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Dear Sirs and Mesdames:

Re: Pfizer BioNTech COVID-19 Vaccine for use in children 5 through 11 years of age

Please find attached a copy of the Pfizer EUA Amendment Request for Pfizer BioNTech COVID-19 Vaccine (Pfizer Vaccine) for use in children 5 through 11 years of age.

This letter constitutes a request on behalf of Canadian parents of 5 to 11 year old children that a criminal investigation be immediately opened with regard to fraudulent submissions of Pfizer Corp. regarding the provision of the Pfizer Vaccine to children 5 through 11 years of age.

The attached document has been reviewed by a number of expert physicians specializing in pediatrics, epidemiology, and pathology, all of whom are of the view that the data submitted by Pfizer in support of its FDA EUA Amendment Request is fraudulent. Specifically, the most glaring and obvious example of this fraud, contrary to s. 380(1) of the *Criminal Code of Canada*, is found

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at Table 14 on p. 34 of the FDA briefing document. That table claims that the Pfizer Vaccine, if provided in a two-dose regimen to 5 to 11 year old children will prevent between 0 and 3 deaths of children per million fully-vaccinated children. That same table goes on to admit that the Pfizer Vaccine will cause between 53 and 106 excess myocarditis cases, 29 to 58 excess myocarditis hospitalizations, and 17 to 34 excess myocarditis ICU admissions.

This same table then remarkably makes the fraudulent and completely scientifically unsupportable claim that the Pfizer Vaccine will then cause **0 EXCESS MYOCARDITIS DEATHS** and fraudulently and misleadingly does not discuss or acknowledge any other potential causes of death. We are advised by our team of expert physicians that the potential causes of death ignored by Pfizer in its emergency use authorization application include anaphylaxis, pericarditis, capillary thrombosis, clotting disorders, strokes and transverse myelitis, to name a few.

In consultation with expert anaesthesiologists and pathologists, we are advised that other risks of death associated with the 17 to 34 "excess myocarditis ICU admissions" include respiratory infections and death associated with ventilators and other ICU-related mortality. This ignores the issue of children with injuries to their hearts significant enough to merit ICU admission not even surviving transport to hospital by ambulance.

It has been well documented that with regard to Pfizer's initial emergency use authorization application in the United States, that data regarding death related to transverse myelitis was scrubbed from the initial application and that Pfizer's original application for 12 to 18 year olds which was similarly fraught with fraudulent mis-statements as to the safety profile of the Pfizer Vaccine.

To suggest to the parents of Canada that this product is safe and will not kill or injure more Canadian 5 to 11 year old children than the notional 0 to 3 "prevented COVID-19 deaths" alluded to by Pfizer in its FDA EUA Application constitutes a fraud on the Canadian public and the Canadian Government.

On a related note, given Pfizer's clear admission of the limited benefit of the Pfizer Vaccine versus the risk of "Excess Myocarditis ICU Admissions", this product should not be approved by any responsible regulator on an emergency basis without at least 5 years of extremely limited testing in randomized controlled trials where parents whose children are being vaccinated are fully and properly informed that the risks to their children from the Pfizer Vaccine by far exceed the risk to those children from contracting COVID-19.

We respectfully request that the Royal Canadian Mounted Police and the Attorney General of Canada confirm that a criminal investigation is being opened with regard to these allegations.

Our office remains available to assist by providing access to the expert physicians that have reviewed this document in support of this criminal complaint.

On a related note, we respectfully request that the Prime Minister of Canada immediately release copies of the Pfizer and Moderna vaccine supply contracts. We are advised that these contracts contain exclusions of liability that confirm that neither Pfizer nor Moderna warrant the safety of

these products on the basis that the products were developed in haste, without adequate studies or testing, under emergency conditions.

Clearly, given that there is not a single documented case of any 5 to 11 year old child in Canada absent severe pre-existing comorbidities having died from COVID-19, there is clearly no urgency in licensing or approving a product that is more likely to kill children than it is to save them from any COVID-19-related mortality.

This letter serves as a notice of liability to Prime Minister Trudeau and Dr. Theresa Tam that in the event that these products are approved absent a complete criminal investigation being conducted, and that any child is harmed or killed by these products, a further complaint with regard to UNLAWFULLY CAUSING BODILY HARM under s. 269 of the *Criminal Code or Canada* or HOMICIDE or a complaint under the *War Crimes and Crimes Against Humanity Act* will be forthcoming as against any party approving the Pfizer Vaccine for 5 to 11 year old children.

Thank you in advance for your prompt acknowledgement of this criminal complaint.

Yours very truly,

RATH & COMPANY

Jeffrey R. W. Rath, B.A. (Hons.), LL.B. (Hons.)
Barrister & Solicitor

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

FDA Briefing Document

EUA amendment request for Pfizer-BioNTech COVID-19 Vaccine for use in children 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. This EUA request initially included safety data from 1,518 BNT162b2 recipients and 750 placebo (saline) recipients 5-11 years of age who are enrolled in the Phase 2/3 portion (Cohort 1) of an ongoing randomized, double-blinded, placebo-controlled 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 cutoff for this cohort. Safety data from an additional 1,591 BNT162b2 recipients and 788 placebo recipients enrolled in the Phase 2/3 portion (Cohort 2) of the trial were provided later during FDA's review of the EUA amendment request to allow for more robust assessment of serious adverse events and other adverse events of interest (e.g., myocarditis, pericarditis, anaphylaxis). The median duration of follow-up in Cohort 2 was 2.4 weeks post Dose 2 at the time of the October 8, 2021 data cutoff for this cohort. Vaccine effectiveness was inferred by immunobridging SARS-CoV-2 50% neutralizing antibody titers (NT50, SARS-CoV-2 mNG microneutralization assay). Neutralizing antibody titers at 1 month post-Dose 2 in children 5-11 years of age were compared to neutralizing antibody titers 1 month post-Dose 2 among a subset of study participants 16-25 years of age randomly selected from efficacy study C4591001 who had previously received two doses of 30 µg BNT162b2. A supplemental descriptive analyses of vaccine efficacy (VE) among Cohort 1 participants (following accrual of 19 total confirmed COVID-19 cases) was also provided during FDA's review of the EUA amendment request.

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 GMTs measured at 1 month after Dose 2 in study C4591007 Phase 2/3 Cohort 1 participants 5-11 years of age vs. GMTs at 1 month after Dose 2 in a randomly selected subset of study C4591001 Phase 2/3 participants 16-25 years of age, 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 the supplemental descriptive efficacy analysis, VE against symptomatic COVID-19 after 7 days post Dose 2 up to October 8, 2021 (data cutoff) was 90.7% (2-sided 95% CI: 67.4%, 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 cutoff, none of these cases met the criteria for severe COVID-19.

Solicited local and systemic adverse reactions (ARs) reported among Cohort 1 participants generally occurred more frequently after Dose 2, with the most commonly reported solicited ARs being 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 most resolved within 1 to 2 days after onset. The most frequently reported unsolicited adverse event (AE) in Cohort 1 BNT162b2 recipients was lymphadenopathy (n=13; 0.9%). 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%). Overall, from the combined safety database of 3,109 BNT162b2 recipients (Cohorts 1 and 2), 4 participants reported serious adverse events; all were considered by the study investigator and FDA as unrelated to vaccination. 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 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 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.

This October 26, 2021 VRPBAC meeting is being held to discuss whether, based on the totality of scientific evidence available, the benefits of the Pfizer-BioNTech COVID-19 Vaccine when administered as a 2-dose series (10 µg each dose, 3 weeks apart) outweigh its risks for use 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

[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.

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 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
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	Same population(s) as those eligible to receive a booster dose of the vaccine used for primary vaccination	October 20, 2021

Sponsor	Authorized Use (Interval)	Indicated Population	Date of EUA or EUA Amendment
	vaccine (same interval as authorized for a booster dose of the vaccine used for primary vaccination)		

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	Reissued September 16, 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]
• Sotrovimab	May 26, 2021	
• Casirivimab/imdevimab	Reissued September 9, 2021	
		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
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 vaccine efficacy 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 cutoff 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

Two cases of myocarditis have been reported in BNT162b2 recipients in study C4591001:

- A male participant ≥55 years of age, with no medical history, reported myocarditis 28 days after Dose 2 of BNT162b2; the event was assessed by the investigator as not related to the study intervention and was ongoing at the time of the data cutoff.
- 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 240 million doses of the Pfizer-BioNTech COVID-19 Vaccine have been administered in the U.S. (CDC COVID Data Tracker, accessed on October 22, 2021). Among all COVID-19 vaccines, 205,046 individuals less than 12 years of age have received at least one dose and 125,656 are fully vaccinated (CDC COVID Data Tracker, accessed on October 22, 2021).

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 in 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 does 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.

Anaphylaxis

Post-authorization surveillance has identified a risk of anaphylaxis, occurring at a rate similar to reported rates of anaphylaxis following licensed preventive vaccines, primarily in individuals with history of prior severe allergic reactions to other medications or foods.[42][43] Anaphylaxis is an important identified risk in the pharmacovigilance plan (PVP) 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 PVP 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 1,518 BNT162b2 and 750 placebo (saline) Phase 2/3 participants 5-11 years of age in ongoing clinical study, C4591007, of which a total of 1,444 (95.1%) had safety follow-up ≥2 months after Dose 2 at the time of a September 6, 2021 data cutoff, and data from an additional 1,591 BNT162b2 and 788 placebo participants with a median duration of follow-up of 2.4 weeks post-Dose 2 at the time of an October 8, 2021 data cutoff. 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. Each dose of this formulation contains 10 µg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 that is formulated in lipid particles and supplied as a frozen suspension in multiple dose vials.

To provide a vaccine with an improved stability profile, 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 and excludes sodium chloride and potassium chloride. The packaged vials for the new formulation are stored frozen at -90°C to -60°C. The frozen vials may be thawed and stored at refrigerator at 2°C to 8°C for up to 10 weeks.

The Pfizer-BioNTech COVID-19 Vaccine does not contain preservative. The vial stoppers are not made with natural rubber latex. For the 10-µg RNA dose, each 1.3-mL filled via vial must be diluted with 1.3mL 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.

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 vaccine efficacy 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 1528 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 cutoff 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; at the time of this Briefing Document was prepared, FDA has not fully verified the underlying data or Pfizer-BioNTech's conclusions from this analysis.

  - Cohort 2: A second cohort of 1,591 BNT162b2 (10 µg) recipients and 778 placebo recipients had a median duration of follow-up of 2.4 weeks post-Dose 2 at the time of data cutoff (October 8, 2021). Safety data from this cohort were provided for further assessment of SAEs and AEs of clinical interest. Data verification is in process, but not yet finished at the time this briefing book was completed.

- 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: 1,528	Ongoing

N=Number of randomized participants as of data cutoff dates July 16, 2021 (all Phase 1 participants), September 6, 2021 (Phase 2/3 Cohort 1: 1,518 BNT162b2, 750 placebo; includes participants starting March 24, 2021) and October 8, 2021 (Phase 2/3 cohort 2: 1,591 BNT162b2, 788 placebo; first subject in this second cohort randomized August 15, 2021).
*First participant, first visit was March 24, 2021.

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.

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 cutoff date (Phase 1: of July 16, 2021; Phase 2/3: September 6, 2021). AEs were categorized by frequency and maximum severity according to system organ class (SOC) and preferred term (PT), according to MedDRA, 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 cutoff dates:

- All Phase 1 participants: July 16, 2021
- Phase 2/3 Cohort 1: September 6, 2021; includes participants starting March 24, 2021
- Phase 2/3 Cohort 2: October 8, 2021; first subject in this cohort was randomized August 15, 2021

7.3 Disposition of Phase 2/3 participants

Cohort 1

Cohort 1 was comprised 1,528 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; 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 Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.

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

Cohort 2

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 cutoff, most participants (98.7%) had received both Dose 1 and Dose 2. Seven participants in the BNT162b2 group did not receive vaccine, for a Safety Population of 1,591. One participant in the BNT162b2 group discontinued from the vaccination period due to AEs of pyrexia and neutropenia that worsened from baseline (see Section 7.6.7, 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 safety population of participants who received BNT162b2 10 µg in Phase 2/3 study C4591007 Cohort 1 are summarized in Table 5 below. Participants were predominately White, with a mean age of approximately 8 years. Of the BNT162b2 recipients, 11.5% met the definition of obesity, 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: 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)
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)
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)
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.

Demographic and baseline characteristic categories with 0 participants in any treatment group are not shown to avoid inadvertent unblinding through public disclosure.
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 Visit 1 and no medical history of COVID-19.
f. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.

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 year-old vs. 7-8 year-old vs. 9-11 year-old), 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.

7.5.3 Efficacy evaluation

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 cutoff of October 8, 2021. The evaluable efficacy population included 1,450 participants randomized to BNT162b2 and 736 participants randomized to placebo.

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: 67.4%, 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.

7.6 Safety results

Please see the Appendix for Phase 1 study results.

Overview of adverse events: Phase 2/3

In C4591007 Phase 2/3 Cohort 1, e-diary data were collected on 1,511 participants 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 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 AEswere 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		
Any AE	166/1518 (10.9)	69/750 (9.2)
Unsolicited non-serious AE	166/1518 (10.9)	68/750 (9.1)
SAE	0/1518 (<0.1)	1/750 (0.1)
From Dose 1 through cutoff date[a] or participant unblinding[b]		
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. Sept 13, 2021 for 1,518 BNT162b2 and 750 placebo; Oct 8, 2021 for the additional 1,591 BNT162b2 and 788 placebo.
b. Three participants (2 BNT162b2, 1 placebo) turned 12 years of age during the course of the study and elig ble to received 30 µg BNT162b2 under EUA; for this reason, the participants were unblinded to their treatment assignment.

7.6.1 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).

7.6.2 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%), 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. Adverse reactions in BNT162b2 recipients that were graded as severe included 4 local reactions (3 participants with redness, 1 participant with swelling) and 1 systemic reaction (1 participant with muscle pain).

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 Dose 1 N=1,511 %	Placebo Dose 1 N=749 %	BNT162b2 Dose 2 N=1,501 %	Placebo Dose 2 N=741 %
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
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.
[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: 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 Dose 1 N=1,511 %	Placebo Dose 1 N=749 %	BNT162b2 Dose 2 N=1,501 %	Placebo Dose 2 N=741 %
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

Event	BNT162b2 Dose 1 N=1,511 %	Placebo Dose 1 N=749 %	BNT162b2 Dose 2 N=1,501 %	Placebo Dose 2 N=741 %
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
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.

[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°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.

f Severity was not collected for use of antipyretic or pain medication.

Table 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

	BNT162b2 10 µg Dose 1	Placebo Dose 1	BNT162b2 10 µg Dose 2	Placebo Dose 2
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
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

	BNT162b2 10 µg Dose 1	Placebo Dose 1	BNT162b2 10 µg Dose 2	Placebo Dose 2
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.

7.6.3 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.

7.6.4 Unsolicited adverse events

Information about unsolicited AEs was collected from Dose 1 to 1 month post-Dose 2. No unsolicited AEs were reported by ≥1% of participants.

In Cohort 1, the most common unsolicited AE was lymphadenopathy, which was reported in 13 (0.9%) participants in the BNT162b2 group, and 1 participant in the placebo group (0.1%). Additional unsolicited AEs reported more commonly in the BNT162b2 group than in the placebo group included otitis externa in 7 participants (0.5%), arthropod bite, nasal congestion, oropharyngeal pain, and rash in 5 participants (0.3%), each. In BNT162b2 recipients, the following AEs were considered Grade 3 in severity: 1 tic, 1 rash (bilateral pleomorphic light eruption on arms). No Grade 4 (life-threatening AEs) were observed in the study. In Cohort 2, lymphadenopathy was reported in 6 (0.4%) vaccine recipients and 3 placebo recipients (0.4%).

7.6.5 SAEs

In Cohort 1, 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, 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.

7.6.6 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 cutoff 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 (CNS) 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%). See Table 13, below.

As in Cohort 1, SMQ analyses in Cohort 2 showed an imbalance of AEs in the BNT162b2 group compared to the placebo with respect to hypersensitivity, with 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. 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-Schonlein 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.

Table 13. Standard MedDRA Query of Adverse Events by System Organ Class and Preferred Terms, Phase 2/3, Participants 5-11 Years, Safety Population, Vaccine Group as Administered, Cohort 1, Study C4591007

SMQ	Overall SMQ System Organ Class Preferred Term	BNT162b2 10 µg (N[a]=1,518) n[b] (%)	Placebo (N[a]=750) n[b] (%)
Any	Participants with any unsolicited AEs within SMQ	19 (1.25)	6 (0.80)
Angioedema (SMQ)	Any unsolicited AEs within Angioedema (SMQ)	4 (0.26)	3 (0.40)
	Eye disorders	0	1 (0.13)
	Periorbital oedema	0	1 (0.13)
	General disorders and administration site conditions	1 (0.07)	0
	Swelling face	1 (0.07)	0
	Skin and subcutaneous tissue disorders	3 (0.20)	3 (0.40)
	Urticaria	3 (0.20)	3 (0.40)
Arthritis (SMQ)	Any unsolicited AEs within Arthritis (SMQ)	1 (0.07)	0
	Musculoskeletal and connective tissue disorders	1 (0.07)	0
	Synovitis	1 (0.07)	0
Convulsions (SMQ)	Any unsolicited AEs within Convulsions (SMQ)	0	0
Demyelination (SMQ)	Any unsolicited AEs within Demyelination (SMQ)	0	0
Hypersensitivity (SMQ)	Any unsolicited AEs within Hypersensitivity (SMQ)	14 (0.92)	4 (0.53)
	Eye disorders	1 (0.07)	1 (0.13)
	Conjunctivitis allergic	1 (0.07)	1 (0.13)
	General disorders and administration site conditions	1 (0.07)	0
	Injection site rash	1 (0.07)	0
	Immune system disorders	0	1 (0.13)
	Hypersensitivity	0	1 (0.13)
	Skin and subcutaneous tissue disorders	12 (0.79)	2 (0.27)
	Dermatitis	1 (0.07)	0

SMQ	Overall SMQ System Organ Class Preferred Term	BNT162b2 10 µg (N^a=1,518) n^b (%)	Placebo (N^a=750) n^b (%)
	Dermatitis allergic	1 (0.07)	0
	Dermatitis contact	3 (0.20)	0
	Eczema	1 (0.07)	1 (0.13)
	Rash	5 (0.33)	0
	Rash erythematous	0	1 (0.13)
	Rash macular	1 (0.07)	0
	Rash pruritic	1 (0.07)	0
Peripheral neuropathy (SMQ)	Any unsolicited AEs within Peripheral neuropathy (SMQ)	0	0
Vasculitis (SMQ)	Any unsolicited AEs within Vasculitis (SMQ)	0	0

Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any unsolicited AEs within SMQ," n = the number of participants reporting at least 1 occurrence of any unsolicited AEs within SMQ.

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.

7.6.7 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 cutoff 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.

7.7 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 cutoff. 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 cutoff 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 cutoff was 90.7% (2-sided 95% CI: 67.4%, 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 cutoff, 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 AE in BNT162b2 recipients was lymphadenopathy (n=13; 0.9%). More BNT162b2 recipients (n=14; 0.92%) reported hypersensitivity-related AEs (primarily rash and dermatitis) than placebo recipients (n=4; 0.53%). 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 (40.1°C) 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 BENEFIT-RISK ASSESSMENT FOR CHILDREN 5-11 YEARS OF AGE

FDA conducted a 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) visits 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 vaccine efficacy of 70% against COVID-19 cases and 80% against COVID-19 associated hospitalization based on real-world data 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 between COVID-NET's reporting areas and the recent trajectory of the pandemic. This difference will lead to a conservative estimate of benefits in the model. The model assumes the 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 data from Optum health claim database for the period 12/10/2020 –

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 is 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 may be a conservative overestimate.

The model results indicate that the benefits of the vaccine are highly dependent on the incidence of COVID-19. To account for uncertain dynamics of the pandemic, the benefits and risks were assessed under six scenarios: Scenario 1 with COVID-19 incidence as of September 11, 2021, Scenario 2 with COVID-19 incidence close to the recent peak of the Delta variant surge at the end of August 2021, Scenario 3 with COVID-19 incidence close to the lowest recorded incidence in June 2021, Scenario 4 with the same COVID-19 incidence as Scenario 1 and an assumption of 90% vaccine efficacy against cases and 100% efficacy against hospitalizations based on the preliminary descriptive efficacy analysis from study C4591007 Phase 2/3 Cohort 1, Scenario 5 with a 3x multiple of the death rate to more closely match the cumulative death rate for 5-11 years old seen in CDC Data Tracker, and Scenario 6 with the same COVID-19 incidence and assumed vaccine efficacy as Scenario 1 but 50% of the myocarditis cases as Scenario 1.

The results of the benefit-risk assessment are summarized in Table 14 below. The results predict that under Scenarios 1 (Sept 11, 2021 Incidence), 2 (Delta surge peak incidence), 4 (high efficacy), and 5 (higher COVID-19 death rate, per the CDC COVID-19 Data Tracker), the benefits of the Pfizer-BioNTech COVID-19 Vaccine 2-dose primary series clearly outweigh the risks for ages 5-11 years. Under Scenario 3 (lowest 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 lowest 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 14. Model-Predicted Benefit-Risk Outcomes of Scenarios 1-6 per One Million Fully Vaccinated Children 5-11 Years Old

	Benefits				Risks			
Sex	Prevented COVID-19 Cases	Prevented COVID-19 Hospitalizations	Prevented COVID-19 ICU Admissions	Prevented COVID-19 Deaths	Excess Myocarditis Cases	Excess Myocarditis Hospitalizations	Excess Myocarditis ICU Admissions	Excess Myocarditis Deaths
Males & Females								
Scenario 1	45,773	192	62	1	106	58	34	0
Scenario 2	54,345	250	80	1	106	58	34	0
Scenario 3	2,639	21	7	0	106	58	34	0
Scenario 4	58,851	241	77	1	106	58	34	0
Scenario 5	45,773	192	62	3	106	58	34	0
Scenario 6	45,773	192	62	1	53	29	17	0
Males only								
Scenario 1	44,790	203	67	1	179	98	57	0
Scenario 2	54,345	250	82	1	179	98	57	0
Scenario 3	2,639	21	7	0	179	98	57	0
Scenario 4	57,857	254	83	1	179	98	57	0
Scenario 5	44,790	203	67	3	179	98	57	0
Scenario 6	44,790	203	67	1	89	49	29	0
Females only								
Scenario 1	45,063	172	54	1	32	18	10	0
Scenario 2	54,345	250	78	2	32	18	10	0
Scenario 3	2,639	21	7	0	32	18	10	0
Scenario 4	57,938	215	67	2	32	18	10	0
Scenario 5	45,063	172	54	4	32	18	10	0
Scenario 6	45,063	172	54	1	16	9	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.

9 PHARMACOVIGILANCE ACTIVITIES

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

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

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 AESIs, 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."

10 TOPIC FOR VRBPAC DISCUSSION

The VRBPAC will convene on October 26, 2021, to discuss 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.

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12 APPENDIX: 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 cutoff 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 38.9°C 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 39.7° 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 Internal Review Committee's decision to discontinue the 30 μg dosage and proceed to Phase 2/3 at the 10 μg dosage.