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

Identifying Information

Application Type	EUA (Event-driven EUA request) Amendment
Application Number	EUA 27034, Amendment 528
Sponsor	Pfizer, Inc., on behalf of Pfizer and BioNTech
Submission Date	April 26, 2022
Receipt Date	April 26, 2022
Signatory Authority	Peter Marks, M.D., Ph.D., Director, CBER, and Acting Director, CBER/OVRR
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Review Completion Date	May 17, 2022
Established Name/Other names used during development	Pfizer-BioNTech COVID-19 Vaccine/ BNT162b2
Dosage Forms/Strengths and Route of Administration	A 0.2 mL suspension (10 µg BNT162b2) for intramuscular injection
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Use: A single booster dose administered at least 5 months after completing a Pfizer-BioNTech COVID-19 Vaccine primary series.
Intended Population for Booster dose	ndividuals 5 through 11 years of age

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1 EXECUTIVE SUMMARY

On April 26, 2022, Pfizer submitted a request to FDA to amend its emergency use authorization (EUA) to allow for the use of a booster dose 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 regimen is a single booster dose containing 10 µg mRNA administered at least 5 months after completion of primary vaccination with BNT162b2. Pfizer's EUA request includes safety data from a total of 401 5-11 year-old participants who received the booster dose in an open-label extension of the Phase 2/3 portion of the ongoing study C4591007 by February 22, 2022; all of these study participants had ≥1 month of safety follow-up after the booster dose (data cut-off March 22, 2022). Most of the 401 participants (86.8%) received Dose 3 between 8 and 9 months after completion of the 2-dose primary series (range 5 to 9 months).

Immunogenicity (inferred vaccine effectiveness) was assessed by descriptive comparisons of SARS-CoV-2 50% neutralizing antibody titers (NT50) at 1 month after a booster dose and 1 month after completion of a 2-dose BNT162b2 primary series. The analyses included evaluations of SARS-CoV-2 GMTs and seroresponse rates against the USA_WA1/2020 reference strain, using a microneutralization assay, and the Omicron variant, using a non-validated fluorescence focus reduction neutralization test (FFRNT). NT50 GMTs post-booster dose against the reference strain and the Omicron variant were higher than those pre-booster dose and post-Dose 2. The seroresponse rate after a booster dose (defined as a ≥4-fold rise in NT50 from pre-booster dose to post-booster dose) was 86.6% as compared to the seroresponse rate after completion of the BNT162b2 primary series of 100%. This difference in seroresponse rates likely reflected the impact of prior vaccination with the primary series. The increases in neutralizing antibody titers elicited by the booster dose were similar in magnitude to those that previously supported emergency use authorization of a booster dose for use in adults (and for which inferred effectiveness has been corroborated by data on COVID-19 outcomes from observational studies).

The proportions of participants who reported solicited local and systemic adverse reactions (ARs) following the booster dose were similar to the proportions of participants from this population who reported ARs following Dose 2. The most commonly reported solicited ARs following administration of the Pfizer-BioNTech COVID-19 Vaccine were pain at the injection site (73.9%), fatigue (45.6%), and headache (34.0%). All local and systemic reactions were mild to moderate in severity, with a median onset within 2 days following vaccination and a median duration of approximately 2 days after onset. The most frequently reported unsolicited adverse event (AE) was lymphadenopathy (n=10, 2.5%) which occurred within 2 days of vaccination and had a median duration of 6 days. There were no reported hypersensitivity reactions related to the vaccine, cases of myocarditis/pericarditis, cases of anaphylaxis, serious adverse events (SAEs) or deaths. Subgroup analyses were not performed as subgroups would have been too small to draw meaningful conclusions.

FDA reviewed a quantitative benefit-risk assessment submitted by the Sponsor and agrees that the known and potential benefits of a booster dose outweigh its known and potential risks for children 5-11 years of age. Assuming a pre-boost vaccine efficacy (VE) of 20%, the Sponsor predicts that during a 6-month period following vaccination the booster dose would avert 16,124 cases of COVID-19 (range: 8,356-20,312) based on the pandemic average COVID-19 incidence rate (approximately 1,500 cases per week per million population from March 7, 2020, through April 9, 2022) and 152,304 cases of COVID-19 (range: 78,976-191,788) based on the Omicron peak incidence rate. Assuming a pre-boost VE against hospitalization of 70%, the Sponsor

predicts 16 prevented hospitalizations (range: 0-16) based on the pandemic average COVID-19 incidence rate and 132 (range: 48-160) hospitalizations based on the Omicron peak incidence rate. With regard to risks, the Sponsor predicted 0 to 12 myocarditis/pericarditis cases per million booster doses within a 21-day risk window following vaccination.

While most study participants 5-11 years of age in the Phase 2/3 booster dose portion of study C4591007 received the booster dose at 8-9 months after completion of the 2-dose primary series, it is reasonable to extrapolate effectiveness of the booster dose in this age group when administered as soon as 5 months after completion of the primary series, based on data from and experience with use of booster doses in older age groups. Alignment of the authorized booster dose interval with that authorized for older age groups (i.e., 5 months) would help to simplify operational and communication aspects of public health vaccination programs.

Considering the statutory requirements and the totality of data available at this time to support effectiveness of a booster dose of the Pfizer-BioNTech COVID-19 Vaccine and to inform known and potential benefits and known and potential risks associated with the booster dose, the review team recommends authorization of the Pfizer-BioNTech COVID-19 Vaccine under EUA for use as a booster dose administered at least 5 months after the primary series in individuals 5 through 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. 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 April 1, 2022, has caused over 488 million cases of COVID-19, including 6.1 million deaths worldwide.[7] In the U.S., more than 79 million cases and 977 thousand deaths have been reported to the Centers for Disease Control and Prevention (CDC). [8,9] Of the total COVID-19 cases reported in the U.S. to date, 6.7% occurred among individuals 5-11 years of age.[10]

Following EUA of the first COVID-19 vaccine in December 2020, COVID-19 cases and deaths in the U.S. declined sharply during the first half of 2021. The emergence of the Delta variant, variable implementation of public health measures designed to control spread, and continued transmission among unvaccinated individuals were major factors in the resurgence of COVID-19 in the U.S., leading to the Delta variant-associated peak in September of 2021 and the more recent surge in cases attributed to the Omicron variant. The proportion of total cases in children 5-11 years of age has risen since the start of the pandemic, constituting 8.4% of cases reported to CDC during the week of April 16, 2022.[11] As of the week ending March 26, 2022, the Omicron variant comprised all of the tested strains in the U.S.[12] Among cases of COVID-19 in individuals less than 18 years of age from the COVID-NET network, approximately 8,005 have

resulted in hospitalization.[13] As of April 17, 2022, 351 deaths from COVID-19 have been reported in the U.S. in the 5-11 year age group.[14]

The most common underlying medical conditions among hospitalized children were obesity (31.9%), neurologic disorders (14.8%), and asthma (14.5%). Obesity was associated with increased risk of severe disease. Available evidence suggests that highest risk groups include children with special healthcare needs, including genetic, neurologic, metabolic conditions, or with congenital heart disease.[15] 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.[16,17]

Following observation of an increased incidence of myocarditis in 2020 compared with 2019, several studies have suggested an association between COVID-19 and myocarditis.[18,19] While the overall incidence of myocarditis following COVID-19 is low, persons with COVID-19 have a nearly 16-fold increase in risk for myocarditis, compared to individuals without COVID-19. Myocarditis may also present as part of the multisystem inflammatory syndrome in children (MIS-C), usually 3 to 5 weeks after a SARS-CoV-2 infection. MIS-C is a rare but serious COVID-19-associated condition that occurs in less than 1% of children with confirmed SARS-CoV-2 infection.[20] MIS-C presents with persistent fever, laboratory evidence of inflammation, and at least two affected organs. In severe cases, hypotension and shock can occur. 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.[21] Up to 66.7% of patients with MIS-C had cardiac involvement, [22] including left ventricular dysfunction, mitral or tricuspid regurgitation, coronary artery aneurysms, and/or arrhythmias.[23] 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.[24] Limited data are available on long-term outcomes in MIS-C.

3 AUTHORIZED AND APPROVED VACCINES AND THERAPIES FOR COVID-19

3.1 Comirnaty and Pfizer-BioNTech COVID-19 Vaccine

Comirnaty (COVID-19 Vaccine, mRNA) contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 that is formulated in lipid particles. The vaccine is administered intramuscularly as two doses 3 weeks apart, with each 0.3 mL dose of the approved formulation containing 30 µg mRNA. Under Emergency Use Authorization (EUA), the vaccine is called the Pfizer-BioNTech COVID-19 Vaccine, and the formulation authorized for use in individuals 12 years of age and older contains 30 µg mRNA in each 0.3 mL dose. The Pfizer-BioNTech COVID-19 Vaccine formulation authorized for use in children 5-11 years of age contains 10 µg mRNA in each 0.2 mL dose. During clinical development, the vaccine was called BNT162b2.

Comirnaty is approved as a 2-dose primary series for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. The Pfizer-BioNTech COVID-19 Vaccine is authorized under EUA as: a 2-dose primary series for individuals 5 years of age and older; a third primary series dose for individuals 5 years of age and older with certain immunocompromising conditions; a homologous first booster dose administered at least 5 months after completion of primary vaccination to individuals 12 years of age and older; a heterologous first booster dose administered after completion of primary vaccination to

individuals 18 years of age and older (the dosing interval is the same as that authorized for a booster dose of the vaccine used for primary vaccination); a homologous second booster dose administered at least 4 months after a first booster dose to individuals 50 years of age and older and individuals 12 years of age and older with certain immunocompromising conditions; and a heterologous second booster dose administered at least 4 months after a first booster dose to individuals 50 years of age and older and individuals 18 years of age and older with certain immunocompromising conditions.

The Pfizer-BioNTech COVID-19 Vaccine safety and effectiveness data supporting approval of Comirnaty and emergency use authorization of Pfizer-BioNTech COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

3.2 Other COVID-19 vaccines

Spikevax manufactured by Moderna is approved for active immunization to prevent COVID-19 in individuals 18 years of age and older. The primary immunization series consists of 2 doses administered 1-month apart. The vaccine is authorized for emergency use (as the Moderna COVID-19 Vaccine) as: a 2-dose primary series for individuals 18 years of age and older; a third primary series dose for individuals 18 years of age and older with certain immunocompromising conditions; a homologous or heterologous first booster dose administered after completion of primary vaccination to individuals 18 years of age and older (the authorized dosing interval for a homologous booster is at least 5 months after completion of a primary series, and the authorized interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination); and a homologous or heterologous second booster dose administered at least 4 months after the first booster dose to individuals 50 years of age and older and individuals 18 years of age and older with certain immunocompromising conditions. Safety and effectiveness data supporting approval of Spikevax and authorization of Moderna COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

The Janssen COVID-19 Vaccine is authorized for use in individuals 18 years of age and older for whom other FDA-authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, or who elect to receive the Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine.[25] The vaccine is authorized for use in these individuals as a single primary vaccination dose and as a single homologous or heterologous booster dose (the dosing interval for a homologous booster is at least 2 months after the single primary vaccination dose, and the dosing interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination).

3.3 Other therapies for COVID-19

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

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

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

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

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

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

4 RATIONALE FOR BOOSTER DOSES FOR COVID-19 VACCINES IN CHILDREN 5-11 YEARS OF AGE

The emergence of the highly transmissible Omicron variant (B.1.1.529) of SARS-CoV-2 in December 2021 resulted in several waves of COVID-19 cases in many parts of the world and, in the U.S., coincided with a rapid increase in COVID-19-associated hospitalizations among all age groups, including children 5-11 years of age.[26] Observational studies have indicated waning effectiveness of mRNA COVID-19 vaccine primary series against symptomatic infection over time for all age groups for which they are authorized, as well as reduced and more rapidly waning effectiveness against symptomatic infection caused by the Omicron variant.[27] These data do not provide clear evidence of waning effectiveness against serious COVID-19 outcomes such as hospitalization and death, including for COVID-19 caused by the Omicron variant, in immunocompetent pediatric and younger adult populations. However, estimates of primary series vaccine effectiveness against serious outcomes have been lower for during the Omicron predominant period as compared to the Delta predominant period across pediatric and adult age groups evaluated. While data on primary series vaccine effectiveness against COVID-19 hospitalization caused by the Delta variant are not available for ages 5-11 years, vaccine effectiveness against COVID-19 hospitalization caused by the Omicron variant in this age group has been estimated at 68% to 74% over a median follow-up period of approximately 1 month, which is lower than estimates for primary series vaccine effectiveness against COVID-19 hospitalization caused by the Delta variant in adolescents and adults (approximately 90% in immunocompetent individuals). Data from observational studies have also indicated higher

estimates of vaccine effectiveness against COVID-19 and serious outcomes in adults and adolescents among those who have received a booster dose than among those who have received only a primary series.[28,29]

In summary, the available evidence indicates a gradual reduction of vaccine effectiveness following the primary series in immunocompetent individuals from all age groups, and that a first booster dose may optimize (increase and prolong) protection against serious disease outcomes. These findings support consideration of expanding use of booster doses to individuals in the 5-11-year-old age group who are now 5 months or more past completion of their primary series.

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

On April 26, 2022, Pfizer and BioNTech submitted a request to amend this EUA to include use of a booster dose of the Pfizer-BioNTech COVID-19 Vaccine (0.2 mL, containing 10 µg mRNA) in individuals 5-11 years of age. The request is supported by:

- Safety data from 401 study C4591007 Phase 2/3 participants 5-11 years of age who received a booster dose (Dose 3) of BNT162b2 and had ≥1 month of safety follow-up after Dose 3 (data cut-off date: March 22, 2022)
- SARS-CoV-2 neutralizing antibody responses measured at 1 month after booster dose (Dose 3) descriptively compared to neutralizing antibody titers prior to Dose 3 and to the neutralizing antibody responses of participants 5-11 years of age who completed a 2-dose BNT162b2 primary series in the same study. Efficacy against COVID-19 was also assessed descriptively in participants 5-11 years of age.

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 authorize 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.

6.2 Regulatory considerations for a booster doses of COVID-19 vaccines

The benefit of a booster dose must be weighed against potential risk. Available data should support the effectiveness of the booster dose, particularly against currently circulating SARS-CoV-2 variants, and benefit should be considered relative to the benefit provided by completion of the primary series.

The Guidance for Industry, Emergency Use Authorization for Vaccines to Prevent COVID-19 (originally issued in October 2020 and last updated March 2022) describes data that could support the safety and effectiveness of modified COVID-19 vaccines directed against a variant of concern. Certain immunobridging approaches for modified vaccines described in the guidance are well established for inferring vaccine effectiveness and have been applied to support EUA of COVID-19 vaccine booster doses for use in adults. For an age group for which the effectiveness of a primary series has been demonstrated and has supported emergency use authorization and/or approval of the vaccine for use in that age group, effectiveness of a booster dose may be inferred from immunogenicity data (neutralizing antibody response data in the case of COVID-19 vaccines) generated in a clinical trial conducted in that age group. Under this approach, an immunobridging analysis that demonstrates statistically non-inferior neutralizing antibody responses following the booster dose as compared to those following the primary series would support effectiveness of the booster dose. Safety evaluation of the booster dose should include a sufficient number of study participants to characterize reactogenicity and should assess other adverse events reported during the immunogenicity evaluation period. While this safety evaluation would not be adequately powered to characterize uncommon but potentially serious adverse reactions, such as myocarditis/pericarditis, safety evaluation of the booster dose would be informed by much more expansive pre- and post-authorization safety data for the vaccine when administered as a primary series and as a booster dose to other age groups. Once authorized for use in a new age group, post-authorization studies should be conducted to assess longer-term safety for serious and other medically important adverse events associated with the booster dose.

7 FDA REVIEW OF CLINICAL TRIAL SAFETY AND EFFECTIVENESS DATA

7.1 Overview of study C45910007

The EUA amendment request contains safety and descriptive immunogenicity analyses of data collected from children 5-11 years of age enrolled in the ongoing Phase 1/2/3, randomized, placebo-controlled study, C4591007. A subset of BNT162b2 recipients from the Phase 2/3 portion received a booster dose (Dose 3) of BNT162b2 (10µg mRNA) five to nine months after completing the primary series (Dose 2). The comparator group for immunogenicity analyses are Phase 2/3 participants 5-11 years of age from this study with Dose 2 data.

Supporting data from study C4591007, Phase 2/3

- 401 BNT162b2 (10 µg) booster dose recipients (3-dose set) and 67 Dose 2 recipients (2-dose set) 5-11 years of age

- Safety data from 401 BNT162b2 (10 µg) booster dose participants vaccinated by February 22, 2022; the median duration of follow-up after Dose 3 was 1.3 months (range: 1 month to 1.8 months).

- Immunogenicity data from a subset of 67 evaluable participants who had booster dose (Dose 3) data available and no evidence of prior SARS-CoV-2 infection up to 1 month after the booster dose.

- The comparator group for immunogenicity included 67 participants randomly selected from the 2-dose analysis set and 29 participants in the 3-dose analysis set (96 participants total) with evaluable immunogenicity data following 2 doses of 10 µg BNT162b2.

Table 1. Data Submitted in Support of Safety and Immunogenicity of a Pfizer-BioNTech COVID-19 Vaccine Booster Dose in Children 5-11 Years of Age, Study C4591007

Data Type	Dose 3 Participants[1] N=401	2-Dose Immunogenicity Set[2] N=67	Total
Safety data, n	401	N/A	401
Evaluable immunogenicity data following Dose 3, n	115	N/A	115
Evaluable immunogenicity data following booster dose and no evidence of prior SARS-CoV-2 infection[3], n	67	N/A	67
Evaluable immunogenicity data following Dose 2 and no evidence of prior SARS-CoV-2 infection[3], n	29	67	96

N= total number of participants in analysis set
n = number of participants with specified characteristics
1 Participants 5 – 11 years of age who were vaccinated with a 10µg booster dose by February 22, 2022. Safety data analysis cut-off date: March 22, 2022.
[2] Participants randomly selected from the Dose 2 analysis set used for immunobridging analyses for the primary series. No further information was provided regarding the selection process
[3] No evidence of prior SARS-CoV-2 infection as defined in Section 7.2 of this memo.

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 booster dose portion of the Phase 2/3 study in children 5-11 years of age. The designs of the Phase 1 and Phase 2/3 primary series portions of the study are described in the Division Memo for Pfizer-BioNTech COVID-19 Vaccine primary series in 5-11 years of age.[30]

For the booster dose portion of the study, all children were enrolled at U.S. sites, had completed a 2-dose primary series of BNT162b2 (10 µg mRNA) and were offered a BNT162b2 (10 µg mRNA) booster dose at least 5 months after completion of the primary series. The booster portion was designed as an open-label extension of the Phase 2/3 portion of the study. No participants were excluded from the booster dose portion of the study. COVID-19 cases were recorded as adverse events, and the incidence was not evaluated as a study endpoint. There were no cases of COVID-19 reported after the booster dose in BNT162b2 recipients through the date of data cut-off.

Immunogenicity evaluation

The SARS-CoV-2 50% neutralizing antibody (NT50) geometric mean titer (GMT) against the reference strain (USA_WA1/2020) in a subset of participants without prior SARS-CoV-2 infection up to 1 month after a booster dose of BNT162b2 was compared descriptively to the post-Dose 2 NT50 GMT in a subset of C4591007 participants in the same age group. Supplemental immunogenicity analyses based on the all-available immunogenicity population were also performed. Sera were tested using the SARS-CoV-2 mNG microneutralization assay. No statistical hypothesis testing was pre-specified for the booster analyses.

SARS-CoV-2 NT50 titers against the Omicron variant were also evaluated in a subset of the evaluable 3-dose (n=17) and 2-dose (n=29) immunogenicity populations using a non-validated fluorescence focus reduction neutralization test (FFRNT) assay. No statistical hypothesis testing was pre-specified.

Safety evaluation

Reactogenicity (solicited local and systemic adverse reactions)

The participants' parents or the participants themselves recorded in an e-diary reactogenicity assessments and antipyretic/pain medication use from Day 1 through Day 7 following each dose. 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 3 through 1 month after Dose 3, and SAEs from Day 1 to 6 months after Dose 3, or the data cut-off date (March 22, 2022). AEs are categorized by frequency and maximum severity according to MedDRA System Organ Class and Preferred Term (PT), and relationship to the study intervention was assessed. Deaths are recorded to the end of the study.

Adverse events of clinical interest

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

Analysis populations

In the context of this EUA amendment request, the safety database was comprised of participants 5-11 years old vaccinated by February 22, 2022. The immunogenicity population started with the first 130 participants 5-11 years old who received Dose 3 and completed the 1-month post-Dose 3 visit prior to March 15, 2022. The data analysis cut-off date was March 22, 2022.

- Safety population: participants who received a 10-µg booster (third) dose of BNT162b2.
- All-available immunogenicity population: All participants who received the booster dose of the study intervention with at least 1 valid and determinate immunogenicity result.
- Evaluable immunogenicity population:

- 3-dose: participants who received Doses 1, 2, and 3 of BNT162b2 (10 µg) within the pre-defined windows, had a 1 month post-Dose 3 assay result from a blood sample collected within a pre-defined window after Dose 3, and had no important protocol deviations through 1 month post-Dose 3. Of participants in the evaluable immunogenicity population, a participant with no evidence of past SARS-CoV-2 infection up to 1 month post-Dose 3 was defined as having: a negative N-binding antibody (serum) result at the Dose 1, 1 month post-Dose 2 (if available), Dose 3, and 1 month post-Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and at any unscheduled visit prior to 1 month post-Dose 3; and no medical history of COVID-19.

  Comparator: participants who received Doses 1 and 2 within the pre-defined windows, had a 1 month post-Dose 2 assay result from a blood sample collected within pre-defined window after Dose 2, and had no important protocol deviations through 1 month post-Dose 2. Of participants in the evaluable immunogenicity population, a participant with no evidence of past SARS-CoV-2 infection up to 1-month post-Dose 2 was defined as having: a negative N binding antibody (serum) result at the Dose 1 and 1-month post-Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and at any unscheduled visit prior to 1 month post-Dose 2; and no medical history of COVID-19.

– The comparator group for the primary immunogenicity analyses was comprised of:
  - participants from the 3-dose analysis set with evaluable post-Dose 2 data as defined above, of which participants, of which 29 had no evidence of SAR-CoV-2 infection up to 1- month after Dose 2.
  - participants (2-dose set, n=67) from the Dose 2 evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection up to 1- month after Dose 2 that was used for immunobridging analyses for the primary series. These phase 2/3 participants received Doses 1 and 2 of BNT162b2 (10 µg) and had evaluable post-Dose 2 data as defined above.

7.3 Disposition of Phase 2/3 booster dose participants (3-dose set)

Of the 425 participants who were initially included in the 3-dose set, 24 participants were excluded as these participants were ≥12 years at the time of the third dose vaccination and received the 30-µg booster dose. Most of the remaining 401 participants (86.8%) received Dose 3 between 8 and 9 months after completion of the 2-dose primary series (range 5 to 9 months).

Safety population

Of the 425 enrolled participants, 401 were age 5-11 years old and had safety data through at least 1 month following vaccination (median of 1.3 months, range 1.0 to 1.8 months).

Immunogenicity populations

Immunogenicity analyses for the primary objectives were based on evaluable participants 5-11 years old without evidence of prior SARS-CoV-2 infection up to 1 month after booster dose (3-dose set). The comparator group (Dose 2 evaluable immunogenicity population) was comprised of 67 participants randomly selected from the evaluable Dose 2 population previously used for immunobridging analyses for the primary series (2-dose set) and 29 participants enrolled in the booster dose portion of the study, had evaluable immunogenicity data 1 month post-Dose 2, and no evidence of SARS-CoV-2 infection up to 1-month after Dose 2.

Table 2. Disposition of Immunogenicity Populations, Phase 2/3 Booster Study Participants 5-11 Years of Age, Immunogenicity Set, Study C4591007

Disposition	BNT162b2 (10 µg) 3-Dose Set n[a] (%)	BNT162b2 (10 µg) 2-Dose Set n[a] (%)	Total n[a] (%)
Randomized[b]	123 (100.0)	67 (100.0)	190 (100.0)
Dose 2 all-available immunogenicity population	30 (24.4)	67 (100.0)	97 (51.1)
Excluded because participant did not have a valid and determinate immunogenicity result after Dose 2	93 (75.6)	0	93 (48.9)
Dose 3 all-available immunogenicity population	118 (95.9)		118 (62.1)
Excluded because participant did not have a valid and determinate immunogenicity result after Dose 3	5 (4.1)		5 (2.6)
Dose 2 evaluable immunogenicity population	30 (24.4)	67 (100.0)	97 (51.1)
Without evidence of infection up to 1 month after Dose 2[c]	29 (23.6)	67 (100.0)	96 (50.5)
Excluded from Dose 2 evaluable immunogenicity population[d]	93 (75.6)	0	93 (48.9)
Did not receive Dose 2 within 19-42 days after Dose 1	2 (1.6)	0	2 (1.1)
Did not have a valid and determinate immunogenicity result within 28-42 days after Dose 2	93 (75.6)	0	93 (48.9)
Did not have blood draw at visit 1 month post-Dose 2	91 (74.0)	0	91 (47.9)
Blood draw within the window but no valid and determinate immunogenicity result obtained in laboratory	2 (1.6)	0	2 (1.1)
Dose 3 evaluable immunogenicity population	115 (93.5)		115 (60.5)
Without evidence of infection up to 1 month after Dose 3[c]	67 (54.5)		67 (35.3)
Excluded from Dose 3 evaluable immunogenicity population[d]	8 (6.5)		8 (4.2)
Did not receive Dose 2 within 19-42 days after Dose 1	2 (1.6)		2 (1.1)
Did not have a valid and determinate immunogenicity result within 28-42 days after Dose 3	6 (4.9)		6 (3.2)
Did not have blood draw at visit 1 month post-Dose 3	1 (0.8)		1 (0.5)
Blood draw 1 month post-Dose 3 outside of window (28-42 days after Dose 3)	1 (0.8)		1 (0.5)
Blood draw within the window but no valid and determinate immunogenicity result obtained in laboratory	4 (3.3)		4 (2.1)

Note: The 3-dose immunogenicity set included the first 130 participants received Dose 3 and completed 1 month post-Dose 3 visit prior to March 15, 2022; 30 of these participants had a blood sample collected at 1 month post-Dose 2. Seven participants received an age-appropriate dose of BNT162b2 30 µg and were excluded from further analyses.
The Dose 2 immunogenicity set used for immunogenicity comparisons included 29 participants from the 3-dose analysis set and an additional 67 participants who were randomly selected from the Dose-2 evaluable immunogenicity population previously used for immunobridging analyses for the primary series; all participants had no evidence of SARS-CoV-2 infection up to 1 month post-Dose 2.
a. n = Number of participants with the specified characteristic, or the total sample.
b. These values are the denominators for the percentage calculations.
c. No evidence of prior SARS-CoV-2 infection as defined in Section 7.2.
d Participants may have been excluded for more than 1 reason.

Comorbidities at baseline

Comorbidities were defined as described in Kim et al. MMWR 2020.[31] Participants with any comorbidity, including obesity, constituted 29.7% of the safety population receiving the booster dose. The most common comorbidities at baseline in the 3-dose set were non-drug related

allergies (21.9%), obesity (9.7%), attention deficit hyperactivity disorder (8.5%), asthma (7.7%), eczema (7.0%), neurologic disorders (5.7%), cardiac conditions (including congenital cardiac disease, 1.8%), and drug hypersensitivities (2.5%). Other comorbidities included Henoch-Schoenlein purpura (n=1).

7.4 Demographic and baseline characteristics

Demographic characteristics for the Phase 2/3 study C4591007 booster dose safety population are summarized in Table 3 below. Overall, participants were predominately White, with a mean age of approximately 8 years. Of the BNT162b2 recipients, 9.7% were obese, 5.5% had evidence of prior SARS-CoV-2 infection, and 29.7% had comorbidities placing them at increased risk of severe COVID-19. All participants were enrolled in the United States. There were no participants with a history of HIV infection.

Table 3. Demographic and Other Baseline Characteristics, Phase 2/3 Participants 5-11 Years of Age Who Received Dose 3 of BNT162b2, Safety Population, Study C4591007

Characteristic	BNT162b2 (10 µg) (N[a]=401) n[b] (%)
Sex	
Male	210 (52.4)
Female	191 (47.6)
Race	
White	281 (70.1)
Black or African American	29 (7.2)
American Indian or Alaska Native	8 (2.0)
Asian	31 (7.7)
Native Hawaiian or other Pacific Islander	1 (0.2)
Multiracial	46 (11.5)
Not reported	5 (1.2)
Ethnicity	
Hispanic or Latino	92 (22.9)
Not Hispanic or Latino	306 (76.3)
Not reported	3 (0.7)
Age at Dose 1	
Mean years (SD)	7.9 (1.75)
Median (years)	8.0
Min, max	5, 11
Obese[c]	
Yes	39 (9.7)
No	362 (90.3)
Baseline Evidence of Prior SARS-CoV-2 Infection	
Negative[d]	379 (94.5)
Positive[e]	22 (5.5)
Comorbidities[f]	
Yes	119 (29.7)
No	282 (70.3)

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
d. As defined in Section 7.2
e. Positive N-binding ant body result at Dose 1, positive NAAT result at Dose 1, or medical history of COVID-19.
f. 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 1 of the prespecified comorbidities based on MMWR Morb Mortal Wkly Rep. 2020;69(32):1081-8 and/or obesity (BMI ≥ 95th percentile).

The demographic and baseline characteristics of the Dose 3 evaluable immunogenicity population were similar to the overall characteristics of the all-available booster dose population, and 4.3% had baseline evidence of prior SARS-CoV-2 infection.

Comparator group for immunogenicity: The 67 participants who were not enrolled in the booster dose portion of the study but were included in the comparator 2-dose set had generally similar age, sex, race, and pre-existing co-morbidities to the 3-dose set. Fewer participants identified as Hispanic or Latino (2-dose set: 11.9%, 3-dose set: 25.2%). Most participants (70.1%) had been enrolled in the U.S. with the others having been enrolled in Finland (10.4%), Spain (10.4%), and Poland (9.0%). None of these participants had a history of prior SARS-CoV-2 infection.

One participant (0.2%) received a concomitant vaccine (influenza) after receiving Dose 3 of the study vaccine.

7.5 Immunogenicity results

7.5.1 Primary immunogenicity objectives

Immunogenicity of the BNT162b2 booster dose was assessed descriptively, based on analyses of GMT ratio and seroresponse rates for neutralizing antibody titers to the reference strain. Among the 67 participants in the 3-dose evaluable subset, the booster dose was administered at 7 to 9 months after the second primary series dose.

GMTs of neutralizing antibody titers to the reference strain

Among evaluable 5-11-year-old participants without prior evidence of SARS-CoV-2 infection up to 1 month post-booster (Dose 3), the ratio of SARS-CoV-2 50% neutralizing GMTs 1 month post-booster compared to 1 month post-Dose 2 was 2.17 (95% CI: 1.76, 2.68) (Table 4, below). Although no statistical hypothesis testing was pre-specified, the lower bound of the 95% CI around the GMT ratio was 1.76 and would have met usual immunobridging statistical success criteria for non-inferiority (>0.67), simple superiority (>1.0) and super-superiority (>1.5).

Table 4. SARS-CoV-2 NT50 GMTs[a] at 1 Month Post-Dose 2, Pre-Booster, 1 Month Post-Booster in Phase 2/3 Participants 5-11 Years of Age Without Evidence of SARS-CoV-2 Infection, Evaluable Immunogenicity Population[b], Study C4591007

Post-Dose 2 N[c] = 96 GMT (95% CI)	Pre-Booster N[d] = 67 GMT (95% CI)	Post-Booster N[d] = 67 GMT (95% CI)	GMR[d] Post-Booster/Post-Dose 2 (95% CI)
1253.9 (1116.0, 1408.9)	270.1 (229.1, 320.6)	2720.9 (2280.1, 3247.0)	2.17 (1.76, 2.68)

a. SARS-CoV-2 mNeonGreen virus microneutralization assay (SARS-CoV-2 mNG NT), reference strain: recombinant USA_WA1/2020. NT50= 50% neutralizing titer. LLOQ = 41
b. Evaluable immunogenicity population pertaining to Phase 2/3 BNT162b2 participants 5-11 years of age (study C4591007): pre- and 1 month post-booster based on Dose 3 evaluable population. Post-Dose 2 based on Dose 2 evaluable population.
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. GMR= Geometric Mean Ratio

Analyses of NT50 GMTs in the all-available immunogenicity populations of the 3-dose and 2-dose set were generally comparable to the results in the evaluable immunogenicity populations. Pre-booster and post-booster GMTs were higher in the all-available population, presumably due to inclusion of participants with prior SARS-CoV-2 infection: Post-Dose 2: 1276.9 (95% CI, 1131.6, 1440.8), N=97; Pre-Booster: 521.3 (95% CI, 417.8, 650.6); Post-Booster 3212.6 (95% CI, 2802.5, 3682.8).

Proportions of participants with a 4-fold rise in NT50 GMTs to the reference strain

Seroresponse rates among participants without evidence of prior SARS-CoV-2 infection are presented in Table 5.

The seroresponse rate from pre-booster dose to 1 month post-booster dose was lower than the seroresponse rate after the primary series (from baseline pre-Dose 1 to 1 month post-Dose 2), reflecting that a ≥4-fold increase in titer is more difficult to achieve from a booster dose administered to a previously vaccinated individual than from a primary series administered to an individual who is naïve to both SARS-CoV-2 infection and COVID-19 vaccination. The seroresponse rates using pre-Dose 1 as the baseline were comparable across study groups (Table 5). Although no statistical hypothesis testing was pre-specified, the usual statistical success criteria for non-inferiority (>-10%) would have been met using the pre-Dose 1 baseline for the booster dose seroresponse analysis but would not have been met when using the pre-Dose 3 baseline (as this analysis does not account for baseline differences).

Table 5. Seroresponse Rates[a,b] at 1 Month Post-Booster Dose (Dose 3) and 1 Month Post-Primary Series (Dose 2), Phase 2/3 Participants 5-11 Years of Age Without Evidence of SARS-CoV-2 Infection, Evaluable Immunogenicity Population[c,] , Study C4591007

Baseline[d]	Seroresponse Rate Post-Primary Series N= 96 % [e,g] (95% CI)	Seroresponse Rate Post-Booster N= 67 % [f,g] (95% CI)	Difference[h] (95% CI)
Pre-Booster	--	86.6 (76.0, 93.7)	-13.4 (-23.6, -7.2)
Pre-Dose 1	100.0 (96.2, 100.0)	98.5 (92.0, 100.0)	-1.5 (-8.0, 2.4)

a. SARS-CoV-2 mNeonGreen virus microneutralization assay-NT50, reference strain: recombinant USA_WA1/2020.
b. Seroresponse was defined as achieving a ≥4-fold rise from indicated baseline to either 1 month post-primary series (Dose 2) or 1 month post-booster (Dose 3). If the baseline measurement was below the LLOQ, a postvaccination assay result ≥4 × LLOQ was considered a seroresponse.
c. Evaluable immunogenicity population pertaining to Phase 2/3 BNT162b2 participants 5-11 years of age (study C4591007): Pre-booster and post-booster based on Dose 3 evaluable population, Pre-Dose 1 and post-primary series based on Dose 2 evaluable population.
d. Baseline sample used to determine seroresponse.
e. Proportion of participants with a ≥4- fold rise in NT50 GMT from pre-dose 1 to 1-month post-Dose 2
f. Proportion of participants with a ≥4-fold rise in NT50 GMT from indicated baseline to 1-month post-booster
g. %: 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 indicated baseline and 1 month after post-booster or post-primary series (as indicated).
h. Difference in proportion of participants with ≥4-fold rise from pre-dose 1 or pre-booster (as indicated) to post- booster dose as compared to seroresponse rate post-primary series.

7.5.2 Exploratory immunogenicity analyses against the Omicron variant

Pfizer submitted exploratory descriptive analyses of data from a subset of participants without evidence of prior SARS-CoV-2 infection from the evaluable populations in the 3-dose set: n=29 at 1 Month post-Dose 2 and n=17 at 1 Month post-Dose 3. GMTs were determined using a non-validated SARS-CoV-2 fluorescence focus reduction neutralization test (FFRNT) assay with the reference strain (USA-WA1/2020) and the Omicron variant; the relative sensitivity of the two assays is not known.

Table 6. SARS-CoV-2 Neutralizing GMTs[a] at 1 Month Post- Booster and 1 month Post-Primary Series in Participants Without Evidence of SARS-CoV-2 Infection, Evaluable Immunogenicity Population[b], Study C4591007

Assay Target	Post-Dose 2 N=29 GMT (95% CI)	Post-Dose 3 N=17 GMT (95% CI)
Omicron variant	27.6 (22.1, 34.5)	614.4 (410.7, 919.2)
Reference strain	323.8 (267.5, 392.1)	1702.8 (1282.6, 2260.7)
GMR[c] (95% CI)	0.09 (0.07, 0.10)	0.36 (0.28, 0.47)

a. SARS-CoV-2 fluorescence focus reduction neutralization test (FFRNT), SARS-CoV-2 strains: recombinant USA_WA1/2020 (reference), B.1.1.529 (Omicron).
b. N = number of participants with valid and determinate assay results for the specified assays at the given dose/sampling time point.
c. GMR= geometric mean ratio of neutralizing antibody titers to Omicron variant/ neutralizing antibody titers to reference strain in each study group

7.6 Safety results

Overview of adverse events: Phase 2/3

In the C4591007 booster dose extension, e-diary data on reactogenicity (local and systemic reactions) were collected from 371 of the 401 BNT162b2 booster dose recipients. Technical issues prevented collection of e-diary data from the entire safety population. Overall, injection site reactions occurring within 7 days of vaccination with the BNT162b2 booster dose were common, occurring in approximately 75% of participants after the Dose 3. Systemic AEs occurred in approximately 59% of BNT162b2 booster dose recipients.

No participants in the safety population withdrew because of AEs, and there were no deaths or SAEs reported. There were no immediate unsolicited AEs in the study. Other unsolicited AEs occurred in 9% of participants. See Table 7 below.

Table 7. Safety Overview, Phase 2/3 Participants 5-11 Years of Age Who Received Dose 3, Safety Population, Study C4591007

Event	BNT162b2 (10 µg) n[b]/N[a] (%)
Immediate unsolicited AE within 30 minutes after Dose 3	0
Solicited injection site reaction within 7 days of Dose 3	278/371 (74.9)
Solicited systemic AE within 7 days of Dose 3	220/371 (59.3)
From Dose 3 through 1 month after Dose 3	
Any AE	36/401 (9.0)
Unsolicited non-serious AE	36/401 (9.0)
SAE	0

Event	BNT162b2 (10 µg) n[b]/N[a] (%)
From Dose 3 through cutoff date	
Withdrawal due to AEs	0
SAE	0
Deaths	0

Note: MedDRA (v24.1) coding dictionary applied.
Note: Immediate AE refers to an AE reported in the 30-minute observation period after vaccination.
a. N = number of administered participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.

7.6.1 Solicited adverse reactions

The most frequently reported local ARs included pain at the injection site (73.9%), swelling (16.4%) and redness (15.6%). The most frequently reported systemic ARs included fatigue (45.6%), headache (34.0%), and muscle pain (18.3%). All reported local and systemic ARs were mild-to-moderate in severity, with median onset 2 days post-vaccination, and resolved within 1 to 2 days after onset. The proportions of participants in the Safety Population who reported solicited adverse reactions (ARs) after Dose 3 were generally comparable to the proportions of participants in the Safety Population who reported ARs after Doses 1 and 2.

Table 8 and Table 9 summarize the frequencies, severities, and durations of ARs reported within 7 days after Dose 3 compared to corresponding ARs reported after Doses 1 and 2.

Table 8. Frequency of Solicited Local Reactions Within 7 Days After Vaccination, by Dose Number, Among Phase 2/3 Participants 5-11 Years of Age Who Received Dose 3, Safety Population[a], Study C4591007

Event	BNT162b2 (10 µg) Dose 1 (N=398) n[b] (%)	BNT162b2 (10 µg) Dose 2 (N=399) n[b] (%)	BNT162b2 (10 µg) Dose 3 (N=371) n[b] (%)
Redness[c]			
Any	46 (11.6)	66 (16.5)	58 (15.6)
Mild	34 (8.5)	35 (8.8)	38 (10.2)
Moderate	12 (3.0)	30 (7.5)	19 (5.1)
Severe	0	1 (0.3)	1 (0.3)
Grade 4	0	0	0
Swelling[c]			
Any	38 (9.5)	56 (14.0)	61 (16.4)
Mild	24 (6.0)	25 (6.3)	30 (8.1)
Moderate	14 (3.5)	31 (7.8)	31 (8.4)
Severe	0	0	0
Grade 4	0	0	0
Pain at the injection site[d]			
Any	309 (77.6)	288 (72.2)	274 (73.9)
Mild	255 (64.1)	220 (55.1)	177 (47.7)
Moderate	54 (13.6)	67 (16.8)	95 (25.6)
Severe	0	1 (0.3)	2 (0.5)
Grade 4	0	0	0
Any local reaction[e]	315 (79.1)	296 (74.2)	278 (74.9)

Note: Reactions were collected in the electronic diary (e-diary) and unscheduled clinical assessments from Day 1 through Day 7 after each vaccination.
Note: Grade 4 reactions were classified by the investigator or medically qualified person.
Note: All randomized participants who received at least 1 dose of the study intervention.
a. N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of participants with the specified characteristic.

c. Mild (Grade 1): ≥0.5 to 2.0 cm; moderate (Grade 2): >2.0 to 7.0 cm; severe (Grade 3): >7.0 cm; Grade 4: necrosis (redness and swelling categories) or exfoliative dermatitis (redness category only).
d. Mild (Grade 1): does not interfere with activity; moderate (Grade 2): interferes with activity; severe (Grade 3): prevents daily activity; Grade 4: emergency room visit or hospitalization for severe pain at the injection site.
e. Any local reaction: any redness ≥0.5 cm, any swelling ≥0.5 cm, or any pain at the injection site.

Table 9. Frequency of Solicited Systemic Adverse Events Within 7 Days After Vaccination, by Dose Number, Among Phase 2/3 Participants 5-11 Years of Age, Safety Population[a], Study C4591007

Event	BNT162b2 (10 µg) Dose 1 (N=398) n[b](%)	BNT162b2 (10 µg) Dose 2 (N=399) n[b](%)	BNT162b2 (10 µg) Dose 3 (N=371) n[b](%)
Fever			
≥38.0℃	14 (3.5)	35 (8.8)	25 (6.7)
≥38.0℃ to 38.4℃	9 (2.3)	14 (3.5)	17 (4.6)
>38.4℃ to 38.9℃	4 (1.0)	14 (3.5)	5 (1.3)
>38.9℃ to 40.0℃	1 (0.3)	6 (1.5)	3 (0.8)
>40.0℃	0	1 (0.3)	0
Fatigue[c]			
Any	149 (37.4)	186 (46.6)	169 (45.6)
Mild	101 (25.4)	105 (26.3)	99 (26.7)
Moderate	47 (11.8)	77 (19.3)	63 (17.0)
Severe	1 (0.3)	4 (1.0)	7 (1.9)
Grade 4	0	0	0
Headache[c]			
Any	94 (23.6)	120 (30.1)	126 (34.0)
Mild	77 (19.3)	85 (21.3)	76 (20.5)
Moderate	17 (4.3)	33 (8.3)	47 (12.7)
Severe	0	2 (0.5)	3 (0.8)
Grade 4	0	0	0
Chills[c]			
Any	24 (6.0)	41 (10.3)	39 (10.5)
Mild	17 (4.3)	33 (8.3)	23 (6.2)
Moderate	7 (1.8)	7 (1.8)	15 (4.0)
Severe	0	1 (0.3)	1 (0.3)
Grade 4	0	0	0
Vomiting[d]			
Any	8 (2.0)	7 (1.8)	9 (2.4)
Mild	8 (2.0)	7 (1.8)	6 (1.6)
Moderate	0	0	3 (0.8)
Severe	0	0	0
Grade 4	0	0	0
Diarrhea[e]			
Any	27 (6.8)	26 (6.5)	18 (4.9)
Mild	26 (6.5)	23 (5.8)	15 (4.0)
Moderate	1 (0.3)	3 (0.8)	2 (0.5)
Severe	0	0	1 (0.3)
Grade 4	0	0	0
New or worsened muscle pain[c]			
Any	32 (8.0)	50 (12.5)	68 (18.3)
Mild	23 (5.8)	33 (8.3)	40 (10.8)
Moderate	9 (2.3)	16 (4.0)	28 (7.5)
Severe	0	1 (0.3)	0
Grade 4	0	0	0

Event	BNT162b2 (10 µg) Dose 1 (N=398) n[b](%)	BNT162b2 (10 µg) Dose 2 (N=399) n[b](%)	BNT162b2 (10 µg) Dose 3 (N=371) n[b](%)
New or worsened joint pain[c]			
Any	15 (3.8)	22 (5.5)	25 (6.7)
Mild	9 (2.3)	18 (4.5)	14 (3.8)
Moderate	6 (1.5)	4 (1.0)	11 (3.0)
Severe	0	0	0
Grade 4	0	0	0
Any systemic event[f]	202 (50.8)	230 (57.6)	220 (59.3)
Use of antipyretic or pain medication[g]	53 (13.3)	87 (21.8)	114 (30.7)

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) and unscheduled clinical assessments from Day 1 through Day 7 after each dose. Grade 4 events were classified by the investigator or medically qualified person.
Note: All randomized participants who received at least 1 dose of the study intervention.
a. N = number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
b. n = Number of participants with the specified characteristic.
c. Mild (Grade 1): does not interfere with activity; moderate (Grade 2): some interference with activity; severe (Grade 3): prevents daily activity; Grade 4: emergency room visit or hospitalization for severe fatigue, severe headache, severe chills, severe muscle pain, or severe joint pain.
d. Mild (Grade 1): 1 to 2 times in 24 hours; moderate (Grade 2): >2 times in 24 hours; severe (Grade 3): requires intravenous hydration; Grade 4: emergency room visit or hospitalization for severe vomiting.
e. Mild (Grade 1): 2 to 3 loose stools in 24 hours; moderate (Grade 2): 4 to 5 loose stools in 24 hours; severe (Grade 3): 6 or more loose stools in 24 hours; Grade 4: emergency room visit or hospitalization for severe diarrhea.
f. Any systemic event: any fever ≥38.0℃, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
g. Severity was not collected for use of antipyretic or pain medication.

Most local and systemic ARs occurred within 2 days post-vaccination and lasted a median of 2 days.

7.6.2 Unsolicited adverse events

All booster participants vaccinated prior to February 22, 2022 (N=401) had safety follow-up from Dose 3 through the data cut-off date of March 22, 2022 (median follow-up of 1.3 months). Non-serious adverse events (AEs) were reported by 9.0% (N=36) of booster dose recipients, and 52.7% (n=19) of these AEs were assessed by the investigator as related to vaccination. The most commonly reported AEs (by PT) were lymphadenopathy (2.5%), injection site pain (1.7%), and headache (0.7%). Many of the reported AEs were consistent with the solicited ARs (e.g., injection site pain, headache, and fatigue).

Lymphadenopathy was reported by 10 participants. All reported lymphadenopathy cases were mild in severity and considered by the study investigator to be related to study intervention. Most (80%) occurred in the axillary nodes of the limb used for vaccination. All occurred within 2 days of vaccination and had a median duration of 6 days (range 2 to 9 days; with one case not resolved at date of data cutoff).

An additional 19 participants were vaccinated with a booster dose after the February 22, 2022 date noted above. These participants were not included in the safety analyses provided with this EUA application. There were no reports of severe ARs, severe AEs, or related AEs in this group of participants.

7.6.3 Severe AEs and SAEs

A severe AE occurred in a 5-year-old female with a history of fever as high as 40.3°C after Dose 2 of the primary series. She developed a fever to 39.0°C on the day she received Dose 3. The

fever was accompanied by bilateral lower extremity arthralgia and mild dizziness. Her symptoms resolved within 3 days of onset with treatment for her fever. The AE was considered severe based on the participant's reported maximum temperature.

No SAEs were reported by any participant after the booster dose.

7.6.4 AEs of clinical interest

Standardized MedDRA Queries (SMQs) were conducted to evaluate for constellations of unsolicited AEs among 5-11 year-old booster dose recipients through cut-off date of March 22, 2022. SMQs (narrow and broad in scope) were conducted on adverse event PTs that could represent various conditions, including but not limited to angioedema, arthritis, cardiomyopathy, ischemic heart disease, cardiac arrhythmia, cardiac failure, central nervous system vascular disorders, convulsions, demyelination, embolic and thrombotic events, hearing and vestibular disorders, hematopoietic cytopenias, hypersensitivity, peripheral neuropathy, thrombophlebitis, and vasculitis. For example, the cardiomyopathy SMQ includes PTs that may be related to myocarditis and pericarditis, such as chest pain, palpitations, dyspnea, syncope, troponin elevation, ECG with ST elevation or PR depression, pericardiac rub, or echocardiographic findings.

This search identified one participant who reported an AE within the hypersensitivity SMQ. This was for a mild facial rash that occurred 11 days following the booster dose. The rash was attributed to wearing a face mask and was considered unrelated to the study vaccine by the investigator and FDA.

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

7.7 Study C4591007 Phase 2/3 booster summary

The clinical data submitted with this EUA request come from ongoing study C4591007. Immunogenicity of the 10 µg BNT162b2 booster dose was assessed in a subset of 67 participants 5-11 years of age with no evidence of prior SARS-CoV-2 infection up to 1 month after the booster dose. Effectiveness of the booster dose against the reference strain was inferred based on immunogenicity analyses of antibody responses at 1 month following booster dose and of antibody response at 1 month following Dose 2 of 5-11 year old participants who completed a 2-dose primary series, as assessed by SARS-CoV-2 NT50 GMTs and seroresponse rates (≥4-fold rise) elicited by the vaccine.

Descriptive analyses showed a higher NT50 GMT against the reference strain (USA_WA1/2020), as assessed by mNG microneutralization assay, at 1 month following Dose 3 as compared to NT50 GMT prior to Dose 3 and at 1 month post-Dose 2, in a subset of participants from the same study. The proportion of participants with a 4-fold rise in NT50 GMTs before and after the booster dose was less than the proportion of participants with a 4-fold rise in NT50 GMTs before and after the primary series; however, the proportions of participants with a 4-fold rise between pre-Dose 1 and post-Dose 2 or post-Dose 3 were generally comparable. The NT50 GMT against both the reference strain and Omicron variant, evaluated using the non-validated FFRNT assay, was also higher in a subset of the 3-dose set at 1 month post-Dose 3 as compared to 1 month post-Dose 2. The NT50 GMT against Omicron was lower than the GMT against the reference strain at both time points, but the fold-increase from post-Dose 2 to post-Dose 3 was greater for Omicron than for the reference strain (approximately 22-fold as compared to approximately 5-fold); however, the relative sensitivities of these non-validated assays is not known.

The reactogenicity reported after the BNT162b2 booster dose (Dose 3), assessed in 401 participants 5-11 years of age, was similar to the reactogenicity observed after the second primary series dose (Dose 2). The most frequently reported unsolicited adverse event (AE) was lymphadenopathy, which was reported in 10 booster dose recipients (2.5%). No SAEs, withdrawals due to AEs, myocarditis/pericarditis or anaphylaxis were reported among participants in the safety population.

8 FDA REVIEW OF OTHER INFORMATION SUBMITTED

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

The Sponsor submitted a benefit-risk (B-R) assessment for use of a BNT162b2 booster dose in children 5-11 years of age. The key benefits assessed include preventable COVID-19 cases and hospitalizations due to COVID-19. The key risks include excess myocarditis/pericarditis cases associated with vaccination. The Agency asked the Sponsor to address several concerns related to B-R model input assumptions and to perform sensitivity analysis related to uncertainty of remaining vaccine protection from the primary series and vaccine-related myocarditis risk among the target age group. The Sponsor provided an updated the B-R assessment according to FDA's comments. Assuming a pre-boost vaccine efficacy (VE) of 20%, the Sponsor predicts that during a 6-month period following vaccination, the booster dose would avert 16,124 cases of COVID-19 (range: 8,356-20,312) based on the pandemic average COVID-19 incidence rate (approximately 1,500 cases per week per million population from March 7, 2020, through April 9, 2022) and 152,304 cases of COVID-19 (range: 78,976-191,788) based on the Omicron peak incidence rate. Additionally, assuming a pre-boost VE against hospitalization of 70%, the Sponsor predicts prevented hospitalizations of 16 (range: 0-16) based on the pandemic average COVID-19 incidence rate and 132 (range: 48-160) based on the Omicron peak incidence rate. Regarding risks, the Sponsor predicted 0 to 12 myocarditis/pericarditis cases per million booster doses within 21-day risk window post vaccination. Based on review of Sponsor's B-R assessment, FDA reviewers agree with the Sponsor's conclusions that the known and potential benefits of a booster dose outweigh its known and potential risks for children 5-11 years of age (see Section 10 below).

8.2 Chemistry, manufacturing, and control (CMC) information

The Sponsor did not submit any new CMC information with this EUA amendment. Therefore, as determined during review of the EUA Amendment request for use of the Pfizer-BioNTech COVID-19 Vaccine in individuals 5 through 11 years of age, the Pfizer-BioNTech COVID-19 Vaccine is manufactured with sufficient quality and consistency to support the proposed use under EUA.[32]

8.3 Pharmacovigilance activities

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

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

Pfizer-BioNTech plans to conduct passive and active surveillance to monitor the post-authorization safety for the Pfizer-BioNTech COVID-19 Vaccine, including:

- Mandatory reporting by the Sponsor under the EUA for the following events to VAERS within 15 days: SAEs (irrespective of attribution to vaccination); COVID-19 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.

The Sponsor also plans to conduct the following post-authorization observational studies. These studies will encompass the evaluation of children 5-11 years of age and third/booster doses and include active surveillance safety studies using large health insurance claims and/or electronic health record database(s):

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

  Objective: To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general 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 determine whether an increased risk of prespecified adverse events of special interest (AESI), including myocarditis/pericarditis, exists following administration of at least one dose of the Pfizer-BioNTech COVID-19 Vaccine.

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

  Objective: To describe the clinical course (treatment, survival, hospitalizations, long-term cardiac outcomes) of myocarditis or pericarditis among individuals diagnosed with myocarditis and/or pericarditis after receiving at least 1 dose of the Pfizer-BioNTech COVID-19 Vaccine and among individuals diagnosed with myocarditis and/or pericarditis who had no prior COVID-19 vaccination.

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

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

Pfizer-BioNTech also plans to conduct Study C4591014 entitled “Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study Kaiser Permanente Southern California” which includes individuals 5-11 years of age and analyses for vaccine effectiveness among individuals with greater than two doses of BNT162b2.

8.4 Clinical assay information

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

Additionally, a fluorescence focus reduction neutralization test (FFRNT) was used to determine neutralizing titers against the reference USA_WA1/2020 strain and the B.1.1.529 Omicron variant (a recombinant virus with Omicron variant spike gene on the mNeonGreen USA_WA1/2020 genetic background). The FFRNT is a non-validated assay and was used for exploratory purposes only.

8.5 Inspection of clinical study sites

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

8.6 EUA prescribing information and fact sheets

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

9 POST-EUA AND POST-LICENSURE SAFETY SURVEILLANCE

As of May 2, 2022, more than 340 million doses of the Pfizer-BioNTech COVID-19 Vaccine have been administered in the U.S. (CDC COVID Data Tracker, accessed on May 3, 2022). Among those 5-11 years of age, 10,143,428 individuals have received at least one dose of COVID-19 vaccine and 8,214,105 individuals are fully vaccinated.

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, stimulated reporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported event was actually due to the vaccine.

As of May 3, 2022, VAERS received 737,018 reports (including 381,025 U.S. reports) following Pfizer-BioNTech COVID-19 Vaccine, of which 10,405 U.S. reports were described as involving children 5-11 years of age, 14,995 U.S. reports were in children 12-15 years of age, and 8,056 U.S. reports were in adolescents 16-17 years of age. The top ten most frequently reported MedDRA Preferred Terms (PTs) included:

- Most frequent PTs among all ages: SARS-CoV-2 test, headache, fatigue, pyrexia, COVID-19, dizziness, pain, nausea, chills, pain in extremity.

- Most frequent PTs in persons ≤17 years of age: dizziness, pyrexia, headache, syncope, product storage error, nausea, product administered to patient of inappropriate age, chest pain, fatigue, vomiting.

- Most frequent PTs in persons 5-11 years of age: incorrect dose administered, product preparation issue, product administered to patient of inappropriate age, product storage error, pyrexia, vomiting, headache, syncope, dizziness, fatigue.

Note that a report may have one or more PTs. Among U.S. VAERS reports for individuals 5-11 years of age, the majority (96.1%) were non-serious.

Safety concerns identified from post-authorization safety surveillance data in VAERS are summarized below. Anaphylaxis, myocarditis, and pericarditis are existing safety concerns that have been added to the product Fact Sheets. Review of passive surveillance AE reports and the Sponsor's periodic safety reports did not indicate any new safety concerns. Most AEs are labeled events and consistent with the safety profile for this vaccine. No unusual frequency, clusters, or other trends for AEs were identified that would suggest a new safety concern, including among the reports described in children 5-11 years of age.

Anaphylaxis

Post-authorization surveillance has identified a risk of anaphylaxis, primarily in individuals with history of prior severe allergic reactions to other medications or foods.[33,34]Anaphylaxis is an important identified risk in the pharmacovigilance plan and included in the Warnings sections of the vaccine Fact Sheets and Prescribing Information. The estimated crude reporting rate for anaphylaxis following Pfizer-BioNTech COVID-19 Vaccine for all ages in the U.S. is 4.7 cases per million doses administered based on VAERS data as of May 3, 2022, which is similar to estimated rates for other vaccines.[35]

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 adult males under 40 years of age than among females and older males and have been highest in males 16-17 years of age. Rates of verified cases per million doses within 7-days following Dose 2 administration were ~70.2 cases among males ages 16-17 years, 45.7 cases among males ages 12-15 years, and 4.3 cases among males ages 5-11 years.[36] Although some cases of vaccine-associated myocarditis/pericarditis have required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae and outcomes in affected individuals, or whether the vaccine might be associated initially with subclinical myocarditis (and if so, what are

the long-term sequelae). A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established. Myocarditis and pericarditis were added as important identified risks in the pharmacovigilance plan and included in the Warnings sections of the vaccine Fact Sheets and Prescribing Information. The Sponsor is conducting additional post-authorization/post-marketing studies to assess known serious risks of myocarditis and pericarditis as well as to identify an unexpected serious risk of subclinical myocarditis.

VAERS reporting rates of myocarditis in individuals ages 12-29 years following booster exceeded the background rate but were lower compared to the rates following administration of the second primary series dose of Pfizer-BioNTech COVID-19 Vaccine.[37]

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

10.1 Known and potential benefits

Available data support the benefit of a booster dose of Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) in children 5-11 years of age for the prevention of COVID-19. Immunogenicity data indicate higher neutralizing antibody titers against SARS-CoV-2, including against the Omicron variant, in children 5-11 years of age who received a booster dose of BNT162b2 as compared to children 5-11 years old who received the Pfizer-BioNTech COVID-19 Vaccine primary series. This observation is similar to the neutralizing antibody responses observed in adults following a booster dose and is considered in the context of real-world evidence in adults and adolescents supporting increased effectiveness of BNT162b2 against COVID-19 and associated serious outcomes following a booster dose as compared to following a 2-dose primary series.[38,39] The totality of evidence therefore supports a similar benefit in younger children 5-11 years of age.

Although study participants 5-11 years of age in the immunogenicity analyses received the BNT162b2 booster dose at 7 to 9 months after completion of the 2-dose primary series, it is reasonable to extrapolate effectiveness of the booster dose in this age group when administered a soon as 5 months after completion of the primary series, based on data from and experience with use of booster doses in older age groups. Alignment of the authorized booster dose interval with that authorized for older age groups (i.e., 5 months) would help to simplify operational and communication aspects of public health vaccination programs.

Since the overall burden of COVID-19 (most notably more serious outcomes such as hospitalization and death) is lower in children 5-11 years of age compared with adults, the individual-level and population-level benefits of a booster dose, in particular among healthy vaccine recipients at low risk of severe COVID-19, are expected to be lower in children 5-11 years of age than in adults and would depend largely on the incidence of COVID-19 (see Section 8.1). Nonetheless, given the uncertainty of the COVID-19 pandemic and likelihood of continued SARS-CoV-2 transmission, widespread deployment of the vaccine for use among children 5-11 years of age may have a substantial effect on COVID-19-associated morbidity and mortality in this age group. With the continued relaxation of other preventive measures to minimize SARS-CoV-2 transmission (e.g., mask mandates, social distancing, and isolation of infected individuals), the added benefits of a booster dose in this age group might be even greater. Furthermore, longer-term post-COVID symptoms (“long COVID”) can cause significant morbidity after initially mild infection, including in younger children, and risk factors for these symptoms remain unknown.

10.2 Uncertainties related to benefits

The uncertainties associated with benefits of a booster dose of the Pfizer-BioNTech COVID-19 Vaccine, when used in children 5-11 years of age, include the following:

- Duration of protection: in older age groups, waning neutralizing antibody titers, including after booster doses, have been associated with waning protection against asymptomatic infection and less severe COVID-19. However, protection against more severe COVID-19 has been observed to date to be durable among younger adults and adolescents.

- Effectiveness in populations at high risk of severe COVID-19, including children with certain immunocompromising medical conditions: while such conditions may adversely impact vaccine effectiveness, a booster dose is still likely to improve protection in these populations compared to that conferred by the primary series alone.

- Benefits in children previously infected with SARS-CoV-2 relative to those who have not been previously infected: current seroprevalence data indicate that up to 70% of the population 5-11 years of age has been infected during one of the recent waves associated with Delta or Omicron variants. While previous infection provides some protection against re-infection, available evidence suggests that this protection is not durable, and availability of a booster dose would be a benefit to children (and their caregivers) who seek additional protection. Furthermore, booster vaccination with a vaccine based on the ancestral strain may broaden immunity against future variants compared to the immunity conferred by infection with the Delta or Omicron variant.

- Future vaccine effectiveness as influenced by characteristics of the pandemic, including emergence of new variants: it is possible that new variants will emerge that require additional booster doses with modified vaccines that are better antigenically matched to those variants.

10.3 Known and potential risks

Following the booster dose of BNT162b2 in children 5-11 years of age, the reported rates of solicited local and systemic adverse reactions were similar to those reported following the doses 1 and 2 of the primary series. Lymphadenopathy was reported more frequently in booster dose recipients than after Dose 1 (2.5% vs. 0.9%). The unsolicited AEs rate and nature of the reported AEs do not suggest any new safety concerns compared with AEs reported after the first 2 vaccine doses. Although many study participants 5-11 years of age received the BNT162b2 booster dose at 8 to 9 months after the second primary series dose, and almost all received the BNT162b2 booster dose at 7 to 9 months after the second primary series dose, it is reasonable to extrapolate safety of the booster dose in this age group when administered a soon as 5 months after completion of the primary series, based on data from and experience with use of booster doses in older age groups. Alignment of the authorized booster dose interval with that authorized for older age groups (i.e., 5 months) would help to simplify operational and communication aspects of public health vaccination programs.

Anaphylaxis, primarily among individuals with a history of severe allergic reactions to other medications or foods, has been documented to occur at a rate of approximately 5 cases per million doses among vaccine recipients 16 years of age and older (similar in magnitude to reported rates of anaphylaxis following licensed preventive vaccines). Risk of allergic reactions, including the potential for severe allergic reactions and the need for vaccine providers to be able to manage them should they occur and a contraindication for use in individuals with known

allergy to any component of the vaccine, are described in the vaccine Fact Sheets and Prescribing Information. Additionally, risk of anaphylaxis/severe allergic reactions will be further evaluated as part of the pharmacovigilance plan for the vaccine.

Myocarditis/pericarditis is a known risk associated with the Pfizer-BioNTech COVID-19 Vaccine and is greatest among males 16-17 years of age compared with both younger and older age groups. In contrast to myocarditis in the pre-COVID era, most reported cases of vaccine-associated myocarditis have involved rapid resolution of symptoms with conservative management; however, the long-term sequelae of vaccine-associated myocarditis, if any, remain to be determined. The risk of vaccine-associated myocarditis/pericarditis following primary series doses is much lower among children 5-11 years of age than adolescents[40,41], and the risk of myocarditis in adolescents and adults following a booster dose is lower than the risk associated with the second primary series dose. No cases of myocarditis or pericarditis were reported among the 401 booster dose recipients in study C4591007. However, this safety database is not large enough to quantify the frequency of this uncommon adverse reaction, and post-authorization safety surveillance is needed to further assess this risk following a booster dose in children 5-11 years of age.

10.4 Uncertainties related to risks

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

- Risk of myocarditis/pericarditis, as described in detail in Section 10.3 above.
- Safety in certain subpopulations: available data are insufficient to make conclusions about the safety of the vaccine in certain subpopulations such as immunocompromised children.
- Safety data available in children previously infected with SARS-CoV-2 are limited, due to lower seroprevalence of SARS-CoV-2 in young children.
- Adverse reactions that are very uncommon or that require longer follow-up to be detected. Active and passive safety surveillance will continue during the post authorization period to detect new safety signals.

11 OVERALL SUMMARY AND RECOMMENDATIONS

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

- As summarized in Section 7 of this review, the CBRN agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of available scientific evidence, a single booster dose of Pfizer-BioNTech COVID-19 Vaccine, when administered to children 5-11 years of age, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2. Vaccine effectiveness was inferred from descriptive analyses of immunogenicity data based on the NT50 GMTs 1 month post-Dose 2, prior to Dose 3, and at 1 month following Dose 3. Although not evaluated in pre-specified hypothesis testing, the

descriptive comparisons of neutralizing antibodies following the second primary series dose and booster dose among children 5-11 years of age support similar conclusions about booster dose effectiveness as the immunobridging analyses previously used for inferring effectiveness of a first booster dose in adults 18 years of age and older (which have since been corroborated by vaccine effectiveness data from observational studies of a BNT162b2 booster dose in adolescents and adults).

- Based on the data summarized in Section 7 and benefits and risks in Section 10 of this review, the known and potential benefits of a booster dose of the vaccine outweigh the known and potential risks when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 5-11 years of age. Known and potential benefits include reduction in the risk of symptomatic COVID-19 and associated serious sequelae. Potential benefits that could be further evaluated but are not necessary to support an EUA include prevention of COVID-19 in individuals with previous SARS-CoV-2 infection, reduction in asymptomatic SARS-CoV-2 infection and reduction of SARS-CoV-2 transmission. Known and potential risks include common local and systemic adverse reactions (notably injection site reactions, fatigue, headache, muscle pain, chills, fever and joint pain), lymphadenopathy, and hypersensitivity reactions (e.g., rash, pruritis, urticaria, angioedema), and rarely anaphylaxis and myocarditis/pericarditis (based on experience in Pfizer-BioNTech COVID-19 Vaccine recipients 12 years of age and older). Risks that should be further evaluated include quantifying the rate of vaccine-associated myocarditis/pericarditis in this age group and surveillance for other adverse reactions that may become apparent with more widespread use of the vaccine and with longer duration of follow-up. Acknowledging the current uncertainties around benefits and risks, FDA concurs that the Sponsor's quantitative analysis using conservative assumptions predicts that the known and potential benefits of a booster dose of the vaccine outweigh the known and potential risks in children 5-11 years of age.

- Comirnaty and Spikevax are the only FDA-approved vaccines indicated for active immunization for prevention of COVID-19 caused by SARS-CoV-2. No COVID-19 vaccine is currently approved for use as a booster dose in children 5-11 years of age.

Based on the considerations outlined above, the review team recommends authorization of the Pfizer-BioNTech COVID-19 Vaccine under EUA for use as a booster dose (10 µg administered at least 5 months after completion of the primary series) in children 5-11 years of age.

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