Emergency Use Authorization (EUA) for an Unapproved Product
Review Memorandum

Identifying Information

Application Type	EUA (Event-driven EUA request) Amendment
Application Number	EUA 27034, Amendment 324
Sponsor	Pfizer, Inc., on behalf of Pfizer and BioNTech
Submission Date	October 6, 2021
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Review Completion Date	October 29, 2021
Established Name/Other names used during development	Pfizer-BioNTech COVID-19 Vaccine/ BNT162b2
Dosage Forms/Strengths and Route of Administration	A 0.2 mL suspension (10 µg BNT162b2) for intramuscular injection
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
Intended Population	ndividuals 5 through 11 years of age

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1 EXECUTIVE SUMMARY

On October 6, 2021, Pfizer submitted a request to FDA to amend its emergency use authorization (EUA) to expand use of Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) for prevention of COVID-19 caused by SARS-CoV-2 in individuals 5 through 11 years of age (hereafter 5-11 years of age). The proposed dosing regimen is a 2-dose primary series, 10 µg mRNA/per dose, administered 3 weeks apart. To provide a vaccine with an improved stability profile and greater ease of use at vaccine distribution sites, authorization was also requested for a modified formulation of the Pfizer-BioNTech COVID-19 Vaccine that uses a tromethamine (Tris)/Sucrose buffer instead of the phosphate-buffered saline (PBS)/Sucrose buffer as used in the previous formulation. Analytical comparability assessment, which uses laboratory testing to demonstrate that a change in product formulation is not expected to impact safety or effectiveness of the product, demonstrated that the Tris/Sucrose formulation is comparable to the previously authorized/ approved BNT162b2 PBS/Sucrose formulation.

Pfizer's EUA request includes safety data from 5-11-year-old participants in the Phase 2/3 portion of the ongoing randomized, observer-blinded, placebo-controlled clinical trial C4591007. The request initially included safety data from 1,518 recipients of BNT162b2 and 750 recipients of saline placebo, over 95% of whom had ≥2 months of safety follow-up after Dose 2 (Cohort 1; data cut-off September 6, 2021). To allow for more robust assessment of serious adverse events and adverse events of interest (e.g., myocarditis, pericarditis, anaphylaxis), Pfizer subsequently provided safety data from an additional 1,591 BNT162b2 recipients and 788 placebo recipients who were enrolled into the trial later and whose median duration of follow-up was 2.4 weeks post-Dose 2 (Cohort 2; data cut-off October 8, 2021).

Vaccine effectiveness was inferred by immunobridging SARS-CoV-2 50% neutralizing antibody titers (NT50, SARS-CoV-2 mNG microneutralization assay) among study participants 5-11 years of age (Phase 2/3 Cohort 1 of study C4591007) compared to those among a randomly selected subset of study participants 16-25 years of age (Phase 2/3 of study C4591001). The immunogenicity analyses evaluated neutralizing antibody titers against the USA_WA1/2020 reference strain, as assessed by microneutralization assay, among study participants with no evidence of prior SARS-CoV-2 infection up to 1 month post-Dose 2. Immunobridging endpoints and statistical success criteria were as follows:

- SARS-CoV-2 neutralizing antibody geometric mean titers (GMTs) measured 1 month after Dose 2, with immunobridging success criteria of >0.67 for the lower bound of the 95% confidence interval around the GMT ratio (5-11 years of age / 16-25 years of age), and a point estimate of the GMT ratio ≥1.0.

- Percentage of participants with seroresponse (≥4-fold rise from baseline [pre-Dose 1]), with immunobridging success criterion of >-10% for the lower bound of the 95% confidence interval around the difference (5-11 years of age minus 16-25 years of age) in seroresponse rates.

Immunobridging statistical success criteria, as described above, were met. Subgroup analyses of immunogenicity by age, gender, race and ethnicity, obesity and baseline SARS-CoV-2 status showed no notable differences as compared with the overall study population, although some subgroups were too small to draw meaningful conclusions. Descriptive immunogenicity analyses, based on an exploratory 50% plaque reduction neutralization test (PRNT), showed that a 10 µg BNT162b2 primary series elicited PRNT neutralizing titers against the reference

strain and B.1.617.2 (Delta) strain in participants 5-11 years of age (34 BNT162b2, 4 placebo) with no evidence of SARS-CoV-2 infection up to 1 month post-Dose 2.

In a supplemental descriptive efficacy analysis, vaccine efficacy (VE) against symptomatic COVID-19 after 7 days post-Dose 2 up to October 8, 2021 (data cut-off) was 90.7% (2-sided 95% CI: 67.7%, 98.3%) in participants 5-11 years of age without evidence of prior SARS-CoV-2 infection. Totals of 3 cases of COVID-19 occurred in the BNT162b2 group and 16 in the placebo group, most of which occurred during July-August 2021 when the Delta variant was prevalent in the United States. At the time of the data cut-off, none of these cases met the criteria for severe COVID-19.

Solicited local and systemic adverse reactions (ARs) were more frequently reported after Dose 2. The most commonly reported solicited ARs following administration of any primary series dose were pain at the injection site (84.3%), fatigue (51.7%), and headache (38.2%). Most local and systemic reactions were mild to moderate in severity, with median onset 2 days post-vaccination, and most resolved within 1 to 2 days after onset. The most frequently reported unsolicited adverse event (AE) in Cohort 1, lymphadenopathy was reported in 13 BNT162b2 recipients (0.9%); in Cohort 2, lymphadenopathy was reported in 6 BNT162b2 recipients (0.4%). In Cohort 1, more BNT162b2 recipients (n=14; 0.92%) reported hypersensitivity-related AEs (primarily skin and subcutaneous disorder including rash and dermatitis) than placebo recipients (n=4; 0.53%). For Cohort 2, hypersensitivity reactions were reported in 9 participants (0.6%) in the BNT162b2 group; events included a Type IV hypersensitivity reaction and other rashes. Regarding serious adverse events (SAEs), one event (fracture) was reported in Cohort 1 and 3 events (infective arthritis, foreign body ingestion, and epiphyseal fracture) were reported in Cohort 2; all were considered by the study investigator and FDA as unrelated to vaccination. There were no reports of myocarditis/pericarditis or anaphylaxis, and no deaths. Subgroup safety analyses by gender, race and ethnicity, obesity and baseline SARS-CoV-2 status showed no notable differences as compared with the overall study population, although some subgroups were too small to draw meaningful conclusions.

FDA conducted a quantitative benefit-risk analysis to evaluate predicted numbers of symptomatic COVID-19 cases, hospitalizations, ICU admissions, and deaths that would be prevented per million fully vaccinated children 5-11 years of age over a 6-month period, as compared with predicted numbers of vaccine-associated excess myocarditis cases, hospitalizations, ICU admissions and deaths per million fully vaccinated children 5-11 years of age. The model conservatively assumed that the risk of myocarditis/pericarditis associated with the 10 µg dose in children 5-11 years of age would the same as the estimated risk associated with the 30 µg dose in adolescents 12-15 years of age from Optum healthcare claims data. While benefits of vaccination were highly dependent on COVID-19 incidence, the overall analysis predicted that the numbers of clinically significant COVID-19-related outcomes prevented would clearly outweigh the numbers of vaccine-associated excess myocarditis cases over a range of assumptions for COVID-19 incidence. At the lowest evaluated COVID-19 incidence (corresponding to the June 2021 nadir), the predicted number of vaccine-associated myocarditis cases was greater than the predicted number of COVID-19 hospitalizations prevented for males and for both sexes combined. However, in consideration of the different clinical implications of hospitalization for COVID-19 versus hospitalization for vaccine-associated myocarditis, and benefits related to prevention of non-hospitalized cases of COVID-19 with significant morbidity, the overall benefits of the vaccine may still outweigh the risks even under this low incidence scenario, which incorporates very conservative assumptions. If the myocarditis/pericarditis risk in this age group is lower than the conservative assumption used in the model, the benefit-risk balance would be even more favorable.

At the VRBPAC meeting held on October 26, 2021, the Committee discussed and then voted on whether, based on the totality of scientific evidence available, the benefits of the Pfizer-BioNTech COVID-19 Vaccine when administered as a 2-dose series (10 µg each dose, 3 weeks apart) outweigh its risks for use in children 5-11 years of age. The vote was 17-0 in favor of the authorization, with 1 abstention.

Based on the totality of the scientific evidence available at this time to support the conclusion that the Pfizer-BioNTech COVID-19 vaccine may be effective, and that the known and potential benefits outweigh the known and potential risks associated with the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 5-11 years of age, the review team recommends authorization of the Pfizer-BioNTech COVID-19 vaccine under EUA for use as a 2-dose series (10 µg each dose, 3 weeks apart) in children 5-11 years of age.

2 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. The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus). SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV). 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 (ARDS), 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 October 15, 2021, has caused approximately 239 million cases of COVID-19, including 4.8 million deaths worldwide.[7] In the United States, more than 44 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 722,000 deaths. [8,9] Of the total COVID-19 cases reported in the United States to date, 22.3% occurred among individuals <18 years of age, with 8.7% occurring among 5-11-year-olds.[10] Following emergency use authorization of COVID-19 vaccines in December 2020, COVID-19 cases and deaths in the United States declined sharply during the first half of 2021; however, beginning in late June 2021 a rise in cases was observed, including in children, associated with the highly transmissible Delta variant that is now predominant in the United States.[11] As of the week ending October 2, 2021, the Delta variant comprised greater than 99% of tested strains in the United States.[12] During the last week in August 2021, new COVID-19 infections in individuals less than 18 years of age surpassed those in adults 18 to 64 years of age for the first time during the pandemic.[13] In the United States, COVID-19 cases occurring in children 5-11 years now constitute 39% of cases in individuals younger than 18 years of age.[14] Among cases of

COVID-19 in individuals less than 18 years of age from the COVID-NET network[a], approximately 4,300 have resulted in hospitalization.[15] As of October 17, 2021, 691 deaths from COVID-19 have been reported in the United States in individuals less than 18 years of age, with 146 deaths in the 5-11 year age group.[16]

The most common underlying medical conditions among hospitalized children were chronic lung disease (29%), obesity (25%) and neurologic disorders (23%). A total of 68% of hospitalized children had more than one underlying condition. Obesity and feeding tube dependence were 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.[17] 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.[18,19]

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 infection is low, persons with COVID-19 have a nearly 16-fold increase in risk for myocarditis, compared to individuals without COVID-19. The risk is lowest among individuals 25-39 years and higher in persons less than 16 years and older than 50 years of age.[22] 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.[23] MIS-C presents with persistent fever, laboratory evidence of inflammation, and at least 2 affected organs. In severe cases, hypotension and shock can occur. Most patients have laboratory markers indicating damage to the heart.[24] During the pandemic, a rise in MIS-C cases has generally lagged behind a rise observed in COVID-19 infections by several weeks,[25] with one study demonstrating the peak in MIS-C cases occurring 31 days following the peak in laboratory-confirmed COVID-19 cases.[26] Between May 2020 and October 4, 2021, the CDC received reports of 5,217 cases and 46 deaths that met the definition for MIS-C; the median age of participants was 9 years with half of the cases occurring in children ages 5 to 13 years. Males comprised 60% of cases, and 61% were reported in children who were reported as Hispanic or Black.[27] Up to 66.7% of patients with MIS-C had cardiac involvement, [28] including left ventricular dysfunction, mitral or tricuspid regurgitation, coronary artery aneurysms, and/or arrhythmias.[29] 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.[30] Limited data are available on long-term outcomes in MIS-C.

While children and adolescents appear less susceptible to SARS-CoV-2 infection and generally have a milder COVID-19 disease course as compared with adults,[31,32] adolescents and adults have similar SARS-CoV-2 viral loads in their nasopharynx, so adolescents may play a role in community transmission.[33,34] Transmission of SARS-CoV-2 virus from children can occur in both household and school settings.[35,36] In schools, transmission depends on the transmission rates locally, variants circulating in the community, vaccination rates, and other preventive mitigation

[a] COVID-NET covers approximately 10% of the U.S. population; The current network covers nearly 100 counties in the 10 Emerging Infections Program (EIP) states (CA, CO, CT, GA, MD, MN, NM, NY, OR, and TN) and four additional states through the Influenza Hospitalization Surveillance Project (IA, MI, OH, and UT); see https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html.

strategies. Transmission between school staff members may be more common than transmission involving students.[37] There is evidence that SARS-CoV-2 transmission is greater in secondary and high schools than elementary schools.[38,39] Outbreaks of COVID-19 have been reported in settings where children congregate, such as summer youth camps.[40,41]

In addition to morbidity and mortality on an individual level, the continuing spread of SARS-CoV-2 has caused significant challenges and disruptions in worldwide healthcare systems, economies, and many aspects of human activity (travel, employment, education). Other impacts of COVID-19 on children include limited access to basic services such as healthcare and child protective services, and social isolation due to disruption of school, sports, and social group gatherings. The emergence of the Delta variant, variable implementation of public health measures designed to control spread, and continued transmission among unvaccinated individuals are major factors in the recent resurgence of COVID-19. While recently reported cases appear to be declining relative to the Delta variant-associated peak globally and in the United States, the longer-term effect of the Delta variant and the potential role of other variants on the future course of the pandemic is uncertain.

3 AUTHORIZED AND APPROVED VACCINES AND THERAPIES FOR COVID-19

FDA has issued EUAs for three COVID-19 vaccines as shown in Table 1 below. The Pfizer-BioNTech COVID-19 Vaccine is also FDA approved for use as a 2-dose primary series in individuals 16 years of age and older, under the trade name COMIRNATY (see Section 4).

Table 1. Emergency Use Authorizations of COVID-19 Vaccines

Sponsor	Authorized Use (Interval)	Indicated Population	Date of EUA or EUA Amendment
Pfizer-BioNTech	2-dose primary series (3 weeks apart)	Individuals ≥16 years of age	December 11, 2020
		Individuals ≥12 years of age	May 10, 2021
Pfizer-BioNTech	3rd primary series dose (at least 1 month after the second dose)	Individuals ≥12 years of age with compromised immune systems due to solid organ transplantation or conditions considered to have an equivalent level of immunocompromise	August 12, 2021
Pfizer-BioNTech	Booster dose (at least 6 months after completing a primary series of COMIRNATY and/or Pfizer-BioNTech COVID-19 Vaccine)	• Individuals 65 years of age and older • Individuals 18 through 64 years of age and at high risk of severe COVID-19 • Individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2	September 22, 2021
Moderna	2-dose series (4 weeks apart)	2-dose primary series in adults ≥18 years of age	December 18, 2020
Moderna	3rd dose (at least 1 month after the second dose)	Individuals ≥12 years of age with compromised immune systems due to solid organ transplantation or conditions considered to have an equivalent level of immunocompromise	August 12, 2021

Sponsor	Authorized Use (Interval)	Indicated Population	Date of EUA or EUA Amendment
Moderna	Booster dose (at least 6 months after completing a primary series of Moderna COVID-19 Vaccine	• Individuals 65 years of age and older • Individuals 18 through 64 years of age and at high risk of severe COVID-19 • Individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2	October 20, 2021
Janssen	Single dose	Individuals ≥18 years of age	February 27, 2021
Janssen	Booster dose	Individuals ≥18 years of age	October 20, 2021
Pfizer, Moderna and Janssen	Single heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine (same interval as authorized for a booster dose of the vaccine used for primary vaccination)	Same population(s) as those eligible to receive a booster dose of the vaccine used for primary vaccination	October 20, 2021

Remdesivir is the only product currently approved by the FDA for treatment of COVID-19 requiring hospitalization, and its approved use is limited to individuals 12 years of age and older. Prior to its approval, remdesivir was authorized for emergency use in adults and pediatric patients and remains authorized for emergency use in hospitalized pediatric patients who are not included in the indicated population under licensure.

Emergency use authorizations of COVID-19 pharmacological products for post-exposure prophylaxis and/or treatment of COVID-19 are as follows:

Table 2. Emergency Use Authorized Pharmacological Products for Post-exposure Prophylaxis and/or Treatment of COVID-19

Product	Date of EUA	Authorized Use and Population
SARS-CoV-2-targeting Monoclonal Antibodies		
• Bamlanivimab/etesevimab • Sotrovimab • Casirivimab/imdevimab	Reissued September 16, 2021 May 26, 2021 Reissued September 9, 2021	All three products are indicated for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years and older at high risk for progressing to severe COVID-19[a] Casirivimab/imdevimab is also authorized for post-exposure prophylaxis (prevention) for COVID-19 in patients at high risk for progressing to severe COVID-19[b]
Antiviral Drugs		
• Remdesivir	Reissued October 22, 2020 (following FDA approval in adults and some pediatric patients)	Treatment of COVID-19 in hospitalized pediatric patients weighing at least 3.5 kg to <40 kg, or <12 years of age weighing at least 3.5 kg, or ≥12 years and weighing at least 40 kg

Product	Date of EUA	Authorized Use and Population
Immune Modulators		
• Baricitinib	Reissued July 29, 2021	Treatment of COVID-19 in hospitalized patients[b] receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO
• Actemra	June 24, 2021	
COVID-19 Convalescent Plasma	Reissued March 9, 2021	Treatment of hospitalized patients with COVID-19

a Indicated for adults and pediatric patients 12 years of age and older weighing at least 40 kg
b Indicated for adults and pediatric patients 2 years and older
ECMO extracorporeal membrane oxygenation, EUA emergency use authorization
Source: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs Accessed August 2, 2021.

4 COMIRNATY (COVID-19 VACCINE, mRNA)

On August 23, 2021, FDA approved COMIRNATY (COVID-19 Vaccine, mRNA) made by BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.). COMIRNATY is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The vaccine is administered IM as a series of two doses (0.3 mL each) 3 weeks apart, with each dose containing 30 µg mRNA. COMIRNATY contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein of SARS-CoV-2 that is formulated in lipid particles. COMIRNATY is the only vaccine or medical product that is FDA approved for prevention of COVID-19. COMIRNATY is also authorized under EUA for use as a 2-dose primary series in individuals 12 years of age and older, for use as a third primary series dose in individuals 12 years of age and older with certain immunocompromising conditions, and for use as a single booster dose administered at least 6 months after completion of a primary series to individuals 65 years of age and older, individuals 18 through 64 years of age at increased risk of severe COVID-19, and individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2. The vaccine authorized under EUA is also known as the Pfizer-BioNTech COVID-19 Vaccine. During clinical development, the vaccine was called BNT162b2.

COMIRNATY is supplied as a concentrated multi-dose liquid formulation (0.45 mL volume) stored frozen at -90°C to -60°C in a 2 mL Type 1 glass vial. A sterile diluent, 0.9% Sodium Chloride Injection, USP, is supplied separately and is stored at 20°C to 25°C. The COMIRNATY Multiple Dose Vial is thawed in a refrigerator (2°C to 8°C) for 2 to 3 hours or at room temperature (up to 25°C) for 30 minutes. Once at room temperature, the COMIRNATY Multiple Dose Vial is diluted with 1.8 mL of the diluent. After dilution, each vial of COMIRNATY contains six doses of 0.3 mL of vaccine. COMIRNATY does not contain preservative.

4.1 Efficacy of a 2-dose primary series of COMIRNATY in individuals 16 years of age and older

Efficacy of BNT162b2 for the prevention of COVID-19 occurring at least 7 days after completion of a 2-dose primary series was evaluated in an ongoing Phase 3 study, C4591001, in approximately 44,000 participants randomized 1:1 to receive two doses of either BNT162b2 or placebo, 3 weeks apart. Participants were enrolled with stratification by age (younger adults: 18 through 55 years of age; older adults: over 55 years of age). The population for the VE analysis that supported approval of COMIRNATY included participants 16 years of age and older who

had been enrolled from July 27, 2020, and who were followed for the development of COVID-19 during blinded placebo-controlled follow-up through as late as March 13, 2021. Overall, 60.8% of participants in the BNT162b2 group and 58.7% of participants in the placebo group had ≥4 months of follow-up time after the primary series in the blinded placebo-controlled follow-up period. The overall VE against COVID-19 in subjects without evidence of prior SARS-CoV-2 infection was 91.1% (95% CI: 88.8 to 93.1). The overall VE against COVID-19 in subjects with or without evidence of prior SARS-CoV-2 infection was 90.9% (95% CI: 88.5 to 92.8).

4.2 Safety of a 2-dose primary series of COMIRNATY in individuals 16 years of age and older

In study C4591001, the most commonly reported solicited adverse reactions (occurring in ≥10% of participants) among BNT162b2 vaccine recipients 16 through 55 years of age following any dose were pain at the injection site (88.6%), fatigue (70.1%), headache (64.9%), muscle pain (45.5%), chills (41.5%), joint pain (27.5%), fever (17.8%), and injection site swelling (10.6%). The most commonly reported solicited adverse reactions in BNT162b2 vaccine recipients 56 years of age and older following any dose were pain at the injection site (78.2%), fatigue (56.9%), headache, (45.9%), muscle pain (32.5%), chills (24.8%), joint pain (21.5%), injection site swelling (11.8%), fever (11.5%), and injection site redness (10.4%).

Among participants 16 through 55 years of age, SAEs from Dose 1 up to the participant unblinding date in ongoing follow-up were reported by 0.8% of BNT162b2 recipients and 0.9% placebo recipients. In a similar analysis, in participants 56 years of age and older serious adverse events (SAEs) were reported by 1.8% of BNT162b2 recipients and 1.7% of placebo recipients who received at least 1 dose of BNT162b2 or placebo, respectively. In these analyses, 58.2% of study participants had at least 4 months of follow-up after the primary series. There were no notable patterns between treatment groups for specific categories of SAEs (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2. From Dose 1 through the March 13, 2021 data cut-off date, there were a total of 38 deaths, 21 in the BNT162b2 group and 17 in the placebo group. None of the deaths were considered related to vaccination.

4.3 Effectiveness and safety of a 2-dose primary series of Pfizer-BioNTech COVID-19 Vaccine in adolescents 12-15 years of age

On May 10, 2021, FDA authorized the use of Pfizer-BioNTech COVID-19 Vaccine in individuals 12-15 years of age based on safety and effectiveness data from an ongoing Phase 2/3 randomized, double-blinded and placebo-controlled trial of the Pfizer-BioNTech COVID-19 Vaccine in 2,260 participants 12-15 years of age.

Vaccine effectiveness in the adolescent age group was inferred by immunobridging based on a comparison of SARS-CoV-2 50% neutralization antibody titers (SARS-CoV-2 mNG microneutralization assay) at 1 month after Dose 2 in participants 12-15 years of age with those of young adults 16-25 years of age (the most clinically relevant subgroup of the study population in whom VE has been demonstrated). In the planned immunobridging analysis, the geometric mean ratio (GMR) of neutralizing antibody titers (adolescents to young adults) was 1.76 (95% CI: 1.47, 2.10), meeting the success criterion (lower bound of the 95% CI for the GMR >0.67). In a descriptive immunogenicity analysis, seroresponse rates among participants without prior evidence of SARS-CoV-2 infection were seen in 97.9% of adolescents and 100% of young adults (difference in seroconversion rates: -2.1%; 95% CI: -6.0%, 0.9%). Immunogenicity outcomes were consistent across demographic subgroups, such as baseline SARS-CoV-2 status, comorbidities, ethnicity, race and sex. In the supplemental efficacy analysis, VE after 7

days post-Dose 2 was 100% (95% CI 75.3; 100.0) in participants 12-15 years of age without prior evidence of SARS-CoV-2 infection and 100% in the group of participants with or without prior infection. VE between Dose 1 and Dose 2 was 75.0% (95% CI 7.4; 95.5), with divergence of cumulative incidence of COVID-19 cases in BNT162b2 vs. placebo groups beginning at approximately 14 days after Dose 1. Although based on a small number of cases in descriptive analyses, the supplementary VE data provided compelling direct evidence of clinical benefit in addition to the immunobridging data.

Safety data from a total of 2,260 adolescents 12-15 years of age randomized to receive vaccine (N=1,131) or placebo (N=1,129) with a median of greater than 2 months of follow-up after the second dose suggest a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. The most common solicited adverse reactions after any dose included injection site pain (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), all of which were generally mild to moderate and lasted a few days. Severe solicited local and systemic adverse reactions occurred in up to 2.4% of 12-15-year-old BNT162b2 recipients, were more frequent after Dose 2 (most common: fatigue 1.3%, headache 1.0%, chills 0.4%) than after Dose 1 (most common: fatigue 2.4%, headache 2.0%, chills 1.8%) and more frequent after any dose in BNT162b2 recipients than age-matched placebo recipients. Among recipients of BNT162b2, severe solicited adverse reactions/events in 12-15-year-olds occurred less frequently than in 16-25-year-olds. No deaths were observed in this age group during the follow-up period. SAEs, while uncommon (<0.5%), represented medical events expected to occur among individuals in this age group and with the underlying conditions represented in the study population, and available data do not suggest a causal relationship to BNT162b2. There were no notable patterns or numerical imbalances between treatment groups for specific categories of non-serious AEs among study participants 12-15 years of age that would suggest a causal relationship to BNT162b2 vaccine.

4.4 Cases of myocarditis/pericarditis reported in BNT162b2 recipients in ongoing clinical trials of BNT162b2

Pericarditis and myopericarditis have been reported in BNT162b2 recipients in study C4591001:

- A male participant ≥55 years of age, with no medical history, reported pericarditis 28 days after Dose 2 of BNT162b2; the event was assessed by the investigator and FDA as not related to the study intervention and was ongoing at the time of the data cut-off.
- A male participant who was randomized to blinded placebo group at age 15 years and subsequently unblinded and crossed over to open label BNT162b2 at age 16 years was diagnosed with myopericarditis beginning 2 days after Dose 2 of BNT162b2. He was hospitalized on Day 3 and treated with IVIG, non-steroidal anti-inflammatory medications and steroids, and discharged the following day. He was followed by a cardiologist and seen for follow up 2 months after vaccination. At that time the cardiologist recommended limited activity. The investigator concluded that the there was a reasonable possibility that the myopericarditis was related to vaccine administration due to the plausible temporal relationship. FDA agrees with this assessment.

4.5 Post-EUA and post-licensure surveillance

As of October 21, 2021, more than 244 million doses of the Pfizer-BioNTech COVID-19 Vaccine have been administered in the U.S. According to the CDC COVID Data Tracker, 205,046 individuals less than 12 years of age have received at least one dose of the Pfizer-BioNTech

COVID-19 Vaccine, and 125,656 have received two doses. It is not known what proportions of these numbers represent unauthorized use of the vaccine and what proportions might reflect errors in reporting of the recipients' ages.

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event (AE) reports following administration of 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, 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 October 18, 2021, VAERS received 442,763 reports (including 270,342 U.S. reports), of which 854 U.S. reports were described as involving children 5-11 years of age, 9,523 U.S. reports were in children 12-15 years of age, and 5,821 U.S. reports were in adolescents 16-17 years of age. The top ten most frequently reported MedDRA Preferred Terms (PTs) included:

- Overall, most frequent PTs: headache, fatigue, pyrexia, SARS-CoV-2 test, dizziness, pain, nausea, chills, pain in extremity, dyspnoea
- Most frequent PTs in in persons ≤17 years of age: dizziness, syncope, headache, pyrexia, nausea, product administered to patient of inappropriate age, chest pain, fatigue, vomiting, loss of consciousness.

Note that a report may have one or more PTs. An additional query of VAERS for U.S. reports by dose number retrieved the following: 127,747 reports after Dose 1; 100,730 reports after Dose 2; and 5,223 reports after dose 3 (data as of October 18, 2021).

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 AE reports and the Sponsor's periodic safety reports did not indicate any new safety concerns, including in adolescents. Most AEs are labeled events and consistent with the safety profile for this vaccine. No unusual frequency, clusters, or other trends for AEs were identified that would suggest a new safety concern, including among the reports described as involving children 5-11 years of age.

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.[4243] 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 in the U.S. is 6.1 cases per million doses at this time based on the above VAERS data.

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 and have been highest in males 12 through 17 years of age (~71.5 cases per million second primary series doses among males age 16-17 years and 42.6 cases per million second primary series doses among males age 12-15 years as per CDC presentation to the ACIP on August 30, 2021). In an FDA analysis of the Optum healthcare claims database, the estimated excess risk of myocarditis/pericarditis approached 200 cases per million fully vaccinated males 16-17 years of age and 180 cases per million fully vaccinated males 12-15 years of age.[44] 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). 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.

5 EUA AMENDMENT REQUEST FOR THE PFIZER-BIONTECH COVID-19 VACCINE FOR USE IN CHILDREN 5-11 YEARS OF AGE

On October 6, 2021, Pfizer and BioNTech submitted a request to amend this EUA to include use of a 2-dose primary series of the Pfizer-BioNTech COVID-19 Vaccine (10 µg each dose, administered 3 weeks apart) in individuals 5-11 years of age for active immunization to prevent COVID-19 caused by severe acute coronavirus 2 (SARS-CoV-2).

The request is accompanied by safety data from the Phase 2/3 portions of study C45910071. This data includes 518 BNT162b2 recipients and 750 placebo (saline) recipients 5-11 years of age, of whom over 95% of participants in each group had ≥2 months of safety follow up after Dose 2 (Cohort 1, September 6, 2021 data cut-off), and data from an additional 1,591 BNT162b2 and 788 placebo recipients who were enrolled into the trial later and whose median duration of follow-up was 2.4 weeks post-Dose 2 (Cohort 2; October 8, 2021 data cut-off). Vaccine effectiveness in children 5-11 years of age was inferred by immunobridging SARS-CoV-2 50% neutralizing antibody titers (NT50, as assessed by SARS-CoV-2 mNG microneutralization assay) among C4591007 study participants 5-11 years of age following completion of a primary series to antibody titers of those of young adults 16-25 years of age who received two doses of 30 µg BNT162b2 in study C4591001. Efficacy against COVID-19 disease was assessed descriptively in study C4591007 participants 5-11 years of age.

Vaccine formulation

Authorization is being requested for a modified formulation of the Pfizer-BioNTech COVID-19 Vaccine. To provide an improved stability profile to the vaccine, the Pfizer-BioNTech COVID-19 Vaccine for use in children 5-11 years of age uses tromethamine (Tris) buffer instead of the phosphate-buffered saline (PBS) as used in the previous formulation. The packaged vials for the new formulation are also stored frozen at -90°C to -60°C; however, the frozen vials may be thawed and stored at refrigerator at 2°C to 8°C for up to 10 weeks. For the 10-µg mRNA dose, each 1.3-mL filled vial must be diluted with 1.3 mL 0.9% sodium chloride for injection to provide 10 doses at 10 µg RNA / 0.2 mL Injection volume. After dilution, the vials should be stored at 2°C to 25°C and should be used within 12 hours. See Section 8.1 Chemistry, Manufacturing, and Controls (CMC) information, for details.

6 EUA REQUIREMENTS, GUIDANCE AND CONSIDERATIONS PERTAINING TO COVID-19 VACCINES

6.1 U.S. requirements to support issuance of an EUA for a biological product

Based on the declaration by the Secretary of the U.S. 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 (CBRN) 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.

6.2 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" February 2021, 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 5-11 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]

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

The Vaccines and Related Biological Products Advisory Committee convened on June 21, 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 a young adult population in which clinical disease endpoint vaccine efficacy 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 (geometric mean titer [GMT] and seroresponse rate) are considered appropriate for comparing the range of neutralizing antibody responses elicited by the vaccine in pediatric vs. 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 adverse reactions (reactogenicity, including injection site and systemic adverse reactions), and less common but medically important adverse reactions. 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 adverse reactions that occur too rarely to be detected in clinical trials.

7 FDA REVIEW OF CLINICAL SAFETY AND EFFECTIVENESS DATA

7.1 Overview of study C45910007

The EUA amendment request contains safety, immunogenicity, and descriptive efficacy data from children 5-11 years of age enrolled in C4591007, an ongoing Phase 1/2/3, randomized, placebo-controlled study. The comparator group for the immunobridging analyses to support vaccine effectiveness in this age group was a random subset 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.

Data from study C4591007

- Phase 2/3: a total of 3,109 BNT162b2 (10 µg) recipients and 1538 placebo recipients 5-11 years of age
  - Cohort 1: 1,518 BNT162b2 (10 µg) recipients and 750 placebo recipients, of whom 1,444 (95.1%) and 714 (95.2%), respectively, had at least 2 months of safety follow-up after completing a 2-dose primary series (data cut-off September 6, 2021). Summary tables for solicited adverse reactions (ARs) and immunogenicity analyses are based on this cohort of subjects. A descriptive efficacy analysis was also based on this cohort.
  - Cohort 2: A second cohort of 1,591 BNT162b2 (10 µg) recipients and 7878 placebo recipients had a median duration of follow up of 2.4 weeks post-Dose 2 at the time of data cut-off (October 8, 2021). Safety data from this cohort were provided for further assessment of SAEs and AEs of clinical interest.
- Phase 1 data to support dosage selection for Phase 2/3 portion of the study

Table 3. Study C4591007*: Participants 5-11 Years of Age (10 µg BNT162b2)

Study Number/ Countries	Description	BNT162b2 N	Placebo (Saline) N	Study Status
C4591007 United States, Finland, Poland, and Spain	Phase 1/2/3 randomized, placebo-controlled; to evaluate safety, immunogenicity and efficacy of COVID-19 vaccine	Phase 1: 16 Phase 2/3: 3,109	Phase 1:0 Phase 2/3: 1,538	Ongoing

N=Number of randomized participants as of data cut-off dates July 16, 2021 (all Phase 1 participants), September 6, 2021 (Phase 2/3 cohort 1: 1,518 BNT162b2, 750 placebo; enrollment started June 7, 2021) and October 8, 2021 (Phase 2/3 cohort 2: 1,591 BNT162b2, 788 placebo; enrollment started August 26, 2021).
*First participant, first visit was March 24, 2021 (Phase 1).

7.2 Study design

Study C4591007 is an ongoing Phase 1/2/3 randomized, observer-blinded, placebo-controlled safety, immunogenicity, and efficacy study. This section presents the design for the Phase 2/3 portion of the study in children 5-11 years of age. Please see Appendix 1 for Phase 1 study design.

Phase 2/3 is being conducted in the United States, Finland, Poland, and Spain. The Phase 2/3 portion of the study did not exclude children with a history of prior SARS-CoV-2 infection or clinical symptoms/signs of COVID-19, children 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).

Participants were randomized 2:1 to receive two doses of 10 µg BNT162b2 or placebo (saline), 3 weeks apart. Participants who turned 12 years of age during the study would have the opportunity to receive the EUA-authorized dose level of 30 µg (12-15 years of age) if they originally received placebo.

Immunogenicity evaluation

Immunobridging was based on SARS-CoV-2 neutralizing antibody responses in study C4591007 Phase 2/3 (Cohort 1) participants 5-11 years of age compared to neutralizing antibody responses in a random subset of study C4591001 participants 16-25 years of age, as measured by 50% neutralizing antibody titers (NT50, SARS-CoV-2 mNG microneutralization assay) against the reference strain (USA_WA1/2020) at 1 month after a primary series. The primary analysis is based on the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 2.

Primary endpoints and statistical success criteria

- Immunobridging success based on GMT was declared if the lower limit (LL) of the 95% CI for the GMT ratio (5-11 years of age / 16-25 years of age) 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 (5-11 years of age minus 16-25 years of age) 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.

Efficacy evaluation

A secondary objective is to evaluate efficacy of BNT162b2 against laboratory-confirmed symptomatic COVID-19 occurring from 7 days after Dose 2 in participants without evidence of prior SARS CoV-2 infection and in participants with or without evidence of prior SARS CoV-2 infection. A descriptive analysis was conducted once 19 confirmed cases had accrued. COVID-19 and severe COVID-19 case definitions are included in Appendix 2.

Safety evaluation

Reactogenicity (solicited local and systemic adverse reactions)

The participants' parents or participants themselves recorded reactogenicity assessments and antipyretic/pain medication use from Day 1 through Day 7 after each dose in an e-diary. Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling) and systemic AEs (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 2, and SAEs from Day 1 to 6 months after Dose 2, or the data cut-off date (Phase 1: July 16, 2021; Phase 2/3: September 6, 2021). AEs were categorized by frequency and maximum severity according to MedDRA System Organ Class and PT, and relationship to the study intervention was assessed. Deaths are recorded to the end of the study.

Adverse events of clinical interest

The occurrence of certain AEs including lymphadenopathy and myocarditis/pericarditis were assessed as part of the safety review, as well as additional AEs requested by FDA (including anaphylaxis, Bell's palsy, appendicitis, pregnancy exposures and outcomes, and MIS-C cases).

Analysis populations

Pertaining to participants 5-11 years of age

- 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.
- Evaluable immunogenicity: All eligible randomized participants who receive two doses of the vaccine to which they are randomized with Dose 2 received within the predefined window, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.
- Evaluable efficacy: All randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1) and have no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2.

Data analysis cut-off dates:

- All Phase 1 participants: July 16, 2021
- Phase 2/3 Cohort 1 (initial): September 6, 2021 (enrollment started June 7, 2021)
- Phase 2/3 Cohort 2: October 8, 2021 (enrollment started August 26, 2021)

7.3 Disposition of Phase 2/3 participants

Cohort 1 (initial enrollment)

Cohort 1 was comprised 1,538 BNT162b2 10 µg participants and 757 placebo participants; 11 (0.7%) BNT162b2 and 6 (0.8%) placebo participants did not receive any study agent. Two BNT162b2 participants (0.1%) and two placebo participants (0.3%) discontinued vaccination before the 1 month post-Dose 2 follow up; none resulted from an AE. Three participants turned 12 years of age during the course of the study and became eligible to receive 30 µg BNT162b2 under EUA; two of these participants received two doses of 10 µg BNT162b2 prior to being unblinded, and the other participant received both doses of placebo before being unblinded and withdrew to receive a COVID-19 vaccine outside of the study; data from these participants were included in endpoint analyses up to the point at which they were unblinded.

Safety population: solicited ARs, unsolicited AEs, SAEs and AEs of clinical interest were assessed in a total of 2,268 (1,518 10 µg BNT162b2, 750 placebo) participants 5-11 years of age; over 95% of participants in each study group completed at least 2 months of safety follow-up after Dose 2. Five BNT162b2 recipients and six placebo recipients withdrew from the study, mainly due to voluntary withdrawal.

Comparator group for immunogenicity: The comparator group for immunobridging analyses consisted of 300 evaluable participants 16-25 years of age who received both doses of BNT162b2 30 µg and were randomly selected from study C4591001 Phase 2/3.

Table 4. Disposition of Immunogenicity Populations, Phase 2/3, Participants 5-11 Years of Age (Study C4591007 Cohort 1) and Participants 16-25 Years of Age (Study C4591001)

Disposition	5-11 years of age BNT162b2 (10 µg) n (%)	5-11 years of age Placebo n (%)	16-25 years of age BNT162b2 (30 µg) n (%)
Randomized to receive BNT162b2[a]	322 (100.0)	163 (100.0)	300 (100.0)
All-available immunogenicity population	311 (96.6)	156 (95.7)	286 (95.3)
Excluded because they did not have at least 1 valid and determinate immunogenicity result after vaccination	11 (3.4)	7 (4.3)	13 (4.3)
Evaluable immunogenicity population	294 (91.3)	147 (90.2)	273 (91.0)
Without evidence of infection up to 1 month after Dose 2[b]	264 (82.0)	130 (79.8)	253 (84.3)
Subjects excluded from evaluable immunogenicity population	28 (8.7)	16 (9.8)	27 (9.0)
Reason for exclusion (subjects may have been excluded for >1 reason)			
Did not receive 2 doses of the vaccine as randomized	3 (0.9)	1 (0.6)	0
Did not receive Dose 2 within 19 to 42 days after Dose 1	3 (0.9)	2 (1.2)	3 (1.0)
Did not have at least 1 valid and determinate immunogenicity result within 28 to 42 days after Dose 2	13 (4.0)	14 (8.6)	21 (7.0)
Did not have blood draw at 1 month after Dose 2 visit	7 (2.2)	6 (3.7)	8 (2.7)
1 Month after Dose 2 blood draw outside of window (28-42 days after Dose 2)	6 (1.9)	8 (4.9)	13 (4.3)
Had important protocol deviation(s) as determined by the clinician	10 (3.1)	0	4 (1.3)

%:n/N. n = number of participants with the specified characteristic. N = number of randomized participants in the specified group; this value is the denominator for the percentage calculations.

a. Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding ant body [serum] negative at pre-Dose 1 and at 1 month post-Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1 and pre-Dose 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.

b. Participants may have been excluded for more than 1 reason.

Efficacy population

Of 2186 participants (1450 BNT162b2 and 736 placebo) in the evaluable efficacy population, 1305 BNT162b2 and 663 placebo participants did not have evidence of SARS-CoV-2 infection from pre-Dose 1 to 7 days post-Dose 2.

Cohort 2 (expansion)

In the Phase 2/3 safety expansion, 1,598 participants were randomized to receive BNT162b2 and 796 were randomized to placebo. At the time of the October 8, 2021, cut-off, most participants (98.7%) had received both Dose 1 and Dose 2. Seven of the randomized BNT162b2 participants did not receive vaccine. One participant in the BNT162b2 group discontinued from the vaccination period due to AEs of pyrexia and neutropenia that worsened from baseline (see Section 7.7.7, AEs leading to withdrawal). Two participants (0.1%) in the BNT162b2 group withdrew from the study before the 1-month period. Neither withdrawal was due to an AE.

Comorbidities at baseline

Comorbidities were defined as described in Kim et al. MMWR 2020.[47] Participants with any comorbidity, including obesity, constituted 20.6% of the BNT162b2 group and 20.3% of placebo group. The most common comorbidities at baseline in the Cohort 1 BNT162b2 group were obesity (11.5%), asthma (7.8%), neurologic disorders (1.3%), and congenital heart disease (1.0%). Other comorbidities included diabetes in 2 participants (0.2%), and one participant each (0.1%) for acute lymphocytic leukemia (immunocompromising conditions), cystic fibrosis, and sickle cell disease.

Demographic characteristics were similar in Cohort 2 as Cohort 1. Overall, 11.1% of participants were obese. Comorbidities including obesity were found in 19.9% of participants. As in Cohort 1, the most common comorbidities were asthma, neurologic disorders and congenital heart disease.

7.4 Demographic and baseline characteristics

Demographic characteristics for the Phase 2/3 study C4591007 Cohort 1 safety population are summarized in Table 5 below. Overall, participants were predominately White, with a mean age of approximately 8 years. Of the BNT162b2 recipients, 11.5% were obese, 8.8% had evidence of prior SARS-CoV-2 infection and 20.6% had comorbidities placing them at increased risk of severe COVID-19. More than 70% of participants were enrolled in the United States.

Table 5. Demographic and Baseline Characteristics, Phase 2/3, Participants 5-11 Years, Safety Population, Study C4591007 Cohort 1

Characteristic	C4591007 BNT162b2 10 µg (N[a]=1518) n[b] (%)	C4591007 Placebo (N[a]=750) n[b] (%)
Sex: Male	799 (52.6)	383 (51.1)
Sex: Female	719 (47.4)	367 (48.9)
Race: White	1204 (79.3)	586 (78.1)
Race: Black or African American	89 (5.9)	58 (7.7)
Race: American Indian or Alaska Native	12 (0.8)	3 (0.4)
Race: Asian	90 (5.9)	47 (6.3)
Race: Native Hawaiian or other Pacific Islander	<1%	<1%
Race: Multiracial	109 (7.2)	49 (6.5)
Race: Not reported	9 (0.6)	7 (0.9)
Ethnicity: Hispanic or Latino	319 (21.0)	159 (21.2)
Ethnicity: Not Hispanic or Latino	1196 (78.8)	591 (78.8)
Ethnicity: Not reported	<1%	<1%
Age: Mean years (SD)	8.2 (1.93)	8.1 (1.97)
Age: Median (years)	8.0	8.0
Obese[c]: Yes	174 (11.5)	92 (12.3)
Obese[c]: No	1343 (88.5)	658 (87.7)
Obese[c]: Missing	<1%	<1%
Baseline Evidence of Prior SARS-CoV-2 Infection: Negative[e]	1385 (91.2)	685 (91.3)
Baseline Evidence of Prior SARS-CoV-2 Infection: Positive[f]	133 (8.8)	65 (8.7)
Comorbidities[d]: Yes	312 (20.6)	152 (20.3)
Comorbidities[d]: No	1206 (79.4)	598 (79.7)
Country: Finland	158 (10.4)	81 (10.8)
Country: Poland	125 (8.2)	60 (8.0)
Country: Spain	162 (10.7)	78 (10.4)

Characteristic	C4591007 BNT162b2 10 µg (N[a]=1518) n[b] (%)	C4591007 Placebo (N[a]=750) n[b] (%)
Country: United States	1073 (70.7)	531 (70.8)

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥ 95th percentile).
e. Negative N-binding antibody result and negative NAAT result at pre-Dose 1 and no medical history of COVID-19.
f. Positive N-binding antibody result at pre-Dose 1, positive NAAT result at pre-Dose 1, or medical history of COVID-19.

The demographic and baseline characteristics of the evaluable immunogenicity and efficacy populations without baseline evidence of SARS-CoV-2 infection were similar to the overall characteristics of Cohort 1 population.

Demographic characteristics in Cohort 2 were similar to Cohort 1.

Comparator group for immunogenicity: The 300 participants ages 16-25 years from study C4591001 were from sites in the United States (64%), Argentina (18%), Brazil (12%), and South Africa/Turkey/Germany (6% combined total).

Less than 0.8% of participants in either group received non-COVID-19 vaccines during the study; most were routine pediatric immunizations including diphtheria, pertussis, tetanus, human papillomavirus vaccine, and meningococcal vaccine.

7.5 Immunogenicity results

7.5.1 Primary immunogenicity objective

Immunogenicity of BNT162b2 was assessed based on analyses of GMTs and seroresponse rates for neutralizing antibody titers to the reference strain (USA_WA1/2020).

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, the ratio of SARS-CoV-2 50% neutralizing GMT in children 5-11 years (10 µg each dose) compared to individuals 16-25 years (30 µg each dose) was 1.04 (95% CI: 0.93, 1.18). The lower bound of the 2-sided 95%CI for GMR was >0.67 and the point estimate was ≥1, which met FDA's requested criteria; see Table 6, below.

Table 6. SARS-CoV-2 Neutralizing GMTs (NT50)[a] at 1 Month Post-Primary Series in Phase 2/3 BNT162b2 (10 µg) Recipients 5-11 Years of Age and Study C4591001 Phase 2/3 Cohort 1 BNT162b2 (30 µg) Recipients 16-25 Years of Age Without Evidence of SARS-CoV-2 Infection up to 1 Month After Dose 2, Evaluable Immunogenicity Population[b]

GMT (95% CI) 5-11 Years of Age Study C4591007 N[c] = 264	GMT (95% CI) 16-25 Years of Age Study C4591001 N[c] = 253	GMT Ratio (95% CI) (5-11 Years of Age / 16-25 Years of Age)[d]
1197.6 (1106.1, 1296.6)	1146.5 (1045.5, 1257.2)	1.04 (0.93, 1.18)

a. SARS-CoV-2 mNeonGreen virus microneutralization assay (SARS-CoV-2 mNG NT), reference strain: recombinant USA_WA1/2020. NT50= 50% neutralizing titer.
b. Evaluable immunogenicity population pertaining to Phase 2/3 BNT162b2 participants 5-11 years of age (study C4591007) and Phase 2/3 BNT162b2 participants 16-25 years of age (study C4591001).
c. 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.
d. 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 are displayed in Table 7 below. Children 5-11 years of age had similar seroresponse (as measured from before vaccination to 1 month after Dose 2) rate as individuals 16-25 years of age. The difference between the two age groups was 0.0% (95% CI: -2.0%, 2.2%). The lower limit of the 95% CI for the difference in seroresponse rate was -2.0%, which was greater than the prespecified margin of -10% and thus immunobridging based on seroresponse rate was met, see Table 7 below.

Table 7. Seroresponse Rates[a,b] at 1 Month Post-Primary Series in Phase 2/3 BNT162b2 (10 µg) Recipients 5-11 Years of Age and Study C4591001 Phase 2/3 Cohort 1 BNT162b2 (30 µg) Recipients 16-25 Years of Age[b] Without Evidence of SARS-CoV-2 Infection up to 1 Month After Dose 2, Evaluable Immunogenicity Population[c]

Seroresponse 5-11 Years of Age Study C4591007 %[d] (95% CI) N= 264	Seroresponse 16-25 Years of Age Study C4591001 %[d] (95% CI) N= 253	% Difference in Seroresponse Rate (Age Group 5-11 Years minus Age Group 16-25 Years)[e] (95% CI)
99.2 (97.3, 99.9)	99.2 (97.2, 99.9)	0 (-2.0, 2.2)

a. SARS-CoV-2 mNeonGreen virus microneutralization assay-NT50, 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 5-11 years of age (study C4591007) and Phase 2/3 BNT162b2 participants 16-25 years of age (study C4591001).
d. %: n/N. n = number of participants with seroresponse for the given assay at the given dose/sampling time point. 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.
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 Geometric Mean Titers

GMTs of SARS-CoV-2 neutralizing titers and seroresponse rates at 1 month after Dose 2 did not vary by demographic subgroup, although some subgroups were too small to evaluate by protocol-specified methods. Specifically, no notable differences in GMTs or seroresponse rates were observed by age (i.e., 5-6 years vs. 7-8 years vs. 9-11 years), sex, race, ethnicity, obesity (Y/N), or SARS-CoV-2 status.

In descriptive post hoc analyses of immunogenicity data based on the presence or absence of comorbidities (defined as described in Kim et al. MMWR 2020[47]), GMT and seroresponse rates among those with comorbidities were comparable to those without comorbidities.

7.5.2 Exploratory immunogenicity analyses against the Delta Variant

In response to FDA's request for immunogenicity data to support effectiveness of a 10 µg BNT162b2 primary series against the Delta variant, Pfizer submitted exploratory descriptive analyses of data from a randomly selected subset of participants (34 BNT162b2 recipients, 4 placebo recipients) with no evidence of infection up to 1 month post-Dose 2. These data were generated using non-validated SARS-CoV-2 plaque reduction neutralization assays with the reference strain (USA-WA1/2020) and the Delta variant; the relative sensitivity of the two assays is not known.

Table 8. SARS-CoV-2 Neutralizing GMTs[a] at Pre-Dose 1 and 1 Month Post-Primary Series in C4591007 Phase 2/3 Cohort 1 Participants 5-11 Years of Age Without Evidence of SARS-CoV-2 Infection up to 1 Month After Primary Series, Evaluable Immunogenicity Population[b]

Assay Target	Time Point	BNT162b2 10 µg N=34 GMT (95% CI)	Placebo N=4 GMT (95% CI)
Reference strain	Pre-Dose 1	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)
	1 month post-Dose 2	365.3 (279.0, 478.4)	10.0 (10.0, 10.0)
Delta variant	Pre-Dose 1	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)
	1 month post-Dose 2	294.0 (214.6, 405.3)	10.0 (10.0, 10.0)

a. SARS-CoV-2 plaque reduction neutralization assay, SARS-CoV-2 strains: recombinant USA_WA1/2020 (reference), B.1.617.2 (Delta).
b. N = number of participants with valid and determinate assay results for the specified assays at the given dose/sampling time point. Participants with no serological or virological evidence of SARS-CoV-2 infection: defined as N-binding ant body [serum] negative from pre-Dose 1 to 1 month post-Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] prior to Dose 1 and Dose 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to 1-month post-Dose 2, and no medical history of COVID-19.

7.6 Efficacy results

Pfizer submitted supplemental, descriptive efficacy data for Phase 2/3 Cohort 1 participants 5-11 years of age, based on a total of 19 confirmed symptomatic COVID-19 cases occurring at least 7 days post-Dose 2, accrued up to the data cut-off of October 8, 2021. The evaluable efficacy population included 1,450 participants randomized to BNT162b2 and 736 participants randomized to placebo, of whom 1305 BNT162b2 and 663 placebo participants did not have evidence of SARS-CoV-2 infection from pre-Dose 1 to 7 days after Dose 2.

In participants 5-11 years of age without evidence of SARS-CoV-2 infection prior to Dose 2, the observed VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 90.7%

(95% CI: 67.7%, 98.3%), with 3 COVID-19 cases in the BNT162b2 group compared to 16 in the placebo group (2:1 randomization BNT162b2 to placebo). All cases of COVID-19 occurred in children without prior history of infection. None of these cases met the criteria for severe infection. Most of the cases occurred in July-August 2021. Comorbidities at baseline (including obesity) were present in total of 20.1% of cases. No virus sequence analyses were available to determine whether these cases were caused by the Delta variant or another variant.

7.7 Safety results

Please see the Appendix 1 for Phase 1 study results.

Overview of adverse events: Phase 2/3

In C4591007 Phase 2/3 Cohort 1, e-diary data were collected from 1,511 BNT162b2 recipients and 749 placebo recipients for reactogenicity (local and systemic reactions). Overall, injection site reactions occurring within 7 days of vaccination with BNT162b2 were common, occurring in approximately 75% of participants after either Dose 1 or Dose 2. Systemic AEs occurred in approximately 50% of BNT162b2 recipients.

No Cohort 1 participants withdrew because of AEs, and there were no deaths reported. SAEs occurred in one participant each from the BNT162b2 and placebo groups, and neither were considered by the investigator or FDA to be related to the investigational agent. Immediate unsolicited AEs were rare in this study, occurring in 0.3% or less after either Dose 1 or Dose 2. See Table 9 below.

Table 9. Safety Overview, Phase 2/3 Cohorts 1 and 2, Participants 5-11 Years, Safety Population, Study C4591007

Event	BNT162b2 10 µg n/N (%)	Placebo n/N (%)
Immediate unsolicited AE within 30 minutes after vaccination		
Dose #1	3/1518 (0.2)	3/750 (0.4)
Dose #2	4/1515 (0.3)	2/746 (0.3)
Solicited injection site reaction within 7 days		
Dose #1	1150/1511 (76.1)	254/749 (33.9)
Dose #2	1096/1501 (73.0)	237/741 (32.0)
Solicited systemic AR within 7 days		
Dose #1	715/1511 (47.3)	334/749 (44.6)
Dose #2	771/1501 (51.4)	272/741 (36.7)
From Dose 1 through 1 month after Dose 2 (cohort 1)[a]		
Any AE	166/1518 (10.9)	69/750 (9.2)
Unsolicited non-serious AE	166/1518 (10.9)	68/750 (9.1)
From Dose 1 through 1 month after Dose 2 (cohort 2)[a]		
Any AE	115/1591 (7.2)	50/788 (6.3)
Unsolicited non-serious AE	113/1591 (7.1)	50/788 (6.3)
From Dose 1 through cut-off date[b] or participant unblinding[c]		
Withdrawal due to AEs	1/3109 (<0.1)	0/1538 (0.0)
SAE	4/3109 (0.1)	1/1538 (0.1)
Deaths	0/3109 (0.0)	0/1538 (0.0)

Note: MedDRA (v24.0) coding dictionary applied.
Note: Immediate AE refers to an AE reported in the 30-minute observation period after vaccination.
%:n/N. n = Number of participants with the specified characteristic. N = number of administered participants in the specified group; this value is the denominator for the percentage calculations.
a. For cohort 1, 95% of participants had at least 2 months follow-up. For cohort 2, 71% of participants had at least 2 weeks follow-up.
b. Oct 8, 2021 for all participants (cohort 1 and cohort 2), N=3109 is the total N for BNT162
c. Three participants (2 BNT162b2, 1 placebo) turned 12 years of age during the course of the study and eligible to received 30 µg BNT162b2 under EUA; for this reason, the participants were unblinded to their treatment assignment.

7.7.1 Immediate AEs

Among the 1,518 Cohort 1 participants who received BNT162b2 Dose 1, a total of 3 reported any immediate AE, and all were injection site pain. Following Dose 2, 4 participants experienced an immediate AE, including 1 with nausea, 1 with injection site pain, 1 with injection site erythema, and 1 with erythema (skin and subcutaneous disorder).

7.7.2 Solicited adverse reactions

Solicited local adverse reactions generally occurred more commonly after Dose 2 and included pain at the injection site (71%), redness (18.5%) and swelling (15.3%). Systemic adverse reactions also occurred more frequently after Dose 2 and included fatigue (39.4%), headache (28.0%), and muscle pain (11.7%). Most local and systemic reactions were mild to moderate in severity, with median onset 2 days post-vaccination, and resolved within 1 to 2 days after onset.

Rates of local and systemic adverse reactions in children 5-11 years of age were generally similar to those in individuals 12 years of age or older enrolled in study C4591001, with pain at the injection site slightly lower in the 5-11 year-old group, but redness and swelling slightly higher. Systemic adverse reactions such as fever, fatigue, headache, chills, and muscle pain were generally reported less frequently and were milder in severity in the 5-11 year-old group compared to individuals 12 years of age or older.

The frequencies of local and systemic adverse reactions within 7 days after each vaccination in participants with evaluable e-diary data are summarized in Tables 10, 11, and 12 below.

Table 10. Frequency of Solicited Local Reactions Within 7 Days After Each Dose, by Severity, Phase 2/3 Cohort 1 Participants 5-11 Years of Age, Safety Population[a], Study C4591007

Event	BNT162b2 10µg Dose 1 N=1,511 %	Placebo Dose 1 N=748 %	BNT162b2 10µg Dose 2 N=1,501 %	Placebo Dose 2 N=740 %
Pain at the injection site[b]				
Any[d]	74.1	31.3	71.0	29.5
Mild	58.9	27.3	52.8	25.9
Moderate	14.9	4.0	17.8	3.5
Severe	0.3	0.0	0.3	0.0
Redness[c]				
Any[d]	14.7	5.7	18.5	5.4
Mild	9.5	4.9	9.5	4.2
Moderate	5.2	0.8	8.8	1.2
Severe	0.0	0.0	0.2	0.0

Event	BNT162b2 10µg Dose 1 N=1,511 %	Placebo Dose 1 N=748 %	BNT162b2 10µg Dose 2 N=1,501 %	Placebo Dose 2 N=740 %
Swelling[c]				
Any[d]	10.5	2.7	15.3	2.7
Mild	5.6	1.7	7.8	2.0
Moderate	4.8	0.9	7.5	0.7
Severe	0.1	0.0	0.0	0.0

%: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; the N used in the percentage calculations for redness and swelling were 749 after Dose 1 and 741 after Dose 2 in the placebo group, due to an e-diary error.

a. Randomized participants in the specified age group who received at least 1 dose of the study intervention.

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 11. Frequency of Solicited Systemic Reactions Within 7 Days After Dose 2 by Severity, Phase 2/3 Cohort 1 Participants 5-11 Years of Age, Safety Population, Study C4501007

Event	BNT162b2 10µg Dose 1 N=1,511 %	Placebo Dose 1 N=748 %	BNT162b2 10µg Dose 2 N=1,501 %	Placebo Dose 2 N=740 %
Fever				
≥38.0°C	2.5	1.3	6.5	1.2
≥38.0°C to 38.4°C	1.5	0.5	3.4	0.7
>38.4°C to 38.9°C	0.8	0.7	2.5	0.4
>38.9°C to 40.0°C	0.2	0.1	0.5	0.1
>40.0°C	0.0	0.0	0.1	0.0
Fatigue[b]				
Any[e]	33.6	31.3	39.4	24.3
Mild	22.0	20.1	21.4	13.0
Moderate	11.3	11.1	17.3	11.2
Severe	0.3	0.1	0.7	0.1
Headache[b]				
Any[e]	22.4	24.1	28.0	18.6
Mild	16.5	17.5	18.7	12.6
Moderate	5.8	6.0	9.1	6.1
Severe	0.1	0.5	0.2	0.0
Chills[b]				
Any[e]	4.6	4.7	9.8	4.3
Mild	3.6	4.0	7.0	3.2
Moderate	1.1	0.7	2.7	0.9
Severe	0.0	0.0	0.1	0.1
Vomiting[c]				
Any[e]	2.2	1.5	1.9	0.8
Mild	1.7	1.5	1.8	0.8
Moderate	0.5	0.0	0.1	0.0
Severe	0.0	0.0	0.0	0.0
Diarrhea[d]				
Any[e]	5.9	4.1	5.3	4.7
Mild	5.2	4.1	4.8	4.3
Moderate	0.7	0.0	0.5	0.4
Severe	0.0	0.0	0.0	0.0

Event	BNT162b2 10µg Dose 1 N=1,511 %	Placebo Dose 1 N=748 %	BNT162b2 10µg Dose 2 N=1,501 %	Placebo Dose 2 N=740 %
New or worsened muscle pain[b]				
Any[e]	9.1	6.8	11.7	7.4
Mild	6.4	4.7	7.7	5.1
Moderate	2.6	2.1	3.9	2.3
Severe	0.1	0.0	0.1	0.0
New or worsened joint pain[b]				
Any[e]	3.3	5.5	5.2	3.6
Mild	2.3	4.1	3.8	2.7
Moderate	1.1	1.3	1.4	0.9
Severe	0.0	0.0	0.0	0.0
Use of antipyretic or pain medication[f]	14.4	8.3	19.7	8.1

%: 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; the N used in the percentage calculations for fever and use of antipyretic or pain medication were 749 after Dose 1 and 741 after Dose 2 in the placebo group, due to an e-diary error.
a. All participants in the specified age group who received at least 1 dose of the study intervention.
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.

Table 12. Characteristics of Solicited Local and Systemic Adverse Reactions, Phase 2/3 Cohort 1, Participants 5-11 Years, Safety Population, Vaccine Group as Administered, Study C4591007

Event	BNT162b2 10 µg Dose 1 n[a]/N[b]	Placebo Dose 1 n[a]/N[b]	BNT162b2 10 µg Dose 2 n[a]/N[b]	Placebo Dose 2 n[a]/N[b]
Any solicited local reaction				
Day of onset: median (min, max)	1.0 (1, 6)	1.0 (1, 6)	1.0 (1, 7)	1.0 (1, 7)
Duration: median (min, max)	2.0 (1, 10)	1.0 (1, 10)	2.0 (1, 11)	1.0 (1, 12)
Persisted beyond 7 days	11/1511	9/749	8/1501	5/741
Redness				
Day of onset: median (min, max)	2.0 (1, 7)	2.0 (1, 5)	2.0 (1, 6)	1.0 (1, 5)
Duration: median (min, max)	1.0 (1, 10)	1.0 (1, 8)	2.0 (1, 10)	1.0 (1, 11)
Persisted beyond 7 days	4/1511	1/749	2/1501	1/741
Swelling				
Day of onset: median (min, max)	2.0 (1, 4)	1.0 (1, 7)	2.0 (1, 4)	1.0 (1, 5)
Duration: median (min, max)	1.0 (1, 8)	1.0 (1, 9)	2.0 (1, 10)	1.0 (1, 12)
Persisted beyond 7 days	1/1511	1/749	2/1501	2/741
Pain at injection site				
Day of onset: median (min, max)	1.0 (1, 6)	1.0 (1, 6)	1.0 (1, 7)	1.0 (1, 7)
Duration: median (min, max)	2.0 (1, 10)	1.0 (1, 10)	2.0 (1, 11)	1.5 (1, 12)
Persisted beyond 7 days	7/1511	8/748	6/1501	5/740
Any solicited systemic reaction				
Day of onset: median (min, max)	2.0 (1, 7)	1.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 22)	1.0 (1, 19)	1.0 (1, 51)	1.0 (1, 10)
Persisted beyond 7 days	29/1511	15/749	30/1501	13/741

	BNT162b2 10 µg Dose 1	Placebo Dose 1	BNT162b2 10 µg Dose 2	Placebo Dose 2
Fever				
Day of onset: median (min, max)	2.0 (2, 7)	2.5 (1, 7)	2.0 (1, 7)	6.0 (2, 7)
Duration: median (min, max)	1.0 (1, 3)	1.0 (1, 3)	1.0 (1, 5)	1.0 (1, 5)
Persisted beyond 7 days	0	0	0	0
Fatigue				
Day of onset: median (min, max)	2.0 (1, 7)	1.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 21)	2.0 (1, 9)	1.0 (1, 14)	1.0 (1, 10)
Persisted beyond 7 days	16/1511	7/748	17/1501	6/740
Headache				
Day of onset: median (min, max)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 22)	1.0 (1, 19)	1.0 (1, 51)	1.0 (1, 9)
Persisted beyond 7 days	12/1511	9/748	10/1501	6/740
Chills				
Day of onset: median (min, max)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 10)	1.0 (1, 7)	1.0 (1, 8)	1.0 (1, 8)
Persisted beyond 7 days	3/1511	0	1/1501	1/740
Vomiting				
Day of onset: median (min, max)	4.0 (1, 7)	4.0 (1, 6)	2.0 (1, 6)	3.0 (2, 6)
Duration: median (min, max)	1.0 (1, 5)	1.0 (1, 1)	1.0 (1, 2)	1.0 (1, 5)
Persisted beyond 7 days	0	0	0	0
Diarrhea				
Day of onset: median (min, max)	3.0 (1, 7)	3.0 (1, 7)	3.0 (1, 7)	4.0 (1, 7)
Duration: median (min, max)	1.0 (1, 8)	1.0 (1, 6)	1.0 (1, 28)	1.0 (1, 9)
Persisted beyond 7 days	1/1511	0	2/1501	2/740
New or worsened joint pain				
Day of onset: median (min, max)	2.0 (1, 6)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 7)	1.0 (1, 4)	1.0 (1, 18)	1.0 (1, 6)
Persisted beyond 7 days	0	0	1/1501	0
New or worsened muscle pain				
Day of onset: median (min, max)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 9)	1.0 (1, 8)	1.0 (1, 9)	1.0 (1, 6)
Persisted beyond 7 days	1/1511	1/748	3/1501	0

a. n = Number of participants with the specified reaction persisted beyond 7 days.
b. N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.

7.7.3 Subgroup analyses of solicited adverse reactions

Subgroup analyses were performed for solicited adverse reactions, comparing BNT162b2 and placebo groups by sex, race, ethnicity, and baseline SARS-CoV-2 status at baseline. No notable differences were observed among the study groups, although certain subgroups such as Black or African American race and Hispanic/Latino ethnicity had too few participants to draw meaningful conclusions.

7.7.4 Unsolicited adverse events

In 1 group of participants (cohort 1; initial enrollment cohort), non-serious adverse events from Dose 1 through up to 30 days after Dose 2 up to the cut-off date of September 06, 2021, in ongoing follow up were reported by 10.9% of Pfizer BioNTech COVID-19 Vaccine (10 mcg modRNA) recipients and by 9.1% of placebo recipients. In this group of participants, >99% had follow-up 30 days post Dose 2. In a second group of participants (cohort 2; expansion cohort) for which the median follow-up was 2.4 weeks (range 0 – 3.7 weeks), non-serious adverse

events from Dose 1 through the cut-off date of October 8, 2021, were reported by 7.1% of Pfizer BioNTech COVID-19 Vaccine (10 mcg modRNA) recipients and by 6.3% of placebo recipients.

In the initial enrollment cohort, from Dose 1 through 30 days after Dose 2, lymphadenopathy was reported in 13 (0.9%) participants in the Pfizer BioNTech COVID-19 Vaccine (10 mcg modRNA) group vs. 1 (0.1%) in the placebo group. In the expansion cohort, from Dose 1 through the cut-off date, lymphadenopathy was reported in 6 (0.4%) participants in the Pfizer BioNTech COVID-19 Vaccine (10 mcg modRNA) group vs. 3 (0.4%) in the placebo group. There were no other notable patterns between treatment groups for specific categories of non-serious adverse events that would suggest a causal relationship to Pfizer BioNTech COVID 19 Vaccine.

7.7.5 SAEs

In Cohort 1 (median of 2.3 months follow-up post Dose 2), SAEs occurred at frequency of 0.1% in both BNT162b2 and placebo recipients. For BNT162b2 recipients, only one SAE was reported, an upper limb fracture. In Cohort 2 (median of 2.4 weeks follow-up post Dose 2), 3 BNT162b2 recipients (0.2%) reported a SAE: 1 infection of the knee, 1 foreign body ingestion, and 1 epiphyseal fracture. All SAEs reported in the study were considered by the study investigator to be unrelated to vaccination. FDA agrees with this assessment.

Deaths: No deaths have occurred during the study in either Cohort 1 or 2.

7.7.6 AEs of clinical interest

FDA conducted Standardized MedDRA Queries (SMQs) to evaluate for constellations of unsolicited AEs among recipients 5-11 years of age in study C4591007 Phase 2/3 Cohort 1 through the September 6, 2021, cut-off date. SMQs (narrow and broad in scope) were conducted on AE Preferred Terms (PTs) that could represent various conditions, including but not limited to angioedema, arthritis, cardiomyopathy, ischaemic heart disease, cardiac arrhythmia, cardiac failure, central nervous system vascular disorders, convulsions, demyelination, embolic and thrombotic events, hearing and vestibular disorders, hematopoietic cytopenias, hypersensitivity, peripheral neuropathy, thrombophlebitis, and vasculitis. For example, the cardiomyopathy SMQ includes PTs that may be related to myocarditis and pericarditis, such as chest pain, palpitations, dyspnea, syncope, troponin elevation, ECG with ST elevation or PR depression, pericardiac rub, or echocardiographic findings.

For Cohort 1, the SMQ analyses resulted in identification of 19 participants with AEs of interest in the SMQs (narrow and broad in scope) in the BNT162b2 group and 6 in the placebo group. The SMQ analyses revealed an imbalance of AEs potentially representing allergic reactions, with 14 participants in the vaccine group (0.92%) reporting hypersensitivity-related AEs (primarily skin and subcutaneous disorder including rash and dermatitis) compared with 4 participants in the placebo group (0.53%).

For Cohort 2, the SMQ analyses with respect to hypersensitivity identified 9 participants in the vaccine group (0.57%) and 4 in the placebo group (0.51%) reporting unsolicited AEs in this category, primarily skin and subcutaneous disorders of rash and dermatitis. The SMQ for angioedema was reported in 3 (0.19%) in the vaccine group compared to 1 (0.13%) in the placebo group. These events included one participant with both angioedema and urticaria, and 3 participants with urticaria.

One participant, a 6-year-old female in the BNT162b2 group, had a non-serious AE of Henoch-Schönlein purpura which was diagnosed 21 days after Dose 1 and was considered non-serious.

No new or unexpected adverse reactions were identified based on these SMQ results.

In Cohorts 1 and 2, “chest pain” was reported in a total of 12 participants: 6 assigned to the BNT162b2 group and 6 assigned to placebo. Chest pain resolved in all participants within 1-2 days of onset. No participants required a cardiac evaluation or ER visit, and none were hospitalized. In each case the AE was considered to be noncardiac in origin.

7.7.7 AEs leading to study withdrawal

In C4591007 Phase 2/3 Cohort 1, there were no AEs leading to withdrawal. In Cohort 2 with a follow up cut-off of October 8, 2021, 1 participant was withdrawn due to AEs of fever 2 days after Dose 1 and worsening of neutropenia (previously diagnosed as benign transient neutropenia. Dose 2 was not administered.

7.8 Study C4591007 Phase 2/3 summary

This EUA request included safety data from 1,518 BNT162b2 recipients and 750 placebo (saline) recipients 5-11 years of age in the Phase 2/3 portion (Cohort 1) of an ongoing clinical trial, C4591007; Among Cohort 1 participants, 95.1% had safety follow up ≥2 months after Dose 2 at the time of the September 6, 2021, data cut-off. Safety data from an additional 1,591 BNT162b2 recipients and 788 placebo recipients from the Phase 2/3 portion of the trial (Cohort 2) were provided for assessment of SAEs and other AEs of interest (e.g., myocarditis, pericarditis, anaphylaxis); the median duration of follow-up was 2.4 weeks post-Dose 2 at the time of the October 8, 2021, data cut-off for Cohort 2.

Immunobridging success criteria were met for geometric mean neutralizing antibody titers and seroresponse rates at 1 month post-Dose 2 against the USA_WA1/2020 reference strain, as assessed by 50% mNG microneutralization assay, among children 5-11 years of age in study C4591007 Cohort 1 compared to study participants 16-25 years of age randomly selected from study C4591001. Subgroup immunogenicity analyses by age, gender, race and ethnicity, obesity and baseline SARS-CoV-2 status showed no notable differences compared to the overall study population, although some subgroups were too small to draw meaningful conclusions. Descriptive immunogenicity analyses, based on 50% plaque reduction neutralization test (PRNT), showed that a 10 µg BNT162b2 primary series elicited PRNT neutralizing titers against the reference strain and B.1.617.2 (Delta) strain in participants 5-11 years of age (34 BNT162b2, 4 placebo). Lastly, in a supplemental descriptive efficacy analysis, VE against symptomatic COVID-19 after 7 days post-Dose 2 as of the October 8, 2021, data cut-off was 90.7% (2-sided 95% CI: 67.7%, 98.3%) in participants 5-11 years of age without prior evidence of SARS-CoV-2 infection; 3 cases of COVID-19 occurred in the BNT162b2 group and 16 in the placebo group. All cases of COVID-19 occurred in participants 5-11 years of age without prior history of SARS-CoV-2 infection, and most occurred during July-August 2021. At the time of data cut-off, no cases met the criteria for severe COVID-19 infection.

Solicited local and systemic ARs generally occurred more frequently after Dose 2, and the most commonly reported solicited ARs were pain at the injection site (71%), fatigue (39.4%), and headache (28%). Most local and systemic reactions were mild to moderate in severity, with median onset 2 days post-vaccination, and resolved within 1 to 2 days after onset. The most frequently reported unsolicited adverse event (AE) in Cohort 1, lymphadenopathy was reported

in 13 BNT162b2 recipients (0.9%); in Cohort 2, lymphadenopathy was reported in 6 BNT162b2 recipients (0.4%). In Cohort 1, more BNT162b2 recipients (n=14; 0.92%) reported hypersensitivity-related AEs (primarily skin and subcutaneous disorder including rash and dermatitis) than placebo recipients (n=4; 0.53%). For Cohort 2, hypersensitivity reactions were reported in 9 participants (0.6%) in the BNT162b2 group; events included a Type IV hypersensitivity reaction and other rashes. Overall, from the combined safety database of 3,109 BNT162b2 participants, 4 BNT162b2 participants reported a SAE, and all of the SAEs were considered unrelated to vaccination. One BNT162b2 recipient withdrew from the study due to fever (40.1ºC) that occurred 2 days after Dose 1 and neutropenia that had worsened from baseline; the neutropenia was related to a pre-existing condition. There were no reports of myocarditis/pericarditis or anaphylaxis, and no participant deaths. Subgroup safety analyses by gender, race and ethnicity, obesity and baseline SARS-CoV-2 status showed no notable differences compared to the overall study population, although some subgroups were too small to draw meaningful conclusions.

8 FDA REVIEW OF OTHER INFORMATION SUBMITTED

8.1 Chemistry, Manufacturing, and Control (CMC) information

The currently authorized/approved Pfizer-BioNTech COVID-19 vaccine, mRNA (BNT162b2), is formulated in phosphate-buffer saline (PBS) containing sodium chloride and potassium chloride (referred to as PBS/Sucrose formulation), and this formulation was used in Study C4591007. To provide a vaccine with an improved stability profile and greater ease of use at vaccine distribution sites, Pfizer/BioNTech have developed a new drug product (DP) formulation using tromethamine (Tris) buffer (referred to as Tris/Sucrose formulation). The new formulation no longer contains sodium chloride and potassium chloride. The BNT162b2 Tris/Sucrose vaccine product is formulated at 0.1 mg/mL of mRNA in 10 mM Tris, 300 mM sucrose, pH 7.4. For use in children 5-11 years of age, the Tris/Sucrose DP is filled at 1.3 mL fill volume in glass vials and requires dilution with 1.3 mL 0.9% sodium chloride for injection prior to administration. After dilution, each vial provides a total of 10 doses of 10-µg mRNA, each in 0.2 mL injection volume.

The Tris/Sucrose DP is currently manufactured using facilities already authorized or approved for the manufacture of the PBS/Sucrose DP. The manufacturing process for the Tris/Sucrose DP uses the same drug substance (DS) and the same lipids and has the same initial steps as for the current PBS/Sucrose formulation, including the steps of (b) (4) and (b) (4) Changes are implemented in the formulation buffer (from PBS to Tris) during the (b) (4) DP formulation unit operations. Subsequent steps of sterile filtration, aseptic filling, labeling and freezing for storage are essentially the same between the two formulations with only adjustments to reflect the different fill volumes. The Tris/Sucrose DP manufacturing process was validated by process-performance qualification (PPQ) execution, including production of 3 PPQ lots filled at 2.25 mL, supporting the 30-µg mRNA dose, and two PPQ lots filled at 1.3 mL, supporting the 10-µg mRNA dose. The validation results demonstrated that with a well-defined process protocol, consistent manufacturing of the BNT162b2 Tris/Sucrose DP can be achieved for both fill volumes.

Analytical comparability was demonstrated for the Tris/Sucrose DP when compared with the currently authorized/approved PBS/sucrose DP based on in-process test results, final DP release test results and characterization test results. Analytical comparability uses laboratory testing to demonstrate that a change in product formulation does not impact a product's safety or effectiveness. In the case of a lipid nanoparticle containing mRNA such as BNT162b2 multiple different release parameters are evaluated, ranging from product appearance to size of

the lipid-nanoparticle to the integrity of the mRNA in the product. Release and characterization tests include tests for purity, composition, and critical attributes of mRNA associated with the activity of the vaccine

In this case, analytical comparability to the current PBS/Sucrose formulation was demonstrated for the Tris/Sucrose DP through a combination of release and characterization testing. Comparability was established for the three PPQ Tris/Sucrose DP lots manufactured at production scale and filled at a volume of 2.25 mL.

The manufacturing specifications for the Tris/Sucrose DP are based on those established for the authorized/approved PBS/Sucrose DP and are not affected by the change from the PBS/Sucrose to the Tris/Sucrose buffer. The analytical procedures for Tris/Sucrose DP release and stability testing are identical to the corresponding PBS/Sucrose procedures with the exception of an update to include minor modifications in sample preparations to account for the difference in mRNA concentration between the two formulations. Validation of each assay method for the Tris/Sucrose DP was performed and the validation results have demonstrated that all the analytical procedures are suitable for their intended use.

Based on the available stability data for the Tris/Sucrose DP and the established 9-month expiry for the PBS/Sucrose DP, the initial shelf-life for the BNT162b2 Tris/Sucrose vaccine product is 6 months when stored frozen between -90°C to -60°C. The available stability data also support storage at 2-8°C for up to 10 weeks once the frozen Tris/Sucrose vaccine has been thawed. At the vaccine administration sites, the 10 µg Tris/Sucrose DP vials can be stored at 2°C to 25°C for up to 24 hours. However, after the first puncture, the vaccines must be used within 12 hours. This proposed in-use shelf-life is supported by compatibility assessment and microbial in-use challenge studies.

Taken together, the analytical comparability assessment demonstrated that the Tris/Sucrose DP lots are comparable to the previously authorized/approved BNT162b2 PBS/Sucrose DP. The results further support the capability of the commercial manufacturing process to produce a consistent Tris/Sucrose DP with acceptable quality.

The manufacture of the Pfizer-BioNTech COVID-19 Vaccine is performed at a number of facilities. For each of these facilities, FDA requested and reviewed information on equipment, facilities, quality systems and controls, container closure systems as well as other information as per the guidance, “Emergency Use Authorization for Vaccines to Prevent COVID-19, February 2021”, to ensure that there is adequate control of the manufacturing processes and facilities.

In particular, the following information was assessed:

- Facilities appear to be adequately designed and maintained and manufacturing process, personnel, air direction and waste flow are suitable for manufacturing.
- Multiple product manufacturing areas and equipment used to manufacture the COVID-19 vaccine were assessed and cleaning and changeover procedures were evaluated and appear adequate. Cross-contamination controls appear suitable to mitigate risk of cross contamination.
- The successful qualification of critical equipment for drug substance and drug product manufacturing was verified.
- Aseptic process information and validation studies were assessed and appear acceptable.

- Drug product solution sterilization by filtration was reviewed and appears acceptable.
- Sterilization and depyrogenation of pertinent equipment and materials, including container/closure components, description and validation studies appear acceptable.
- Utilities qualification studies including HVAC systems, appear adequate. Air cleanliness of the manufacturing cleanrooms were adequately controlled and maintained.
- Container/closure integrity studies to ensure sterility of drug product in the final container were conducted and appear adequate.

FDA also performed inspections at two facilities, reviewed the inspectional histories of all applicable facilities and all available information to ascertain whether each facility meets current good manufacturing practice requirements. We find that all the facilities are adequate to support the use of the Pfizer-BioNTech COVID-19 Vaccine under EUA for individuals five years of age and older.

8.2 Pharmacovigilance activities

Pfizer submitted a revised pharmacovigilance plan to monitor safety concerns that could be associated with BNT162b2 in individuals 5-11 years of age. The plan includes the following safety concerns:

- Important Identified Risks: anaphylaxis, myocarditis, and pericarditis
- Important Potential Risks: Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease.

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 (MIS)
- 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.
- Periodic safety reports containing an aggregate review of safety data including assessment of AEs; vaccine administration errors, whether or not associated with an AE; and newly identified safety concerns.
- Post-authorization observational studies, that would be modified to encompass the evaluation of children 5-11 years of age 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 U.S. population of all ages, pregnant women, the immunocompromised, and persons with a prior history of COVID-19 within selected data sources participating in the U.S. 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 assess the potential increased risk of events of interest, including myocarditis/pericarditis, after being vaccinated with at least one dose of the Pfizer-BioNTech COVID-19 Vaccine.

- Study C4591021 Substudy: Substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY

  Objective: To describe the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within one year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine.

- 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]). Working title: *Myocarditis/pericarditis follow-up study within the Pediatric Heart Network*

  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 5-11 years of age in Study C4591014 entitled “Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study Kaiser Permanente Southern California.”

8.3 Clinical assay information

The SARS-CoV-2 mNG microneutralization assay used in the Phase 2/3 clinical study C4591007 measures neutralizing antibodies (50% inhibition titers) against SARS-CoV-2 using Vero cell monolayers in a 96-well plate format. The SARS-CoV-2 mNG virus is derived from the USA_WA1/2020 strain that had been rescued by reverse genetics and engineered to express a fluorescent reporter gene (mNeonGreen) upon productive infection of cells. The validation protocol (that includes evaluation of dilutional linearity, precision, limits of quantification, and limit of detection) and the results of the validation study, executed at Pfizer Hackensack Meridian Health Center (Nutley, New Jersey), were submitted to support the suitability of the assay for neutralizing antibody assessment against the USA_WA1/2020 strain.

Additionally, a plaque reduction neutralization test (PRNT) was used to determine neutralizing titers against the reference USA_WA1/2020 strain and the SARS-CoV-2 virus Delta variant (a recombinant virus with Delta variant spike gene on the USA_WA1/2020 genetic background). The PRNT is a non-validated assay and was used for exploratory purposes only.

8.4 Inspection of clinical study sites

The review team decided that Bioresearch Monitoring (BIMO) inspections are not needed to support the review of this EUA amendment. Sites under this study had been previously inspected.

8.5 EUA prescribing information and fact sheets

The Full EUA Prescribing Information, Fact Sheet for Health Care Providers Administering Vaccine (Vaccination Providers), and Vaccine Information Fact Sheet for Recipients and Caregivers were reviewed, and suggested revisions were sent to the Sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

For the Fact Sheets applicable for the 12 years and older population, certain information has been updated to reflect changes made to the scope of the October 29, 2021 authorization. For example, certain portions of the fact sheets have been revised to: refer to the use of different color caps; identify the availability of the new formulation; clarify the new age groups for whom the vaccine is authorized; and explain which dosage may be used for individuals who receive their first dose at age 11 and turn 12 years old before their second dose. In addition, we made additional changes to address the potential that the previous versions of the fact sheets created confusion. For example, we removed a sentence from the fact sheets stating that COMIRNATY and the Pfizer-BioNTech COVID-19 Vaccine are "legally distinct with certain differences that do not impact safety or effectiveness." Communicating the legal relationship of the different products did not appear relevant to the target audience of these fact sheets, as the more relevant information for them is that when prepared according to their respective instructions for use, the FDA-approved COMIRNATY and the two EUA-authorized formulations of Pfizer-BioNTech COVID-19 Vaccine for ages 12 years of age and older can be used interchangeably without presenting any safety or effectiveness concerns. We continue to explain in the Letter of Authorization that the original formulation of the Pfizer-BioNTech COVID-19 Vaccine and COMIRNATY are legally distinct with certain differences that do not impact safety or effectiveness.

9 BENEFIT/RISK IN THE CONTEXT OF THE PROPOSED EUA FOR PFIZER-BIONTECH COVID-19 VACCINE IN CHILDREN 5-11 YEARS OF AGE

9.1 Known and potential benefits

Available data support the effectiveness of the Pfizer-BioNTech COVID-19 Vaccine in preventing symptomatic COVID-19 among children 5-11 years of age. The immunobridging analyses from study C4591007 met pre-specified success criteria that allow for inference of vaccine effectiveness in this age group. Furthermore, direct evidence for clinical benefit is provided by a preliminary descriptive analysis of VE against symptomatic COVID-19 of any severity, with a VE point estimate of 90.7% (2-sided 95% CI: 67.7%, 98.3%) compared with placebo. This VE point estimate is similar to the estimated VE among adults in enrolled in the Phase 3 placebo-controlled efficacy trial that supported the original EUA authorization as well as VE estimates in adults from real-world observational studies. While no cases of severe COVID-19 were accrued during study follow-up to date, it is highly likely that vaccine effectiveness against severe COVID-19 among children 5-11 years of age will be even higher than vaccine effectiveness against non-severe COVID-19, as is the case in adults. Prevention of symptomatic COVID-19 will also likely result in prevention of sequelae such as post-COVID symptoms (also known as "long COVID") and MIS-C. Since the overall burden of COVID-19 is lower in children 5-11 years of age compared with adults, the individual-level and population-level benefits of the vaccine, in particular among healthy vaccine recipients at low risk of severe COVID-19, are expected to be lower in children 5-11 years of age than in adults and will depend largely on the incidence of COVID-19 (see Section 9.5). Nonetheless, given the uncertainty of the COVID-19 pandemic and likelihood of continued SARS-CoV-2 transmission during over the ensuing

months, widespread deployment of the vaccine for use among children 5-11 years of age will likely have a substantial effect on COVID-19 associated morbidity and mortality in this age group. The impact of measures currently in place to mitigate against SARS-CoV-2 transmission in settings where children congregate with other children and with adults also contributes to consideration of vaccine benefits in this age group. If these measures were relaxed, the potential benefits of vaccination in this age group would be even greater.

9.2 Data gaps related to benefits

The data gaps associated with benefits of the Pfizer-BioNTech COVID-19 vaccine when used in children 5-11 years of age include the following:

- Duration of protection and potential need for booster doses.
- Effectiveness in certain populations at high risk of severe COVID-19, including highly immunocompromised children.
- Benefits (and in particular the need for a 2-dose primary series) in children previously infected with SARS-CoV-2 relative to those who have not been previously infected; despite these uncertainties, however, available data support that previously infected individuals are susceptible to re-infection.
- Future vaccine effectiveness as influenced by characteristics of the pandemic, including emergence of new variants.
- Vaccine effectiveness against asymptomatic infection.
- Vaccine effectiveness against transmission of SARS-CoV-2.

9.3 Known and potential risks

In children 5-11 years of age, there were higher rates of solicited local and systemic adverse reactions, lymphadenopathy, and hypersensitivity reactions in vaccine recipients than placebo recipients. Overall, the rates of these adverse reactions reported among children 5-11 years of age were lower than those reported among older age groups and likely reflect the lower vaccine mRNA content evaluated in children 5-11 years of age. In considering unsolicited adverse events reported among children 5-11 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 vaccine recipients 16 years of age and older (similar in magnitude to reported rates of anaphylaxis following 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 pharmacovigilance plan 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 5-11 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, most of whom had at least 2 weeks of follow-up post-Dose 2. However, this safety database is not large enough to quantify the frequency of this uncommon adverse reaction. Data supporting that the risk of vaccine-associated myocarditis may be lower among children 5-11 years of age compared with adolescents 16-17 years of age include a lower rate of vaccine-associated myocarditis among adolescents 12-15 years of age compared with adolescents 16-17 years of age, a lower incidence of myocarditis in the pre-COVID era among children 5-11 years of age compared with adolescents, and lower rates of systemic reactogenicity in children 5-11 years of age associated with the lower vaccine mRNA content intended for use in this age group.

9.4 Data gaps related to risks

The data gaps associated with risks of the Pfizer-BioNTech COVID-19 vaccine when used in children 5-11 years of age include the following:

- Risk of myocarditis/pericarditis, as described in detail in Section 9.3 above.
- 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.

9.5 Quantitative benefit-risk assessment for children 5-11 years of age

FDA conducted a quantitative benefit-risk assessment for use of a Pfizer-BioNTech COVID-19 Vaccine 2-dose primary series in children 5-11 years of age. The key benefits assessed include preventable COVID-19 cases, hospitalizations, intensive care unit (ICU) admissions and deaths due to COVID-19. The key risks include excess myocarditis/pericarditis cases, and related hospitalizations, ICU admissions, and deaths attributable to myocarditis/pericarditis. The benefits and risks are assessed per million fully vaccinated individuals with and without stratification by sex, and with comparison to age groups 12-15 years and 16-17 years.

The model assesses the benefits of vaccine protection in a 6-month period after completion of the primary series. The model assumes VE of 70% against COVID-19 cases and 80% against COVID-19 associated hospitalization based on a CDC vaccine effectiveness study for ages 20+ years during circulation of the Delta variant.[48] The incidence rates of COVID-19 cases for the week of September 11, 2021, are obtained from COVID-NET for all sex/age groups. COVID-NET covers approximately 10 percent of the U.S. population. Four-week averages of incidence rate for hospitalizations (week ending on 8/21/2021 to week ending on 9/11/2021) are used due to the variability in rates given the small numbers of hospitalizations per age/sex group. Estimates for the percentage of hospitalizations resulting in ICU admission and the percentage of hospitalized patients who die are based on cumulative rates of hospitalizations, ICU admissions, and deaths for each sex/age groups reported in COVID-NET since March 2020. The death rate among 5-11 year-olds is lower in COVID-NET than in other national data sources such as the CDC COVID-19 Data Tracker. This could be due to geographic differences in case reporting and the recent trajectory of the pandemic. This difference will lead to a conservative estimate of benefits in the model. The model assumes that incidence rates of COVID-19 cases and hospitalizations remain constant over the assessment period of 6 months.

The estimates for excess myocarditis/pericarditis among fully vaccinated individuals ages 12-15 years and ages 16-17 years are based on Optum healthcare claims data for the period 12/10/2020 to 07/10/2021, which is a conservative approach that includes non-confirmed cases. For this analysis the estimate for ages 12-15 years is applied to ages 5-11 years because vaccine-associated myocarditis/pericarditis data are not available for this age group. The proportions of vaccine-attributable myocarditis/pericarditis hospitalizations and ICU admissions are obtained from Vaccine Safety Datalink (12-17 year-old group[49]). Some of these hospitalizations and ICU admissions may be precautionary and therefore not clinically equivalent to COVID-19 hospitalizations and ICU admissions. The dose intended for use in children 5-11 years of age (10 µg), is lower than the dose used under EUA in adolescents 12-15 years of age (30 µg), and the observed systemic reactogenicity associated with the respective antigen contents in clinical trials is lower for children 5-11 years of age as well. Thus, assuming the same rate of vaccine-associated myocarditis for children 5-11 years of age as has been observed for adolescents 12-15 years of age in Optum claims data may be a conservative overestimate.

The model inputs described above were used to develop “Scenario 1,” a base model from which five alternative scenarios were derived to address key uncertainties associated with model inputs. The model’s results indicate that the incidence of COVID-19 is highly influential to the benefits of the vaccine. To account for uncertain dynamics of the pandemic, FDA assesses the benefits and risks under Scenario 2 with COVID-19 incidence close to recent peak, and Scenario 3 with COVID-19 incidence close to the lowest recorded incidence since the beginning of the pandemic. These two scenarios provide likely bounds for potential future states of the pandemic. Scenario 4 (90% vaccine efficacy against cases and 100% efficacy against hospitalizations) tests the impact on benefits and risks of potentially higher vaccine efficacy suggested by the Sponsor’s newly submitted descriptive efficacy analysis (see Section 7.6). Scenario 5 with a 3x multiple of the death rate is used to match the cumulative death rate for 5-11 year-olds seen in CDC Data Tracker. Scenario 6 uses a 50% lower rate of attributable myocarditis than Scenario 1 to address the uncertainty associated with the rate of vaccine-attributable myocarditis in children 5-11 years, for whom the data is not available.

The results of the benefit-risk assessment are summarized in Table 13 below. The results predict that under Scenarios 1 (base), 2 (peak COVID incidence), 4 (high efficacy), and 5 (high COVID death rate), and 6 (low attributable myocarditis rate) the benefits of the Pfizer-BioNTech COVID-19 Vaccine 2-dose primary series outweigh the risks for ages 5-11 years. Under Scenario 3 (low incidence), the model predicts more excess hospitalizations due to vaccine-related myocarditis/pericarditis compared to prevented hospitalizations due to COVID-19 in males and in both sexes combined. However, in consideration of the different clinical implications of hospitalization for COVID-19 versus hospitalization for vaccine-associated myocarditis/pericarditis, and benefits related to prevention of non-hospitalized cases of COVID-19 with significant morbidity, the overall benefits of the vaccine may still outweigh the risks under this low incidence scenario. If the myocarditis/pericarditis risk in this age group is lower than the conservative assumption used in the model, the benefit-risk balance would be even more favorable.

Table 13. Model-Predicted Benefit-Risk Outcomes of Scenarios 1-6 per One Million Fully Vaccinated Children 5-11 Years Old

Sex	**Benefit**: Prevented COVID-19 Cases	**Benefit**: Prevented COVID-19 Hospitaliza-tions	**Benefit**: Prevented COVID-19 ICU Admissions	**Benefit**: Prevented COVID-19 Deaths	**Risk**: Excess Myocarditis Cases	**Risk**: Excess Myocarditis Hospitaliza-tions	**Risk**: Excess Myocarditis ICU Admissions	**Risk**: Excess Myocarditis Deaths
Males & Females								
Scenario 1	45,773	192	62	1	106	92	34	0
Scenario 2	54,345	250	80	1	106	92	34	0
Scenario 3	2,639	21	7	0	106	92	34	0
Scenario 4	58,851	241	77	1	106	92	34	0
Scenario 5	45,773	192	62	3	106	92	34	0
Scenario 6	45,773	192	62	1	53	46	17	0
Males only								
Scenario 1	44,790	203	67	1	179	156	57	0
Scenario 2	54,345	250	82	1	179	156	57	0
Scenario 3	2,639	21	7	0	179	156	57	0
Scenario 4	57,857	254	83	1	179	156	57	0
Scenario 5	44,790	203	67	3	179	156	57	0
Scenario 6	44,790	203	67	1	89	78	29	0
Females only								
Scenario 1	45,063	172	54	1	32	28	10	0
Scenario 2	54,345	250	78	2	32	28	10	0
Scenario 3	2,639	21	7	0	32	28	10	0
Scenario 4	57,938	215	67	2	32	28	10	0
Scenario 5	45,063	172	54	4	32	28	10	0
Scenario 6	45,063	172	54	1	16	14	5	0

Scenario 1: COVID-19 incidence as of September 11, 2021, VE 70% vs. COVID-19 cases and 80% vs. COVID-19 hospitalization.
Scenario 2: COVID-19 incidence at peak of U.S. Delta variant surge at end of August 2021, VE 70% vs. COVID-19 cases and 80% vs. COVID-19 hospitalization.
Scenario 3: COVID-19 incidence as of nadir in June 2021, VE 70% vs. COVID-19 cases and 80% vs. COVID-19 hospitalization.
Scenario 4: COVID-19 incidence as of September 11, 2021, VE 90% vs. COVID-19 cases and 100% vs. COVID-19 hospitalization.
Scenario 5: COVID-19 case incidence as of September 11, 2021, VE 70% vs. COVID-19 cases and 80% vs. COVID-19. hospitalization, COVID-19 death rate 300% that of Scenario 1.
Scenario 6: COVID-19 incidence as of September 11, 2021, VE 70% vs. COVID-19 cases and 80% vs. COVID-19 hospitalization, excess myocarditis cases 50% of Scenario 1.

10 VRBPAC SUMMARY

The 170th meeting of the VRBPAC was held on October 26, 2021, to discuss the data submitted by Pfizer in support of the EUA amendment request and other data to inform benefits and risks of the Pfizer-BioNTech COVID-19 Vaccine in children 5-11 years of age. In addition to presentations from the Center for Disease Control and Prevention on the epidemiology of COVID-19 in children and on known safety signals, Pfizer and the FDA presented data from Study C4591007, and the FDA also presented a benefit-risk analysis modeling use of the vaccine in the intended population. The Committee's discussion focused on the benefits and risks of the vaccine, and associated uncertainties, taking into account the current trend of the pandemic. There was concern expressed that some populations, such as those with comorbidities, might benefit more from the vaccine than healthy children who are generally at low risk of serious complications of COVID-19, in particular those who have previously been infected with SARS-CoV-2 and may already benefit from natural immunity against currently

circulating variants. The voting question presented to the Committee was “Based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 Vaccine when administered as a 2-dose series (10 µg each dose, 3 weeks apart) outweigh its risks for use in children 5-11 years of age.” The vote was 17 yes, 0 no, and 1 abstain. Several of those voting yes explained that they wanted to make the option of vaccination available to this age group based on individual considerations. In explaining their votes a few of the committee members noted their concern that the vaccine might be mandated at this time, given the uncertainties around benefit and risk balance in the setting of decreasing COVID-19 incidence and increasing SARS-CoV-2 seroprevalence in this age group. FDA representatives explained that FDA does not mandate vaccines for the general public and that vaccine mandates are outside the scope of FDA's decision making process. Some members also noted the importance of safety monitoring as well as the importance of obtaining more experience with the vaccine. A few other members noted that the availability of the vaccine will help children directly and potentially help reduce transmission of SARS-CoV-2.

11 OVERALL SUMMARY AND RECOMMENDATIONS

Following review of information submitted in support of the EUA request, the review team concludes that:

- As summarized in Section 6 of this review, the CBRN 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 described in Section 7 of this review, Pfizer-BioNTech COVID-19 Vaccine, when administered as a 2-dose primary series in children 5 -11 years of age, may be effective in preventing serious or life-threatening disease or condition that can be caused by SARS-CoV-2. Vaccine effectiveness was inferred by immunobridging based on a comparison of SARS-CoV-2 50% neutralizing antibody titers at one month after dose 2 in participants 5-11 years of age with those of young adults 16 to 25 years of age, the most clinically relevant subgroup of the study population in whom VE has been demonstrated. In the planned immunobridging analysis, the GMT ratio of neutralizing antibody titers (children to young adults) was 1.04% (95% CI: 0.93, 1.18) meeting the success criterion (lower bound of the 95% CI for the GMT ratio > 0.67 and the point estimate ≥1). In a descriptive immunogenicity analysis, seroresponse rates among participants without prior evidence of SAR-Co-V2 infection were seen in 99.2% percent of children and 99.2% percent of young adults, with a difference in seroconversion rates of 0 (95% CI -2.0, 2,2), meeting the prespecified success criteria of the lower limit of the 95% CI for the difference in seroresponse of greater than -10%. immunogenicity outcomes were consistent across demographic subgroups. Descriptive analyses from a randomly selected subset of participants (34 BNT162b2 recipients, 4 placebo recipients) with no evidence of infection up to 1 month post-Dose 2 demonstrated that a 10 µg primary series elicited PRNT neutralizing titers against both the reference strain and the Delta variant. In a supplemental efficacy analysis, VE after 7 days post-Dose 2 was 90.7% (95% CI: 67.7%, 98.3%); 3 cases of COVID-19 occurred in participants 5-11 years of age without prior history of SARS-CoV-2 infection, and most occurred during July-August 2021. Although based on a small number of cases and descriptive analysis, the supplemental VE data provide compelling direct evidence of clinical benefit in addition to the immunobridging data.

- Based on the data summarized in Section 7 and benefits and risks in Section 9 of this review, the known and potential benefits of the vaccine outweigh the known and potential risks when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 5-11 years of age. Known and potential benefits include reduction in the risk of symptomatic COVID-19 and associated serious sequelae. Potential benefits that could be further evaluated but are not necessary to support an EUA include prevention of COVID-19 in individuals with previous SARS-CoV-2 infection, reduction in asymptomatic SARS-CoV-2 infection and reduction of SARS-CoV-2 transmission. Known and potential risks include common local and systemic adverse reactions (notably injection site reactions, fatigue, headache, muscle pain, chills, fever and joint pain), less commonly lymphadenopathy, and hypersensitivity reactions (e.g., rash, pruritis, urticaria, angioedema), and rarely anaphylaxis and myocarditis/pericarditis (based on experience in Pfizer-BioNTech COVID-19 vaccine recipients 12 years of age and older). Risks that should be further evaluated include quantifying the rate of vaccine-associated myocarditis/pericarditis in this age group and surveillance for other adverse reactions that may become apparent with more widespread use of the vaccine and with longer duration of follow-up. Acknowledging the current uncertainties around benefits and risks, a quantitative analysis using conservative assumptions predicts that overall benefits of vaccination outweigh risks in children 5-11 years of age.

- COMIRNATY is the only FDA approved vaccine indicated for active immunization for prevention of COVID-19 caused by SARS-CoV-2. It is licensed as a 2-dose primary series given 3 weeks apart in individuals 16 years. The Pfizer-BioNTech COVID-19 vaccine is authorized as a 2-dose primary series given weeks apart in adolescents 12-15 years of age. A third dose is authorized for use, as part of the primary series, in immunocompromised individuals 12 years and older. A booster dose administered at least 6 months after completing a primary series is authorized for in use in individuals 65 years of age and older, individuals at high risk of severe COVID-19, and individuals 18-64 years of age with frequent institutional or occupational exposure to SARS-CoV-2. The Pfizer-BioNTech COVID-19 vaccine is authorized for use as a single heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine. No COVID-19 vaccine is currently available for use in children 5-11 years of age.

Based on the considerations outlined above, the review team recommends authorization of the Pfizer-BioNTech COVID-19 Vaccine under EUA for use as a 2-dose primary series (10 µg each dose, 3 weeks apart) in children 5-11 years of age.

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13 APPENDIX 1: C4591007 PHASE 1 (DOSE RANGING) – SUMMARY OF SAFETY AND IMMUNOGENICITY

During study C4591007 Phase 1, BNT162b2 was evaluated in U.S. children 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 SARS-CoV-2 infection. BNT162b2 dosages of 10 µg, 20 µg, then 30 µg were evaluated sequentially (n=16 participants per dosage) based upon the safety evaluation and recommendation by the internal review committee (IRC) to either advance to the subsequent dosage or terminate a specific dosage. Safety evaluation was the same as for Phase 2/3. SARS-CoV-2 50% neutralizing GMTs (SARS-CoV-2 mNG microneutralization assay) were assessed at 7 days after Dose 2.

Altogether, 48/49 (98%) of participants (assigned to the 10 µg, 20 µg, or 30 µg dosage groups combined) received two doses of BNT162b2 and completed the 1 month follow up visit after Dose 2. One BNT162b2 participant (20 µg dosage group) did not receive study vaccine. Following safety review of reactogenicity data from the initial 4 participants in the BNT162b2 30 µg dosage group, the IRC recommended to discontinue the 30 µg dosage, due to high frequencies of solicited ARs, and recommended that the remaining 12 participants receive the dosage selected for Phase 2/3 (i.e., 10 µg) at Dose 2. No participants from Phase 1 withdrew or discontinued from the study.

The frequencies of local and systemic adverse reactions were generally dose number and dosage dependent. Across dosages, systemic adverse reactions were generally mild and moderate in severity and resolved within 1 day of onset. No SAEs, deaths or AEs leading to withdrawal occurred at the time of data cut-off on July 16, 2021, with approximately 3 months of follow up. No participants reported anaphylaxis, myocarditis/pericarditis, or MIS-C. One BNT162b2 (30 µg) recipient reported Grade 1 axillary lymphadenopathy, which started 3 days after Dose 2 and resolved 17 days later; the AE was considered by the study investigator to be related to study intervention.

All four participants who received 30 µg for both doses developed mild-moderate redness and pain at the injection site, and 2 of the 4 participants developed swelling. In addition, all four subjects reported fevers to 38.9ºC with mild to moderate fatigue, and 2 of the 4 developed muscle pain of moderate severity following the second dose. One participant in the 20-µg group reported Grade 3 pyrexia (temperature to 39.7º C, also reported as a systemic adverse reaction, on Day 2 post-Dose 2), which resolved by Day 3. Both 10 and 20 µg dosages elicited similar

immune responses 7 days after Dose 2. In participants 5-11 years of age without evidence of SARS-CoV-2 infection up to 1 month post-Dose 2, the neutralizing antibody GMTs (NT50) at 1 month after Dose 2 were similar in the BNT162b2 10 μg and 20 μg groups (4163 and 4728, respectively).

The higher frequencies of solicited adverse reactions in participants receiving the 20 μg and 30 μg dosages, the favorable AE profile at the 10-μg dosage in participants 5-11 years of age followed for approximately 3 months after Dose 2, and the immunogenicity results demonstrating similar neutralizing antibody responses at the 10 and 20 μg dosages informed the IRC's decision to discontinue the 30-μg dosage and proceed to Phase 2/3 at the 10-μg dosage.

14 APPENDIX 2: COVID-19 AND SEVERE COVID-19 CASE DEFINITIONS

COVID-19

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

- Fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea as defined by ≥3 loose stools/day, vomiting

Severe COVID-19

Confirmed COVID-19 plus at least one of the following symptoms:

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