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

Identifying Information

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Sponsor	Pfizer, Inc., on behalf of Pfizer and BioNTech
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Signatory Authority	David C. Kaslow, M.D., Director, CBER/OVRR
Principal Reviewers	Meghan Maguire Thon, Ph.D., Regulatory Project Manager, OVRR/DVRPA CAPT Michael Smith, Ph.D., Regulatory Project Manager, OVRR/DVRPA Julianne Clifford, Ph.D., Regulatory Project Manager, OVRR/DVRPA Adam Spanier, M.D., Ph.D., MPH, Clinical reviewer, OVRR/DVRPA Ye Yang, Ph.D., Biostatistics reviewer, OBPV/DB Samaneh Bazel, M.D., PVP reviewer, OBPV/DPV Xiao Wang, Ph.D., CMC/Product reviewer, OVRR/DVP Kathleen Jones, Ph.D., CMC/Facility reviewer, OCBQ/DMPQ Laura Fontan, B.S., M.B.A., CMC/Facility reviewer, OCBQ/DMPQ, Hong Yang, Ph.D., Benefit-risk assessment reviewer, OBPV/ABRA Oluchi Elekwachi, PharmD, MPH, Labeling reviewer, OCBQ/DCM/APLB
Review Completion Date	March 14, 2023
Established Name/Names used during development	Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)
Dosage Forms/Strengths and Route of Administration	A 0.2 mL suspension 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 (fourth dose) after completion of primary vaccination with 3 doses of the Pfizer-BioNTech COVID-19 Vaccine in individuals 6 months through 4 years of age
Intended Population	Individuals 6 months through 4 years of age

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1 Executive Summary

On February 28, 2023, Pfizer submitted a request to FDA to amend its Emergency Use Authorization (EUA) to allow for the use of a booster dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), hereafter referred to as Bivalent (WT/OMI BA4/BA.5), for prevention of COVID-19 caused by SARS-CoV-2 in individuals 6 months through 4 years of age (hereafter 6 months-4 years of age).

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to be an ongoing global health challenge, and as of March 10, 2023, has led to over 676 million cases of coronavirus disease 2019 (COVID-19), including over 6.88 million deaths worldwide.[1] The Pfizer-BioNTech COVID-19 Vaccine (hereafter referred to as BNT162b2) is a nucleoside-modified messenger RNA (mRNA) vaccine encoding the full-length spike (S) protein of the original (ancestral/reference) Wuhan-Hu-1 SARS-CoV-2 strain. BNT162b2 was initially authorized under EUA on December 10, 2020, for primary series vaccination of individuals 16 years of age and older and subsequently authorized for primary series for individuals as young as 6 months of age. Also, BNT162b2 was previously authorized for booster vaccination of individuals 5 years of age and older; however, following emergence of the Omicron variant and its sublineages (recently including BA.4/BA.5) and observations of decreased vaccine effectiveness against Omicron sublineages compared to the original strain, formulations of the vaccine containing Omicron components were developed to improve vaccine effectiveness. Following a June 28, 2022, meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss potential changes to COVID-19 vaccine strain composition for use in future vaccination campaigns and subsequent discussions with the World Health Organization (WHO) and other regulatory authorities, FDA recommended that manufacturers develop bivalent COVID-19 vaccines that include a component based on the original strain and a component based on Omicron BA.4/BA.5 for use as a booster dose potentially beginning in fall 2022. On August 31, 2022, FDA authorized the Pfizer BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use under EUA as a single booster dose in individuals 12 years of age and older, with concurrent revision of the authorization for the original (monovalent) BNT162b2 to no longer provide for its use as a booster dose in individuals 12 years of age and older. On October 12, 2022, FDA authorized the Pfizer BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use under EUA as a single booster dose in individuals 5 through 11 years of age, with concurrent revision of the authorization for BNT162b2 to no longer provide for its use as a booster dose in individuals 5 through 11 years of age and older. On December 8, 2022, FDA authorized the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use under EUA as the third dose in the 3-dose primary series for individuals 6 months through 4 years of age, with concurrent revision to remove authorization of BNT162b2 as the third dose in the 3-dose primary series for those individuals. A booster vaccine that is able to elicit improved protection against the Omicron BA.4/BA.5 sublineages, and potentially other sublineages, is an important public health need.

The EUA request contains safety and immunogenicity data from 60 participants 6 months-4 years of age from Study C4591048 (hereafter Study 1048), Substudy B, Group 2, who received the 3 µg Bivalent (1.5 µg WT, 1.5 µg OMI BA.4/BA.5) booster dose at least 2 months after completing a 3-dose BNT162b2 primary series. The median duration of safety follow-up after the booster dose was 1.8 months. Omicron BA.4/BA.5 and the reference strain neutralizing geometric mean titers (GMTs) and seroresponse rates at 1 month after the Bivalent (WT/OMI BA.4/BA.5) booster dose were descriptively summarized. Post-BNT162b2 Dose 3 SARS-CoV-2 neutralizing responses from age-matched Study C4591007 (hereafter Study 1007) Phase 2/3 participants, 6 months-4 years of age, who had received three doses of 3 µg BNT162b2 were

also descriptively summarized and included as a reference. There were no formal statistical comparisons of the immune response between subsets from the two studies. In addition, supportive safety data with a median follow up of 1.6 months were provided for 431 individuals ≥5 years of age who received a Bivalent (WT/OMI BA.4/BA.5) booster dose in studies 1048 [Substudy D Group 2] and C4591044 (hereafter Study 1044) [Cohort 2 Groups 1,2, and 4]. In participants 6 months-4 years of age, the Omicron BA.4/BA.5-specific neutralizing GMT at 1 month after a Bivalent (WT/OMI BA.4/BA.5) booster dose was numerically higher than the GMT after the third BNT162b2 primary dose in Study 1007. Omicron BA.4/BA.5 strain seroresponse rates were similar in the bivalent and BNT162b2 vaccine groups. For the reference strain that is no longer in widespread circulation, the GMT after the third BNT162b2 primary dose was higher than the GMT after a Bivalent (WT/OMI BA4/BA.5) booster dose; this observation in part may be due to a lower quantity of modRNA (1.5 µg) for the original strain in the bivalent (WT/OMI BA4/BA.5) than in BNT162b2 (3 µg). Based on safety data from Study 1048, the frequencies of solicited local and systemic reactions after a 3 µg Bivalent (WT/OMI BA4/BA.5) booster dose were similar to frequencies within the respective age groups reported after completion of a BNT162b2 primary series. The safety profile from participants 5 years and older suggests that Bivalent (WT/OMI BA4/BA.5) administered as a fourth COVID-19 vaccine dose is generally tolerated in individuals who previously received two primary doses and one booster dose of BNT162b2 vaccine.

Given that Bivalent (WT/OMI BA.4/BA.5) is manufactured using the same process as BNT162b2, post-marketing safety data for BNT162b2 were considered relevant to the safety evaluation of Bivalent (WT/OMI BA.4/BA.5). As of March 2, 2023, more than 434 million doses of the Pfizer-BioNTech COVID-19 Vaccines (including BNT162b2 and Bivalent (WT/OMI BA.4/BA.5)) have been administered in the U.S.[2] In recipients of any age and all doses, the most frequently reported preferred terms (PTs) in the Vaccine Adverse Event Reporting System (VAERS) for Bivalent (WT/OMI BA.4/BA.5) were COVID-19, fatigue, headache, pyrexia, pain, chills, cough, pain in extremity, nausea, and dizziness. For important risks identified in the pharmacovigilance plan for BNT162b2, anaphylaxis and myocarditis/pericarditis remain identified risks that are included in product labeling. The Sponsor is conducting additional safety-related post-authorization/postmarketing studies for BNT162b2, including postmarketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. The Sponsor will also conduct post-authorization studies to evaluate the association between the Bivalent (WT/OMI BA.4/BA.5) and a pre-specified list of adverse events of special interests (AESIs) in the general U.S. population.

The totality of scientific evidence available at this time supports the conclusion that, Bivalent (WT/OMI BA.4/BA.5) when administered as a booster dose to individuals 6 months-4 years of age who completed a 3-dose primary series with BNT162b2 may be effective against the currently circulating SARS-CoV-2 variants and that the known and potential benefits outweigh the known and potential risks. Therefore, the review team recommends authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) under EUA for use as a booster dose in individual 6 months-4 years of age administered at least 2 months after completion of a 3-dose primary series with BNT162b2 Vaccine.

2 Background

2.1 SARS-CoV-2 and COVID-19

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 variable respiratory and systemic manifestations. Disease symptoms

vary, with many persons presenting with asymptomatic or mild disease while some others, especially those older than 65 years and those with certain co-morbid conditions,[3] may develop severe respiratory tract disease including pneumonia and acute severe respiratory distress syndrome, leading to multiorgan failure and death. Most adults with COVID-19 recover within 1 to 2 weeks but symptoms may persist for months in some individuals.[4] 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.[5,6] Other symptoms in children include nausea and vomiting, diarrhea, dyspnea, nasal symptoms, rashes, fatigue and abdominal pain.[4] Most children with COVID-19 recover within 1 to 2 weeks. Estimates of asymptomatic infection in children vary from 15% to 50% of infections.[7,8] However, COVID-19-associated hospitalizations and deaths have occurred in individuals 17 years of age and younger, and for some children, COVID-19 symptoms may continue for weeks to months after their initial illness. Moreover, hospitalization and death rates among individuals under 18 years of age are highest in children <2 years of age.[9]

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of March 1, 2023, has led to over 675 million cases of COVID-19 and over 6.8 million deaths worldwide.[1] In the U.S., more than 103 million cases and 1.1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC).[10] Approximately 3.7% of cases occurred in children through 4 years of age.[11]

Since the start of the pandemic caused by the Wuhan-Hu-1 strain of SARS-CoV-2 (also referred to as the ancestral, original, or reference strain), surges in SARS-CoV-2 activity and resultant COVID-19 cases, hospitalizations, and deaths have been associated with a combination of factors, including but not limited to: emergence of variants with greater transmissibility, greater virulence, and/or antigenic mutations, enabling at least partial escape from immunity conferred by prior vaccination or infection; relaxation of public health measures aimed at preventing transmission; and seasonal variation typical of respiratory viruses. Recent surges, both globally and in the U.S., have been associated with rapid spread of highly transmissible SARS-CoV-2 variants, most recently Omicron XBB.1.5, BQ.1 and, and BQ.1.1. The Omicron variant BA.1 became the predominant variant circulating in the U.S. in December 2021, and subsequently evolved into sublineages, including BA.4 and BA.5 sublineages, and more recently the XBB.1.5, BQ.1 and, and BQ.1.1 sublineages. As of March 7, 2023, XBB.1.5 was the currently dominant variant in the U.S. (89.6% of cases), followed by BQ.1.1 (6.7% of cases). With a current daily average of 32,999 cases and 388 deaths due to COVID-19, vaccination to elicit protection against the evolving Omicron sublineages continues to be an important public health need. Moreover, recent studies have demonstrated that XBB.1.5 can evade humoral immunity induced by mRNA vaccines or natural infection and that a bivalent vaccine (ancestral and BA.4/5) is, “more immunogenic than the original vaccine,” with greater responses against circulating omicron sublineages to XBB.1.5 and added protection against symptomatic XBB/XBB.1.5 infection.[12,13]

Throughout this document, the term “sublineage” indicates the SARS-CoV-2 Omicron variant BA.1, BA.4, BA.5, BQ.1, BQ.1.1 and/or XBB lineage, as specified.

2.2 Authorized and Approved Vaccines and Therapies for COVID-19

2.2.1 Comirnaty, Pfizer-BioNTech COVID-19 Vaccine, and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)

Comirnaty (COVID-19 Vaccine, mRNA), manufactured by Pfizer and BioNTech, is approved for use as a 2-dose primary series for active immunization to prevent COVID-19 caused by SARS-

CoV-2 in individuals 12 years of age and older. Comirnaty contains a nucleoside-modified messenger RNA (mRNA) encoding the S protein of the original SARS-CoV-2 strain that is formulated in lipid particles. Under EUA, the vaccine is called the Pfizer-BioNTech COVID-19 Vaccine and is authorized for use as: the first two doses of a 3-dose primary series for individuals 6 months-4 years of age, a 2-dose primary series for individuals 5 years of age and older, and a third primary series dose for individuals 5 years of age and older with certain types of immunocompromise. A bivalent formulation of the vaccine manufactured using the same process, Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), hereafter referred to as Bivalent (WT/OMI BA4/BA.5), is authorized for use as a single booster dose in individuals 5 years of age and older, to be administered at least 2 months after either completion of primary vaccination with an authorized or approved COVID-19 vaccine or receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 Vaccine and as the third dose of the 3-dose primary series in individuals 6 months-4 years of age. The total mRNA content for each of the authorized and/or approved primary series and booster doses is specified for the age group in which the vaccine is being administered: 3 µg in 0.2 mL for 6 months-4 years of age, 10 µg in 0.2 mL for 5-11 years of age, and 30 µg in 0.3 mL for 12 years of age and older. Safety and effectiveness data supporting approval of Comirnaty and authorization of BNT162b2 and Bivalent (WT/OMI BA4/BA.5) are detailed in the decision memoranda available on the FDA website.

2.2.2 Spikevax, Moderna COVID-19 Vaccine, and Moderna COVID-19 Vaccine, Bivalent (WT/OMI BA4/BA.5)

Spikevax (COVID-19 Vaccine, mRNA), manufactured by Moderna, is approved for use as a 2-dose primary series for active immunization to prevent COVID-19 in individuals 18 years of age and older. Spikevax contains nucleoside-modified mRNA that encodes for the full-length spike (S) protein of the original SARS-CoV-2 strain encapsulated in lipid particles. Under EUA, the vaccine is called the Moderna COVID-19 Vaccine and is authorized for use as a 2-dose primary series for individuals 6 months of age and older, and a third primary series dose for individuals 6 months of age and older with certain types of immunocompromise. A bivalent formulation of the vaccine manufactured using the same process, Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), is authorized for use as a single booster dose in individuals 6 years of age and older, to be administered at least 2 months after either completion of primary vaccination with an authorized or approved COVID-19 vaccine or receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 Vaccine. The Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is also authorized for use as a single booster dose in individuals 6 months through 5 years of age, to be administered at least 2 months after completion of primary vaccination with the monovalent Moderna COVID-19 Vaccine. The total mRNA content for each of the authorized and/or approved primary series doses is specified for the age group in which the vaccine is being administered: 25 µg in 0.25 mL for 6 months-5 years of age, 50 µg in 0.5 mL for 6-11 years of age, and 100 µg in 0.5 mL for 12 years old and older. The total mRNA content for the authorized booster dose of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in individuals is 10 mcg in 0.2 mL for 6 months-5 years of age, 25 mcg in 0.25 mL for 6-11 years of age, and 50 µg in 0.5 mL for 12 years of age and older. Safety and effectiveness data supporting approval of Spikevax and authorization of the Moderna COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

2.2.3 Janssen COVID-19 Vaccine

The Janssen COVID-19 Vaccine, a non-replicating adenovirus type 26-vectored vaccine encoding the S protein of SARS-CoV-2 original strain, is authorized for active immunization to

prevent COVID-19 in individuals 18 years of age and older for whom other FDA-authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, or who elect to receive the Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine. The vaccine is authorized for use in these individuals as a single primary vaccination dose and as a first booster dose at least 2 months after completion of primary vaccination with an authorized or approved COVID-19 vaccine. The safety and effectiveness data supporting authorization for the Janssen COVID-19 Vaccine and limitations on its use are detailed in the decision memoranda available on the FDA website.

2.2.4 Novavax COVID-19 Vaccine

The Novavax COVID-19 Vaccine, Adjuvanted, which contains recombinant S protein of the SARS-CoV-2 original strain and Matrix-M adjuvant, is authorized for use as a 2-dose primary series for active immunization to prevent COVID-19 in individuals 12 years of age and older. Novavax COVID-19 Vaccine, Adjuvanted is also authorized for use as a first booster dose administered at least 6 months after completion of primary vaccination with an authorized or approved COVID-19 vaccine in individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and to individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine. Safety and effectiveness data supporting authorization for the Novavax COVID-19 Vaccine, Adjuvanted are detailed in the decision memoranda available on the FDA website.

2.2.5 Therapies for COVID-19

The antiviral remdesivir (Veklury) 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.

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 include the following:

Antivirals: Nirmatrelvir co-packaged with ritonavir tablets (Paxlovid) is authorized for the treatment of mild-to-moderate COVID-19 in certain adults as well as pediatric patients, 12 years of age and older weighing at least 40 kg, who are at high risk for progression to severe COVID-19, including hospitalization or death. Molnupiravir (Lagevrio) is authorized for the treatment of mild-to-moderate COVID-19 in certain adults at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative approved or authorized COVID-19 treatment options are not accessible or clinically appropriate. It is not authorized for use in patients less than 18 years of age.

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

who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

COVID-19 convalescent plasma with high anti-SARS-CoV-2 antibody titer is authorized for emergency use as a treatment for COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings.

Monoclonal antibodies were previously deployed for prophylaxis and for treatment of COVID-19 in older children and adults. However, the currently circulating variants are relatively resistant to neutralization by existing monoclonal antibodies. FDA recently announced that previously authorized monoclonal antibodies (bebtelovimab, sotrovimab, bamlanivimab, etesevimab, casirivimab co-packaged with imdevimab, and tixagevimab co-packaged with cilgavimab) are not authorized in the United States because they are not expected to neutralize Omicron subvariants.

3 Rationale for Bivalent Booster Doses

3.1 Post-Authorization Effectiveness Data Against Clinically Relevant SARS CoV-2 Variants

While the currently authorized and approved monovalent COVID-19 vaccines in the U.S. are based on the original SARS-CoV-2 strain, recently and currently circulating SARS-CoV-2 variants harbor mutations in the S protein that confer at least partial antigenic escape from vaccine-elicited immunity. Nonetheless, currently available monovalent vaccines have retained some level of effectiveness against all epidemiologically important SARS-CoV-2 variants that have emerged to date, with higher level effectiveness preserved against more serious outcomes (hospitalization and death) than against mild symptomatic disease. [14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24]

Results from observational studies that have investigated the effectiveness of primary vaccination with authorized and approved vaccines have shown decreased effectiveness against certain variants (notably Omicron, for which neutralizing antibody titers are decreased compared with the original strain) and waning effectiveness over time.[15,16,17] Although first booster doses with the monovalent original COVID-19 vaccines have restored waning vaccine effectiveness (VE), including against severe disease and hospitalization associated with Omicron,[15,16,17,18] observational studies have also indicated waning effectiveness of the first booster dose over time, mainly against mild disease, with some studies also suggesting waning effectiveness against hospitalization[15,19,20,21] and lower effectiveness among immunocompromised individuals.[22] In studies in Israel with a second booster dose of the Original Pfizer-BioNTech COVID-19 Vaccine in adults 60 years of age and older, a second booster dose improved VE overall (including a reduction in mortality), although effectiveness against mild disease decreased during a 10-week follow-up period.[23,24]

In a recently published report, investigators provided estimates of bivalent COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection with XBB-related sublineages. National pharmacy-based testing was conducted December 1, 2022–January 13, 2023, and it showed the bivalent booster dose VE (compared with 2–4 monovalent doses) to be comparable between XBB/XBB.1.5 sublineage–related infections and BA.5 sublineage–related infections. The authors assert that the results demonstrate that a bivalent mRNA booster dose provides additional protection against symptomatic XBB/XBB.1.5 infection for at least the first 3 months after vaccination in persons who had previously received 2–4 monovalent vaccine doses.[13]

3.2 June 28th VRBPAC, January 26th VRBPAC, and Subsequent Regulatory Discussions

On June 28, 2022, the 175th meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened in open session to discuss whether and how the SARS-CoV-2 strain composition of COVID-19 vaccines should be modified (see FDA website for background materials). The committee heard presentations on the current epidemiology of the COVID-19 Pandemic and SARS-CoV-2 variants in the United States, COVID-19 vaccine effectiveness (CDC), and future COVID-19 Pandemic epidemiology modeling (J. Lessler, University of North Carolina). In addition, available clinical data on modified COVID-19 vaccines were presented by COVID-19 vaccine manufacturers (Pfizer Inc., ModernaTX, and Novavax Inc.) and considerations for vaccine strain composition from the WHO Technical Advisory Group on COVID-19 Vaccine Composition were also presented (K. Subbarao, WHO). FDA perspective on considerations for strain composition for modifications of COVID-19 vaccines was also provided. After these presentations and committee discussions, the VRBPAC voted 19-2 in favor of the inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines in the U.S. Although there was no vote on a more specific strain composition, there was general preference among committee members for a bivalent vaccine with an ancestral strain component and an Omicron variant component and a preference for vaccine coverage of Omicron sublineages BA.4 and BA.5. Several members stressed the need to continue to accumulate additional data on this complex issue.

Following the VRBPAC meeting, FDA and other global regulatory authorities met to discuss preliminary data on adapted vaccines addressing emerging variants and to discuss alignment on the criteria for strain selection and regulatory approaches to address new waves of COVID-19 (see ICMRA website for additional details). Based on emerging clinical data, there was a preference for a bivalent vaccine that incorporated a component based on the original strain and an Omicron variant component to provide greater breadth of immunity against SARS-CoV-2 variants including Omicron, as it is currently unknown which strains will be circulating in the future.

On June 30, 2022, FDA notified COVID-19 vaccine manufacturers of a recommendation to develop a bivalent booster vaccine (Original and Omicron BA.4/BA.5) to improve protection during a potential fall 2022 booster vaccination campaign. FDA requested that sponsors expeditiously begin clinical trials to generate safety and immunogenicity data evaluating a bivalent (Original and Omicron BA.4/BA.5) vaccine in relevant populations. FDA recognized that data in trial participants who would receive the bivalent (Original and Omicron BA.4/BA.5) vaccine would potentially not be available prior to the optimal timeframe for deployment of the vaccine in a potential fall 2022 booster vaccination campaign. Consequently, to address the urgent public health need for COVID-19 vaccine booster doses more closely matched to circulating variants, FDA considered that it may be appropriate to issue an EUA of a bivalent (Original and Omicron BA.4/BA.5) vaccine based primarily on relevant safety and effectiveness data from participants who received an earlier bivalent vaccine (Original and Omicron BA.1), plus supportive pre-clinical animal data for the recommended bivalent vaccine (Original and Omicron BA.4/BA.5), as well as data from use of already authorized vaccines.

At the January 26, 2023, VRBPAC meeting, the committee discussed harmonization of the strain composition for primary series and booster doses, simplification of the immunization schedule, and periodic updates of COVID-19 vaccine strain composition. The committee voted in favor of harmonizing the COVID-19 vaccine strain composition for primary series and booster doses in the U.S. to a single composition. The committee generally agreed that simplification of the immunization schedule was highly desirable and recommended that the simplification be

based on the best available evidence. The committee generally agreed that periodic updates to COVID-19 vaccine strain composition should be considered annually, if not biannually, and that FDA and VRBPAC need to be prepared to consider urgent updates if escape variant strains emerge.

3.3 Rationale for a Bivalent Booster Dose in Children 6 Months Through 4 Years of Age

A booster vaccine that is able to elicit improved protection against the Omicron BA.4/BA.5 sublineages, and potentially other sublineages, is an important public health need.

4 Regulatory Considerations for an Omicron Booster EUA

4.1 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. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's known and potential benefits outweigh its known and potential risks. This includes demonstrating that manufacturing information ensures product quality and consistency.

4.2 FDA Guidance for Industry Related to COVID-19 Vaccines, Including Modified COVID-19 Vaccines

Appendix 2 of the FDA Guidance for Industry, Emergency Use Authorization for Vaccines to Prevent COVID-19 (originally issued in October 2020 and last updated March 2022) discusses an approach to chemistry, manufacturing and controls (CMC) nonclinical and clinical data to support the safety and effectiveness of a modified vaccine to address emerging SARS-CoV-2

variants. Although the approach outlined in Appendix 2 does not specifically address considerations for multivalent modified vaccines, the approach and associated immunogenicity endpoints and analyses for supporting vaccine effectiveness are relevant to bivalent modified vaccines. In discussions with COVID-19 vaccine manufacturers, FDA has advised that effectiveness of a bivalent (original and Omicron variant) vaccine should be supported by immunobridging analyses demonstrating: 1) statistically superior neutralizing geometric mean titers (GMTs) against the Omicron variant elicited by the bivalent vaccine as compared to the previously authorized original vaccine; 2) statistically non-inferior neutralizing antibody seroresponse rates against the Omicron variant elicited by the bivalent vaccine as compared to the previously authorized original vaccine; 3) statistically non-inferior neutralizing antibody GMTs against the original strain elicited by the bivalent vaccine as compared to the previously authorized original vaccine; and 4) statistically non-inferior neutralizing antibody seroresponse rates against the original strain elicited by the bivalent vaccine as compared to the previously authorized original vaccine. FDA also advised vaccine manufacturers that, as discussed in the guidance document for monovalent modified vaccines, safety data to support EUA of a modified bivalent vaccine should include analyses of adverse events collected during the immunogenicity evaluation period. While the guidance encouraged clinical evaluation of modified vaccines across different age groups, the guidance also indicates that extrapolation of data accrued in one age group to support EUA of a modified vaccine in other age groups could be considered.

5 EUA Amendment Request to Authorize a Pfizer-BioNTech COVID-19 Vaccine, Bivalent (WT/OMI BA4/BA.5) Booster Dose for Individuals 6 Months-4 Years of Age who Completed a Primary Series with Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)

5.1 Summary of the EUA Request

On February 28, 2023, Pfizer and BioNTech submitted a request to amend the EUA to include the use of the Bivalent (WT/OMI BA4/BA.5) in individuals 6 months-4 years of age to provide a single booster dose (fourth dose) after completion of primary vaccination with three doses of Pfizer-BioNTech COVID-19 Vaccine, administered at least 2 months following the last dose of the primary series. Each 3-µg dose of the Bivalent (WT/OMI BA4/BA.5) is formulated to contain 1.5 µg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of the original SARS-CoV-2 strain and 1.5 µg of modRNA encoding the S glycoprotein of SARS-CoV-2 Omicron sublineages BA.4 and BA.5 (Omicron BA.4/BA.5). The S-proteins of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical.

The EUA amendment contains:

- Data from Study 1048, Substudy B, Group 2:
    - Safety: 60 participants, 6 months-4 years of age, who received Bivalent (WT/OMI BA.4/BA.5) as a booster dose at least 2 months after completing a 3-dose BNT162b2 primary series. The median duration of safety follow-up after the booster dose was 1.8 months.
    - Immunogenicity: (Omicron BA.4/BA.5, reference strain). 60 participants 6 months-4 years of age who received Bivalent (WT/OMI BA.4/BA.5) as a booster dose at least 2 months after completing a 3-dose BNT162b2 primary series.

- Supportive Bivalent (WT/OMI BA.4/BA.5) booster (fourth) dose safety data in individuals ≥5 years of age who received a 2-dose primary series and one booster dose of BNT162b2.

5.2 Initial Clinical Effectiveness Data in Adults Using the Bivalent mRNA Boosters

CDC recently reported initial effectiveness results using the Bivalent mRNA (Original and Omicron BA.4/BA.5) boosters. The study evaluated symptomatic cases of COVID-19 that were diagnosed from September 14, 2022, to November 11, 2022, in 360,626 adults who presented to the Increasing Community Access to Testing Program for COVID-19 testing.[25] Of those tested, 34% of individuals were diagnosed with COVID-19. Relative vaccine effectiveness of a Bivalent mRNA booster dose compared with that of ≥2 monovalent mRNA vaccine doses among persons for whom 2 to 3 months and ≥8 months had elapsed since last monovalent mRNA dose was 30% and 56% among persons 18 to 49 years of age, 31% and 48% among persons 50 to 64 years of age, and 28% and 43% among persons ≥65 years of age, respectively. The authors concluded that Bivalent mRNA booster doses provide additional protection against symptomatic SARS-CoV-2 in immunocompetent persons who previously received monovalent mRNA vaccines only, with relative benefits increasing with time since receipt of the most recent monovalent mRNA vaccine dose.

6 FDA Review of Safety and Immunogenicity Data from Bivalent Booster Doses

6.1 Study C4591048, Substudy B, Group 2

The EUA amendment request contains safety and immunogenicity analyses of data collected from a subset of individuals 6 months-4 years of age from Substudy B, Group 2 of the ongoing master protocol, Study 1048, designed to evaluate safety and immunogenicity of Bivalent (WT/OMI BA4/BA.5). Substudy B is an open-label study to evaluate the safety and immunogenicity of a third or fourth dose of 3 µg of Bivalent (WT/OMI BA4/BA.5), which consists of 1.5 µg BNT162b2 Original and 1.5 µg BNT162b2 Omicron BA.4/BA.5 components.

As data from all participants in Study 1048 are not yet available, the sections below summarize safety and immunogenicity data from a subset of 60 individuals, 6 months-4 years of age, who received the 3 µg Bivalent (WT/OMI BA4/BA.5) vaccine candidate as a booster dose, after completion of a 3-dose BNT162b2 primary series (Substudy B, Group 2).

6.1.1 Study Design

In Study 1048, Substudy B, approximately 4,100 participants 6 months-4 years of age were enrolled in three groups. Group 2 is comprised of children 6 months-4 years of age, who previously received three 3 µg BNT162b2 primary doses, with the last dose administered 60 to 240 days prior to enrollment in Study 1048.

Substudy B, Group 2 received 1 dose of 3 µg Bivalent (WT/OMI BA4/BA.5). Enrollment was stratified by age, such that approximately 30% of participants were 6 months to <2 years of age and approximately 70% of participants were 2 to 4 years of age.

Immunogenicity Evaluation

Omicron BA.4/BA.5 and the reference strain neutralizing geometric mean titers (GMTs) and seroresponse rates at 1 month after the Bivalent (WT/OMI BA.4/BA.5) booster dose administration were descriptively summarized. Post-BNT162b2 Dose 3 SARS-CoV-2 neutralizing responses from age-matched Study 1007 Phase 2/3 participants, 6 months-4 years of age, who had received three doses of 3 µg BNT162b2 were also descriptively summarized and included as a reference. There were no formal statistical comparisons of the immune response between subsets from the two studies. Sera were tested using the SARS-CoV-2 mNG microneutralization assay to determine Omicron BA.4/BA.5 and reference strain-specific (USA_WA1/2020) neutralizing titers.

Geometric mean titers (GMT) and geometric mean fold rises (GMFR) with 2-sided 95% CIs were calculated. Seroresponse was defined as a ≥4-fold rise from baseline (before the first bivalent booster dose [fourth dose]) for participants in Group 2 of Substudy B. For Study 1007, seroresponse was defined as a ≥4-fold rise from before the third BNT162b2 dose.

Safety Evaluation

Solicited local and systemic reactions were recorded daily for 7 days after study vaccination in an e-diary, as follows:

Children 6 months to <2 years of age (hereafter 6-23 months of age):

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

Children ≥2 to <5 years of age (hereafter 2-4 years of age):

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

Non-serious adverse events (AEs) were collected from the time of bivalent booster vaccination through 1 month after the study vaccination, and serious AEs (SAEs) were collected through 6 months post-vaccination. AEs were categorized by frequency, maximum severity, seriousness, and relationship to study intervention using system organ class (SOC) and preferred term (PT) according to Medical Dictionary for Regulatory Activities (MedDRA).

Myocarditis and pericarditis were designated in Study 1048 protocol as AEs of special interest (AESIs). A list of MedDRA AE terms were evaluated during clinical safety data review and signal detection; these included events of interest for vaccines in general or due to association with COVID-19, taking into consideration health authority lists of AESIs for COVID-19 vaccine that included events potentially indicative of severe COVID-19, multisystem inflammatory syndrome in children (MIS-C), myocarditis, pericarditis, autoimmune, and neuroinflammatory disorders among other events.

Prior SARS-CoV-2 infection was determined by virological testing via nucleic acid amplification test (NAAT) on nasal (anterior nares) swabs and serological testing (N-binding antibody assay) at study baseline and medical history of COVID-19. Participants were surveilled for potential COVID-19 from the first study dose visit onwards.

Statistical Analysis Plan

<u>Safety population</u>

Available safety data as of cutoff date 25 November 2022, were summarized for a subset of 60 participants (the first 24 and 36 participants enrolled in 6-23 months age group and 2-4 years of age group, respectively) in Group 2 of Substudy B.

Safety analyses: Descriptive statistics were provided for each reactogenicity endpoint for each group, including counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. AEs and SAEs were categorized according to MedDRA terms. Counts, percentages, and associated 95% CIs of AEs and SAEs were provided for each group.

Immunogenicity Population
Available immunogenicity data as of cutoff date 25 November 2022, were summarized for a subset of 60 participants in Group 2 of Study 1048 of Substudy B. The cutoff date for the Study 1007 subset was 07 August 2022.

A subset of Study 1007 was comprised of 60 participants 6 months-4 years of age from Phase 2/3 who received a third 3 µg BNT162b2 primary dose and were closest in match by age, prior SARS-CoV-2 infection status (i.e., before Dose 3), and prior dosing interval (i.e., between BNT162b2 Dose 2 and Dose 3) to Study 1048 participants.

6.1.2 Disposition

Safety Population
The safety population was comprised of 24 participants, 6-23 months of age and 36 participants 2-4 years of age who received 3 µg of Bivalent (WT/OMI BA4/BA.5.) No participants were excluded from the safety population. The median duration of safety follow-up time after the Bivalent (WT/OMI BA4/BA.5) booster dose was 1.8 months.

Overall, 96.7% of the 60 participants completed the 1-month post-vaccination visit. No participant in the 6-23 months of age group and 1 participant in the 2-4 years of age group withdrew as a personal decision.

Immunogenicity Population
The evaluable immunogenicity population (with or without evidence of SARS-CoV-2 infection up to 1-month post-bivalent booster dose) included 58 (96.7%) participants 6 months-4 years of age (n=23 [95.8%] 6-23 months of age and n=35 [97.2%] 2-4 years of age.)

The evaluable immunogenicity population from Study 1007 (with or without evidence of infection up to 1-month post-Dose 3) included 54 (90.0%) participants 6 months-4 years of age (n=23 [95.8%] 6-23 months of age and n=31 [86.1%] 2-4 years of age.)

For both groups, the most common reason for exclusion from evaluable immunogenicity population was not having at least 1 valid and determinate immunogenicity result within 28-42 days after vaccination. Complete details of the immunogenicity population are also noted in Table 1.

Table *1*. Immunogenicity Populations in Study C4591048 (Study 1048, Dose 4), and Study C4591007 (Study 1007, Dose 3)

Population Characteristics	Study 1048 6-23 Months n[a] (%)	Study 1048 2-4 Years n[a] (%)	Study 1048 6 months-4 Years n[a] (%)	Study 1007 6-23 Months n[a] (%)	Study 1007 2-4 Years n[a] (%)	Study 1007 6 Months-4 Years n[a] (%)
Randomized[b]	24 (100)	36 (100)	60 (100)	24 (100)	36 (100)	60 (100)
All available immunogenicity population	23 (95.8)	35 (97.2)	58 (96.7)	24 (100.0)	36 (100.0)	60 (100.0)
Excluded from all available immunogenicity population[c]	1 (4.2)	1 (2.8)	2 (3.3)	0	0	0

Population Characteristics	Study 1048 6-23 Months n[a] (%)	Study 1048 2-4 Years n[a] (%)	Study 1048 6 months-4 Years n[a] (%)	Study 1007 6-23 Months n[a] (%)	Study 1007 2-4 Years n[a] (%)	Study 1007 6 Months-4 Years n[a] (%)
Evaluable immunogenicity population	23 (95.8)	35 (97.2)	58 (96.7)	23 (95.8)	31 (86.1)	54 (90.0)
Participants without evidence of infection up to 1 month after study vaccination[d]	12 (50.0)	26 (72.2)	38 (63.3)	13 (54.2)	21 (58.3)	34 (56.7)
Excluded from evaluable immunogenicity population[e]	1 (4.2)	1 (2.8)	2 (3.3)	1 (4.2)	5 (13.9)	6 (10.0)

Source: EUA 27034.719, Word doc 508 Compliant tables – Group 2 1MPD Safety and Immuno, p 3 Table B.3
Notes: Study 1048 includes participants 6 months-4 years of age who received 3 doses of BNT162b2 3 µg 60 to 240 days prior to enrollment.
a. n = number of participants with the specified characteristic
b. This value is the denominator for the percentage calculations
c. Reason for exclusion= did not have at least one valid and determinate immunogenicity result after Dose 4 (Study C4591048) or Dose 3 (Study C4591007)
d. Participants with no serological or virological evidence of past SARS-CoV-2 infection up to 1month post-Dose 4 in Study 1048 or 1month post-Dose 3 in Study 1007. Having no evidence of past SARS-CoV-2 infection up to 1month post-Dose 4 for Study 1048 participants was defined as having a negative serum N-binding ant body result at Dose 4 visit and 1month post-Dose 4 visit; a negative NAAT [nasal swab] result at Dose 4 visit, and any unscheduled visit up to the 1-month post-Dose 4 blood sample collection; and had no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1 month post-Dose 3 for Study 1007 participants was defined as having a negative serum N-binding antibody result at the Dose 1, 1-month post Dose 2 (if available), Dose 3, and 1-month post Dose 3 visits; a negative NAAT [nasal swab] result at the Dose 1, Dose 2, and Dose 3 visits and any unscheduled visit up to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
e. Each of the 16 excluded participants may have been excluded for more than one reason: “Did not have at least one valid and determinate immunogenicity result within 28-42 days after study vaccination” and/ or “1-month post-study vaccination blood draw outside of 28-42 day window”.

6.1.3 Demographic and Other Baseline Characteristics

Safety Population

6-23 months of age

The demographic characteristics of participants 6-23 months of age who received 3 µg Bivalent (WT/OMI BA4/BA.5) are shown in Table 2, below. Overall, 54.2% of participants were White, 4.2% were Black or African American, 20.8% were Asian, and 20.8% were multiracial participants. There were 16.7% Hispanic/Latino participants. The median age was 19 months, and 58.3% of participants were female. Overall, 41.7% of participants had evidence of prior SARS-CoV-2 infection (“baseline positive”). The median interval since the last BNT162b2 vaccination and the Bivalent (WT/OMI BA4/BA.5) was 6.4 months (range 2.1 to 8.6.)

2-4 years of age

The demographic characteristics of participants in the 2-4 years of age group who received 3 µg Bivalent (WT/OMI BA4/BA.5) are shown in Table 2. Overall, 61.1% of participants were White, 5.6% were Black or African American, 11.1% were Asian, and 22.2% were multiracial participants. There were 30.6% Hispanic/Latino participants. The median age was 2 years, and 55.6% of participants were male. Three (8.3%) participants were obese (BMI ≥95th percentile for age). Overall, 19.4% of participants were baseline positive for prior SARS-CoV-2 infection. The median interval since the last BNT162b2 vaccination and the Bivalent (WT/OMI BA4/BA.5) was 7.1 months (range 2.2 to 8.5.)

Table 2. Demographic Characteristics of Safety Population, Recipients of Dose 4 Bivalent BNT162b2, Study C4591048 (Study 1048)

Characteristic	6-23 Months (N[a]=24) n[b] (%)	2-4 Years (N[a]=36) n[b] (%)	6 Months-4 Years (N[a]=60) n[b] (%)
Sex	-	-	-
Male	10 (41.7)	20 (55.6)	30 (50.0)
Female	14 (58.3)	16 (44.4)	30 (50.0)
Race	-	-	-
White	13 (54.2)	22 (61.1)	35 (58.3)
Black or African American	1 (4.2)	2 (5.6)	3 (5.0)
Asian	5 (20.8)	4 (11.1)	9 (15.0)
Multiracial	5 (20.8)	8 (22.2)	13 (21.7)
Ethnicity	-	-	-
Hispanic/Latino	4 (16.7)	11 (30.6)	15 (25.0)
Non-Hispanic/non-Latino	20 (83.3)	25 (69.4)	45 (75.0)
Age at the study vaccination (months/years[c])	-	-	-
Mean (SD)	18.6 (3.57)	2.6 (0.76)	N/A
Median	19.0	2.0	N/A
(Min, max)	(12, 23)	(2, 4)	N/A
Time (months) from Dose 3 to the first study vaccination	-	-	-
Mean (SD)	6.0 (1.98)	6.8 (1.76)	6.5 (1.89)
Median	6.4	7.1	6.9
(Min, max)	(2.1, 8.6)	(2.2, 8.5)	(2.1, 8.6)
≥2 to <3 Months	3 (12.5)	3 (8.3)	6 (10.0)
≥3 to <4 Months	1 (4.2)	0	1 (1.7)
≥4 to <5 Months	3 (12.5)	2 (5.6)	5 (8.3)
≥5 to <6 Months	3 (12.5)	2 (5.6)	5 (8.3)
≥6 to <7 Months	7 (29.2)	10 (27.8)	17 (28.3)
≥7 to <8 Months	1 (4.2)	7 (19.4)	8 (13.3)
≥8 to <9 Months	6 (25.0)	12 (33.3)	18 (30.0)
Obese[d]	-	-	-
Yes	N/A	3 (8.3)	N/A
No	N/A	33 (91.7)	N/A
Baseline SARS-CoV-2 status	-	-	-
Positive[e]	10 (41.7)	7 (19.4)	17 (28.3)
Negative[f]	13 (54.2)	29 (80.6)	42 (70.0)
Missing	1 (4.2)	0	1 (1.7)

Characteristic	6-23 Months (N[a]=24) n[b] (%)	2-4 Years (N[a]=36) n[b] (%)	6 Months-4 Years (N[a]=60) n[b] (%)
Comorbidities[g]	-	-	-
Yes	1 (4.2)	4 (11.1)	5 (8.3)
No	23 (95.8)	32 (88.9)	55 (91.7)

Source: EUA 27034.719, Word doc 508 Compliant tables – Group 2 1MPD Safety and Immuno, p 45 Table P
Notes: Substudy B Group 2 includes participants 6 months-4 years who received 3 doses of BNT162b2 3 µg, 60 to 240 days prior to enrollment.
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. The participant age at the study vaccination is in months for the age group 6-23 months and in years for the age groups 2-4 years and 6 months-4 years
d. 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. Obesity is summarized for participants ≥2 years of age.
e. Positive N-binding ant body result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
f. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
g. Number of participants who have one or more comorbidities that increase the risk of severe COVID-19: defined as participants who had at least one of the prespecified comorbidities based on MMWR 2020;69(32):1081-8 and/or obesity (BMI ≥95th percentile).
Abbreviations: MMWR= Morbidity and Mortality Weekly Report; N/A= not applicable; NAAT= nucleic acid amplification test; N-binding= SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2= severe acute respiratory syndrome coronavirus 2.

Immunogenicity Population

The demographic characteristics of the Study 1048 evaluable immunogenicity population (Table 3) were similar to the safety population.

In participants from Study 1007, the median time since the last prior dose of BNT162b2 and the third BNT162b2 dose was 6.9 months (range 2.2 to 9.1). The demographics were similar to Study 1048 participants, except the percentage of White participants was higher in Study 1007 than Study 1048 (83.3% vs. 58.6%).

Table 3. Demographic Characteristics of Evaluable Immunogenicity Populations, Study C4591048 (Study 1048, Subset of Substudy B Group 2) and Study C4591007 (Study 1007)

Demographic	Study 1048 6-23 Months (N[a]=23) n[b] (%)	Study 1048 2-4 Years (N[a]=35) n[b] (%)	Study 1048 6 Months-4 Years (N[a]=58) n[b] (%)	Study 1007 6 Months-2 Years (N[a]=23) n[b] (%)	Study 1007 2-4 Years (N[a]=31) n[b] (%)	Study 1007 6 Months-4 Years (N[a]=54) n[b] (%)
Sex	-	-	-	-	-	-
Male	9 (39.1)	20 (57.1)	29 (50.0)	14 (60.9)	14 (45.2)	28 (51.9)
Female	14 (60.9)	15 (42.9)	29 (50.0)	9 (39.1)	17 (54.8)	26 (48.1)
Race	-	-	-	-	-	-
White	13 (56.5)	21 (60.0)	34 (58.6)	19 (82.6)	26 (83.9)	45 (83.3)
Black or African American	1 (4.3)	2 (5.7)	3 (5.2)	1 (4.3)	0	1 (1.9)
Asian	5 (21.7)	4 (11.4)	9 (15.5)	1 (4.3)	2 (6.5)	3 (5.6)
Multiracial	4 (17.4)	8 (22.9)	12 (20.7)	2 (8.7)	3 (9.7)	5 (9.3)
Ethnicity	-	-	-	-	-	-
Hispanic/Latino	4 (17.4)	11 (31.4)	15 (25.9)	2 (8.7)	4 (12.9)	6 (11.1)
Non-Hispanic/non-Latino	19 (82.6)	24 (68.6)	43 (74.1)	21 (91.3)	27 (87.1)	48 (88.9)

Demographic	Study 1048 6-23 Months (N[a]=23) n[b] (%)	Study 1048 2-4 Years (N[a]=35) n[b] (%)	Study 1048 6 Months-4 Years (N[a]=58) n[b] (%)	Study 1007 6 Months-2 Years (N[a]=23) n[b] (%)	Study 1007 2-4 Years (N[a]=31) n[b] (%)	Study 1007 6 Months-4 Years (N[a]=54) n[b] (%)
Age at study vaccine dose[c] (months/years[d])	-	-	-	-	-	-
Mean (SD)	18.6 (3.65)	2.6 (0.77)	N/A	18.3 (3.27)	2.6 (0.75)	N/A
Median	19.0	2.0	N/A	19.0	2.0	N/A
(Min, max)	(12, 23)	(2, 4)	N/A	(12, 23)	(2, 4)	N/A
Time (days) from last prior BNT162b2 dose to study vaccine dose[c]	-	-	-	-	-	-
n	23	35	58	23	31	54
Mean (SD)	166.6 (56.68)	190.4 (49.34)	180.9 (53.20)	174.4 (50.93)	191.6 (52.99)	184.3 (52.35)
Median	181.0	196.0	193.5	184.0	200.0	194.0
(Min, max)	(60, 240)	(62, 239)	(60, 240)	(63, 246)	(62, 254)	(62, 254)
60-240 Days	23 (100.0)	35 (100.0)	58 (100.0)	22 (95.7)	28 (90.3)	50 (92.6)
>240 Days	0	0	0	1 (4.3)	3 (9.7)	4 (7.4)
Time (months[e]) from last prior BNT162b2 dose to study vaccine dose[c]	-	-	-	-	-	-
n	23	35	58	23	31	54
Mean (SD)	5.9 (2.02)	6.8 (1.76)	6.5 (1.90)	6.2 (1.82)	6.8 (1.89)	6.6 (1.87)
Median	6.5	7.0	6.9	6.6	7.1	6.9
(Min, max)	(2.1, 8.6)	(2.2, 8.5)	(2.1, 8.6)	(2.3, 8.8)	(2.2, 9.1)	(2.2, 9.1)
≥2 to <3 Months	3 (13.0)	3 (8.6)	6 (10.3)	2 (8.7)	3 (9.7)	5 (9.3)
≥3 to <4 Months	1 (4.3)	0	1 (1.7)	0	2 (6.5)	2 (3.7)
≥4 to <5 Months	3 (13.0)	2 (5.7)	5 (8.6)	3 (13.0)	0	3 (5.6)
≥5 to <6 Months	3 (13.0)	2 (5.7)	5 (8.6)	4 (17.4)	0	4 (7.4)
≥6 to <7 Months	6 (26.1)	10 (28.6)	16 (27.6)	7 (30.4)	6 (19.4)	13 (24.1)
≥7 to <8 Months	1 (4.3)	7 (20.0)	8 (13.8)	2 (8.7)	10 (32.3)	12 (22.2)
≥8 to <9 Months	6 (26.1)	11 (31.4)	17 (29.3)	5 (21.7)	8 (25.8)	13 (24.1)
≥9 Months	0	0	0	0	2 (6.5)	2 (3.7)
Baseline SARS-CoV-2 status	-	-	-	-	-	-
Positive[f]	9 (39.1)	7 (20.0)	16 (27.6)	9 (39.1)	6 (19.4)	15 (27.8)
Negative[g]	13 (56.5)	28 (80.0)	41 (70.7)	13 (56.5)	23 (74.2)	36 (66.7)
Missing	1 (4.3)	0	1 (1.7)	1 (4.3)	2 (6.5)	3 (5.6)

Demographic	Study 1048 6-23 Months (N[a]=23) n[b] (%)	Study 1048 2-4 Years (N[a]=35) n[b] (%)	Study 1048 6 Months-4 Years (N[a]=58) n[b] (%)	Study 1007 6 Months-2 Years (N[a]=23) n[b] (%)	Study 1007 2-4 Years (N[a]=31) n[b] (%)	Study 1007 6 Months-4 Years (N[a]=54) n[b] (%)
Comorbidities[h]	-	-	-	-	-	-
Yes	1 (4.3)	4 (11.4)	5 (8.6)	0	0	0
No	22 (95.7)	31 (88.6)	53 (91.4)	23 (100.0)	31 (100.0)	54 (100.0)

Source: EUA 27034.719, Word doc 508 Compliant tables – Group 2 1MPD Safety and Immuno, p 5 Table E.1
Notes:
Substudy B Group 2 includes participants 6 months-4 years of age who received 3 doses of BNT162b2 3 µg 60 to 240 days prior to enrollment.
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. study vaccine dose defined as Dose 4 for Study 1048) and Dose 3 for Study 1007.
d. The participant age at the study vaccination is in months for the age group 6-23 months and in years for the age groups 2-4 years.
e. Month was calculated as 28 days
f. For Study 1048 Substudy B Group 2: positive N-binding antibody result at Dose 4 visit, positive NAAT result at Dose 4 visit, or medical history of COVID-19. For Study 1007: positive N-binding antibody result at Dose 1, 1 month post–Dose 2 (if available), or Dose 3 visits, positive NAAT result at Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to Dose 3 visit, or medical history of COVID-19.
g. For Study 1048 Substudy B Group 2: negative N-binding antibody result at Dose 4 visit, negative NAAT result at Dose 4 visit, and no medical history of COVID-19. For Study 1007: negative N-binding antibody result at Dose 1, 1 month post-Dose 2 (if available), and Dose 3 visits, negative NAAT result at Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to Dose 3 visit, and no medical history of COVID-19.
h. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19: defined as participants who had at least 1 of the prespecified comorbidities based on MMWR 2020;69(32):1081-8 and/or obesity (BMI ≥95th percentile) for participants of 2-5 years. Comorbidities were assessed at the first study visit for both studies. Abbreviations: BMI = body mass index; N/A = not applicable; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

6.1.4 Vaccine Effectiveness Results

6.1.4.1 Primary Immunogenicity

The median time since the last prior dose of BNT162b2 to study vaccination (i.e., Dose 4 of Bivalent (WT/OMI BA4/BA.5) in Study 1048 and Dose 3 of BNT162b2 in Study 1007) was 6.9 months (range 2.1-8.6) and 6.9 months (range 2.2-9.1), respectively. A total of 27.6% of Study 1048 participants had evidence of prior SARS-CoV-2 infection (“baseline positive”) just prior to the bivalent booster dose (Dose 4). In Study 1007, 27.8% of participants were baseline positive just prior to the third primary monovalent BNT162b2 dose (Dose 3).

Geometric Mean Titers (GMTs)
Table 4 displays the GMTs at baseline (prevaccination) and 1 month post vaccination dose for Omicron BA.4/BA.5 and the reference (Original) strain by age group, baseline COVID-19 status, and vaccine group. Baseline positive for Study 1048 participants was defined as: positive N-binding antibody result at Dose 4 (booster) visit, positive NAAT result at Dose 4 visit, or medical history of COVID-19, and for Study 1007 participants was defined as: positive N-binding antibody result at Dose 1, 1-month post-Dose 2 (if available), or Dose 3 visits, positive NAAT result at Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to Dose 3 visit, or medical history of COVID-19.

Omicron BA.4/BA.5
Regardless of age, prior SARS-CoV-2 infection, or sampling time point, the GMTs against the Omicron BA.4/BA.5 variant were 2.2-3.7 times higher in the Bivalent (WT/OMI BA4/BA.5) group

than in the monovalent BNT162b2 group. Overall, the rise in GMT from prevaccination to 1 month post vaccination was similar across age subgroups (i.e., 6-23 months old, 2-4 years old) and vaccine groups (i.e., post-bivalent booster [Dose 4], post-BNT162b2 primary Dose 3). Regardless of the vaccine received, the rise in GMT from prevaccination to 1 month post dose was higher in the children without evidence of previous SARS-CoV-2 infection than children with evidence of previous infection (10-14 vs. 3-5), but the rise was about three times higher in children receiving Bivalent (WT/OMI BA4/BA.5).

Reference Strain

Regardless of age or prior SARS-CoV-2 infection, the GMTs at prevaccination against the reference (original) strain were 0-4.5 times higher in the Bivalent (WT/OMI BA4/BA.5) group (i.e., pre-booster) than in the original BNT162b2 group (i.e., pre-primary Dose 3.) The rise in GMT from prevaccination to 1 month post dose was similar across age groups (~3.5 fold; pre-bivalent booster GMT 2678 to post-booster GMT 9733) in the Bivalent (WT/OMI BA4/BA.5) group, but lower than the rise in the original BNT162b2 group (8.4-13.6; pre-monovalent BNT162b2 Dose 3 GMT 777 to post-Dose 3 GMT 9057). The rise in GMT from prevaccination to 1 month post dose was numerically higher in the children without evidence of previous COVID-19 infection compared with children with evidence of previous infection (SARS-CoV-2 negative: pre-bivalent booster GMT 76, post-bivalent booster GMT 1075; SARS-CoV-2 positive: pre-bivalent booster GMT 1158, post-bivalent booster GMT 4979); however, this rise was more notable in the children receiving the original BNT162b2 vaccine (14-21 vs. 3-13.6) than children receiving the Bivalent (WT/OMI BA4/BA.5) vaccine (4.6-4.8 vs. 1.5-2.2), which in part may be due to a lower quantity of the modRNA (1.5 µg) for the original strain in the bivalent (WT/OMI BA4/BA.5) vs. BNT162b2 (3 µg).

Table *4*. Geometric Mean Titers by Baseline SARS-CoV-2 Status, Evaluable Immunogenicity Populations, Study C4591048 (Study 1048) and Study C4591007 (Study 1007)

SARS-CoV-2 Status[a]	Study 1048 n[b]	Study 1048 GMT[c] (95% CI[c])	Study 1007 n[b]	Study 1007 GMT[c] (95% CI[c])
6 months-4 years: prevaccination	-	-	-	-
Overall	54	192.5 (120.4, 307.8)	54	70.5 (51.1, 97.2)
Positive[d]	16	1315.4 (789.1, 2192.8)	15	351.7 (195.2, 633.8)
Negative[e]	38	85.7 (56.6, 129.8)	36	38.2 (34.2, 42.8)
6 months-4 years: 1 month post vaccination	-	-	-	-
Overall	58	1695.2 (1151.8, 2494.9)	54	607.9 (431.1, 857.2)
Positive	16	4897.7 (3085.5, 7774.1)	15	1785.9 (1009.4, 3159.9)
Negative	41	1116.0 (701.3, 1776.1)	36	416.2 (287.8, 602.0)
6-23 months: prevaccination	-	-	-	-
Overall	21	243.9 (115.3, 516.1)	23	96.0 (55.3, 166.8)
Positive[d]	9	1157.5 (653.8, 2049.2)	9	368.1 (189.1, 716.9)
Negative[e]	12	75.9 (39.5, 145.7)	13	40.9 (30.0, 55.7)

SARS-CoV-2 Status[a]	Study 1048 n[b]	Study 1048 GMT[c] (95% CI[c])	Study 1007 n[b]	Study 1007 GMT[c] (95% CI[c])
6-23 months: 1 month post vaccination	-	-	-	-
Overall	23	2011.4 (1141.3, 3544.9)	23	625.6 (365.7, 1070.5)
Positive	9	4978.7 (3844.4, 6447.8)	9	1378.6 (568.4, 3343.3)
Negative	13	1074.7 (454.2, 2543.0)	13	351.3 (186.4, 662.4)
2-4 years: prevaccination	-	-	-	-
Overall	33	165.6 (88.3, 310.5)	31	56.1 (38.0, 82.7)
Positive[d]	7	1550.5 (498.2, 4825.5)	6	328.4 (75.7, 1424.1)
Negative[e]	26	90.7 (52.1, 157.9)	23	36.8 (34.2, 39.6)
2-4 years: 1 month post vaccination	-	-	-	-
Overall	35	1514.9 (882.2, 2601.5)	31	595.0 (370.5, 955.6)
Positive[d]	7	4795.4 (1421.9, 16172.9)	6	2633.3 (1212.8, 5717.8)
Negative	28	1135.7 (630.3, 2046.5)	23	458.1 (281.6, 745.1)

Source: EUA 27034.719, Word doc 508 Compliant tables – Group 2 1MPD Safety and Immuno, p 17 Table F.1
Notes:
a: protocol-specified timing for blood sample collection.
b: n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c: GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d: for C4591048 Substudy B Group 2: positive N-binding antibody result at Dose 4 visit, positive NAAT result at Dose 4 visit, or medical history of COVID-19. For C4591007: positive N-binding antibody result at Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visits, positive NAAT result at Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to Dose 3 visit, or medical history of COVID-19.
e: for C4591048 Substudy B Group 2: negative N-binding antibody result at Dose 4 visit, negative NAAT result at Dose 4 visit, and no medical history of COVID-19. For C4591007: negative N-binding ant body result at Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to Dose 3 visit, and no medical history of COVID-19.
Abbreviations: SARS-CoV-2= severe acute respiratory syndrome coronavirus 2; GMT= geometric mean titer; LLOQ= lower limit of quantitation; N-binding= SARS-CoV-2 nucleoprotein-binding; NAAT= nucleic acid amplification test; NT50= 50% neutralizing titer

Geometric Fold Rise

Omicron BA.4/BA.5

The GMFR was similar in the Bivalent (WT/OMI BA4/BA.5) and BNT162b2 groups at 1 month post dose (13.6 vs. 10.7), and there was no difference by age subgroup (6-23 months old, 2-4 years old). Among participants 6 months-4 years of age with or without evidence of SARS-CoV-2 infection, the GMFR at 1 month post dose was 2.0-9.6 times higher in participants who were baseline negative compared with those who were baseline positive in both vaccine groups.

Reference Strain

Overall, the GMFRs were 2.6-3.6 times higher in the BNT162b2 group than in the Bivalent (WT/OMI BA4/BA.5) group; the magnitude of differences in GMFR was largest in the 2-4 years of age subgroup. Among participants 6 months-4 years of age with or without evidence of SARS-CoV-2 infection, the GMFRs at 1 month post dose were 2.2-6.8 times higher in

participants who were baseline negative compared with those who were baseline positive in both vaccine groups.

Seroresponse

Table 5 displays the number and percent of participants achieving a seroresponse at 1 month after vaccination by baseline SARS-CoV-2 status, strain (Omicron BA.4/BA.5, reference), vaccine group, and age. Baseline SARS-CoV-2 status for Study 1048 was defined as: positive N-binding antibody result at Dose 4 visit, positive NAAT result at Dose 4 visit, or medical history of COVID-19, and for Study 1007 the definition was positive N-binding antibody result at Dose 1, 1 month post-Dose 2 (if available), or Dose 3 visits, positive NAAT result at Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to Dose 3 visit, or medical history of COVID-19.

Omicron BA.4/BA.5

Among participants 6 months-4 years of age who were baseline SARS-CoV-2 positive, 56.3% participants in the Bivalent (WT/OMI BA4/BA.5) group and 60.0% participants in the BNT162b2 group achieved seroresponse against the Omicron BA.4/ BA.5 variant at 1 month post-bivalent booster and post-third BNT162b2 primary dose, respectively. Among participants 6 months-4 years of age who were baseline SARS-CoV-2 negative, 76.3% and 63.9% participants in the Bivalent (WT/OMI BA4/BA.5) group and BNT162b2 group, respectively, achieved seroresponse. The seroresponse rate was similar across the two age subgroups who received Bivalent (WT/OMI BA4/BA.5) (6-23m, 2-4y), but among BNT162b2 participants, the seroresponse rate was higher among the subgroup 2-4 years of age than 6-23 months of age (71.0% vs. 47.8%).

Reference Strain

Among participants 6 months-4 years of age, the seroresponse rate was higher at 1 month after the third BNT162b2 primary dose than after Bivalent (WT/OMI BA4/BA.5) booster (fourth) dose (75% vs. 43.9%).

The seroresponse rate was higher among participants who were baseline SARS-CoV-2 negative than those who were baseline positive. Among participants 6 months-4 years of age who were baseline SARS-CoV-2 positive, the seroresponse rate was 18.8% after Bivalent (WT/OMI BA4/BA.5) booster and 33.3% after the third BNT162b2 primary dose. Within the baseline negative group, 53.7% and 91.2% participants in the Bivalent (WT/OMI BA4/BA.5) group and BNT162b2 group, respectively, had a seroresponse.

Table 5. Evaluable Immunogenicity Population With SARS-CoV-2 Neutralization Assay, Omicron BA.4/BA.5 - NT50 (Titer) Seroresponse, 1 Month After Study Vaccination in Studies C4591048 (1048) and C4591007 (1007)

SARS-CoV-2 Status[a]	Study 1048 N[b]	Study 1048 n[c] (%) (95% CI[d])	Study 1007 N[b]	Study 1007 n[c] (%) (95% CI[d])
6 months-4 years	-	-	-	-
Overall	54	38 (70.4) (56.4, 82.0)	54	33 (61.1) (46.9, 74.1)
Positive[e]	16	9 (56.3) (29.9, 80.2)	15	9 (60.0) (32.3, 83.7)
Negative[f]	38	29 (76.3) (59.8, 88.6)	36	23 (63.9) (46.2, 79.2)
6-23 Months	-	-	-	-
Overall	21	14 (66.7) (43.0, 85.4)	23	11 (47.8) (26.8, 69.4)
Positive[e]	9	5 (55.6)	9	4 (44.4)

SARS-CoV-2 Status[a]	Study 1048 N[b]	Study 1048 n[c] (%) (95% CI[d])	Study 1007 N[b]	Study 1007 n[c] (%) (95% CI[d])
		(21.2, 86.3)		(13.7, 78.8)
Negative[f]	12	9 (75.0) (42.8, 94.5)	13	6 (46.2) (19.2, 74.9)
2-4 Years	-	-	-	-
Overall	33	24 (72.7) (54.5, 86.7)	31	22 (71.0) (52.0, 85.8)
Positive[e]	7	4 (57.1) (18.4, 90.1)	6	5 (83.3) (35.9, 99.6)
Negative[f]	26	20 (76.9) (56.4, 91.0)	23	17 (73.9) (51.6, 89.8)

Source: EUA 27034.719, Word doc C4591048-ssb-508-Compliant tables–1MPD, p 37 Table H.1
Note: For participants from Study C4591048 Substudy B Group 2, seroresponse is defined as achieving a ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. Protocol-specified timing for blood sample collection for evaluation after study.
b. N = number of participants with valid and determinate assay results for the specified assay both before Dose 4 (1048)/Dose 3 (1007) and at the given sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given sampling time point.
d. Exact 2-sided CI, based on the Clopper and Pearson method.
e. For Study 1048 Substudy B Group 2: positive N-binding antibody result at Dose 4 visit, positive NAAT result at Dose 4 visit, or medical history of COVID-19. For Study 1007: positive N-binding antibody result at Dose 1, 1-month post Dose 2 (if available), or Dose 3 visits, positive NAAT result at Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to Dose 3 visit, or medical history of COVID-19.
f. For Study 1048 Substudy B Group 2: negative N-binding antibody result at Dose 4 visit, negative NAAT result at Dose 4 visit, and no medical history of COVID-19. For Study 1007: negative N-binding antibody result at Dose 1, 1-month post Dose 2 (if available), and Dose 3 visits, negative NAAT result at Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to Dose 3 visit, and no medical history of COVID-19.
Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; LLOQ= lower limit of quantitation; CI= confidence interval; N-binding= SARS-CoV-2 nucleoprotein-binding; NAAT= nucleic acid amplification test; NT50 = 50% neutralizing titer.

6.1.4.2 Exploratory Immunogenicity Analyses

No data on currently circulating SARS-CoV-2 strains for participants 6 months-4 years were provided in this EUA amendment (aEUA).

6.1.5 Safety Results

Available safety data as of the cutoff date 25 November 2022, are summarized below for the subset of 60 participants in Group 2 of Study 1048, Substudy B. Overall, the median follow-up time after study vaccination was 1.8 months.

6.1.5.1 Solicited Adverse Reactions

No participant in any age group reported an immediate AE within 30 minutes of Bivalent (WT/OMI BA4/BA.5) booster dose. In the 7 days after bivalent booster vaccination among participants 6-23 months of age, solicited injection site reactions were reported in 8.3% of participants (Table 6); solicited systemic AEs were reported in 20.8% of participants (Table 7), which included irritability (18.2%), drowsiness (9.1%), decreased appetite (4.5%), and fever (4.2%).

Table 6. Frequency of Solicited Local Reactions by Maximum Severity, Within 7 Days After the Study Vaccination in 6-23 Months Age Group, Safety Population, Study C4591048 (Study 1048, Subset of Substudy B Group 2)

Local Reaction	N[a]	n[b] (%)
Redness	-	-
Any	24	2 (8.3)
Mild: >0.5 to 2.0 cm	24	2 (8.3)
Moderate: >2.0 to 7.0 cm	24	0
Severe: >7.0 cm	24	0
Grade 4: exfoliative dermatitis or necrosis	24	0
Swelling	-	-
Any	24	1 (4.2)
Mild: >0.5 to 2.0 cm	24	1 (4.2)
Moderate: >2.0 to 7.0 cm	24	0
Severe: >7.0 cm	24	0
Grade 4: necrosis	24	0
Tenderness at the injection site[d]	-	-
Any	23	1 (4.3)
Mild: hurts if gently touched	23	1 (4.3)
Moderate: hurts if gently touched with crying	23	0
Severe: causes limitation of limb movement	23	0
Grade 4: ER visit or hospitalization for severe tenderness	23	0
Any local reaction: any redness >0.5 cm, any swelling >0.5 cm, or any tenderness at the injection site	24	2 (8.3)

Source: EUA 27034.719, Word doc C4591048-ssb-508-Compliant tables–1MPD, p 51 Table R.1
Note: Subset of Substudy B Group 2 includes the first 24 and 36 participants enrolled in ≥6 months to <2 years age group and ≥2 years to <5 years age group, respectively.
Note: Substudy B Group 2 includes participants ≥6 months to <5 years of age who received 3 doses of BNT162b2 3 µg 60 to 240 days prior to enrollment.
Note: Reactions were collected in the electronic diary (e-diary) and at unscheduled clinical assessments from Day 1 through Day 7 after the study vaccination. Reactions reported as adverse events in the case report form within 7 days after the study vaccination were also included in the analysis; the severity of these events is based on the grading scale in the adverse event section of the case report form.
Note: Grade 4 events were classified by the investigator or medically qualified person.
a. N = number of participants reporting at least 1 yes or no response for the specified reaction after the study vaccination.
b. n = Number of participants with the specified characteristic.
Abbreviations: ER= emergency room

Table 7. Frequency of Solicited Systemic Events by Maximum Severity, Within 7 Days After the Study Vaccination in 6-23 Months Age Group, Safety Population, Study C4591048 (Study 1048, Subset of Substudy B Group 2)

Event	N[a]	n[b] (%)
Fever	-	-
≥38.0ºC	24	1 (4.2)
≥38.0ºC to 38.4ºC	24	1 (4.2)
>38.4ºC to 38.9ºC	24	0
>38.9ºC to 40.0ºC	24	0
>40.0ºC	24	0
Decreased appetite	-	-
Any	22	1 (4.5)
Mild: decreased interest in eating	22	1 (4.5)
Moderate: decreased oral intake	22	0
Severe: refusal to feed	22	0
Grade 4: ER visit or hospitalization for severe decreased appetite (loss of appetite)	22	0

Event	N[a]	n[b] (%)
Drowsiness	-	-
Any	22	2 (9.1)
Mild: increased or prolonged sleeping bouts	22	2 (9.1)
Moderate: slightly subdued; interfering with daily activity	22	0
Severe: disabling; not interested in usual daily activity	22	0
Grade 4: ER visit or hospitalization for severe drowsiness (increased sleep)	22	0
Irritability	-	-
Any	22	4 (18.2)
Mild easily consolable	22	3 (13.6)
Moderate requiring increased attention;	22	1 (4.5)
Severe inconsolable; crying cannot be comforted	22	0
Grade 4: ER visit or hospitalization for severe irritability (fussiness)	22	0
Any systemic event: any fever ≥38.0℃, decreased appetite, drowsiness, or irritability	24	5 (20.8)
Use of antipyretic or pain medication[c]	24	2 (8.3)

Source: EUA 27034.719, Word doc 508 Compliant tables – Group 2 1MPD Safety and Immuno, p 55 Table S.1
Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) and at unscheduled clinical assessments from Day 1 through Day 7 after the study vaccination. Events reported as adverse events in the case report form within 7 days after the study vaccination were also included in the analysis; the severity of these events is based on the grading scale in the adverse event section of the case report form.
Note: Grade 4 events were classified by the investigator or medically qualified person.
a. N= number of participants reporting at least 1 yes or no response for the specified event after the study vaccination.
b. n= Number of participants with the specified characteristic.
c. Severity was not collected for use of antipyretic or pain medication

Among participants 2-4 years of age, solicited injection site reactions were reported for 12 (33.3%) participants (Table 8) and systemic AEs were reported for 12 (33.3%) (Table 9), which included fatigue (30.6%), diarrhea (5.6%), headache (2.8%), vomiting (2.8%), new or worsened joint pain (2.8%), and chills (2.8%).

Table 8. Frequency of Solicited Local Reactions by Maximum Severity, Within 7 Days After the Study Vaccination in 2-4 Years Age Group, Safety Population, Study C4591048 (Study 1048, Subset of Substudy B Group 2)

Local Reaction	N[a]	N[b] (%)
Redness	-	-
Any	36	3 (8.3)
Mild: >0.5 to 2.0 cm	36	2 (5.6)
Moderate: >2.0 to 7.0 cm	36	1 (2.8)
Severe: >7.0 cm	36	0
Grade 4: exfoliative dermatitis or necrosis	36	0
Swelling	-	-
Any	36	1 (2.8)
Mild: >0.5 to 2.0 cm	36	0
Moderate: >2.0 to 7.0 cm	36	1 (2.8)
Severe: >7.0 cm	36	0
Grade 4: necrosis	36	0

Local Reaction	N[a]	N[b] (%)
Pain at the injection site	-	-
Any	36	10 (27.8)
Mild: does not interfere with activity	36	8 (22.2)
Moderate: interferes with activity	36	2 (5.6)
Severe: prevents daily activity	36	0
Grade 4: ER visit or hospitalization for severe pain at the injection site	36	0
Any local reaction: any redness ≥0.5 cm, any swelling ≥0.5 cm, or any pain at the injection site	36	12 (33.3)

Source: EUA 27034.719, Word doc 508 Compliant tables – Group 2 1MPD Safety and Immuno, p 53 Table R.2
Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) and at unscheduled clinical assessments from Day 1 through Day 7 after the study vaccination. Events reported as adverse events in the case report form within 7 days after the study vaccination were also included in the analysis; the severity of these events is based on the grading scale in the adverse event section of the case report form.
Note: Grade 4 events were classified by the investigator or medically qualified person.
a. N = number of participants reporting at least 1 yes or no response for the specified reaction after the study vaccination.
b. n = Number of participants with the specified characteristic
Abbreviations: ER= emergency room

Table 9. Frequency of Solicited Systemic Events by Maximum Severity, Within 7 Days After the Study Vaccination in 2-4 Years Age Group, Safety Population, Study C4591048 (Study 1048, Subset of Substudy B Group 2)

Event	N[a]	n[b] (%)
Fever	-	-
≥38.0ºC	36	0
≥38.0ºC to 38.4ºC	36	0
>38.4ºC to 38.9ºC	36	0
>38.9ºC to 40.0ºC	36	0
>40.0ºC	36	0
Fatigue	-	-
Any	36	11 (30.6)
Mild: does not interfere with activity	36	6 (16.7)
Moderate: some interference with activity	36	5 (13.9)
Severe: prevents daily activity	36	0
Grade 4: ER visit or hospitalization for severe fatigue	36	0
Headache	-	-
Any	36	1 (2.8)
Mild: does not interfere with activity	36	1 (2.8)
Moderate: some interference with activity	36	0
Severe: prevents daily activity	36	0
Grade 4: ER visit or hospitalization for severe headache	36	0
Chills	-	-
Any	36	1 (2.8)
Mild: does not interfere with activity	36	1 (2.8)
Moderate: some interference with	36	0
Severe: prevents daily activity	36	0
Grade 4: ER visit or hospitalization for severe chills	36	0
Vomiting	-	-
Any	36	1 (2.8)
Mild: 1 to 2 times in 24 hours	36	1 (2.8)
Moderate: >2 times in 24 hours	36	0
Severe: requires intravenous hydration	36	0
Grade 4: ER visit or hospitalization for hypotensive shock	36	0

Event	N[a]	n[b] (%)
Diarrhea	-	-
Any	36	2 (5.6)
Mild: 2 to 3 loose stools in 24 hours	36	1 (2.8)
Moderate: 4 to 5 loose stools in 24 hours	36	1 (2.8)
Severe: 6 or more loose stools in 24 hours	36	0
Grade 4: ER visit or hospitalization for severe diarrhea	36	0
New or worsened muscle pain	-	-
Any	36	0
Mild: does not interfere with activity	36	0
Moderate: some interference with activity	36	0
Severe: prevents daily activity	36	0
Grade 4: ER visit or hospitalization for severe new or worsened muscle pain	36	0
New or worsened joint pain	-	-
Any	36	1 (2.8)
Mild: does not interfere with activity	36	1 (2.8)
Moderate: some interference with activity	36	0
Severe: prevents daily activity	36	0
Grade 4: ER visit or hospitalization for severe new or worsened joint pain	36	0
Any systemic event: any fever ≥38.0ºC, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain	36	12 (33.3)
Use of antipyretic or pain medication[c]	36	1 (2.8)

Source: EUA 27034.719, Word doc 508 Compliant tables – Group 2 1MPD Safety and Immuno, p 57 Table S.2
Notes: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) and at unscheduled clinical assessments from Day 1 through Day 7 after the study vaccination. Events reported as adverse events in the case report form within 7 days after the study vaccination were also included in the analysis; the severity of these events is based on the grading scale in the adverse event section of the case report form.
Grade 4 events were classified by the investigator or medically qualified person.
a. N = number of participants reporting at least 1 yes or no response for the specified event after the study vaccination.
b. n = Number of participants with the specified characteristic.
c. Severity was not collected for use of antipyretic or pain medication.

6.1.5.2 Unsolicited Adverse Events

Within 30 days after the bivalent booster dose, five unsolicited, non-serious AEs were reported for three (12.5%) participants 6-23 months of age. Mild injection site pain occurring 1 day after vaccination and mild fatigue 3 days after vaccination occurred in one participant, and both AEs were considered related to vaccination by the study investigator and by the FDA. AEs for the other two participants (fever 20 and 24 days after vaccination and diarrhea 31 days after vaccination, respectively), were considered unrelated to the vaccination by the study investigator and by the FDA.

Among participants 2-4 years of age, two AEs were reported in one (2.8%) participant; the injection site warmth and erythema occurred 19 days after vaccination when the participant received an influenza vaccine. These reactions were considered unrelated to the study vaccination by the study investigator and by the FDA.

6.1.5.3 Serious Adverse Events

During the 30 days after a bivalent booster dose, no non-fatal SAEs or deaths occurred in participants 6 months-4 years of age.

6.1.5.4 Adverse Events of Clinical Interest

During the 30 days after a bivalent booster dose, no AEs of lymphadenopathy, rash, anaphylaxis/hypersensitivity, appendicitis, Bell's palsy, and myo/pericarditis were reported in participants 6 months-4 years of age.

6.1.6 Summary of Findings from Study C4591048, Substudy B, Group 2

In participants 6 months-4 years of age, Omicron BA.4/BA.5-specific neutralizing GMTs were higher at 1 month after a 3 µg bivalent BNT162b2 (Original/Omi BA.4/BA.5), administered as a fourth COVID-19 vaccine dose, than the neutralizing GMTs in a subset of participants in Study 1007 Phase 2/3 after the third primary BNT162b2 dose. The seroresponse rate for the Omicron BA.4/BA.5 strain was similar in both vaccine groups, and higher for the reference (Original) strain after the third BNT162b2 primary dose than those who received the bivalent (WT/OMI BA4/BA.5) (75% vs. 43.9%, respectively). The seroresponse rate after a bivalent booster dose was 1-8 times higher among participants who were baseline SARS-CoV-2 negative than among participants who were SARS-CoV-2 positive.

Based on safety data from 60 participants (24 participants 6-23 months of age, 36 participants 2-4 years of age), frequencies of solicited local and systemic reactions after a 3 µg Bivalent BNT162b2 (Original/Omi BA.4/BA.5) booster dose were similar to frequencies within the respective age group reported after completion of a BNT162b2 primary series.

6.2 Supporting Data: Study C4591048, Substudy D, Group 2

6.2.1 Study Design

Study 1048 is a Phase 1/2/3 study to evaluate the safety and immunogenicity of a bivalent BNT162b2 (Bivalent (WT/OMI BA4/BA.5)) RNA-based vaccine candidate. Substudy D was designed to evaluate the safety and immunogenicity of a third or fourth dose of the bivalent (WT/OMI BA4/BA.5) in children 5 to less than 12 years of age who received two or three prior doses of BNT162b2 at 10 µg.

The section presents the safety data for 113 Substudy group 2 participants 5 to less than 12 years of age who received a 10 µg bivalent (WT/OMI BA4/BA.5) booster dose (fourth COVID-19 vaccine dose) 2.6 to 8.5 months after the last BNT162b2 primary dose. The median duration of safety follow-up was 1.6 months (range 1.1 to 2.3 months). The data cutoff date was November 25, 2022.

The safety monitoring was the same as for Study 1048, Substudy B, Group 2. The safety analysis population included participants 5 years to less than 12 years of age who received a fourth dose of the Bivalent (WT/OMI BA4/BA.5), 10 µg.

6.2.2 Disposition

Of the 115 participants enrolled, 113 were vaccinated. Two (1.7%) participants were excluded from the safety population as they withdrew prior to receiving study intervention. Seven did not complete the 1-month post-study vaccination visit.

6.2.3 Demographic and Other Baseline Characteristics

The median age of participants was 9 years (range 5 through 11 years of age), 50.4% were male and 49.6% were female, 58.4% were White, 20.4% were Hispanic/Latino, 19.5% were multi-racial, 11.5% were Asian, and 8.0% were Black or African American.

6.2.4 Safety Results

6.2.4.1 Solicited Adverse Reactions

Fatigue was the most frequently reported systemic event within 7 days after a fourth dose of the Bivalent (WT/OMI BA4/BA.5) 10 µg, followed by headache, muscle pain and less frequently by chills, joint pain, fever, vomiting, and diarrhea. Two (1.8%) participants reported fever >38.9°C to 40°C. No participants reported fever >40.0°C. Antipyretic or pain medication use was reported by 23.4% of participants after study vaccination. Most systemic events were mild or moderate in severity. Incidence of severe systemic events was low (fatigue and headache, 1 participant [0.9%] each) in the 5 years to less than12 years of age group who received a fourth dose of the Bivalent (WT/OMI BA4/BA.5) at 10 µg. No Grade 4 systemic events were reported. The median onset for all systemic events was 2 to 4 days, and all events resolved within a median duration of 1 to 2 days after onset.

6.2.4.2 Unsolicited Adverse Events

Non-serious AEs from the study vaccination through 1 month post-bivalent booster dose were reported in 4 (3.5%) vaccine recipients. Lymphadenopathy 2 days after vaccination was reported in 1 (0.9%) recipient and was considered to be related to the vaccination by the study investigator and by FDA. AEs for the three other recipients were considered to be unrelated to study vaccination by the study investigator and by FDA (influenza infection 17 days after immunization, otitis media 12 days after immunization, and sore throat 29 days after immunization). Overall, the AE profile at 1 month after the bivalent booster dose was generally consistent with solicited local and systemic reactions that occurred within 7 days after completion of a BNT162b2 primary series.

6.2.4.3 Serious Adverse Events

No deaths or SAEs were reported by participants in Group 2 from study vaccination through 1 month after study vaccination. No withdrawals due to AEs, or deaths were reported.

6.2.4.4 Adverse Events of Clinical Interest

From study vaccination up to 1 month post-bivalent booster dose, no AEs of anaphylaxis/hypersensitivity, appendicitis, Bell’s palsy, myo/pericarditis were reported. One AE of lymphadenopathy was reported in a 10-year-old boy and was assessed by the investigator and by FDA as related to study vaccination. The boy had a palpable axillary lymph node (moderate in severity), with onset on Day 2 after study vaccination, located in the same arm as the injection site, and it resolved within 3 days.

6.2.5 Summary of Findings from Study C4591048, Substudy D, Group 2

The safety profile within 7 days post vaccination of a 10 µg Bivalent (WT/OMI BA4/BA.5) booster dose (fourth COVID-19 vaccine dose) was characterized by mostly mild or moderate reactogenicity and few reported AEs and is considered acceptable.

6.3 Supporting Data: Study C4591044 Cohort 2, Group 1, 2, and 4

Study 1044 is a randomized, active-controlled, observer-blind study to evaluate the safety, and immunogenicity of Bivalent (WT/OMI BA4/BA.5) at the 30 and 60 µg dose levels. Cohort 2 was comprised of individuals ≥12 years of age who received three prior doses of 30 µg BNT162b2 then a Bivalent (WT/OMI BA4/BA.5) booster at the 30 µg or 60 µg dose level. The supporting data described in this section come from within Cohort 2, Group 1 (12-17 years), Group 2 (18-55 years), and Group 4 (>55 years). All of the participants had received 3 prior doses of 30 µg BNT162b2, with the most recent dose administered 150 to 365 days prior to receiving a 30 µg dose of Bivalent (WT/OMI BA4/BA.5), which was administered as a second booster dose (Dose 4).

Safety Evaluation
Solicited local and systemic reactions were recorded for 7 days after study vaccination and recorded daily in a e-diary. Non-serious AEs were assessed from the time of study vaccination through 1 month after study vaccination, and SAEs were assessed through 6 months after bivalent booster dose.

Analysis Population
Of the 317 vaccinated participants in Groups 1, 2, and 4, the safety population who received 30 µg bivalent (WT/OMI BA4/BA.5) was comprised of 108 participants 12-17 years of age (Group 1), 104 participants 18-55 years of age (Group 2), and 106 participants >55 years of age (Group 4), respectively. One participant from Group 1 was excluded from the analysis populations because informed consent was not documented. Participants of Study 1044 received the second booster dose a median of 9.9 months (range 5.5 to 14.3 months) after receiving the first booster dose and had a median follow up time of 1.6 months up to a data cutoff date of October 12, 2022.

6.3.1 Demographic and Other Baseline Characteristics

Demographic characteristics of Cohort 2 participants in Groups 1, 2 and 4:

Among Group 1 participants, 85% were White, 8.4% were Black or African American, 2.8% were Asian, 2.8% were multiracial, and other race subgroups were <1%. There were 6.5% Hispanic/Latino participants. The median age was 15.0 years, and 44.9% of participants were female. A total of 6.8% of participants were characterized as obese (BMI ≥95th percentile for participants 12 through 15 years of age and BMI ≥30.0 kg/m2 for participants ≥16 years of age). Overall, 75.7% of participants were SARS-CoV-2 positive at baseline (prior to bivalent booster dose). The median time since the last BNT162b2 dose was 8.3 months.

Among Group 2 participants, 79.6% were White, 8.7% were Black or African American, 9.7% were Asian, 1.9% were multiracial, and other race subgroups were <1%. There were 11.7% Hispanic/Latino participants. The overall median age was 40 years, and 57.3% of participants were female. A total of 25.2% of participants were characterized as obese. Overall, 64.1% of participants were SARS-CoV-2 positive at baseline (prior to bivalent booster dose). The median time since the last BNT162b2 dose was 10.9 months.

Among Group 4 participants, 79.2% were White, 15.1% were Black or African American, 2.8% were Asian, and other race subgroups were <1%. There were 9.4% Hispanic/Latino participants. The overall median age was 65 years, and 38.7% of participants were female. A total of 38.7% of participants were characterized as obese. Overall, 60.4% of participants were

SARS-CoV-2 positive at baseline (prior to bivalent booster dose). The overall median time since last prior dose of original BNT162b2 before study vaccination was 10.9 months.

6.3.2 Safety Results

6.3.4.1 Solicited Adverse Reactions

Group 1
Pain at the injection site (70%) was the most frequently reported local reaction within 7 days after booster dose, with swelling (8%) and redness (6%) at the injection site reported much less frequently. Most local reactions were mild or moderate in severity. Severe local reaction (injection site pain which prevents daily activity) was reported by one (0.9%) participant after 30 µg bivalent (WT/OMI BA4/BA.5) booster vaccination.

Fatigue (67%) was the most frequently reported systemic event within 7 days after booster dose, followed by headache (51%), muscle pain (26%), chills (23%), joint pain (12%), fever (9%), diarrhea (7%), and vomiting (3%). One participant reported fever >38.9°C.

Group 2
Pain at the injection site (79%) was the most frequently reported local reaction within 7 days after bivalent booster dose, with swelling (7%) and redness (6%) at the injection site reported less frequently. Most local reactions were mild or moderate in severity.

Fatigue (63%) was the most frequently reported systemic event within 7 days after booster dose, followed by headache (44%), muscle pain (31%), joint pain (17%), chills (15%), diarrhea (14%), fever (5%), and vomiting (2%). Severe fatigue (prevents daily activity) was reported in two participants, and severe diarrhea (6 or more loose stools in 24 hours) was reported by one participant.

Group 4
Pain at the injection site (56%) was the most frequently reported local reaction within 7 days after booster dose, with swelling (2%) and redness (2%) at the injection site reported less frequently. Most local reactions were mild or moderate in severity.

Fatigue (39%) was the most frequently reported systemic event within 7 days after booster dose, followed by headache (30%), muscle pain (20%) chills (12%), joint pain (11%), diarrhea (9%), fever (8%), and vomiting (1%). Severe fatigue was reported by one participant.

6.3.4.2 Unsolicited Adverse Events

Group 1
In total, 8 (7.5%) participants reported any AE from study vaccination through 1 month after study vaccination. Adverse events assessed as related by the investigator were reported by 6 (5.6%) participants. Most of the AEs were consistent with solicited local and systemic reactions that occurred within 7 days: headache (n=2), fatigue (n=3), myalgia (n=2), injection site pain (n=2), chills (two participants), and injection site erythema (n=2). No life-threatening AEs, withdrawals due to AEs, or deaths were reported. No additional participants reported AEs from 1 month after study vaccination to the cutoff date. One participant reported an immediate AE of injection site erythema within 30 minutes of study vaccination.

Group 2
In total, 3 (2.9%) participants reported any AE from study vaccination through 1 month after study vaccination. Adverse events assessed as related by the investigator were reported by 1

(1%) participant: lymphadenopathy 2 days after vaccination. No life-threatening AEs, withdrawals due to AEs, or deaths were reported. No additional participants reported AEs from 1 month after study vaccination to the cutoff date.

Group 4
In total, 4 (3.8%) participants reported any AE from study vaccination through 1 month after study vaccination. Adverse events assessed as related by the investigator were reported by 1 (0.9%) participant: skin erythema within 3 days of the vaccination. No life-threatening AEs, withdrawals due to AEs, or deaths were reported. No additional participants reported AEs from 1 month after study vaccination to the cutoff date.

6.3.4.3 Serious Adverse Events

No SAEs were reported in Groups 1 and 2. One participant 79 years of age was hospitalized for dyspnea, which started 15 days after vaccination, and the event was ongoing at the time of the data cutoff date October 12, 2022. No further details were provided. The event was considered by the investigator and by FDA to be unrelated to study vaccination.

6.3.4.4 Adverse Events of Clinical Interest

No protocol specified AESIs (myocarditis and pericarditis) were reported through 1 month after study vaccination in Groups 1, 2 or 4.

6.3.3 Summary of Findings from Cohort 2 of Study C4591044

This solicited and unsolicited safety data following bivalent booster vaccination suggests that Bivalent (WT/OMI BA4/BA.5) administered as a fourth COVID-19 dose is generally tolerated in individuals 12 years and older who previously received two primary doses and one booster dose of BNT162b2 vaccine.

6.4 FDA Review of Post-Authorization Safety Data from Bivalent Booster Doses

As of March 2, 2023, more than 434 million doses of Pfizer-BioNTech COVID-19 vaccines (including BNT162b2 and Bivalent (WT/OMI BA.4/BA.5) have been administered in the U.S. More than 34 million of these doses were the bivalent formulation (WT/OMI BA4/BA.5).[26] Among the U.S. population <5 years of age, 1,866,921 individuals have received a first mRNA COVID-19 vaccine dose, 982,935 have completed the primary series, and 65,156 have received an mRNA COVID-19 bivalent booster dose. It is not known what proportions of these numbers represent unauthorized use. The Bivalent (WT/OMI BA4/BA.5) is currently authorized (as of December 8, 2022) for use as the third dose of the 3-dose primary series (after two monovalent doses) among individuals ages 6 months through 4 years of age.

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event (AE) reports following administration of Bivalent (WT/OMI BA4/BA.5) and the results are briefly summarized below. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, stimulated reporting, variable report quality as well as accuracy 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.

Anaphylaxis
Post-authorization surveillance for BNT162b2 identified a risk of anaphylaxis, occurring at a rate similar to reported rates of anaphylaxis following licensed preventive vaccines. These reactions

occurred primarily in individuals with history of prior severe allergic reactions to other medications or foods.[13, 27] 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. As of March 02, 2023, there have been 23 U.S. reports of anaphylaxis/anaphylactoid reaction following receipt of the Bivalent (WT/OMI BA4/BA.5) among individuals of all ages (based on an automated search); there were no reports of anaphylaxis among individuals <5 years of age. Preferred terms (PTs) included in the automated VAERS query were as follows: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and anaphylactoid shock. The estimated crude reporting rate for anaphylaxis following the Bivalent (WT/OMI BA4/BA.5) for all ages in the U.S. is 0.7 cases per million doses administered, which is similar to estimated rates for other vaccines.[28]

Myocarditis and pericarditis

Post-EUA safety surveillance reports received by FDA and CDC identified increased rates of myocarditis and pericarditis, particularly 0-7-days following administration of the second primary series dose or first booster dose of BNT162b2. Reporting rates for reports verified to meet the CDC case definition of myocarditis and pericarditis in VAERS have been generally higher among males under 40 years of age than among females and older males.[29] CDC is conducting enhanced surveillance for VAERS case reports using patient and healthcare provider surveys to assess functional status and clinical outcomes among individuals reported to have developed myocarditis after mRNA COVID-19 vaccination. Information is not yet available about potential longer-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.

An automated query of the VAERS database as of March 07, 2023, did not return any reports of myocarditis/pericarditis following a bivalent booster dose among individuals less than 12 years of age.

Myocarditis and pericarditis were added as important identified risks in the PVP and included in the vaccine Fact Sheets and Prescribing Information (Section 5 Warnings and Precautions, 5.2 Myocarditis and Pericarditis, Section 6.2 Post Authorization Experience) for the original and bivalent Pfizer-BioNTech COVID-19 Vaccine. The Sponsor is conducting additional post-authorization/ postmarketing studies to assess known serious risks of myocarditis and pericarditis for the original and bivalent Pfizer-BioNTech COVID-19 Vaccine as well as to identify an unexpected serious risk of subclinical myocarditis for the original Pfizer-BioNTech COVID-19 Vaccine. To help ensure appropriate monitoring of such risks and protect public health, the Sponsor and vaccination providers will be required, under the conditions of authorization, to report all cases of myocarditis and pericarditis (regardless of seriousness) to VAERS. Because some cases of myocarditis or pericarditis following vaccine administration are conservatively managed and may not meet the definition of serious adverse events, this will help ensure that all cases are reported by the Sponsor and vaccination providers.

Review of the above VAERS data, as well as ongoing review of VAERS data and the Sponsor's periodic safety reports, did not identify patterns suggesting new safety concerns for the Bivalent (WT/OMI BA4/BA.5). Most AEs are labeled events, including anaphylaxis and myocarditis/pericarditis, and are consistent with the known safety profile for the original vaccine. In addition, the sponsor submitted a summary of post-authorization AE reports for the bivalent vaccine among all individuals stratified by age group, including individuals ≥6 months to <5 years of age. Review of the sponsor's data did not identify new clinical safety concerns.

Medication errors were among the most-commonly reported events (majority without co-reported clinical AEs) and the sponsor has employed mitigation strategies to address this risk. The clinical AEs reported were consistent with the known safety profile of the original monovalent vaccine such as labeled reactogenicity events (fatigue, headache, pyrexia, chills, arthralgia, and myalgia in decreasing order of frequency), or those noted with SARS-CoV-2 infection (e.g., PT COVID-19, Drug ineffective). There were no deaths in children ≥6 months to <5 years of age and only one foreign SAE report of angioedema was noted in this age group. No unusual frequency, clusters, or other trends for AEs were identified that would suggest new safety concerns for the bivalent vaccine.

7 FDA Review of Other Information Submitted in Support of the EUA Amendment

7.1 Chemistry, Manufacturing, and Controls (CMC) Information

The Sponsor did not submit any new CMC/facilities information with this aEUA as there are no changes to CMC or facilities. Therefore, as determined during review of the aEUA request for use of the Bivalent (WT/OMI BA4/BA.5) as the third dose of the primary vaccination series in individuals 6 months-4 years of age, the Bivalent (WT/OMI BA4/BA.5) is manufactured with sufficient quality and consistency to support the proposed use under EUA.

7.2 Pharmacovigilance Activities

Pfizer is conducting safety-related post-authorization/post-marketing studies for the monovalent vaccine, including post-marketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. Pfizer submitted a revised PVP to monitor safety concerns that could be associated with the Bivalent (WT/OMI BA4/BA.5) vaccine. 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.

Sponsor pharmacovigilance activities
The Sponsor will conduct passive and active surveillance to monitor the post-authorization safety for the Bivalent (WT/OMI BA4/BA.5), including:

- Mandatory reporting by the Sponsor under the EUA for the following events to VAERS within 15 days: SAEs (irrespective of attribution to vaccination); myocarditis; pericarditis; multisystem inflammatory syndrome (MIS) in children and adults; COVID-19 resulting in hospitalization or death
- 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 to evaluate the association between Bivalent (WT/OMI BA4/BA.5) and a pre-specified list of adverse events of special interest (AESIs), including myocarditis and pericarditis, along with deaths and hospitalizations, and severe COVID-19. The studies should be conducted in large scale databases with an active comparator. This condition of authorization under the EUA, to conduct post-authorization observational studies, will encompass the evaluation of Bivalent (WT/OMI BA4/BA.5), including in individuals <12 years of age, in the following studies:

- C4591036: Pediatric Heart Network Study: Ongoing low Interventional Cohort Study of Myocarditis/Pericarditis Associated with Comirnaty in persons less than 21 years of age.

- C4591051: Planned, non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 bivalent Omicron-modified vaccine in the United States.
- C4591052: Planned post-authorization approval active surveillance study among individuals in Europe receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) bivalent Omicron-modified vaccine.

The Sponsor also plans to include vaccine effectiveness analyses among individuals in all authorized age groups who receive the Bivalent (WT/OMI BA4/BA.5) in the ongoing Study C4591014 entitled “Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study Kaiser Permanente Southern California”.

Other pharmacovigilance activities
Mandatory reporting by vaccination providers to VAERS, and to the extent feasible, to the Sponsor, for the following events:

- Vaccine administration errors whether or not associated with an AE
- Serious AEs (irrespective of attribution to vaccination)
- Myocarditis
- Pericarditis
- Cases of multisystem inflammatory syndrome in children and adults
- Cases of COVID-19 that result in hospitalization or death

Active surveillance of vaccine recipients via the v-safe program: v-safe is a smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine parents/guardians (or the recipient) for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports medically significant AE.

7.3 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.

8 Benefit/Risk in the Context of the Proposed EUA For Pfizer-BioNTech COVID-19 Vaccine, Bivalent (WT/OMI BA4/BA.5)

8.1 Discussion of Benefits, Risks, and Uncertainties

COVID-19 is caused by SARS-CoV-2, and the virus has been responsible for over 103 million cases of COVID-19 and over 1.1 million deaths in the U.S. Since the start of the pandemic, there has been a succession of COVID-19 variants including Beta, Delta, Omicron BA.1, Omicron BA.5, and most recently Omicron BQ.1, BQ1.1, and XBB.1.5. As of March 7, 2023, XBB.1.5 was the currently dominant variant in the U.S. (89.6% of cases), followed by BQ.1.1 (6.7% of cases). Current treatment options for COVID-19 in individuals 6 months through 4 years of age include antiviral medications, convalescent plasma, and immune modulators approved or authorized for the management of individuals with COVID-19. However, such

treatments may not prevent complications from COVID-19 including post-acute sequelae of COVID-19 (long COVID).

In addition to the currently authorized and approved treatments, FDA-approved and authorized vaccines provide protection to individuals against COVID-19 and play an important role in controlling the pandemic and reducing the societal and economic interruption caused by the pandemic. For children 6 months through 4 years of age who completed their primary series before December 8, 2022, with 3 doses of the monovalent BNT162b2, a bivalent vaccine dose is not currently authorized. The authorized monovalent mRNA-based vaccines from Moderna and Pfizer-BioNTech are based on the original (ancestral) strain of SARS-CoV-2 and initially had effectiveness of up to 90 to 95% against symptomatic disease when the ancestral strain was circulating. However, a succession of viral variants and waning of individual immunity has led to a reduction in vaccine effectiveness over time. In the setting of the viral variants that have emerged, boosting with available vaccines (based on the ancestral strain) has been able to restore some degree of protection against serious and symptomatic disease, but it appears that effectiveness against symptomatic disease declines more rapidly than that against serious disease, as has been illustrated by studies conducted in the United States,[29, 30] Israel,[19] Qatar,[16] Portugal,[31] and England.[10]

Available data support the benefit of a Bivalent (WT/OMI BA4/BA.5) booster dose in children 6 months-4 years of age for the prevention of COVID-19. Descriptive immunogenicity data indicate an increase in neutralizing antibody titers against SARS-CoV-2, including against Omicron BA.4/BA.5 variant, in children 6 months-4 years of age who received a Bivalent (WT/OMI BA4/BA.5) booster dose. This observation is similar to the neutralizing antibody responses that have been observed in the context of real-world evidence in adolescents and adults following a booster dose and supports effectiveness of a Bivalent (WT/OMI BA4/BA.5) booster dose against COVID-19 and associated serious outcomes. The totality of evidence therefore supports a similar benefit in children 6 months-4 years of age.

Based on previous experience and available evidence, including safety, immunogenicity, and effectiveness data obtained with the BNT162b2 in individuals 6 months- 4 years of age, vaccination with the Bivalent (WT/OMI BA4/BA.5) booster dose is expected to elicit an improved immune response to the BA.4 and BA.5 variants compared to BNT162b2. An initial study performed during the time when BA.4 and BA.5 were circulating indicated that the Bivalent (WT/OMI BA4/BA.5) was relatively more effective than BNT162b2 as booster dose in adults.[2] That noted, it is uncertain exactly how the magnitude of the increase in antibody response to the Bivalent (WT/OMI BA4/BA.5) booster dose will translate into effectiveness against specific COVID-19 outcomes, including symptomatic and serious disease with the recently dominant Omicron XBB.1.5 variant, and this uncertainty is likely to be even greater for variants that may emerge in the future.

Additional booster doses may be associated with transient local and systemic symptoms like those seen with primary series and booster doses given previously. The most notable uncommon side effect of the mRNA COVID-19 vaccines has been myocarditis. Based on the data from the BEST Initiative as of 10/8/2022, within a week after the second dose of Pfizer COVID-19 Vaccine primary series, the crude observed ratio (with adjustment for claims processing delay) of myocarditis or pericarditis was 0.73 cases per 100,000 vaccine doses among individuals 5-11 years of age, and 0.95 cases per 100,000 vaccine doses among male individuals 5-11 years of age (unpublished data, based on fewer than 10 cases). The myocarditis associated with the administration of mRNA COVID-19 vaccines has been mild and transient in most cases (>95%). Limited clinical evaluation of bivalent mRNA COVID-19 vaccine

formulations has not suggested any new safety concerns for this age group in addition to those previously characterized. In addition, passive and active surveillance systems will be utilized to continuously monitor adverse reactions and any emerging safety concerns post EUA. The rate of myocarditis in individuals 6 months through 4 years of age is expected not to be higher, and perhaps may be lower, than that observed in the 5-11 years of age group.

The totality of the available evidence indicates that administration of Bivalent (WT/OMI BA.4/BA.5) as a booster (fourth) dose given at least two months after the most recent COVID-19 vaccination for individual 6 months through 4 years who completed primary vaccination with Pfizer-BioNTech COVID-19 Vaccine will likely increase the immune response against current and emerging SARS-CoV-2 variants and does not suggest any new safety concerns for this age group. Table 10 provides a summary of the benefit-risk considerations in a standard FDA format.

Table 10. Summary of Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• COVID-19 caused by SARS-CoV-2 has been responsible for over 103 million cases and over 1 million deaths in the U.S. • There has been a succession of variants (including Omicron BA.1, BA.4, BA.5, BQ.1, BQ1.1, XBB.1.5, and other subvariants) that have led to a reduction in vaccine effectiveness. • Although the available COVID-19 vaccines based on the original (ancestral) strain continue to provide some protection against hospitalization and death, their overall effectiveness appears to have decreased.	• COVID-19 is a serious disease associated with significant morbidity and mortality from initial infection and additional morbidity from post-acute sequelae of COVID-19 (long COVID) in a subset of those individuals • Certain available COVID-19 vaccines initially had high effectiveness (90-95%) against symptomatic disease; however, vaccine effectiveness has declined in the setting of the new Omicron variant in combination with waning individual immunity; this effect is most clearly observed in older individuals, but decreased vaccine effectiveness, especially after the primary series, is also apparent in pediatric age groups. [32]
Current Treatment Options	• Treatment options for individuals 6 months-4 years of age are limited, especially for those under 2 years of age. • An antiviral medication, immune modulators, and convalescent plasma have been approved or authorized for the management of individuals with COVID-19. • There are currently two authorized mRNA COVID-19 vaccines for use as a primary series in individuals 6 months through 4 years of age. • There is currently no booster dose authorized for individuals 6 months-4 years of age who completed a primary BNT162b2 series. A booster dose of Moderna COVID-19 Vaccine, Bivalent (Original plus Omicron BA.4/BA.5) is only authorized for individuals 6 months-5 years of age who completed primary vaccination with the Moderna COVID-19 Vaccine.	• Currently available treatments may not prevent COVID19 and complications, including post-acute sequelae of COVID-19. • Vaccines play an important role in pandemic control and provide important protection against COVID-19 and complications.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The immunogenicity and safety of booster vaccines against Beta, Delta, and Omicron BA.1 variants were previously evaluated by both current mRNA vaccine manufacturers; however, these vaccines were not deployed in the U.S. because of SARS-CoV-2 variant evolution. • How well the observed immune responses to the Bivalent (WT/OMI BA4/BA.5) as a booster (fourth dose) in individuals 6 months through 4 years of age will translate into vaccine effectiveness against COVID-19, including symptomatic and serious disease caused by currently circulating SARS-CoV-2 variants, remains uncertain	• The totality of the available evidence indicates that use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and BA.4/BA.5) as a booster (fourth dose) will likely increase the broad immune response against SARS-CoV-2 variants.
Risk and Risk Management	• Booster doses may be associated with transient local and systemic symptoms similar to those seen with primary series. • The most notable uncommon side effect has been myocarditis. • The highest risk of myocarditis was observed among male young adults and adolescents.	• The myocarditis associated with the administration of mRNA COVID-19 vaccines has been mild and transient in most cases (>95%). • Post-deployment monitoring for adverse events using both passive and active surveillance systems will be utilized to assess myocarditis risk and any new safety concerns.

8.2 Conclusions Regarding Benefit-Risk

For individuals 6 months through 4 years of age, the known and potential benefits of Bivalent (WT/OMI BA4/BA.5) for a booster dose after completion of a three-dose monovalent primary series outweigh the known and potential risks, considering the totality of available evidence and the outstanding uncertainties. The benefit-risk profile of available mRNA COVID-19 vaccines is well understood following the administration of over one billion doses. FDA's previous benefit-risk assessments based on real-world evidence clearly demonstrate that the benefits of available mRNA COVID-19 vaccines outweigh their risks. During the current phase of COVID-19 caused largely by continued evolution of Omicron variants (e.g., BQ.1.1, XBB.1.5), addition of a booster (fourth) dose of COVID-19 Vaccine, Bivalent is expected to have a favorable benefit-risk profile, potentially helping to restore protection against serious outcomes from COVID-19, and possibly reducing symptomatic disease that may be followed by debilitating post-acute COVID-19 syndrome.

9 Overall Summary and Recommendations

The review team considered information submitted in support of the EUA request and VRBPAC recommendations from the June 28, 2022, and the January 26, 2023, meetings. The review team also considered the following in its assessment of authorization of the Bivalent (WT/OMI BA4/BA.5) as a booster (fourth) dose for individuals 6 months through 4 years of age that completed primary vaccination with Pfizer-BioNTech COVID-19 Vaccine:

- As summarized in Section 2 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.

- The scientific evidence available to support this EUA request includes the following:
  - previously reviewed data on immunogenicity of a booster dose with the bivalent vaccine (Original and Omicron BA.1) in individuals greater than 55 years of age, [33]

  - data on the safety and immunogenicity following the Bivalent (WT/OMI BA4/BA.5) booster (fourth dose) in children 6 months-4 years of age who previously completed primary vaccination with three doses of Pfizer-BioNTech COVID-19 Vaccine,
  - supportive Bivalent (WT/OMI BA.4/BA.5) booster dose (fourth dose) safety data in individuals ≥5 years of age who received a 2-dose primary series and one booster dose of BNT162b2, and
  - postmarketing safety surveillance data with primary series and booster doses of the original Pfizer-BioNTech COVID-19 Vaccine, and booster doses of the Pfizer COVID-19 Vaccine, Bivalent (WT/OMI BA4/BA.5)

- Based on the totality of available scientific evidence, it is reasonable to conclude that the Bivalent (WT/OMI BA4/BA.5) as a booster dose, following three doses of the BNT162b2 as a primary series, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages derived from BA.5. Recent studies have demonstrated that XBB.1.5 can evade humoral immunity induced by mRNA vaccines or natural infection and that a bivalent vaccine (ancestral and BA.4/5) bivalent vaccine is more immunogenic than the original vaccine, with greater responses against circulating omicron sublineages to XBB.1.5.[13] Vaccine effectiveness is based on previously reviewed data on immunogenicity of a booster dose with the bivalent vaccine (Original and Omicron BA.1) in individuals greater than 55 years of age and descriptive clinical immunogenicity data in children 6 months-4 years of age who received a bivalent booster dose at a median of 6.9 months (range: 2.2-8.6) after a 3-dose monovalent BNT162b2 primary series.

- Based on FDA's review of the available scientific evidence, including the data summarized in Section 6 and assessment of benefits and risks in Section 8 of this review, the known and potential benefits of the Bivalent (WT/OMI BA4/BA.5) as a booster (fourth) dose, following three doses of the Pfizer-BioNTech COVID-19 Vaccine as a primary series, outweigh the known and potential risks. Known and potential benefits include reduction in the risk of symptomatic COVID-19 and associated serious sequelae, including from COVID-19 due to Omicron variants derived from BA.5. It is uncertain how any increase in antibody response to a bivalent (Original and BA.4/BA.5) booster vaccine, will translate into effectiveness against COVID-19 outcomes, including symptomatic disease, as new derivatives of Omicron BA.5 circulate. However, these uncertainties must be balanced against available evidence demonstrating waning protection from COVID-19 vaccine monovalent primary series, decreased effectiveness of currently available monovalent COVID-19 vaccines against Omicron BA.5, from which BQ.1, BQ.1.1, and XBB.1.5 are evolved, compared to previous strains, and the time that would be needed to accrue additional clinical trial data with the Bivalent (WT/OMI BA4/BA.5) to more directly assess effectiveness. Additional uncertainties include effectiveness against future SARS-CoV-2 variants, effectiveness against asymptomatic SARS-CoV-2 infection and SARS-CoV-2 transmission, and effectiveness in certain high-risk populations such as severely immunocompromised individuals. Known and potential risks include generally self-limited common local and systemic adverse reactions (notably fatigue, injection site reactions, irritability, drowsiness, decreased appetite, diarrhea, fever, headache, vomiting, joint pain, and chills) based on experience in Pfizer-BioNTech COVID-19 Vaccine recipients 6 months through 4 years of age. 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 widespread use of the vaccine and with longer duration of follow-up.

- The Bivalent (WT/OMI BA4/BA.5) is currently authorized under EUA for use as a single booster dose administered at least 2 months after either completion of primary vaccination with any FDA authorized or approved COVID-19 vaccine or the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine in individuals 5 years of age and older. COVID-19 vaccines that contain an Omicron component are not currently approved or authorized for use as a booster dose in individuals 6 months through 4 years of age who have completed a 3-dose primary series with BNT162b2.

- Review of VAERS data and the Sponsor's periodic safety reports, did not identify patterns suggesting new safety concerns for the Bivalent (WT/OMI BA4/BA.5) for this age group. Most AEs are labeled events, including anaphylaxis and myocarditis/pericarditis, and consistent with the known safety profile for the original vaccine. In addition, the sponsor submitted a summary of post-authorization AE reports for the bivalent vaccine among all individuals stratified by age group, including individuals ≥6 months to <5 years of age. Review of the sponsor's data did not identify new clinical safety trends. The clinical AEs reported were consistent with the known safety profile of the original monovalent vaccine such as labeled common reactogenicity events, or those noted with SARS-CoV-2 infection. Medication errors were among the most-commonly reported events (majority without co-reported clinical AEs) and the sponsor has employed mitigation strategies to address this risk. No unusual frequency, clusters, or other trends for AEs were identified that would suggest new safety concerns for the bivalent vaccine.

Based on the considerations outlined above, the review team recommends authorization of the Bivalent (WT/OMI BA4/BA.5) under EUA for use as a booster (fourth) dose given at least 2 months after the most recent COVID-19 vaccination for individual 6 months through 4 years who completed primary vaccination with BNT162b2.

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