). The difference between the two age groups was 1.2% (95% CI: −1.5, 4.2). The LL of the 95% CI for the difference in seroresponse rate was −1.2%, which was greater than the prespecified margin of −10%, and thus immunobridging based on seroresponse rate was met.

Table 15. Seroresponse Rates[a,b] After Three Primary Series Doses in BNT162b2 (3 µg) Recipients 2-4 Years of Age (1 Month After Dose 3) and BNT162b2 (30 µg) Recipients 16-25 Years of Age[b] (1 Month After Dose 2) Without Evidence of SARS-CoV-2 Infection, Phase 2/3 Evaluable Immunogenicity Populations[c], Studies C4591007 and C4591001

2-4 Years of Age Study C4591007 N=141 Seroresponse rate (%[d]) (95% CI)	16-25 Years of Age Study C4591001 N=170 Seroresponse Rate (%[d]) (95% CI)	% Difference in Seroresponse Rate (Age Group 2-4 Years Minus Age Group 16-25 Years)[e] (95% CI)
100.0 (97.4, 100.0)	98.8 (95.8, 99.9)	1.2 (−1.5, 4.2)

Source: EUA 27034.556 eua-amendment-6m-4y-safety-immuno.pdf. Table 23, Page 114.
Abbreviations: CI=confidence interval; LLOQ=lower limit of quantitation; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2
N=Number of subjects with valid and determinate assay results for the specified assay within the specified window for blood samples collected at baseline (pre-Dose 1) and 1 month after primary series.
n=number of participants with seroresponse for the given assay at the given dose/sampling time point.
Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)] of past SARS-CoV-2 infection [(i.e., N-binding antibody [serum] negative at Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab]

at Dose 1, Dose 2, and Dose 3 (Study 3) study visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection)] and had no medical history of COVID-19 were included in the analysis.
a. SARS-CoV-2 mNeonGreen virus microneutralization assay (SARS-CoV-2 mNG NT), reference strain: recombinant USA_WA1/2020
b. Seroresponse defined as at least 4-fold rise relative to pre-Dose 1; if the baseline measurement was below LLOQ, a postvaccination titer of ≥4 × LLOQ was considered a seroresponse
c. Evaluable immunogenicity population pertaining to Phase 2/3 BNT162b2 participants 2-4 years of age (study C4591007) and Phase 2/3 BNT162b2 participants 16-25 years of age (study C4591001)
e. Immunobridging statistical success is declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%.

Subgroup analyses of GMTs and seroresponse rates: GMTs of SARS-CoV-2 neutralizing titers and seroresponse rates at 1 month after Dose 3 by age group were similar. No notable differences in GMTs or seroresponse rates were observed by sex, race, or ethnicity. Participants in both age groups with positive SARS-CoV-2 status at baseline had numerically higher GMTs before vaccination and at 1 month after Dose 3 compared to those negative at baseline, which is consistent with immunogenicity results observed in older age groups. However, the numbers of participants with positive baseline SARS-CoV-2 status were limited to 6 participants in the 6-23 months age group and 13 participants in the 2-4 years age group.

Table 16. Subgroup Analyses of Geometric Mean SARS-CoV-2 Neutralizing Titers, Phase 2/3 Participants 6-23 Months of Age (1 Month After Dose 3) and 16-25 Years of Age (1 Month After Dose 2), All-Available Immunogenicity Population, Studies C4591007 and C4591001

Subgroup	6-23 Months of Age BNT162b2 (3 µg) n[a], GMT[b]	16-25 Years of Age BNT162b2 (30 µg) n[a], GMT[b]	GMR[c] (95% CI[c])
Sex: Male	79, 1650.9	95, 1262.0	1.31 (1.07, 1.60)
Sex: Female	67, 1749.2	97, 1172.1	1.49 (1.18, 1.89)
Race: White	113, 1737.8	145, 1231.7	1.41 (1.18, 1.68)
Race: Black or African American	2, 777.0	19, 1210.8	0.64 (0.23, 1.77)
Race: American Indian or Alaska Native	1, 2715.0	3, 1716.0	1.58 (NE, NE)
Race: Asian	15, 1958.3	15, 914.8	2.14 (1.27, 3.62)
Race: Native Hawaiian/Pacific Islander	0, NE	2, 2012.3	NE (NE, NE)
Race: Multiracial	15, 1309.5	7, 1213.5	1.08 (0.63, 1.85)
Race: Not reported	0, NE	1, 1845.0	NE (NE, NE)
Ethnicity: Hispanic or Latino	18, 1719.0	59, 1108.9	1.55 (1.02, 2.36)
Ethnicity: Not Hispanic or Latino	127, 1681.4	133, 1266.4	1.33 (1.12, 1.57)
Ethnicity: Not reported	1, 3750.0	0, NE	NE (NE, NE)
Baseline SARS-CoV-2: Positive[d]	6, 3794.8	8, 2507.9	1.51 (0.76, 3.01)
Baseline SARS-CoV-2: Negative[e]	139, 1633.6	184, 1178.1	1.39 (1.19, 1.62)
Baseline SARS-CoV-2: Missing	1, 2325.0	0, NE	NE (NE, NE)

Source: EUA 27024.554 Safety-Immunogenicity_508_Tables. Table H.1.1
Abbreviations: GMR=geometric mean ratio; GMT=geometric mean titer
Note: All-available population refers to Dose 3 all-available immunogenicity population for C4591007 and Dose 2 all-available immunogenicity population for C4591001.
a. n=Number of participants with valid and determinate assay results for SARS-CoV-2 serum neutralizing titer 50 at the given dose/sampling time point.
b. GMTs was calculated by exponentiating the mean logarithm of the titers. Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-Sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Vaccine Group [6 months to <2 years] - Comparison Group [16-25 years]) and the corresponding CI (based on the Student t distribution).
d. Positive N-binding ant body result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
e. Negative N-binding antibody result and negative NAAT result at Visit 1 and no medical history of COVID-19.

Table 17. Subgroup Analyses of Geometric Mean SARS-CoV-2 Neutralizing Titers, Phase 2/3 Participants 2-4 Years of Age (1 Month After Dose 3) and 16-25 Years of Age (1 Month After Dose 2), All-Available Immunogenicity Population, Studies C4591007 and C4591001

Subgroup	2-4 Years of Age BNT162b2 (3 µg) n[a], GMT[b]	16-25 Years of Age BNT162b2 (30 µg) n[a], GMT[b]	GMR[c] (95% CI[c])
Sex: Male	97, 1531.4	95, 1262.0	1.21 (0.98, 1.50)
Sex: Female	120, 1756.6	97, 1172.1	1.50 (1.25, 1.80)
Race: White	158, 1684.5	145, 1231.7	1.37 (1.17, 1.59)
Race: Black or African American	10, 1893.0	19, 1210.8	1.56 (0.90, 2.72)
Race: American Indian or Alaska Native	0, NE	3, 1716.0	NE (NE, NE)
Race: Asian	24, 1384.8	15, 914.8	1.51 (0.76, 3.01)
Race: Native Hawaiian/Pacific Islander	0, NE	2, 2012.3	NE (NE, NE)
Race: Multiracial	22, 1778.9	7, 1213.5	1.47 (0.94, 2.29)
Race: Not reported	3, 900.1	1, 1845.0	0.49 (NE, NE)
Ethnicity: Hispanic or Latino	25, 1839.7	59, 1108.9	1.66 (1.17, 2.35)
Ethnicity: Not Hispanic or Latino	191, 1629.7	133, 1266.4	1.29 (1.10, 1.50)
Ethnicity: Not reported	1, 1533.0	0, NE	NE (NE, NE)
Obese[d]: Yes	11, 1366.9	37, 1163.5	1.17 (0.71, 1.94)
Obese[d]: No	205, 1661.6	155, 1228.5	1.35 (1.17, 1.57)
Obese[d]: Missing	1, 4129.0	0, NE	NE (NE, NE)
Baseline SARS-CoV-2: Positive[e]	13, 3574.5	8, 2507.9	1.43 (0.84, 2.41)
Baseline SARS-CoV-2: Negative[f]	204, 1572.8	184, 1178.1	1.34 (1.16, 1.53)

Source: EUA 27024.554 Safety-Immunogenicity_508_Tables. Table H.1.2
Abbreviations: GMR=geometric mean ratio; GMT=geometric mean titer
Note: All-available population refers to Dose 3 all-available immunogenicity population for C4591007 and Dose 2 all-available immunogenicity population for C4591001.
a. n=Number of participants with valid and determinate assay results for SARS-CoV-2 serum neutralizing titer 50 at the given dose/sampling time point.
b. GMTs was calculated by exponentiating the mean logarithm of the titers. Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-Sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Vaccine Group [2 to <5 years] - Comparison Group [16-25 years]) and the corresponding CI (based on the Student t distribution).
d. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart for participants 2 to <5 years of age or BMI ≥30 kg/m2 for participants 16 to 25 years of age. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
e. Positive N-binding ant body result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
f. Negative N-binding antibody result and negative NAAT result at Visit 1 and no medical history of COVID-19.

Exploratory analyses of immunogenicity against Delta and Omicron variants

In response to FDA's request for additional immunogenicity data to support effectiveness of three 3-µg primary series doses of BNT162b2 against the Delta and Omicron variants, Pfizer submitted exploratory descriptive analyses of SARS-CoV-2 neutralizing GMTs from a randomly selected subset of participants 6 months through 4 years of age (66 BNT162b2 recipients) without evidence of SARS-CoV-2 infection up to 1 month post-Dose 3 (Table 18). These data were generated using non-validated SARS-CoV-2 FFRNT assays with the reference strain USA-WA1/2020 (reference), B.1.617.2 (Delta), and BA.1 (Omicron); the relative sensitivity of the assays is not known.

The descriptive analyses indicate that post-Dose 3 in both age groups, neutralizing antibody GMTs against the reference strain and against the Delta variant were similar, while neutralizing antibody GMTs against the Omicron variant were notably lower. Post-dose 3 GMTs were lower in the 2-4 years age group compared with the 6-23 months age group for the reference strain and both variants. Geometric mean-fold rise (post-Dose 3 vs. pre-Dose 3) was similar for both variants compared with the reference strain and similar between age groups.

Table 18. Geometric Mean Fold Rises of SARS-CoV-2 Neutralizing GMTs Before Dose 3 and at 1 Month After Three Doses in Participants 6 Months Through 4 Years of Age, Phase 2/3 Evaluable Immunogenicity Population[b] Subsets, Study C4591007

Assay Target	C4591007 6-23 Months BNT162b2 3 µg N=32	C4591007 2-4 Years BNT162b2 3 µg N=34
USA WA1/2020 (Reference strain)	--	--
Post-Dose 3 GMT (95% CI)	640.0 (502.6, 815.0)	471.4 (344.6, 644.8)
GMFR (95% CI)	6.2 (4.7, 8.2)	6.7 (5.1, 8.9)
B.1.617.2 (Delta variant)	--	--
Post-Dose 3 GMT (95% CI)	606.3 (455.5, 806.9)	471.4 (341.2, 651.1)
GMFR (95% CI)	6.4 (4.6, 9.1)	6.9 (4.9, 9.8)
B.1.1.529 (Omicron variant)	--	--
Post-Dose 3 GMT (95% CI)	127.5 (90.2, 180.1)	82.5 (55.4, 122.9)
GMFR (95% CI)	7.8 (6.0, 10.2)	5.9 (3.9, 9.0)

Source: EUA 27034.556 eua-amendment-6m-4y-safety-immuno.pdf. Tables 27, 28, 37 and 38, Pages 125, 127, 152 and 154.
Abbreviations: CI=confidence interval; GMFR=geometric mean fold rises; GMT=geometric mean titer; NAAT=nucleic acid amplification test; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
N=number of participants with valid and determinate assay results for the specified assays at the given dose/sampling time point.
a. SARS-CoV-2 fluorescent focus reduction neutralization test assay, SARS-CoV-2 strains: recombinant USA_WA1/2020 (reference), B.1.617.2 (Delta), and BA.1 (Omicron).
b. Participants with no serological or virological evidence of SARS-CoV-2 infection: defined as N-binding antibody [serum] negative from pre-Dose 1 to 1 month post-Dose 2 or 3, SARS-CoV-2 not detected by NAAT [nasal swab] prior to Dose 1, 2 and 3, and negative NAAT [nasal swab] result at any unscheduled visit prior to 1 month post-Dose 2 or 3, and no medical history of COVID-19
c. Geometric Mean Fold Rise: GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

Results in the evaluable immunogenicity population (regardless of evidence of prior infection) and the all-available immunogenicity population were generally similar, noting that inclusion of individuals with prior SARS-CoV-2 infection typically results in elevated baseline (before vaccination) and post-vaccination neutralizing titers compared with individuals without evidence of prior infection.

4.2.6.2. Descriptive efficacy analyses

Participants 6-23 months of age

A preliminary descriptive efficacy analysis of COVID-19 cases occurring at least 7 days post-Dose 3 among participants 6-23 months of age in the Dose 3 evaluable efficacy population included a total of 3 confirmed cases accrued in participants with and without evidence of prior SARS-CoV-2 infection up to the data cutoff of April 29, 2022. The Dose 3 evaluable efficacy population included 376 participants randomized to BNT162b2 and 179 participants randomized to placebo. The VE estimate in this preliminary analysis was 75.6% (95% CI: -369.1%, 99.6%), with 1 COVID-19 case in the BNT162b2 group compared to 2 in the placebo group (2:1 randomization BNT162b2 to placebo).

All post Dose 3 cases occurred from February-April 2022, during circulation of the Omicron variant in the US. None of the participants with confirmed COVID-19 had a comorbidity that increases the risk of severe disease.

Participants 2-4 years of age

A preliminary descriptive efficacy analysis of COVID-19 cases occurring at least 7 days post-Dose 3 among participants 2-4 years of age in the Dose 3 evaluable efficacy population included a total of 7 confirmed cases accrued in participants with or without evidence of prior

SARS-CoV-2 infection up to the data cutoff of April 29, 2022. The Dose 3 evaluable efficacy population with and without evidence of prior SARS CoV-2 infection included 589 participants randomized to BNT162b2 and 271 participants randomized to placebo. The VE estimate in this preliminary analysis was 82.4% (95% CI: -7.6%, 98.3%), with 2 COVID-19 cases in the BNT162b2 group compared to 5 in the placebo group (2:1 randomization BNT162b2 to placebo). One confirmed case in the placebo group occurred in a participant with evidence of SARS-CoV-2 infection prior to 7 days post-Dose 3.

All post-Dose 3 cases occurred from February-April 2022, during circulation of the Omicron variant in the US. Comorbidities at baseline were present in only 1 confirmed COVID-19 case (asthma in one placebo recipient).

Subgroup analyses of VE were not conducted because of the limited number of confirmed COVID-19 cases that occurred 7 days after Dose 3. Nine of the 10 cases were in participants who were seronegative at baseline, and one (a placebo recipient) had missing serostatus.

In a combined analysis of both age groups, VE was 80.4% (95% CI: 14.1%, 96.7%) with 3 cases in the BNT162b2 group and 7 cases in the placebo group. Interpretation of post-Dose 3 efficacy data for both age groups, and for the age group of 6 months through 4 years overall, is limited for the following reasons:

- Vaccine efficacy post Dose 3 cannot be precisely estimated due to the limited number of cases accrued during blinded follow-up, as reflected in the wide confidence intervals associated with the estimates.
- These descriptive efficacy data are preliminary, as the protocol specified 21 cases have not yet been achieved.
- There were highly variable dosing intervals between doses 2 and 3, with median intervals of 112 (range 56 to 245) days among participants 6-23 months of age and 77 (range 42 to 239) days among participants 2-4 years of age in the Dose 3 evaluable efficacy population.
- The median blinded follow-up time post Dose 3 in the analyses was only 35 days for participants 6-23 months of age and 40 days for participants 2-4 years of age.

Severe COVID-19

One COVID-19 case in a participant 6-23 months of age met the criteria for severe COVID-19 because of an increased heart rate (HR) of 172 beats per minute (bpm), with normal cutoff for this age at 156 bpm) in a 14-month-old placebo recipient without evidence of prior SARS-CoV-2 infection. The participant reported symptoms of fever, rhinorrhea, sneezing and new or increased cough. Initial central lab COVID-19 testing was negative within 5 days of symptom onset; however, because of increased cough, repeat central lab testing was repeated 9 days after the first test and was positive. BioFire testing identified coinfection with human rhinovirus/enterovirus. Nine days later, the participant went to the emergency department (ED) after a generalized tonic-clonic seizure lasting approximately 5-10 minutes. Vital signs in the ED included a temperature of 38.4°C, HR 172 bpm, with the following symptoms noted: cough, runny nose and congestion; no diagnostic tests were performed, and the participant was discharged home the same day, after observation. All symptoms were reported as resolved 8 days after the ED visit. Because the participant had not returned back to baseline prior to the ED visit for febrile seizure, the investigator thought the fever could be attributable to COVID-19 illness.

Seven cases in participants 2-4 years of age met the criteria for severe COVID-19: 6 in the BNT162b2 group, of which 2 cases occurred post unblinding, and 1 in the placebo group. All cases occurred post Dose 2 (range 32-208 days post Dose 2), and none occurred post-Dose 3. In the BNT162b2 group, 5 of the 6 cases met criteria for a severe case based on 1 criterion: increased heart rate (n=2) or increased respiratory rate (n=3), all of which were considered by the investigator as not clinically significant based on examination at the illness visit and contributing circumstances such as the participant crying during examination. All cases occurred post Dose 2 (range 32-208 days post Dose 2). The final severe COVID-19 case in a BNT162b2 recipient occurred 99 days post-Dose 2 in a 2-year-old participant who had increased respiratory rate (RR), decreased SpO_2 as severe case criteria and was hospitalized due to COVID-19. The participant reported fever, new or increased cough, and new or increased shortness of breath, with at least 1 symptom ongoing as of the last report. During the urgent care visit, the participant had hypoxemia and was hospitalized with wheeze on lung auscultation. BioFire testing was positive for parainfluenza virus 3, in addition to the positive central laboratory COVID-19 result. The participant received oxygen via nasal canula, inhaled salbutamol and oral steroids while hospitalized, then was discharged home 3 days later.
In the placebo group, a 2-year-old participant met severe criteria because of decreased SpO_2 (88% on room air) with symptoms of new or increased cough and nasal congestion.

Multiple cases of confirmed COVID-19
Six participants 6-23 months of age (3 BNT162b2 recipients and 3 placebo recipients) developed more than one virologically and clinically confirmed episodes of symptomatic COVID-19 disease. All BNT162b2 recipients received 3 doses of assigned study intervention, 1 placebo recipient received 2 doses of placebo only, and 2 original placebo recipients received 2 doses of placebo followed by 3 doses of open-label BNT162b2. The interval between the episodes ranged from 1-4 months, with shorter intervals if the first episode occurred in January 2022 or later (during Omicron circulation). All participants with multiple episodes were negative at baseline for prior SARS-CoV-2 infection. Coinfections with other respiratory viruses were present in 1 BNT162b2 recipient (enterovirus) and 3 placebo recipients (adenovirus, enterovirus, endemic coronavirus, RSV).

Six participants 2-4 years of age (5 BNT162b2 recipients and 1 placebo recipient) developed more than one virologically and clinically confirmed episode of symptomatic COVID-19 disease. All of these participants received 3 doses of assigned study intervention, except for one participant in the BNT162b2 group who received 2 doses of BNT162b2. The interval between the episodes ranged from 1-4 months, with shorter intervals if the first episode occurred in January 2022 or later (during Omicron circulation). All participants with multiple episodes were negative at baseline for prior SARS-CoV-2 infection.

4.2.6.3. Post hoc efficacy analyses

Vaccine efficacy from Dose 1
An analysis of the number of confirmed COVID-19 cases following Dose 1 was conducted with the all-available efficacy population, for all participants regardless of evidence of prior infection through 7 days after Dose 3, at selected time intervals during and following completion of the primary series.

Table 19. First COVID-19 Occurrence Any Time After Dose 1, Blinded Follow-Up Period, Participants 6-23 Months of Age, All-Available Efficacy Population, Study C4591007

Efficacy Endpoint	BNT162b2 3 µg (N[a]=1178) Cases, n1[b] Surveillance Time[c], (n2[d])	Placebo (N[a]=598) Cases, n1[b] Surveillance Time[c], (n2[d])	Vaccine Efficacy % (95% CI[e])
First COVID-19 occurrence after Dose 1	98 0.456, (1027)	58 0.232, (524)	14.0 (-21.2, 38.4)
Dose 1 to before Dose 2	13 0.063, (1027)	5 0.032, (524)	-29.7 (-364.7, 56.6)
Dose 2 to <7 days after Dose 2	3 0.019, (1002)	3 0.010, (517)	48.4 (-285.0, 93.1)
≥7 Days after Dose 2 to before Dose 3	80 0.338, (998)	48 0.173, (512)	14.5 (-24.9, 41.0)
Dose 3 to <7 days after Dose 3	1 0.006, (336)	0 0.003, (147)	UND (NA, NA)
≥7 Days after Dose 3	1 0.030, (277)	2 0.015, (139)	75.5 (-370.1, 99.6)

Source: EUA 27034.554 Efficacy 508 tables. Table E.D.1.
Abbreviations: NA=not applicable; VE=Vaccine Efficacy; UND=Undefined.
a. N=number of participants in the specified group.
b. n1=Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period for the overall row and from start to the end of range stated for each interval.
d. n2=Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Table 20. First COVID-19 Occurrence Any Time After Dose 1, Participants 2 to <5 Years of Age, All-Available Efficacy Population, Study C4591007

Efficacy Endpoint	BNT162b2 3 µg (N[a]=1835) Cases, n1[b] Surveillance Time[c], (n2[d])	Placebo (N[a]=915) Cases, n1[b] Surveillance Time[c], (n2[d])	Vaccine Efficacy % (95% CI[e])
First COVID-19 occurrence after Dose 1	127 0.661, (1673)	92 0.323, (834)	32.6 (10.8, 48.8)
Dose 1 to before Dose 2	21 0.100, (1673)	8 0.050, (834)	-32.1 (-244.8, 43.8)
Dose 2 to <7 days after Dose 2	4 0.031, (1639)	5 0.016, (819)	60.1 (-85.6, 92.1)
≥7 Days after Dose 2 to before Dose 3	100 0.464, (1630)	74 0.228, (814)	33.6 (9.1, 51.3)
Dose 3 to <7 days after Dose 3	0 0.010, (553)	0 0.004, (222)	NE
≥7 Days after Dose 3	2 0.056, (481)	5 0.025, (209)	82.3 (-8.0, 98.3)

Source: EUA 27034.554 Efficacy 508 tables. Table E.D.2.
Abbreviations: NE=not estimable; VE=Vaccine Efficacy.
a. N=number of participants in the specified group.
b. n1=Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period for the overall row and from start to the end of range stated for each interval.
d. n2=Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

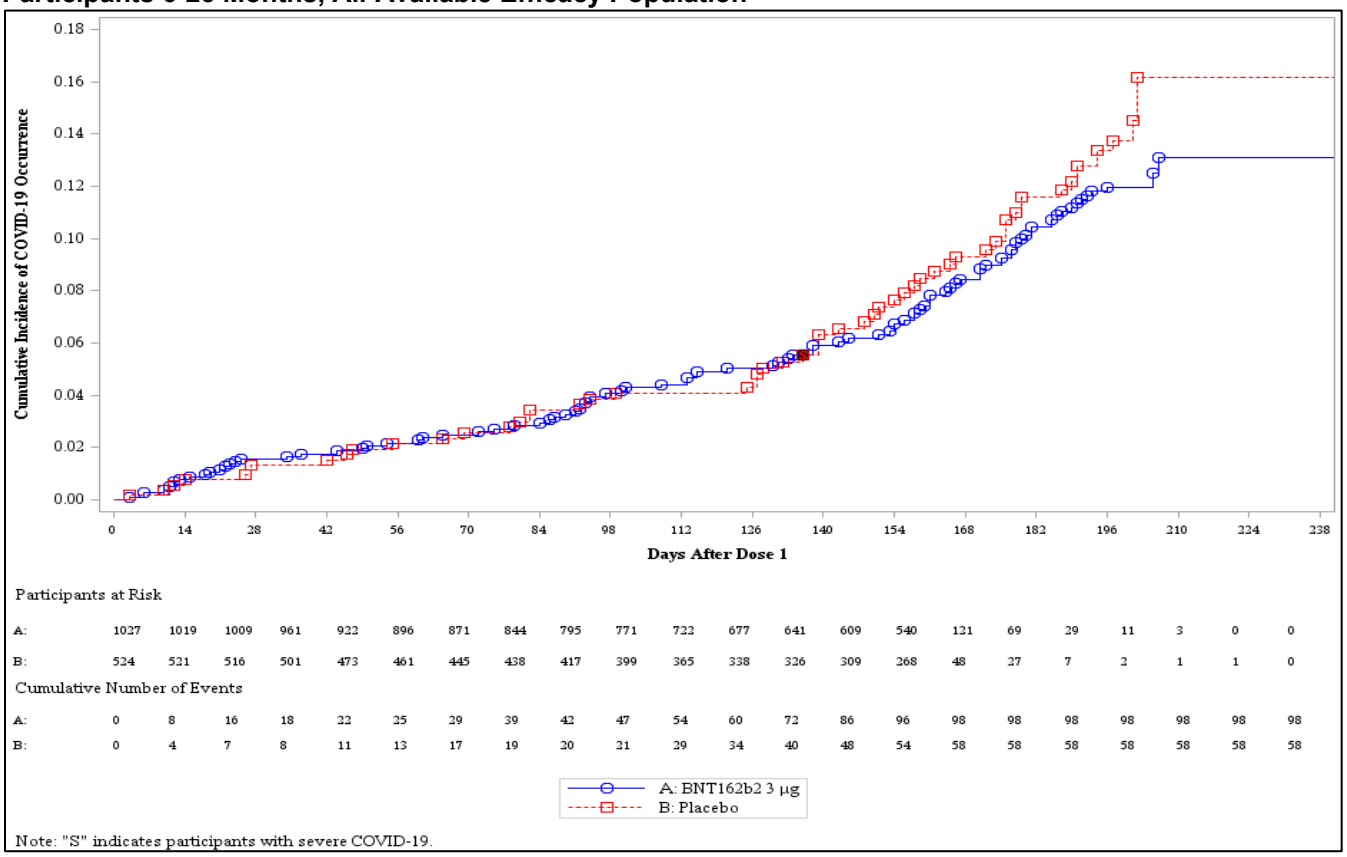
The estimated VE for the prevention of COVID-19 disease after Dose 1 in the all-available efficacy population is 14.0% (95% CI: -21.2%-38.3%) for participants 6-23 months of age and 32.6% (95% CI: 10.8%-48.8%) for participants 2-4 years of age.

The post-hoc analysis of cases accumulated after Dose 1, after Dose 2 and before Dose 3, suggests modest protection against COVID-19 following two doses in the older age group, but interpretation is limited by wide confidence intervals. It is not possible to conclude a difference between efficacy post-Dose 3 as compared to efficacy post-Dose 2 based on COVID-19 cases accrued in the study as of the April 29, 2022, cutoff date.

Cumulative incidence curves

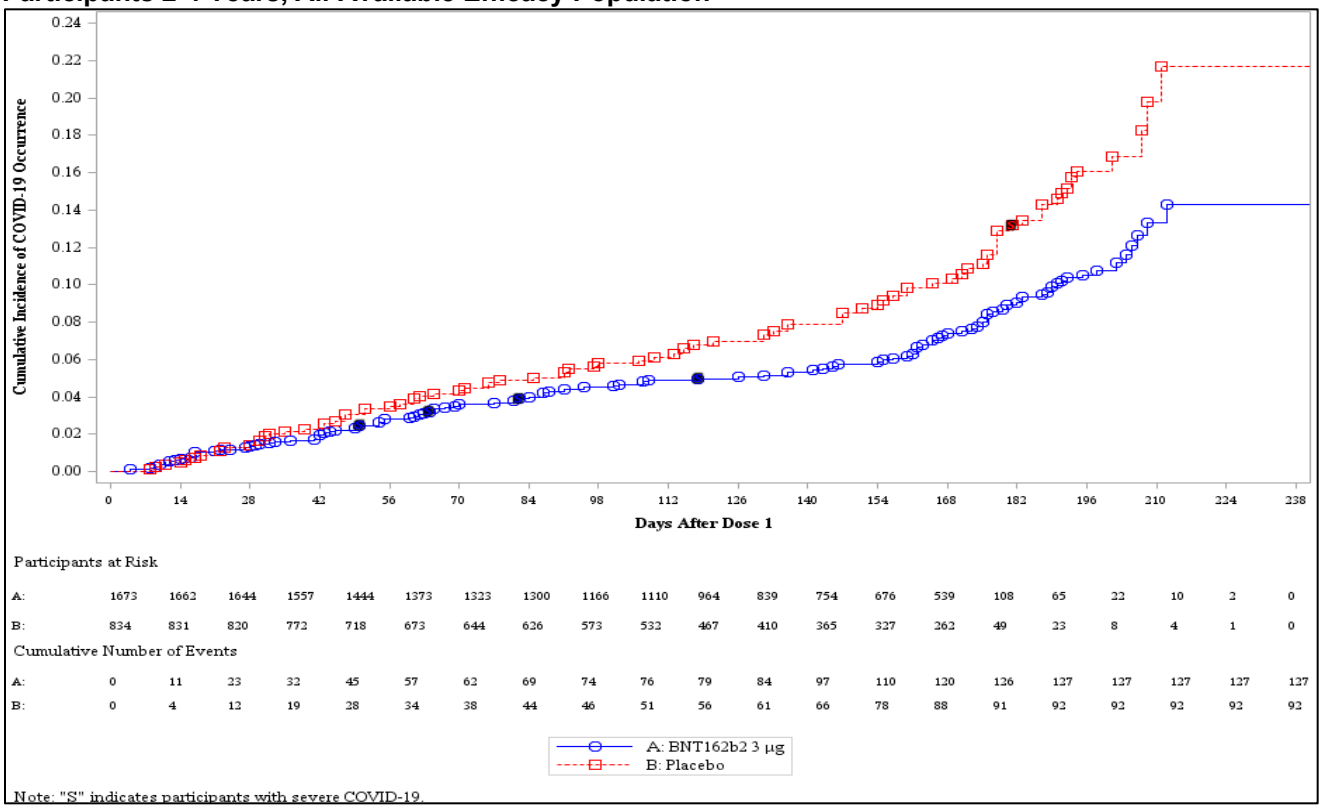
Based on the cumulative incidence curves for the all-available efficacy population after Dose 1, (Figure 1 and Figure 2), COVID-19 disease onset appears to occur similarly for both BNT162b2 and placebo groups until after Dose 3, at which time point, the curves begin to diverge.

Figure 1. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Participants 6-23 Months, All-Available Efficacy Population



Source: Source: EUA 27034.554 Efficacy 508 tables.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Participants 2-4 Years, All-Available Efficacy Population



Source: Source: EUA 27034.554 Efficacy 508 tables.

4.2.7. Phase 2/3 safety results

4.2.7.1. Phase 2/3 overview of adverse events

From Dose 1 to the data cutoff or participant unblinding (whichever was earlier) among BNT162b2 recipients 6 months through 4 years of age, the frequency of immediate unsolicited AEs after any dose was <0.5%, frequencies of solicited injection site reactions within 7 days after any dose ranged from 20.5%-36.3%, and frequencies of solicited systemic reactions after any dose ranged from 30.8%-61.0%. Six BNT162b2 recipients and 1 placebo recipient withdrew from the study due to AEs. SAEs were reported in 17 BNT162b2 recipients 6-23 months of age, and none were considered by the study investigator or FDA to be related to the vaccine. Of the 12 BNT162b2 recipients 2-4 years of age. There were no deaths reported. See Table 21 and Table 22 below for summary counts and frequencies of adverse events after each dose.

Table 21. Adverse Events in Participants 6-23 Months of Age, Blinded Follow-Up, Phase 2/3 Safety Population, Study C4591007

Event	BNT162b2 3 µg	Placebo
Immediate unsolicited AE within 30 minutes after vaccination, n/N (%)	--	--
Dose 1	3/1178 (0.3)	0/598 (0)
Dose 2	3/1166 (0.3)	3/596 (0.5)
Dose 3	0/386 (0)	0/184 (0)

Event	BNT162b2 3 µg	Placebo
Solicited injection site reaction within 7 days, n/N (%)	--	--
Dose 1	279/1173 (23.8)	104/595 (17.5)
Dose 2	248/1147 (21.6)	79/591 (13.4)
Dose 3	75/365 (20.5)	26/170 (15.3)
Solicited systemic reaction within 7 days, n/N (%)	--	--
Dose 1	715/1173 (61.0)	346/595 (58.2)
Dose 2	640/1147 (55.8)	298/591 (50.4)
Dose 3	188/365 (51.5)	77/170 (45.3)
From Dose 1 through 1 month after Dose 3, n/N (%)	--	--
Any AE	355/1178 (30.1)	162/598 (27.1)
Unsolicited non-serious AE	343/1178 (29.1)	157/598 (26.3)
From Dose 1 through cutoff date or participant unblinding, n/N (%)	--	--
Withdrawal due to AEs	3/1178 (0.3)	0/598 (0)
SAE	17/1178 (1.4)	14/598 (2.3)
Death	0/1178 (0)	0/598 (0)

Source: EUA 27024.554 Safety-Immunogenicity_508_Tables. Table Q1, Page 15.
Abbreviations: AE=adverse event; n=number of participants with the specified characteristic. N=number of administered participants in the specified group (the denominator for the percentage calculations); SAE=serious adverse event.
Note: Medical Dictionary for Regulatory Activities (v25.0) coding dictionary applied.
Note: Immediate AE refers to an AE reported in the 30-minute observation period after vaccination.
%: n/N

Table 22. Adverse Events in Participants 2-4 Years of Age, Blinded Follow-Up, Phase 2/3 Safety Population, Study C4591007

Event	BNT162b2 3 µg	Placebo
Immediate unsolicited AE within 30 minutes after vaccination, n/N (%)	--	--
Dose 1	5/1835 (0.3)	3/915 (0.3)
Dose 2	4/1819 (0.2)	1/907 (0.1)
Dose 3	0/606 (0)	0/280 (0)
Solicited injection site reaction within 7 days, n/N (%)	--	--
Dose 1	648/1825 (35.5)	229/909 (25.2)
Dose 2	645/1779 (36.3)	205/878 (23.3)
Dose 3	174/552 (31.5)	41/262 (15.6)
Solicited systemic reaction within 7 days, n/N (%)	--	--
Dose 1	693/1825 (38.0)	354/909 (38.9)
Dose 2	599/1779 (33.7)	283/878 (32.2)
Dose 3	170/552 (30.8)	77/262 (29.4)
From Dose 1 through 1 month after Dose 3, n/N (%)	--	--
Any AE	344/1835 (18.7)	171/915 (18.7)
Unsolicited non-serious AE, n/N (%)	339/1835 (18.5)	169/915 (18.5)
From Dose 1 through cutoff date or participant unblinding, n/N (%)	--	--
Withdrawal due to AEs	3/1835 (0.2)	1/915 (0.1)
SAE	12/1835 (0.7)	8/915 (0.9)
Death	0/1835 (0)	0/915 (0)

Source: EUA 27024.554 Safety-Immunogenicity_508_Tables. Table Q2, Page 16.
Abbreviations: AE=adverse event; n=number of participants with the specified characteristic. N=number of administered participants in the specified group (the denominator for the percentage calculations); SAE=serious adverse event.
Note: Medical Dictionary for Regulatory Activities (v25.0) coding dictionary applied.
Note: Immediate AE refers to an AE reported in the 30-minute observation period after vaccination.
%: n/N

Analyses that included adverse events reported after a participant was unblinded did not suggest any meaningful differences in the safety profile. No events that were reported after unblinding were serious or considered possibly related to study intervention.

4.2.7.2. Immediate adverse events

Of 1,178 BNT162b2 recipients 6-23 months of age, 3 participants reported AEs within 30 minutes after Dose 1: vomiting, injection site erythema and hematoma (n=1 each). After Dose 2, 3 BNT162b2 recipients reported injection site erythema, injection site swelling and rash.

Of 1,835 BNT162b2 recipients 2-4 years of age, 5 participants reported immediate AEs following received Dose 1: erythema in 2 participants, and injection site bruising, injury associated with device and skin abrasion in 1 participant each. Following Dose 2, four immediate reactions were reported by 1 BNT162b2 recipient each: injection site pain, injection site erythema, rash erythematous and urticaria.

None of the BNT162b2 recipients in either age group reported an immediate AE after Dose 3, or anaphylaxis/severe allergic reaction within 30 minutes after any dose.

4.2.7.3. Solicited adverse reactions

Participants 6-23 months of age

Overall, frequencies of any solicited local adverse reaction (AR) were higher in BNT162b2 recipients than placebo recipients, and frequencies were similar after Dose 1 and 2 but slightly lower after Dose 3. Tenderness at the injection site was the most frequently reported local reaction after each BNT162b2 dose (15.0%-16.6%), with redness (7.1%-10.6%) and swelling (2.7%-3.7%) at the injection site reported less frequently. Frequencies of any solicited systemic AR in BNT162b2 recipients were generally similar after Dose 1, 2 or 3, and included irritability (43.6%-51.2%), drowsiness (19.9%-27.0%), decreased appetite (20.2%-22.2%) and fever (6.8%-7.4%). Most local and systemic reactions were mild to moderate in severity, with median onset of 1-2 days postvaccination, and resolved within 1-2 days after onset. Solicited local and systemic reactions in BNT162b2 recipients that were graded as severe occurred in ≤1.1% of participants across groups and doses, and all but one were systemic reactions. No Grade 4 local or systemic reactions were reported after any dose.

Rates of local ARs in participants 6-23 months of age (3 µg dose level) were all lower than those in individuals 5-11 years of age[49] (10 µg dose level) enrolled in the same study. Fever was reported more frequently and with higher severity in participants 6-23 months of age compared to individuals 5-11 years of age. Three vaccine recipients 6-23 months of age reported a fever >40.0°C:

- a 19-month-old with fever of 40.6°C on Day 2 after Dose 1, with fevers of 39°C and 38.1°C on the subsequent days, and a concurrent nonserious AE of exanthema subitum reported on Day 2 after Dose 1 (attributed to a viral infection) that resolved in 4 days;
- an 11-month-old with fever starting on Day 1 after Dose 2 and persisting through Day 5 (temperatures on Days 1 to 5 were: 39.2°C, 39.5°C, 40.5°C, 38.4°C, 39.1°C), Grade 3 drowsiness on Days 1-2 and Days 5-6 post-Dose 2, and Grade 3 irritability on Days 2 and 5 post-Dose 2; the participant was diagnosed with roseola at an unscheduled illness visit;
- a 13-month-old with fever of 40.5°C on Day 3 and 39.5°C on Day 4 after Dose 3, with resolution of fever by Day 6 (no temperature reported on Day 5).

The frequencies of local and systemic ARs within 7 days after each vaccination in participants with evaluable e-diary data are summarized in Table 23 and Table 24. The characteristics of the systemic and local reactions are presented in Table 25.

Table 23. Frequency of Solicited Local Reactions, by Severity, Within 7 Days After Each Dose in Participants 6-23 Months of Age, Phase 2/3 Safety Population[a], Study C4591007

Event	BNT162b2 Dose 1 N=1159-1173	Placebo Dose 1 N=591-595	BNT162b2 Dose 2 N=1137-1147	Placebo Dose 2 N=590-591	BNT162b2 Dose 3 N=362-365	Placebo Dose 3 N=170
Tenderness at the injection site[b], %	--	--	--	--	--	--
Any[d]	16.6	11.2	15.0	8.5	16.0	11.8
Mild	15.6	10.3	13.5	7.1	14.1	10.0
Moderate	0.9	0.8	1.4	1.4	1.9	1.8
Severe	0	0	0.1	0	0	0
Redness[c], %	--	--	--	--	--	--
Any[d]	10.6	7.4	9.3	6.6	7.1	5.3
Mild	9.7	6.9	8.5	6.1	4.7	4.7
Moderate	0.9	0.5	0.9	0.5	2.2	0.6
Severe	0	0	0	0	0.3	0
Swelling[c], %	--	--	--	--	--	--
Any[d]	3.9	2.5	3.9	1.5	2.7	1.8
Mild	3.4	2.2	3.4	1.4	1.9	1.8
Moderate	0.5	0.3	0.5	0.2	0.8	0
Severe	0	0	0	0	0	0
Any local reaction[d]	23.8	17.5	21.6	13.4	20.5	15.3

Source: EUA 27034.556 c4594007-dose3-tables-ns-listings-6mo-4yr-safety.pdf. Pages 128-132.
%: n/N. n=number of participants in the specified age group with the specified reaction. N=number of participants in the specified age group reporting at least 1 yes or no response for the specified reaction after the specified dose.
a. All participants in the specified age group who received at least 1 dose of the study intervention with evaluable e-diary data.
b. Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
c. Mild: 0.5 to ≤2.0 cm; moderate: 2.0 to ≤7.0 cm; severe: >7.0 cm.
d. Any local reaction: any redness >0.5 cm, any swelling >0.5 cm, or any pain at the injection site.

Table 24. Frequency of Solicited Systemic Reactions, by Severity, Within 7 Days After Each Dose in Participants 6-23 Months of Age, Phase 2/3 Safety Population[a], Study C4591007

Event	BNT162b2 Dose 1 N=1159-1173	Placebo Dose 1 N=591-595	BNT162b2 Dose 2 N=1137-1147	Placebo Dose 2 N=590-591	BNT162b2 Dose 3 N=362-365	Placebo Dose 3 N=170
Fever, %	--	--	--	--	--	--
≥38.0°C	7.2	7.2	7.4	6.1	6.8	5.9
≥38.0°C to 38.4°C	3.6	3.7	3.6	3.0	3.8	4.1
>38.4°C to 38.9°C	2.0	2.4	1.7	1.9	1.4	1.2
>38.9°C to 40.0°C	1.6	1.0	2.0	1.2	1.4	0.6
>40.0°C	0.1	0.2	0.1	0	0.3	0
Irritability[b], %	--	--	--	--	--	--
Any[e]	51.2	47.2	47.4	40.7	43.6	37.6
Mild	21.1	17.9	18.7	15.1	15.5	15.9
Moderate	29.4	29.3	28.1	24.7	27.9	21.8
Severe	0.6	0	0.6	0.8	0.3	0
Drowsiness[c], %	--	--	--	--	--	--
Any[e]	27.0	29.3	23.8	21.2	19.9	12.9
Mild	21.7	22.0	17.7	16.6	13.8	8.8
Moderate	5.2	6.9	5.8	4.4	5.8	3.5
Severe	0.2	0.3	0.4	0.2	0.3	0.6

Event	BNT162b2 Dose 1 N=1159-1173	Placebo Dose 1 N=591-595	BNT162b2 Dose 2 N=1137-1147	Placebo Dose 2 N=590-591	BNT162b2 Dose 3 N=362-365	Placebo Dose 3 N=170
Decreased Appetite[d], %	--	--	--	--	--	--
Any[e]	22.2	21.2	22.2	18.0	20.2	13.5
Mild	11.9	12.4	13.8	10.7	11.6	7.6
Moderate	10.0	8.6	8.0	7.1	7.5	5.9
Severe	0.3	0.2	0.4	0.2	1.1	0
Any systemic event[e]	61.0	58.2	55.8	50.4	51.5	45.3
Use of antipyretic or pain medication[f], %	24.0	19.7	21.2	18.8	19.2	16.5

Source: EUA 27034.556 c4594007-dose3-tables-ns-listings-6mo-4yr-safety.pdf. Pages 202, 215.
%: n/N. n=Number of participants with the specified reaction. N=Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
a. All participants in the specified age group who received at least 1 dose of the study intervention with evaluable e-diary data.
b. Mild: easily consolable; Moderate: requiring increased attention; Severe: inconsolable; crying, cannot be comforted.
c. Mild: increased or prolonged sleeping bouts; Moderate: slightly subdued, interfering with daily activity; Severe: disabling; not interested in usual daily activity.
d. Mild: decreased interest in eating; Moderate: decreased oral intake; Severe: refusal to eat.
e. Any systemic event: any fever ≥38.0℃, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
f. Severity was not collected for use of antipyretic or pain medication.

Table 25. Characteristics of Solicited Local and Systemic Reactions in Participants 6-23 Months of Age, Phase 2/3 Safety Population[a], Study C4591007

Event	BNT162b2 Dose 1	Placebo Dose 1	BNT162b2 Dose 2	Placebo Dose 2	BNT162b2 Dose 3	Placebo Dose 3
Any solicited local reaction	--	--	--	--	--	--
Day of onset, median (min, max)	1.0 (1, 6)	1.0 (1, 4)	1.0 (1, 5)	1.0 (1, 6)	1.0 (1, 4)	1.0 (1, 6)
Duration, median (min, max)	1.0 (1, 10)	1.0 (1, 6)	1.0 (1, 6)	1.0 (1, 10)	1.0 (1, 9)	1.0 (1, 5)
Persisted beyond 7 days, n/N (%)	3/1173 (<0.1)	0	0	2/591 (0.3)	1/365 (0.3)	0
Any solicited systemic reaction	--	--	--	--	--	--
Day of onset, median (min, max)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration, median (min, max)	2.0 (1, 39)	2.0 (1, 21)	2.0 (1, 29)	2.0 (1, 34)	2.0 (1, 19)	2.0 (1, 52)
Persisted beyond 7 days, n/N (%)	45/1173 (3.8)	30/595 (5.0)	37/1147 (3.2)	21/591 (3.6)	9/365 (2.5)	7/170 (4.1)

Source: EUA 27034.556 c4594007-dose3-tables-ns-listings-6mo-4yr-safety.pdf. Pages 202, 215.
Abbreviations: AR=adverse reaction; max=maximum; min=minimum; n=number of participants with the specified reaction persisted beyond 7 days; N=number of participants reporting at least one yes or no response for the specified reaction after the specified dose.
a. All participants in the specified age group who received at least 1 dose of the study intervention with evaluable e-diary data.

Participants 2-4 years of age

Solicited local and systemic ARs in BNT162b2 recipients generally occurred at similar frequencies after Dose 1, 2 or 3. Pain at the injection site was the most frequently reported local reaction after each BNT162b2 dose (26.7%-31.0%). Most local and systemic reactions were mild to moderate in severity, with median onset 1-2 days postvaccination, and resolved within 1-2 days after onset. ARs in BNT162b2 recipients that were graded as severe were <0.5% after any dose. No Grade 4 reactions were reported after any dose.

Rates of local ARs in participants 2-4 years of age (3 µg dose level) were all lower than those in individuals 5-11 years of age[50] (10 µg dose level) enrolled in the same study. Systemic ARs such as fatigue, headache, chills, and muscle pain were generally reported less frequently and were milder in severity in 2-4-year-old participants compared to 5-11-year-old participants. Fever was reported more frequently and with higher severity in 2-4-year-old participants than in 5-11-year-old participants. Three vaccine recipients 2-4 years of age reported a fever >40.0°C:

- a 3-year-old was reported to have fever of 40.8°C on Day 2 after Dose 1, which persisted with fevers of 40.7°C, 40.5°C and 38.4°C on the subsequent days and resolved on Day 6 without other concurrent AEs reported. The fever was also reported as a nonserious AE of pyrexia considered as related to study intervention by the investigator and led to withdrawal.
- a 4-year-old was reported to have fever starting on Day 3 after Dose 2 and persisting through Day 7 (temperatures on Days 1 to 5 were: 39.2°C, 39.5°C, 40.5°C, 38.4°C, 39.1°C) with a concurrent Grade 2 SAE of calf pain on Day 6 and a nonserious Grade 2 AE of rash (chest, upper back, and ear) on Day 7 after Dose 2. When the participant defervesced, the rash then developed, which indicated a possible viral infection. (See Section 7.3.7.6 for additional details of SAEs)
- A 4-year-old was reported to have fever on Days 5 through 7 post-Dose 2, ranging from 38.7°C to 40.3°C. No other AEs were reported, and no medication use was reported.

The frequencies of local and systemic ARs within 7 days after each vaccination in participants with evaluable e-diary data are summarized in Table 26 and Table 27. The characteristics of the systemic and local reactions are presented in Table 28.

Table 26. Frequency of Solicited Local Reactions, Within 7 Days After Each Dose in Participants 2-4 Years of Age, Phase 2/3 Safety Population[a], Study C4591007

Event	BNT162b2 Dose 1 N=1813-1825	Placebo Dose 1 N=905-909	BNT162b2 Dose 2 N=1772-1779	Placebo Dose 2 N=877-878	BNT162b2 Dose 3 N=547-552	Placebo Dose 3 N=262
Pain at the injection site[b], %	--	--	--	--	--	--
Any[d]	30.8	20.6	31.0	20.3	26.7	13.4
Mild	28.8	19.7	29.0	19.3	23.8	12.6
Moderate	2.0	0.8	2.0	0.9	2.9	0.8
Severe	0	0.1	0	0.1	0	0
Redness[c], %	--	--	--	--	--	--
Any[d]	8.8	8.5	11.4	5.7	10.9	3.4
Mild	7.5	7.4	9.6	4.9	9.6	2.7
Moderate	1.2	1.0	1.7	0.8	1.3	0.8
Severe	0.1	0.1	0.1	0	0	0
Swelling[c], %	--	--	--	--	--	--
Any[d]	3.7	2.9	5.7	2.1	3.1	1.1
Mild	3.2	2.3	4.6	1.8	2.9	1.1
Moderate	0.4	0.6	1.2	0.2	0.2	0
Severe	0	0	0	0	0	0
Any local reaction[d]	35.5	25.2	36.3	23.3	31.5	15.6

Source: EUA 27034.556 c4594007-dose3-tables-ns-listings-6mo-4yr-safety.pdf. Pages 164-169.
%: n/N. n=number of participants in the specified age group with the specified reaction. N=number of participants in the specified age group reporting at least 1 yes or no response for the specified reaction after the specified dose.
a. All participants in the specified age group who received at least 1 dose of the study intervention with evaluable e-diary data.
b. Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
c. Mild: 0.5 to ≤2.0 cm; moderate: 2.0 to ≤7.0 cm; severe: >7.0 cm.
d. Any local reaction: any redness >0.5 cm, any swelling >0.5 cm, or any pain at the injection site.

Table 27. Frequency of Solicited Systemic Reactions, Within 7 Days After Each Dose in Participants 2-4 Years of Age, Phase 2/3 Safety Population[a], Study C4591007

Event	BNT162b2 Dose 1 N=1813-1825	Placebo Dose 1 N=905-909	BNT162b2 Dose 2 N=1772-1779	Placebo Dose 2 N=877-878	BNT162b2 Dose 3 N=547-552	Placebo Dose 3 N=262
Fever, %	--	--	--	--	--	--
≥38.0°C	5.2	5.3	4.9	5.2	5.1	4.2
≥38.0°C to 38.4°C	3.1	2.6	2.3	1.9	2.9	1.5
>38.4°C to 38.9°C	1.3	1.8	1.5	2.4	1.4	1.5
>38.9°C to 40.0°C	0.7	0.9	1.1	0.9	0.7	1.1
>40.0°C	0.1	0	0.1	0	0	0
Fatigue[b], %	--	--	--	--	--	--
Any[e]	29.7	30.6	25.7	22.9	24.5	21.8
Mild	18.5	19.4	15.1	13.7	15.9	13.4
Moderate	10.9	10.6	10.2	8.9	8.2	8.4
Severe	0.3	0.6	0.5	0.3	0.4	0
Headache[b], %	--	--	--	--	--	--
Any[e]	4.5	4.9	4.6	4.1	4.9	4.2
Mild	3.5	3.9	3.6	2.6	3.5	3.8
Moderate	1.0	0.9	1.0	1.4	1.5	0.4
Severe	0	0.1	0	0.1	0	0
Chills[b], %	--	--	--	--	--	--
Any[e]	2.3	2.4	3.0	2.6	3.3	2.7
Mild	1.5	1.8	2.0	1.9	2.6	2.7
Moderate	0.6	0.7	1.0	0.7	0.5	0
Severe	0.2	0	0	0	0.2	0
Vomiting[c], %	--	--	--	--	--	--
Any[e]	3.0	2.7	3.4	3.3	1.6	3.8
Mild	2.4	1.5	3.1	3.0	1.3	3.4
Moderate	0.6	1.1	0.3	0.3	0.4	0.4
Severe	0	0	0	0	0	0
Diarrhea[d], %	--	--	--	--	--	--
Any[e]	7.7	8.0	6.7	7.3	5.1	5.0
Mild	7.2	7.1	5.9	6.5	3.8	3.8
Moderate	0.5	0.9	0.7	0.8	1.3	1.1
Severe	0	0	0.1	0	0	0
New or worsened muscle pain[b], %	--	--	--	--	--	--
Any[e]	2.4	1.7	2.6	2.4	2.0	1.5
Mild	1.8	1.4	1.9	1.9	1.9	1.5
Moderate	0.5	0.2	0.7	0.5	0.5	0
Severe	0.1	0	0	0	0	0

Event	BNT162b2 Dose 1 N=1813-1825	Placebo Dose 1 N=905-909	BNT162b2 Dose 2 N=1772-1779	Placebo Dose 2 N=877-878	BNT162b2 Dose 3 N=547-552	Placebo Dose 3 N=262
New or worsened joint pain[b], %	--	--	--	--	--	--
Any[e]	0.8	2.0	1.4	1.0	1.3	0.8
Mild	0.7	1.4	1.0	0.7	0.9	0.8
Moderate	0.1	0.6	0.3	0.3	0.2	0
Severe	0	0	0	0	0.2	0
Any systemic reaction[e]	38.0	38.9	33.7	32.2	30.8	29.4
Use of antipyretic or pain medication[f], %	10.8	9.1	9.9	8.4	8.5	6.9

Source: EUA 27034.556 c4594007-dose3-tables-ns-listings-6mo-4yr-safety.pdf. Pages 170-180.
%: n/N. n=Number of participants with the specified reaction. N=Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
a. All participants in the specified age group who received at least 1 dose of the study intervention with evaluable e-diary data.
b. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
c. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.
d. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.
e. Any systemic event: any fever ≥38.0°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
f. Severity was not collected for use of antipyretic or pain medication.

Table 28. Characteristics of Solicited Local and Systemic Reactions in Participants 2-4 Years of Age, Phase 2/3 Safety Population[a], Study C4591007

Event	BNT162b2 Dose 1	Placebo Dose 1	BNT162b2 Dose 2	Placebo Dose 2	BNT162b2 Dose 3	Placebo Dose 3
Any solicited local reaction	--	--	--	--	--	--
Day of onset, median (min, max)	1.0 (1, 7)	1.0 (1, 6)	1.0 (1, 7)	1.0 (1, 6)	1.0 (1, 6)	1.0 (1, 7)
Duration, median (min, max)	1.0 (1, 9)	1.0 (1, 20)	1.0 (1, 31)	1.0 (1, 10)	1.0 (1, 14)	1.0 (1, 11)
Persisted beyond 7 days, n/N (%)	4/1825 (0.2)	3/909 (0.3)	11/1779 (0.6)	2/878 (0.2)	1/552 (0.2)	1/262 (0.4)
Any solicited systemic reaction	--	--	--	--	--	--
Day of onset, median (min, max)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration, median (min, max)	1.0 (1, 26)	1.0 (1, 18)	1.0 (1, 29)	1.0 (1, 32)	1.0 (1, 15)	1.0 (1, 9)
Persisted beyond 7 days, n/N (%)	23/1825 (1.3)	13/909 (1.4)	21/1779 (1.2)	8/878 (0.9)	4/552 (0.7)	3/262 (1.1)

Source: EUA 27034.556 c4594007-dose3-tables-ns-listings-6mo-4yr-safety.pdf. Pages 153, 160, 207
Abbreviations: max=maximum; min=minimum; n=number of participants with the specified reaction persisted beyond 7 days; N=number of participants reporting at least one yes or no response for the specified reaction after the specified dose.
a. All participants in the specified age group who received at least 1 dose of the study intervention with evaluable e-diary data.

Additional analyses of the solicited local and systemic 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.

A total of 120 participants with e-diary data received 3 µg BNT162b2 Dose 1 and 2, turned 5 years of age, then were unblinded and received Dose 3 at the 10 µg dose level in an open-label manner. In a separate analysis of these participants, there was a dose level dependent increase

in local reactions after Dose 3 compared to after Dose 2 (Table 29). There was also a dose level-dependent increase in certain systemic reactions after Dose 3 compared to after Dose 2, including fever, fatigue and headache, while other systemic reactions remained similar or showed no clear pattern after each subsequent dose (Table 30).

Table 29. Frequency of Solicited Local Reactions, Within 7 Days After Dose 2 and 3 in Participants 2-4 Years of Age and Participants Who Turned 5 Years of Age and Received BNT162b2 10 µg Dose 3, Phase 2/3 Safety Population[a], Study C4591007

Event	2-4 Years 3 µg Dose 2 N=120	5 Years 10 µg Dose 3 N=111
Pain at the injection site[b], %	--	--
Any[d]	35.0	53.2
Mild	34.2	44.1
Moderate	0.8	8.1
Severe	0	0.9
Redness[c], %	--	--
Any[d]	11.7	16.2
Mild	10.8	8.1
Moderate	0	8.1
Severe	0.8	0
Swelling[c], %	--	--
Any[d]	4.2	6.3
Mild	3.3	3.6
Moderate	0.8	2.7
Severe	0	0
Any local reaction[d]	40.0	58.6

Source: Adapted from EUA 27034.556 c4591007-dose3-tables-ns-listings-6mo-4yr-safety.pdf. Table p148.
%: n/N. n=number of participants in the specified age group with the specified reaction. N=number of participants in the specified age group reporting at least 1 yes or no response for the specified reaction after the specified dose.
a. All participants in the specified age group who received at least 1 dose of the study intervention with evaluable e-diary data.
b. Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
c. Mild: 0.5 to ≤2.0 cm; moderate: 2.0 to ≤7.0 cm; severe: >7.0 cm.
d. Any local reaction: any redness >0.5 cm, any swelling >0.5 cm, or any pain at the injection site.

Table 30. Frequency of Solicited Systemic Reactions, Within 7 Days After Dose 3 in Participants 2-4 Years of Age and Participants Who Turned 5 Years of Age and Received BNT162b2 10 µg Dose 3, Phase 2/3 Safety Population[a], Study C4591007

Event	2-4 Years 3 µg Dose 2 N=120	5 Years 10 µg Dose 3 N=111
Fever, %	--	--
≥38.0°C	2.5	12.6
≥38.0°C to 38.4°C	0.8	6.3
>38.4°C to 38.9°C	1.7	5.4
>38.9°C to 40.0°C	0	0.9
>40.0°C	0	0
Fatigue[b], %	--	--
Any[e]	24.2	34.2
Mild	17.5	17.2
Moderate	6.7	16.2
Severe	0	0.9

Event	2-4 Years 3 µg Dose 2 N=120	5 Years 10 µg Dose 3 N=111
Headache[b], %	--	--
Any[e]	4.2	12.6
Mild	4.2	9.9
Moderate	0	2.7
Severe	0	0
Chills[b], %	--	--
Any[e]	4.2	2.7
Mild	2.5	1.8
Moderate	0.8	0.9
Severe	0	0
Vomiting[c], %	--	--
Any[e]	3.3	2.7
Mild	2.5	1.8
Moderate	0.8	0.9
Severe	0	0
Diarrhea[d], %	--	--
Any[e]	8.3	3.6
Mild	7.5	3.6
Moderate	0.8	0
Severe	0	0
New or worsened muscle pain[b], %	--	--
Any[e]	5.0	3.6
Mild	4.2	1.8
Moderate	0.8	1.8
Severe	0	0
New or worsened joint pain[b], %	--	--
Any[e]	1.7	0
Mild	1.7	0
Moderate	0	0
Severe	0	0
Any systemic reaction[e]	35.0	45.0
Use of antipyretic or pain medication[f], %	8.4	6.9

Source: Adapted from EUA 27034.556 c4591007-dose3-tables-ns-listings-6mo-4yr-safety.pdf. Table p198.
%: n/N. n=Number of participants with the specified reaction. N=Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
a. All participants in the specified age group who received at least 1 dose of the study intervention with evaluable e-diary data.
b. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
c. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.
d. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.
e. Any systemic event: any fever ≥38.0℃, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
f. Severity was not collected for use of antipyretic or pain medication.

4.2.7.4. Unsolicited adverse events

Information about unsolicited AEs was collected from Dose 1 through 1 month after each dose.

The frequencies of unsolicited non-serious AEs reported were similar in the BNT162b2 and placebo groups in both age groups: 29.1% vs. 26.3% in participants 6-23 months of age and 18.5% vs. 18.5% in participants 2-4 years of age, respectively. The most commonly observed AEs were consistent with those reported as solicited ARs (local and systemic reactogenicity)

and/or were consistent with events frequently reported in this age group, including infections and injuries, that were not considered related to study vaccination.

Adverse events considered related to BNT162b2 included lymphadenopathy and hypersensitivity are discussed in Section 4.2.7.6 with Adverse events of clinical interest. SAEs are discussed in Section 4.2.7.5.

4.2.7.5. Serious adverse events

Information about SAEs was collected from Dose 1 up to 6 months post-Dose 3.

Participants 6-23 months of age

Among participants 6-23 months of age, SAEs were reported in 17 (3.1%) participants in the BNT162b2 group and 14 (2.3%) in the placebo group, most of which were gastrointestinal or respiratory illnesses/infections that occur commonly in this age group.

SAEs reported in the BNT162b2 group included RSV bronchiolitis (5 participants), pneumonia (2 participants), gastroenteritis (2 participants), lower respiratory tract infection (2 participants), and the following events were each reported once (a participant can report more than one event): anal abscess, anaphylaxis, lower respiratory tract infection, viral lower respiratory tract infection, metapneumovirus infection, rhinovirus infection, rotavirus gastroenteritis, viral gastroenteritis, accidental overdose, febrile convulsion, seizure. None of the SAEs in the BNT162b2 group were considered by the study investigator or by FDA to be related to vaccination, given the time to onset after vaccination and/or plausible alternate etiology.

SAEs reported in the placebo group included bronchiolitis or RSV bronchiolitis (3 participants) and cyanosis (2 participants) the following events were each reported once (a participant can report more than one event): vomiting, anaphylaxis, norovirus gastroenteritis, rotavirus gastroenteritis, tonsillitis, viral infection, pneumomediastinum, respiratory distress, feeding intolerance, hypoglycemia, head injury, second degree burns, and thermal burns.

Narratives for SAEs of clinical interest in BNT162b2 recipients are as follows:

- One 21-month-old BNT162b2 recipient was reported to have an SAE of anaphylaxis 14 days after Dose 1. The participant had a known history of nut allergy and was taken to the emergency department for treatment of an anaphylactic reaction (hives, wheezing, nausea and vomiting) one day after eating nuts. FDA agrees that this SAE was unrelated to BNT162b2
- One 6-month-old BNT162b2 recipient was reported to have an SAE of seizure (eye rolling upwards) that occurred 2 days after Dose 2, preceded by symptoms of a respiratory tract infection and temperature of 38.0°C. The participant was evaluated in the emergency department and admitted to the hospital for evaluation of seizure: with eye rolling upwards noted once on an otherwise normal physical/neurological examination. A head ultrasound was normal and SARS-CoV-2 “swab” was negative. Laboratory abnormalities included a slightly elevated C-reactive protein (20 mg/L, normal range not provided), and elevated white blood cells (20.8K). An electroencephalogram (EEG) was performed during physiologic sleep and showed focal evidence of seizure activity. No further information was provided about management of symptoms, including use of antipyretic medications prior to or during the acute presentation of seizure. The participant went home from the hospital the same day, with follow-up appointment in neurology clinic. The parent noticed a few episodes of eye rolling per day, with resolution of symptoms 17 days after onset; the participant was withdrawn from the study by parental request. During follow-up in neurology clinic 2 months

after the event, the final diagnosis was convulsions, not elsewhere classified. While the clinical presentation suggests that the seizure may have been related to an infectious process that began prior to Dose 2, a febrile seizure related to vaccination cannot be definitively excluded based on available information.

- One 21-month-old BNT162b2 recipient was reported to have an SAE of febrile convulsion which occurred 38 days post Dose 1, which was attributed to ear inflammation and resolved the next day. FDA agrees that this SAE was unrelated to BNT162b2.

Participants 2-4 years of age

Among participants 2-4 years of age, SAEs were reported by 12 (0.7%) participants in the BNT162b2 group: appendicitis (2 participants), dehydration (2 participants), and the following events were each reported once (a participant can report more than one event): pyrexia, pain in the extremity, focal peritonitis, status epilepticus, epilepsy, febrile convulsion, rotavirus gastroenteritis, viral gastroenteritis, dehydration, gastroenteritis, diarrhea, upper respiratory tract infection and lower respiratory tract infection. Two SAEs reported by the same participant were considered at least possibly related to vaccination by the study investigator (see narrative below). The remaining SAEs were considered by the study investigator and by FDA to be unrelated to the study vaccine due to the time to onset after vaccination and/or plausible alternative etiology. The 8 (0.9%) placebo recipients who had SAEs reported the following: adenovirus gastroenteritis, gastroenteritis, rotavirus gastroenteritis, foreign body, papilledema, epilepsy, febrile convulsion, and bronchial hyperactivity.

- A 4-year-old BNT162b2 recipient was reported to have SAEs of pyrexia and pain in the extremity. Fever (Tmax of 40.3°C) started 2 days after Dose 2. The participant was brought to the emergency department for further evaluation of fever and discharged the same day. The fever persisted for another 3 days, and the participant was hospitalized for further evaluation of fever, with new onset moderate pain in extremity (right calf pain characterized as an SAE), causing a limp. Physical examination was otherwise normal. Labs included white blood cells 1.8K, platelets 137K, creatinine phosphokinase 491 International Units/L (to 1,878 on Day 7, normal range not provided), erythrocyte sedimentation rate 17 (normal 0-15). Evaluation for other specific viral infections and urine culture for bacteria were negative. Treatment included oral ibuprofen and paracetamol for fever and pain. The fever resolved on Day 7, followed by appearance of a non-pruritic urticarial “purpura”-type rash on face, chest, and upper back. The participant was discharged from the hospital on Day 7. The rash resolved on Day 8, calf pain resolved on Day 9, and the participant fully recovered on Day 10 and returned to daycare without medications. A final diagnosis was not provided.

Based on the temporal relationship to BNT162b2 Dose 2, the study investigator considered the pyrexia to be related to vaccination and the calf pain possibly related to the study vaccine. Given the constellation and progression of symptoms, FDA considered the events to be consistent with symptoms due to an unspecified viral infection, e.g., viral myositis.

Two BNT162b2 recipients reported SAEs of appendicitis, both of which were considered by the study investigator and FDA to be unrelated to vaccination; narratives are provided below:

- A 4-year-old was reported to have SAEs of acute appendicitis (moderate in severity) and mild localized peritonitis, both with onset on 105 days post-Dose 2. This participant was subsequently unblinded upon turning 5 years of age and received open-label Dose 3 of BNT162b2 10-µg approximately 6 months after Dose 2 and no AEs were reported post-Dose 3.

- A 4-year-old was reported to have an SAE of severe appendicitis with onset 11 days post-Dose 2. The event was reported as resolved the same day following appendectomy. This participant reported no other AEs after any dose.

The three SAEs of status epilepticus, febrile convulsion, and epilepsy were considered by the study investigator and FDA to be unrelated to vaccination; narratives are provided below.

- A 4-year-old BNT162b2 recipient with a history of seizures, failure to thrive, gastroesophageal reflux, hypotonia, and lissencephaly was reported to have an SAE of status epilepticus with onset Day 18 after Dose 1. The participant was diagnosed with a urinary tract infection that was considered by the study investigator to have precipitated the seizures; the event resolved within 3 days. The participant was also diagnosed with a non-serious AE of hypoglycemia on Day 18 that resolved within 2 days. This participant withdrew from the study due to the AE before receiving Dose 2.
- A 2-year-old BNT162b2 recipient had a febrile convulsion 21 days post-Dose 1, which resolved the same day, with unknown cause after evaluation in an emergency department. The participant received Dose 2 3 days later without additional AEs reported.
- A 4-year-old BNT162b2 recipient, with a family history of febrile seizures, experienced seizure-like activity 47 days after BNT162b2 Dose 2 and went to the emergency department. The participant had received influenza vaccine 3 days prior to the onset of symptoms. The participant was hospitalized, and no further seizures were noted. EEG subsequently showed abnormal results. An SAE of suspected epilepsy was reported, considered by the study investigator as unrelated to the BNT162b2 vaccine but possibly related to influenza vaccination.

4.2.7.6. Adverse events of clinical interest

FDA conducted Standardized MedDRA Queries (SMQs) to evaluate for constellations of unsolicited AEs among vaccine recipients 6 months through 4 years of age in Phase 2/3 of study C4591007 through the April 29, 2022, cutoff date. SMQs (narrow and broad in scope) were conducted using PTs that could represent various conditions, including but not limited to angioedema, arthritis, convulsions, demyelination, hypersensitivity, peripheral neuropathy, and vasculitis.

No new or unexpected ARs were identified based on these SMQ results for either age group. No cases of myocarditis/pericarditis or vaccine-related anaphylaxis were reported in either age group through the data cutoff.

Participants 6-23 months of age

SMQ analyses of *Angioedema* and *Hypersensitivity* throughout the follow up period yielded similar incidence of events in vaccine and placebo recipients [n=9 (0.8%) vs. n=4 (0.7%) and n=25 (2.1%) vs. n=12 (2.0%), respectively, for Angioedema and Hypersensitivity], with urticaria as the primary PT under the SMQ *Angioedema* [n=8 (0.7%) vaccine vs. n=3 (0.5%) placebo recipients]. Most (n=21, 1.8%) events in the SMQ *Hypersensitivity* were common skin and subcutaneous tissue disorders for this age, such as rash, eczema/atopic dermatitis, maculo-papular rash, erythematous rash, and contact dermatitis.

Two unrelated events of anaphylaxis occurred in one BNT162b2 recipient with known peanut allergy, attributed to a reaction to walnut exposure, and in one placebo recipient with known food allergies, which was attributed to egg allergy; both were also reported as SAEs. Additionally, an unrelated event of serum sickness (full body rash) was reported in 1 BNT162b2

recipient, 31 days after Dose 2, which was attributed to amoxicillin treatment. FDA concurs with the investigators that these events were unlikely to be related to vaccination.

Lymphadenopathy was reported by 2 (0.2%) BNT162b2 recipients 6-23 months of age and no placebo recipients.

- A 12-month-old was noted to have a neck mass 24 days after Dose 2, which was considered not related to the vaccine by the study investigator. A diagnosis of swollen lymph node of unknown etiology was made with an ultrasound. No other symptoms were reported, and the status of the event was ongoing at the time of the data cutoff. FDA concurs with the investigator's assessment.
- A 19-month-old had mild enlarged left groin lymph node 2 days after Dose 2, administered in the left thigh, which resolved after 3 days. The event was considered related to vaccination by the study investigator and by FDA.

Convulsions were reported at a similar incidence in the BNT162b2 (n=4, 0.3%) and placebo (n=1, 0.2%) groups. These included: 2 events of seizure in the BNT162b2 group, one of which occurred 3 days post-Dose 2 and was reported as an SAE (Section 4.2.7.5), and the other was a nonserious event with onset 164 days post-Dose 2; and 2 events of febrile convulsion in the BNT162b2 group, one of which was reported as an SAE (Section 4.2.7.5), and both of which occurred >30 days after vaccination. All were considered by the study investigator and by FDA as not related to study intervention.

Participants 2-4 years of age

SMQ analyses of *Angioedema* throughout the follow up period yielded similar incidences of events between vaccine and placebo recipients [n=7 (0.4%) vs n=4 (0.5%)]. SMQ analyses of *Hypersensitivity* yielded more events in the BNT162b2 group compared to the placebo group [n=16 (0.9%) vs n=4 (0.4%)]. Most (n=11, 0.6%) events in the SMQ for *Hypersensitivity* were common skin and subcutaneous tissue disorders for this age, such as rash, eczema/atopic dermatitis, and contact dermatitis.

Lymphadenopathy was reported by 1 BNT162b2 recipient and no placebo recipients 2-4 years of age. The lymphadenopathy occurred behind the left ear of a 2-year-old participant 2 days after Dose 2, with resolution in 6 days, and was considered related to vaccination by the study investigator and by FDA.

Convulsions were reported at the same incidence in the BNT162b2 (n=4, 0.2%) and placebo (n=2, 0.2%) groups. In the BNT162b2 group, 1 event of status epilepticus occurred 18 days post-Dose 1 in a participant with history of seizures, in the setting of a urinary tract infection (also reported as an unrelated SAE which led to withdrawal). In the BNT162b2 group, this also included 1 event of epilepsy reported 48 days post-Dose 2 as an SAE, and 2 events of febrile convulsion, one of which occurred 21 days post-Dose 1 (reported as an SAE); the other event (non-serious) occurred 42 days post-Dose 2. All events were considered by the study investigator and FDA as not related to study intervention. SAEs are discussed in Section 4.2.7.5.

Two events of appendicitis were reported, both in the BNT162b2 group and both reported as SAEs (Section 4.2.7.5). In one case, the participant had acute appendicitis and localized peritonitis with onset 105 days post-Dose 2 with resolution the next day. In the other case, the participant had appendicitis with onset 11 days post-Dose 2 that resolved the same day. Both events were considered by the study investigator and FDA as not related to study intervention.

4.2.7.7. Adverse events leading to study withdrawal

Study withdrawals due to AEs in participants 6 months through 4 years of age were reported in 6 BNT162b2 recipients and 1 placebo recipient.

Participants 6-23 months of age

Among participants 6-23 months of age, 3 BNT162b2 recipients and no placebo recipients withdrew from the study due to an AE. One BNT162b2 recipient developed fever (>40°C) 2 days post-Dose 1 that resolved in 3 days, with concurrent exanthema subitem (viral infection) that resolved in 4 days. Another BNT162b2 recipient with a history of eczema developed a generalized rash 5 days after receiving Dose 1, which resolved by Day 9. Additionally, 1 BNT162b2 recipient reported pyrexia 3 days post Dose 3 that resolved in 3 days. All adverse events were considered related to the vaccine by the study investigator and FDA.

Participants 2-4 years of age

Among participants 2-4-years of ag, 3 BNT162b2 recipients and 1 placebo recipient withdrew from the study due to an AE. One BNT162b2 recipient with a history of seizures was hospitalized for status epilepticus (attributed to a urinary tract infection) that occurred 18 days post-Dose 1. Another BNT162b2 participant experienced a non-serious AE of pyrexia (maximum temperature 40.8°C), which occurred 2 days post-Dose 1 and resolved in 5 days; this AE was considered by the study investigator and FDA to be related to vaccination. Additionally, 1 BNT162b2 recipient had a nonserious AE of mild urticaria which occurred 2 days post Dose 1 and resolved in 4 days which led to study withdrawal; this AE was considered related to vaccination by the study investigator and FDA.

4.2.7.8. Subgroup analyses of safety

Subgroup analyses were performed for solicited local and systemic ARs, unsolicited AEs, and serious AEs, comparing BNT162b2 and placebo groups by sex, race and ethnicity. No notable differences were observed between subgroups, although certain subgroups such as Black or African American race and Hispanic/Latino ethnicity had too few participants to draw meaningful conclusions.

The percentage of participants 6-23 months old and 2-4 years old who reported e-diary data and who were baseline SARS-CoV-2 positive was 7.5% and 12.6%, respectively. Subgroup analyses of solicited ARs in each age group, by baseline SARs-CoV-2 status, showed similar reactogenicity profiles. No notable differences were found in the type, frequency and severity of unsolicited AEs or serious AEs in this age group in seropositive subjects relative to seronegative subjects.

4.3. Summary of study C4591007 Phase 2/3

This EUA request included data from 1,178 BNT162b2 recipients and 598 placebo recipients 6-23 months of age and 1,835 BNT162b2 recipients and 915 placebo recipients 2-4 years of age in the Phase 2/3 portion of an ongoing clinical trial, C4591007. Among participants 6 months through 4 years of age, the median follow up was 2.1 months after Dose 3 (inclusive of both blinded and open-label follow-up) at the time of the April 29, 2022, data cutoff.

Immunobridging success criteria were met for both age groups of 6-23 months and 2-4 years based on SARS-CoV-2 neutralizing antibody GMTs and seroresponse rates at 1-month post-Dose 3 evaluated against the USA_WA1/2020 reference strain and compared to participants 16-25 years of age randomly selected from study C4591001. Subgroup immunogenicity

analyses by age, gender, race, and ethnicity showed no notable differences compared to the overall study population, although some subgroups were too small to draw meaningful conclusions, and participants seropositive for SARS-CoV-2 at baseline had higher post-Dose 3 antibody titers than participants seronegative for SARS-CoV-2 at baseline. Additional descriptive immunogenicity analyses, based on 50% FFRNT, showed that post-Dose 3 neutralizing antibody GMTs against the Omicron variant were lower than those against the ancestral strain and Delta variant.

In a preliminary descriptive efficacy analysis of 3 COVID-19 cases in participants 6-23 months of age, VE against COVID-19 at least 7 days post-Dose 3 was 75.6% (95% CI: -369.1%, 99.6%), with 1 COVID-19 case in the BNT162b2 group and 2 in the placebo group (2:1 randomization BNT162b2 to placebo). In a similar preliminary descriptive efficacy analysis of 7 COVID-19 cases in participants 2-4 years of age with and without evidence of prior SARS-CoV-2 infection, VE was 82.4% (95% CI: -7.6%, 98.3%) with 2 cases in the BNT162b2 group and 5 in the placebo group (2:1 randomization BNT162b2 to placebo). In a combined analysis of both age groups, VE was 80.4% (95% CI: 14.1%, 96.7%) with 3 cases in the BNT162b2 group and 7 cases in the placebo group. All COVID-19 cases in these analyses occurred in participants without evidence of prior SARS-CoV-2 infection, during February 2022 through April 2022, when the Omicron variant was prevalent in the United States. From Dose 1 through the data cutoff, 1 placebo recipient 6-23 months of age and 7 participants 2-4 years of age (6 BNT162b2 recipients and 1 placebo recipient) met the criteria for severe COVID-19, with only one hospitalization for severe COVID-19 disease in a BNT162b2 recipient 99 days post-Dose 2.

Solicited local ARs generally occurred at similar frequencies after each dose and solicited systemic ARs occurred at slightly decreasing frequencies with each successive dose. The most commonly reported solicited ARs after any dose for participants 6-23 months of age were irritability (51.2%), drowsiness (27.0%), decreased appetite (22.2%), and tenderness at the injection site (16.6%). The most commonly reported solicited ARs after any dose for participants 2-4 years of age were pain at the injection site (30.8%), fatigue (29.7%), and injection site redness (11.4%). Most local and systemic reactions were mild to moderate in severity, with median onset 1-2 days post vaccination, and a median duration of 1-2 days after onset. Subgroup safety analyses of reactogenicity by baseline SARS-CoV-2 status showed no notable differences as compared with the overall study population.

In participants 6-23 months of age, the frequencies of unsolicited non-serious AEs reported were similar in the BNT162b2 and placebo groups (29.1% versus 26.3%). In participants 2-4 years of age, the frequencies of unsolicited non-serious AEs reported were the same in the BNT162b2 and placebo groups (18.7% versus 18.7%). The most commonly observed unsolicited AEs were consistent with those reported as solicited adverse events (local and systemic reactogenicity) and/or were consistent with events frequently reported in this age group, including infections and injuries. Lymphadenopathy was observed following vaccination in two BNT162b2 recipients 6-23 months of age and one BNT162b2 recipient 2-4 years of age; no cases were reported in the placebo group. From the combined safety database of 3,013 BNT162b2 recipients 6 months through 4 years of age, 1% of participants (n=29) reported SAEs, as compared to 1.5% of participants (n=22) in the combined safety database of 1,513 placebo recipients 6 months through 4 years of age. Two SAEs (pyrexia [>40°C] and pain in extremity) which occurred in the same participant were considered by the study investigator as possibly related to vaccination; FDA considers viral myositis to be a plausible alterative etiology. Three participants in the BNT162b2 group withdrew from the study due to pyrexia (>40°C); these AEs were classified as non-serious. There were no reports of myocarditis/pericarditis, no cases of anaphylaxis considered caused by vaccination, and no deaths.

5. Pharmacovigilance activities

Pfizer submitted a revised pharmacovigilance plan to monitor safety concerns that could be associated with BNT162b2 in individuals 6 months through 4 years of age. The PVP includes the important identified risks of anaphylaxis, myocarditis, and pericarditis. Pfizer-BioNTech plans to conduct passive and active surveillance to monitor the post-authorization safety for the Pfizer-BioNTech COVID-19 Vaccine, including:

- Mandatory reporting by the Sponsor under the EUA for the following events to VAERS within 15 days: SAEs (irrespective of attribution to vaccination); COVID-19 disease resulting in hospitalization or death; multisystem inflammatory syndrome

- Adverse event reporting in accordance with regulatory requirements for the licensed vaccine, Comirnaty

Additionally, following approval of Comirnaty, the Sponsor was also asked to submit reports of myocarditis and pericarditis as 15-day reports to VAERS.

The Sponsor will submit periodic safety reports containing an aggregate review of safety data including assessment of adverse events; vaccine administration errors, whether or not associated with an adverse event; and newly identified safety concerns.

Post-authorization observational studies will be conducted, which encompass the evaluation of children 6 months through 4 years of age, and include active surveillance safety studies using large health insurance claims and/or electronic health record database(s):

- Study C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States

  - Objective: To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general US population of all ages, pregnant women, the immunocompromised, and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System.

- Study C4591021: Post-conditional approval active surveillance study among individuals in Europe receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine

  - Objective: To determine whether an increased risk of prespecified AESI, including myocarditis/pericarditis, exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 Vaccine.

- Study C4591021 Substudy (currently C4591038): Substudy to describe the natural history of myocarditis and pericarditis following administration of Comirnaty

  - Objective: To describe the clinical course of myocarditis/pericarditis, including treatment, survival, hospitalization, and long-term cardiac outcomes of myocarditis and pericarditis among individuals diagnosed with myocarditis and/or pericarditis after receiving at least one dose of the Pfizer-BioNTech COVID-19 Vaccine and among individuals diagnosed with myocarditis and/or pericarditis who had no prior COVID-19 vaccination, using a cohort study design.

Study C4591036: Prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination (in collaboration with Pediatric Heart Network [PHN]).

Objective: To characterize the clinical course, risk factors, resolution, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis/pericarditis.

Pfizer-BioNTech also plans to include vaccine effectiveness analyses among individuals 6 months through 4 years of age in study C4591014 entitled “Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study Kaiser Permanente Southern California.”

6. Benefit-risk in the context of the proposed EUA for Pfizer-BioNTech COVID-19 Vaccine in children 6 months through 4 years of age

6.1. Known and potential benefits

Available data support the effectiveness of the Pfizer-BioNTech COVID-19 Vaccine 3-dose primary series (3 µg each dose) in preventing COVID-19 in the age group of 6 months through 4 years. For each of the age groups of 6-23 months and 2-4 years, vaccine effectiveness was inferred by immunobridging, based on a comparison of neutralizing antibody responses with formal hypothesis testing, to a comparator group of participants 16-25 years of age from a clinical endpoint efficacy study in which observed VE was 91.2% (95% CI: 88.3, 93.5) in participants 16-55 years of age.[51] Post-licensure and post-authorization observational studies of Comirnaty and Pfizer-BioNTech COVID-19 Vaccine, respectively, have demonstrated decreased effectiveness of a primary series against the currently predominant Omicron variant compared with effectiveness against the ancestral strain and variants (Alpha, Delta) that were predominant during pre-authorization trials in adults and older pediatric age groups. Consistent with this observation, descriptive immunogenicity analyses based on an exploratory 50% FFRNT in participants 6 months through 4 years of age indicate lower neutralizing titers against the Omicron variant than against the ancestral strain and Delta variant. Available preliminary descriptive VE data from the ongoing Phase 2/3 study from 555 participants 6-23 months of age and 860 participants 2-4 years of age who received 3 doses of BNT162b2 were suggestive of greater effectiveness against COVID-19 disease due to Omicron than following the first 2 doses of the primary series, but definitive conclusions are limited by a small number of cases that precluded a reliable estimate of post-Dose 3 VE.

Among infants and children 6 months through 4 years of age, rates of hospitalization and death due to COVID-19 are higher than among children and adolescents 5-17 years of age, and comparable to individuals 18-25 years of age, underscoring the benefit of an effective COVID-19 vaccine in this age group. In older pediatric age groups, the vaccine has been demonstrated to prevent hospitalization and other serious sequelae such as MIS-C with greater effectiveness against these more serious outcomes, including during the current Omicron-predominant period. Given the uncertainty of the COVID-19 pandemic and likelihood of continued SARS-CoV-2 transmission during the ensuing months, deployment of the vaccine for use among children 6 months through 4 years of age will likely have a beneficial effect on COVID-19 associated morbidity and mortality in this age group.[52]

6.2. Uncertainties related to benefits

The uncertainties associated with benefits of the Pfizer-BioNTech COVID-19 vaccine when used in children 6 months through 4 years of age include the following:

- Duration of vaccine effectiveness: the blinded, placebo-controlled evaluation period for descriptive efficacy analyses was limited, and waning of protection following a primary series has been observed in older age groups.
- Need for a booster dose: based on experience with adults, it is likely that a booster dose will be needed in addition to the three-dose primary series to increase robustness, breadth, and duration of protection against currently circulating and emerging SARS-CoV-2 variants in children 6 months through 4 years of age. A booster dose could be considered for authorization with submission of supportive data in a future amendment to the EUA.
- Effectiveness in certain populations at high risk of severe COVID-19, including immunocompromised individuals.
- Benefits in individuals previously infected with SARS-CoV-2: descriptive post-Dose 3 efficacy analyses do not include cases in previously infected participants. However, observational data with other COVID-19 vaccines have demonstrated an added benefit of vaccination to protection conferred by natural immunity.[53] Additionally, for individuals previously infected with the Omicron variant of SARS-CoV-2, a vaccine based on the ancestral strain S protein could provide a greater breadth of protection against SARS-CoV-2 variants.
- Effectiveness in preventing post-acute sequelae of COVID-19: available data are not conclusive on the effectiveness of COVID-19 vaccines currently in use against long-term sequelae of COVID-19 among individuals who are infected despite vaccination. Additional evaluation is needed to assess the effect of this vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.
- Future vaccine effectiveness as influenced by characteristics of the pandemic, including emergence of new variants: the continued evolution of the pandemic, including changes in the virus infectivity, antigenically significant mutations to the S protein, and changes in practice of nonpharmacologic interventions to mitigate against transmission, will likely influence vaccine effectiveness over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical.
- Vaccine effectiveness against asymptomatic infection and transmission of SARS-CoV-2: Available data for COVID-19 vaccines currently in use has demonstrated that effectiveness against asymptomatic infection is lower and less durable than effectiveness against symptomatic COVID-19. Available data also do not indicate high-level or durable effectiveness against transmission of SARS-CoV-2 from vaccinated individuals with breakthrough infections.

6.3. Known and potential risks

In study participants 6 months through 4 years of age, there were numerically higher rates of solicited local and systemic ARs in BNT162b2 recipients than in placebo recipients. Overall, the rates of these ARs reported among participants 6 months through 4 years of age were lower than those reported among older age groups and likely reflect the lower vaccine mRNA content evaluated in participants 6 months through 4 years of age. In considering unsolicited AEs reported among participants 6 months through 4 years of age, the available safety data from a total database of over 3,000 vaccine recipients do not suggest any new safety concerns compared with the safety profile described in older age groups.

Anaphylaxis, primarily among individuals with a history of severe allergic reactions to other medications or foods, has been documented to occur at a rate of approximately 6 cases per million doses among BNT162b2 recipients 16 years of age and older (similar in magnitude to reported rates of anaphylaxis following other licensed preventive vaccines). Risk of allergic reactions, including the potential for severe allergic reactions and the need for vaccine providers to be able to manage them should they occur and a contraindication for use in individuals with known allergy to any component of the vaccine, are described in the vaccine Fact Sheets and Prescribing Information. Additionally, risk of anaphylaxis/severe allergic reactions will be further evaluated as part of the PVP for the vaccine.

Myocarditis/pericarditis, in particular in the first week following Dose 2, is a known risk associated with the Pfizer-BioNTech COVID-19 Vaccine and is greatest among adolescent males 16-17 years of age compared with both younger and older age groups. In contrast to myocarditis in the pre-COVID era, most reported cases of vaccine-associated myocarditis have involved rapid resolution of symptoms with conservative management; however, the long-term sequelae of vaccine-associated myocarditis, if any, remain to be determined. The risk of vaccine-associated myocarditis/pericarditis among children 6 months through 4 years of age is unknown at this time. No cases of myocarditis or pericarditis were reported among over 3,000 vaccine recipients in the clinical trial, some of whom had at least 1 month of follow-up post-Dose 3. However, this safety database is not large enough to quantify the frequency of this uncommon AR. Data supporting that the risk of vaccine-associated myocarditis may be lower among children 6 months through 4 years of age compared with adolescents 16-17 years of age include a lower rate of vaccine-associated myocarditis reported to VAERS in males 5-11 years of age than for males 12-15 and 16-17 years of age, and lower rates of systemic reactogenicity in participants 6 months through 4 years of age associated with the lower vaccine mRNA content intended for use in this age group.

6.4. Uncertainties related to risks

The uncertainties associated with risks of the Pfizer-BioNTech COVID-19 vaccine when used in children 6 months through 4 years of age include the following:

- Risk of myocarditis/pericarditis, as described in detail in Section 6.3 above, including:
  - Incidence of myocarditis/pericarditis in children 6 months through 4 years of age.
  - Short-term and potential long-term sequelae and outcomes in affected individuals
  - Whether the vaccine is associated with subclinical myocarditis, and if so, whether there are long-term sequelae.
  - Mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established.
- Safety in certain subpopulations
  - Available data are insufficient to make conclusions about the safety of the vaccine in certain subpopulations such as immunocompromised children.
  - Safety data in children previously infected with SARS-CoV-2 are limited; however, available data do not suggest increased reactogenicity or other safety concerns among previously infected children.
- Adverse reactions that are very uncommon or that require longer follow-up to be detected. Active and passive safety surveillance will continue during the post authorization period to detect new safety signals, Section 5, Pharmacovigilance Activities.

7. Topic for VRBPAC Discussion

The VRBPAC will convene on June 15, 2022, to discuss whether, based on the totality of scientific evidence available, the benefits of the Pfizer-BioNTech COVID-19 Vaccine, when administered as a three-dose primary series, outweigh its risks for use in infants and children 6 months through 4 years of age.

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9. Appendix A: Study C4591007 Phase 1 information

9.1. Phase 1: Dose-finding and dose selection design

For Phase 1, BNT162b2 was evaluated in children in the US who were not at high risk of SARS-CoV-2 exposure, did not have medical conditions that represented risk factors for severe COVID-19, and did not have serologic/virologic evidence of prior SARS-CoV-2 infection. BNT162b2 dose levels of 3 µg and 10 µg were evaluated in an age de-escalation, open-label manner for each age group (2-4-years first, followed by 6-23 months), sequentially based upon the safety evaluation and recommendation by the internal review committee to either advance to the subsequent dose level or terminate a specific dose level, with the plan to administer 2 doses, 3 weeks apart to all participants. Safety evaluation included reactogenicity (solicited local reactions and systemic events) 7 days after each dose and AEs through 1 month after Dose 2, for each dose level. The data analysis cutoff date for Phase 1 was July 16, 2021. SARS-CoV-2 50% neutralizing GMTs (SARS-CoV-2 mNG microneutralization assay) were assessed at an early timepoint (at 7 days after Dose 2) to facilitate dose selection.

Based on the 10-µg safety assessments for children 5-11 years of age in C4591007, dose finding was initiated at 10 µg in 2-4-year-olds. Following review by the internal review committee of safety data in 2-4-year-olds for up to 7 days after Dose 1, dosing commenced at the 3-µg dose level in participants 6-23 months of age.

9.2. Phase 1: Safety results

Participants 2-4 years of age
Two dose levels (3 µg and 10 µg) were evaluated in 48 participants 2-4 years of age (n=16 for 3 µg and n=32 for 10 µg). Solicited local and systemic ARs were mostly mild to moderate and short-lived. In general, the frequency and/or severity of solicited ARs increased with increasing dose level and number of injections.

Pain at the injection site was the most commonly reported local reaction for both dose levels. The proportion of participants with pain at the injection site was higher in the 10-µg group compared to the 3-µg group after Dose 1 and Dose 2: 10 µg (62.5% and 53.1%) versus 3 µg (31.3% and 37.5%). Participants in the 10-µg group reported redness and swelling within 7 days after Dose 1 and Dose 2 [redness: 10 µg (28.1% and 15.6%); swelling: 10 µg (9.4% and 3.1%)]; none of the participants in the 3-µg group reported redness or swelling within 7 days after either dose. No Grade 4 local reactions were reported.

Fatigue was the most commonly reported systemic reaction for both dose levels. The proportion of participants with fatigue was higher in the 10-µg compared to the 3-µg dose level group after Dose 1 and Dose 2: 10 µg (46.9% and 59.4%) versus 3 µg (25.0% and 25.0%).

Fever was more common and more severe in the 10-µg group than in the 3-µg group after Dose 1 and Dose 2: 10 µg (18.8% and 18.8%) versus 3 µg (0% and 6.3%). Severe fever (>38.9°C to 40°C) was reported in the 10-µg group by 2 (6.3%) participants within 7 days after Dose 1 and 2 (6.3%) participants and none in the 3-µg group. All systemic events except fever were mild or moderate in severity post-Dose 1 and 2.

From Dose 1 to 1 month after Dose 2, one or more AEs were reported by 25.0% of participants in the 3-µg group and 37.5% of participants in the 10-µg group. A higher proportion of AEs in the 10-µg group than in the 3-µg dose level group were considered by the study investigator as

related to study intervention (21.9% vs. 12.5%). In the 10-µg group, the AEs reported were injection site pain (n=3), costochondritis (n=1), lymphadenopathy (n=1), abdominal discomfort (n=1), abdominal pain (n=1), and injection site bruising (n=1), whereas the 3-µg group reported only injection site pain (n=2). None of the participants reported a severe AE or SAE, and no deaths were reported during the study.

Participants 6-23 months of age
The 3-µg dose level was evaluated in 16 participants 6-23 months of age. Local and systemic reactogenicity were mostly mild and resolved within 1 or 2 days. Redness (18.8%) and swelling (6.3%) were the most common local reactions within 7 days after Dose 1. Tenderness at injection site (6.3%) was the only local reaction within 7 days after Dose 2. All local reactions were mild in severity. Drowsiness (25.0%) and irritability (43.8%) were the most frequent systemic events reported within 7 days after Dose 1. Irritability (31.3%), fever (12.5%), and decreased appetite (12.5%) were more common within 7 days after Dose 2. All systemic events within 7 days after Dose 1 were mild or moderate in severity, and those within 7 days after Dose 2 were mild in severity.

From Dose 1 to 1 month after Dose 2 in participants 6-23 months of age, one or more AEs were reported by 12.5% of participants who received 3 µg BNT162b2. One 16-month-old participant reported Grade 1 urticaria on Day 1 post-Dose 1, which resolved in 2 days and was considered related to the study intervention. No severe AEs, SAEs or deaths were reported.

9.3. Phase 1: Immunogenicity results

For both age groups (6-23 months, 2-4 years), the SARS-CoV-2 neutralizing GMTs SARS-CoV-2 neutralizing GMTs at the 3-µg level were similar, and numerically higher than GMTs at 1 month post-Dose 2 (30 µg) from participants 16-25 years of age (study C4591001). In participants 2-4 years of age, the SARS-CoV-2 neutralizing antibody response was dose-dependent, and SARS-CoV-2 neutralizing GMTs at 7 days post-Dose 2 at the 10-µg level were similar to GMTs at 1 month post-Dose 2 (30 µg) from adolescents 12-15 years of age (study C4591001) and numerically higher than GMTs post-Dose 2 (30 µg) in participants 16-25 years of age (study C4591001). Sera from participants in study C4591007 and the comparator groups were tested contemporaneously with the same assay.

9.4. Phase 1: Dose selection decision

Because the 3-µg dose level was better tolerated than the 10-µg dose level in children 2-4 years of age, the 3-µg dose level was selected for evaluation in children 6-23 months of age. The 3-µg dose selected for both age groups in the Phase 2/3 portion of study C4591007 was also supported by the preliminary immunogenicity results.

10. Appendix B: COVID-19 case definitions

COVID-19
The case definition for a confirmed case of COVID-19 was the presence of at least one of the following symptoms and a positive SARS-CoV-2 nucleic acid amplification test within 4 days of the symptomatic period:

- Fever
- New or increased cough
- New or increased shortness of breath
- Chills
- New or increased muscle pain
- New loss of taste or smell
- Sore throat
- Diarrhea
- Vomiting
- Inability to eat/poor feeding

Severe COVID-19
The case definition for a severe COVID-19 case included a confirmed COVID-19 case with at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (RR and HR, by age,[1] $SpO_2 \leq 93\%$ on room air at sea level, or PaO_2/FiO_2 <300 mm Hg)
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to an ICU
- Death

For participants <5 years of age, positive RT-PCR cases confirmed by the central laboratory or valid local test also underwent BioFire testing for coinfection with other respiratory pathogens.

[1] 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.