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

Identifying Information

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Application Number	EUA 27034, Amendment 731 and 732
Sponsor	Pfizer, Inc., on behalf of Pfizer and BioNTech
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Review Completion Date	April 17, 2022
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 (for 6 months through 4 years) A 0.2 mL suspension for intramuscular injection (for 5 years through 11 years of age) A 0.3 mL suspension for intramuscular injection (for 12 years of age and older) (For dosing regimen, dose, and schedule, refer to Section 5.1)
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
Intended Population	Individuals 6 months of age and older

Table of Contents

1 Executive Summary

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to be an ongoing global health challenge. As of April 12, 2023, SARS-CoV-2 has led to over 763 million cases of coronavirus disease 2019 (COVID-19), including 6.9 million deaths worldwide. The Pfizer-BioNTech COVID-19 Vaccine (also known as BNT162b2) is a nucleoside-modified messenger RNA (mRNA) vaccine encoding the full-length spike (S) protein of the original (ancestral) Wuhan-Hu-1 SARS-CoV-2 strain. The Pfizer-BioNTech COVID-19 Vaccine was initially authorized under Emergency Use Authorization (EUA) on December 11, 2020, for primary series vaccination of individuals 16 years of age and older and subsequently authorized for primary series vaccination of individuals 6 months to 15 years of age. The vaccine was also previously authorized for booster vaccination of individuals 5 years of age and older; however, following emergence of the Omicron variant and its sublineages (most recently BA.4/BA.5 and related sublineages) 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. 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) Pfizer-BioNTech COVID-19 Vaccine to no longer include use as a booster dose in individuals 12 years of age and older, and 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 years through 11 years of age, with concurrent revision of the authorization for the original (monovalent) Pfizer-BioNTech COVID-19 Vaccine to no longer include use as a booster dose in individuals 5 years through 11 years of age. 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 a third primary series dose in individuals 6 months through 4 years of age, with concurrent revision of the authorization for the original (monovalent) Pfizer-BioNTech COVID-19 Vaccine to no longer include use as a third primary series dose individuals 6 months through 4 years of age. Finally, on March 14, 2023, FDA authorized the Pfizer-BioNTech COVID-19 Vaccine, Bivalent for use in individuals 6 months through 4 years of age to provide a single booster dose at least 2 months after completion of primary vaccination with 3 doses of Pfizer-BioNTech COVID-19 Vaccine.

Although the available evidence suggests that the Original Pfizer-BioNTech COVID-19 Vaccine (monovalent vaccine) continues to provide protection against serious disease from COVID-19, since the authorizations of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) as boosters in children and adults, data have emerged indicating that the bivalent vaccine provides improved protection compared to the Original Pfizer-BioNTech COVID-19 Vaccine. In addition, data from several studies provide evidence that two or more exposures to the SARS-CoV-2 Spike protein through vaccination and/or infection provide sufficient pre-existing immunity such that administration of a single dose of an authorized bivalent COVID-19 vaccine would likely induce or restore the expected protective immunity for a defined duration in immunocompetent individuals. Additionally, data from the Centers for Disease Control and Prevention (CDC) indicate that most individuals over 4 years of age have either received COVID-19 vaccination, experienced infection with SARS-CoV-2, or have experienced both. In addition, simplification of the vaccination regimen is warranted. FDA expects that simplification of the immunization schedules may contribute to more facile vaccine deployment, fewer vaccine administration errors, and less complex communication, all

potentially leading to improved vaccine coverage rates and, ultimately, to enhanced public health.

Pfizer-BioNTech has submitted a request on April 7, 2023, to amend the EUA for consolidating the fact sheets and to update the dosing and administration schedule for Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to provide for the use of the Pfizer BioNTech COVID-19 Vaccine, Bivalent as a three-dose schedule for children 6 months through 4 years of age and as a single dose for individuals 5 years of age and older. In addition, Pfizer-BioNTech requested to amend the EUA to provide for authorization of an additional dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals 65 years of age and older and one or more additional doses for certain immunocompromised individuals.

Given that the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is manufactured using the same process as Original Pfizer-BioNTech COVID-19 Vaccine, postmarketing safety data for Original Pfizer-BioNTech COVID-19 Vaccine were considered relevant to the safety evaluation of this vaccine. Review of postmarketing safety data indicate a similar safety profile of the Original Pfizer-BioNTech COVID-19 Vaccine and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). As of April 5, 2023, more than 366 million doses of the original Pfizer-BioNTech COVID-19 Vaccine have been administered in the US, and 35,690,430 booster doses of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Of the total doses of either the Original or Bivalent formulation given in the US, 2,792,884 have been administered to individuals 6 months through 5 years of age and 63,145,813 have been administered to individuals 6 through 17 years of age, and 332,754,043 doses administered to adults 18 years of age and older (data lock point Apr 5, 2023).

In recipients of any age and all doses, the most frequently reported preferred terms (PTs) in the Vaccine Adverse Event Reporting System (VAERS) were headache, pyrexia, fatigue, chills, pain, pain in extremity, nausea, dizziness, myalgia, and injection site pain. For important risks identified in the pharmacovigilance plan for Pfizer-BioNTech COVID-19 Vaccine, anaphylaxis and myocarditis/pericarditis are identified risks that are included in product labeling. The Sponsor is conducting additional safety-related post-authorization/postmarketing studies for the Original Pfizer-BioNTech COVID-19 Vaccine, including postmarketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. The Sponsor is also conducting planned post-authorization studies to evaluate the association between the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and a pre-specified list of adverse events of special interest (AESIs) in all authorized ages in the general US population.

The totality of scientific evidence available currently supports moving to a single vaccine composition for all vaccine doses, consisting for the time being of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Review of the totality of the available evidence on prior exposure to SARS-CoV-2 and vaccination against COVID-19 suggests that most individuals may only need to receive one dose of a bivalent COVID-19 vaccine to restore protective immunity for a period of time. Additional doses of a bivalent COVID-19 vaccine may be reasonably expected to induce the expected protective immunity for those who have a low likelihood of prior SARS-CoV-2 infection (the very young) or those who may not generate a protective immune response (older adults and immunocompromised individuals). At this time the available evidence indicates that those 6 months through 4 years of age should still receive three doses of Pfizer BioNTech COVID-19 Vaccine, Bivalent 0, 21 days and ≥8 weeks after the second dose; those 65 years of age and older may receive a second dose at least 4 months following administration of a prior bivalent COVID-19 vaccine, and individuals 5 years of age

and older with certain kinds of immunocompromise (solid organ transplant recipients and those determined to have a similar level of immunocompromise), may receive an additional vaccine dose at least 2 months following administration of a prior bivalent COVID-19 vaccine and subsequent doses at the discretion of the healthcare provider.

Taken together, the review team recommends discontinuation of use of the monovalent Pfizer-BioNTech COVID-19 in the United States and use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) administered in an appropriate schedule based on age, previous vaccination status, and risk of COVID-19-associated severe disease, hospitalization, and death.

2 Background

2.1 SARS-CoV-2 Virus 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. As of April 12, 2023, SARS-CoV-2 has led to over 762 million cases of coronavirus disease 2019 (COVID-19), including 6.8 million deaths worldwide.[1] 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,[2] 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.[3] 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.[4,5] 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.[6,7] 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.

In the US, more than 104 million cases and 1.1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC).[8] Approximately 4% of cases occurred in children less than 5 years of age and 14% of cases occurred in children and adolescents 5 through 17 years of age.[9] 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 US, have been associated with rapid spread of highly transmissible SARS-CoV-2 variants, most recently Omicron. The Omicron BA.1 variant became the predominant variant circulating in the US in December 2021, and while COVID-19 cases, hospitalizations, and deaths in the US have declined since the peak of the Omicron surge in January 2022, the Omicron variant continues to evolve into sublineages, including the recent BA.4 and BA.5 sublineages, and most recently the XBB.1.5 sublineage which accounts for nearly all reported COVID-19 cases in the US currently.[10] In addition, population-level evidence suggests an increased reinfection risk associated with the Omicron variant and its sublineages compared to earlier SARS-CoV-2 variants.[11] Additionally, available evidence demonstrates

waning of immunity elicited by COVID-19 primary vaccination and booster doses and reduced effectiveness of currently available vaccines based on the original SARS-CoV-2 strain against COVID-19 caused by the currently dominant Omicron variant sublineages (see Section 3.1 below). Since the introduction of the bivalent COVID-19 (Original + BA.4/BA.5) boosters, multiple studies have demonstrated that bivalent vaccine booster doses have provided improved protection against symptomatic disease, hospitalization, and death from the more recently evolved Omicron sublineages that have included BA.4, BA.5, BQ.1.1, and XBB.1.5, documenting the benefit of updating the strain composition of the vaccines.

Throughout this document, the term "sublineage" indicates the SARS CoV-2 Omicron variant BA.1, BA.4, BA.5, BQ.1.1, or XBB.1.5 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 two-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 Emergency Use Authorization (EUA), the vaccine is called the Pfizer-BioNTech COVID-19 Vaccine and is authorized for use as a: part of a 3-dose primary series for individuals 6 months through 4 years of age, a two-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), 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 or receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 vaccine. For children 6 months through 4 years of age, the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is authorized as a single booster dose after completion of primary vaccination with three doses of Pfizer-BioNTech COVID-19 Vaccine and as the third dose of a 3-dose primary series. 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 (primary series and booster doses) for 6 months through 4 years of age, 10 µg in 0.2 mL for 5 through 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 the Pfizer-BioNTech COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/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 (Original and Omicron BA.4/BA.5)

Spikevax (COVID-19 Vaccine, mRNA), manufactured by Moderna, is approved for use as a two-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 months through 5 years of age, to be administered at least 2 months after either completion of primary vaccination with Moderna COVID-19 Vaccine, or for those 6 years of age or older at least 2 months after completion of primary vaccination or 2 months after receipt of the most recent booster dose with an authorized or approved monovalent 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 through 5 years of age, 50 µg in 0.5 mL for 6 through 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 6 months through 5 years of age and older is 10 µg in 0.2 mL, for use in individuals 6 years through 11 years of age is 25 µg in 0.25 mL, and for use in individuals 12 years of age and older is 50 µg in 0.5 mL. 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 homologous or heterologous booster dose (the dosing interval for a booster is 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 two-dose primary series for active immunization to prevent COVID-19 in individuals 12 years of age and older, and as a first booster dose in the following individuals: Individuals 18 years and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and 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 Veklury (remdesivir) is currently approved by the FDA for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 testing who are hospitalized, or who are not hospitalized and have mild-to-moderate COVID-19 and are at high risk for severe COVID-19. The immune modulator Olumiant (baricitinib) is currently approved for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). The immune modulator Actemra

(tocilizumab) is currently approved for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

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:

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

SARS-CoV-2-targeting monoclonal antibodies: Several SARS-CoV-2-targeting monoclonal antibodies have been authorized under EUA but are not currently authorized due to the high frequency of circulating SARS-CoV-2 variants that are non-susceptible to them. These include: sotrovimab; REGEN-COV (casirivimab and imdevimab) (both authorized for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death); and bebtelovimab, was previously authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years of age and older weighing at least 40 kg with positive results of direct SARS-CoV-2 testing, who are at high risk for progression to severe COVID-19 and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. For a similar reason, Evusheld (tixagevimab co-packaged with cilgavimab) is not currently authorized under EUA as pre-exposure prophylaxis for prevention of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg).

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

Gohibic (vilobelimab) is authorized for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation (IMV) or ECMO. Vilobelimab a recombinant chimeric monoclonal IgG4 antibody that specifically binds to the soluble human complement split product C5a after cleavage from C5 to block its interaction with the C5a receptor, both of which are components of the complement system thought to contribute to inflammation and worsening of COVID-19.

Kineret (anakinra) is authorized for the treatment of COVID-19 in hospitalized adults with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR). Anakinra is an Interleukin-1 (IL-1) receptor

antagonist. IL-1 is involved in inflammatory diseases and additionally, IL-1 is linked to acute severe lung inflammation in COVID-19.
COVID-19 convalescent plasma with high 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.

3 Rationale for Bivalent Strain Composition

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

While the currently authorized and approved COVID-19 vaccines in the US 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 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.[12,13,14,15,16,17,18,19,20,21,22]

Results from observational studies that investigated the effectiveness of primary vaccination with originally authorized and approved monovalent vaccines showed decreased effectiveness against certain variants (notably Omicron, for which neutralizing antibody titers were found to be decreased compared with the original strain) and waning effectiveness over time.[12,13,14] Although first booster doses have restored waning vaccine effectiveness (VE), including against severe disease and hospitalization associated with Omicron,[12,13,14,15] 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[12,16,17,18] and lower effectiveness among the immunocompromised individuals.[19] In Israeli experience with a second monovalent booster dose of the 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.[21,22]

Following introduction of the Bivalent (Original and Omicron BA.4/BA.5) mRNA COVID-19 vaccines, studies have demonstrated that when given to adults a single bivalent booster vaccine increases immunogenicity against currently circulating variants and reduces symptomatic disease, hospitalization, and death.[23,24,25,26,27,28]

The improved protection against currently circulating variants provided by the bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines compared with the monovalent Original COVID-19 vaccines provides support for the transition to use of bivalent vaccines for all doses for mRNA COVID-19 vaccines as well as support for periodic updates of the strain composition of COVID-19 vaccines.

3.2 January 26, 2023, VRBPAC and Subsequent Regulatory Discussions

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 unanimously voted in favor of harmonizing the COVID-19 vaccine strain composition for primary series and booster doses in the US 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.

In March 2023, FDA notified COVID-19 vaccine manufacturers that they should plan to implement the proposals discussed at the VRBPAC and supported by the committee's vote and discussion. Specifically, FDA noted that the process of moving to a single vaccine strain composition, i.e., Original and Omicron BA.4/BA.5 for all mRNA-based COVID-19 vaccines, should also involve consolidation of the various provider and patient fact sheets for different age groups into one provider and one patient fact sheet for each vaccine, and simplification of the vaccination regimens to the extent appropriate. Specifically, given the current state of immunity of the population, including natural acquired, vaccine-induced, and hybrid (combined natural infection in the setting of at least one COVID-19 vaccination) immunity, FDA suggested moving to a single vaccination for most individuals for each of the authorized bivalent vaccines, with modifications for the very young, those 65 years and older, and those with certain forms of immunocompromise. The current EUA request was made in response to this recommendation by FDA.

4 Regulatory Considerations for EUA of a Bivalent COVID-19 Vaccine with an Omicron Component

4.1 US Requirements to Support Issuance of an EUA for a Biological Product

The Secretary of the US Department of Health and Human Services (HHS) has determined that there is a public health emergency or a significant potential for a public health emergency, that affects, or has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19. Based on that determination, and the Secretary's declaration that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, 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 expectations.

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 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 nor simplification of authorized dosing regimens and schedules, the approach and associated immunogenicity endpoints and analyses for supporting vaccine effectiveness are relevant to bivalent modified vaccines. 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.

The guidance recommended that studies to demonstrate effectiveness of a monovalent modified COVID-19 vaccine administered for primary vaccination use a dose and dosing regimen that is the same as the authorized prototype vaccine, and a study is underway for the use of a three-dose regimen of the Pfizer BioNTech COVID-19 Vaccine, Bivalent in individuals 6 months through 4 years of age. At this time, FDA considers it reasonable to authorize a three-dose regimen of the Pfizer BioNTech COVID-19 Vaccine, Bivalent in previously unvaccinated individuals 6 months through 4 years of age given the anticipated favorable benefit-risk balance of this regimen in that age group. FDA also considers it reasonable to authorize additional doses of the Pfizer BioNTech COVID-19 Vaccine, Bivalent in individuals 65 years of age and older and certain immunocompromised individuals given the anticipated favorable benefit-risk balance of additional doses in those individuals. This is based upon the accumulated experience with primary series, first booster doses, and second booster doses of the Pfizer BioNTech COVID-19 Vaccine, and booster doses of the Pfizer BioNTech COVID-19 Vaccine, Bivalent and Pfizer BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.1) (see Section 6).

5 EUA Amendment Request to Consolidate the Fact Sheets and Update Dosing and Administration for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent

5.1 Summary of the EUA Request

On April 7, 2023, Pfizer/BioNTech requested revisions to the current Pfizer/BioNTech COVID-19 Vaccine EUA Fact Sheets for the use of the bivalent (original and Omicron BA.4/BA.5) Pfizer-BioNTech COVID-19 Vaccine for all doses and all ages. The request to update the dosing and administration schedule for Pfizer-BioNTech COVID-19 Vaccine Bivalent (Original and Omicron BA.4/BA.5) included the use of the bivalent vaccine as a 3-dose schedule for children 6 months through 4 years of age and a single dose vaccination schedule for individuals 5 years of age and older, consistent with the following tables.

Table 1. Dosing for Individuals 6 Months of Age and Older Not Previously Vaccinated With a COVID-19 Vaccine

Age	Pfizer-BioNTech COVID-19 Vaccine, Bivalent Vial Cap and Label Border Color	Dose and Dosing Regimen
6m-4y	Maroon	3 doses, 0.2 mL each Dose 1: Week 0 Dose 2: Week 3 Dose 3: ≥8 weeks after Dose 2
5-11y	Orange	Single dose, 0.2 mL
12-64y	Gray	Single dose, 0.3 mL
≥65 years	Gray	Single dose, 0.3 mL One additional dose, 0.3 mL, may be administered ≥4 months after first dose of an authorized bivalent COVID-19 vaccine

Table 2. Dosing for Individuals 6 Months Through 4 Years of Age Previously Vaccinated With the Monovalent Pfizer-BioNTech COVID-19 Vaccine

Age	Number of Previous Doses of Pfizer-BioNTech COVID-19 Vaccine	Pfizer-BioNTech COVID-19 Vaccine, Bivalent Vial Cap and Label Border Color	Dose and Dosing Regimen
6m-4y	1 previous dose	Maroon	2 doses, 0.2 mL each Dose 1: 3 weeks after receipt of Pfizer-BioNTech COVID-19 Vaccine Dose 2: ≥8 weeks after Dose 1
6m-4y	2 previous doses	Maroon	Single dose, 0.2 mL ≥8 weeks after receipt of second dose of Pfizer-BioNTech COVID-19 Vaccine
6m-4y	3 previous doses	Maroon	Single dose, 0.2 mL ≥2 months after receipt of third dose of Pfizer-BioNTech COVID-19 Vaccine

Table 3. Dosing for Individuals 5 Years of Age and Older Previously Vaccinated With 1 or More Doses of a Monovalent COVID-19 Vaccine

Age	Pfizer-BioNTech COVID-19 Vaccine, Bivalent Vial Cap and Label Border Color	Dose and Dosing Regimen
5-11y	Orange	Single dose, 0.2 mL ≥2 months after monovalent COVID-19 vaccine
12-64y	Gray	Single dose, 0.3 mL ≥2 months after monovalent COVID-19 vaccine
≥65 years	Gray	Single dose, 0.3 mL ≥2 months after monovalent COVID-19 vaccine One additional dose, 0.3 mL, may be administered ≥4 months after first dose of an authorized bivalent COVID-19 vaccine

In addition, the EUA request encompassed a single additional age-appropriate dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent for individuals with certain kinds of immunocompromise 5 years of age and older at least 2 months following the initial dose of a bivalent COVID-19 vaccine. The EUA request also encompassed additional age-appropriate doses of Pfizer BioNTech COVID 19 Vaccine, Bivalent at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances.

5.2 FDA Approach to Harmonizing Strain Composition and Simplifying the Immunization Schedule

FDA expects that simplification of COVID-19 vaccine composition and immunization schedules may contribute to more facile vaccine deployment, fewer vaccine administration errors, and less complex communication, all potentially leading to improved vaccine coverage rates and, ultimately, to enhanced public health. Described below is the approach taken to harmonize the vaccine strain composition [e.g., currently Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)] for all doses and all ages and to simplify the immunization schedule with aged-based dose regimens and adjustments for additional doses in certain populations with increased risk of severe COVID-19 outcomes.

5.2.1 Harmonizing Strain Composition

Multiple variants of SARS-CoV-2 have emerged since the beginning of the pandemic. After the emergence and rapid global spread of the Omicron variant (B.1.1.529, also referred to as the BA.1 sublineage) and more recent predominance of the Omicron BA.4 and BA.5 sublineages (hereafter referred to as BA.4/BA.5 due to the shared structure of their spike glycoproteins), along with clinical trial and real-world data indicating waning protection following primary series and booster doses of available COVID-19 vaccines, and reduced effectiveness of currently available original (monovalent) COVID-19 vaccines against Omicron BA.4/BA.5, 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.

Recent pre-clinical data supports the improved antibody response of bivalent vaccines (compared to monovalent vaccine) against Omicron variants when used in naïve animals,[29] as does recent clinical and real-world effectiveness from studies with bivalent vaccines.

Extrapolation of these data to support authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was considered in the context of the totality of available evidence, which included:

- Extensive knowledge of the safety and efficacy of the mRNA COVID-19 vaccine platform;
- Safety, immunogenicity, efficacy, and observational effectiveness data from the original (monovalent) Pfizer-BioNTech COVID-19 Vaccine (BNT162b2); and
- Immunogenicity data from two other modified (monovalent) vaccine candidates manufactured using the same process as BNT162b2 (containing Beta and Omicron BA.1 mRNA components, respectively), which are not reviewed in detail in the EUA memorandum dated August 31, 2022 , but which, as reported by the Sponsor and as similar to the data for the Bivalent BA.1 (Original and Omicron BA.1) vaccine reviewed in the aforementioned memorandum, showed statistically significant increases in neutralizing antibody GMTs, as compared to the original BNT162b2 vaccine, to the variant components included in the modified vaccines.

Together, these data informed FDA's assessment of the effectiveness and the known and potential benefits and risks of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

Based upon the accumulated experience with primary series, first booster doses, and second booster doses (homologous and heterologous) of the Pfizer-BioNTech COVID-19 Vaccine, FDA determined that it was reasonable to extrapolate the available safety, efficacy, immunogenicity, and real-world evidence supporting a favorable benefit-risk balance for first and second booster doses of monovalent (ancestral) mRNA COVID-19 vaccines to conclude a favorable benefit-risk balance for use of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) as a single dose in individuals 5 years of age and older administered at least 2 months after receipt of a monovalent COVID-19 vaccine.

As mentioned in Section 4.2 above, FDA considers that safety and effectiveness data for a bivalent COVID-19 vaccine accrued in a certain age group could be extrapolated to support emergency use authorization in other age groups. Accumulated experience with mRNA COVID-19 vaccines has demonstrated that while some differences in safety profile and magnitude of neutralizing antibody responses are apparent across various age groups, there is an overall similarity in safety profile and immune response across age groups. FDA therefore considers that it is reasonable to extrapolate safety and effectiveness data for a bivalent COVID-19 vaccine to any age group for which available evidence has supported (or would support) emergency use authorization of a prior COVID-19 vaccine manufactured by the same process as the bivalent vaccine.

5.2.2 Simplification of Immunization Schedule

One approach to immunization schedule simplification relies upon evidence that two or more exposures to the SARS-CoV-2 Spike protein through vaccination and/or infection provide sufficient pre-existing immunity such that administration of a single dose of an authorized bivalent COVID-19 vaccine would likely induce or restore the expected protective immunity for a defined duration in immunocompetent individuals.

Evidence supportive of this approach includes the following:

- Seroprevalence surveys estimate that almost all the US population 5 years of age and older now have antibodies (from vaccination and/or infection) against SARS-CoV-2 (Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC; 2023, March 31. https://covid.cdc.gov/covid-data-tracker).
- Multiple studies that report that at least two exposures to S protein, through vaccination and/or infection, provide some degree of protective immunity. High-level summaries of some of these published studies are provided as follows:
    - Powell et al. 2022[28] reported that previous infection with any SARS-CoV-2 variant alone provided some protection in adolescents against symptomatic reinfection with another variant, while vaccination added to this protection. Vaccination alone provided low-to-moderate protection against symptomatic Omicron infection in adolescents with waning protection after each dose. Authors note that hybrid immunity (from previous infection irrespective of variant plus vaccination) offered the highest protection against Omicron infection.

- Hansen at al. 2022[27] reported that previous Omicron infection in triple vaccinated individuals in Denmark provided high-level protection against BA.5, supporting the notion that vaccination can boost preexisting hybrid immunity and lead to protection against infection by variants.
- Flury et al. 2022[24] reported that hybrid immunity and booster vaccination in health professionals were associated with reduced risk of fewer reported symptoms during SARS-CoV-2 infection during the Delta and Omicron waves in Switzerland. Booster vaccination in uninfected individuals was associated with reduction in risk of symptomatic Omicron infection while this immunity was found to wane over time.
- Chin et al. 2022[26] reported data from effectiveness studies in two high-risk populations in a prison system. Preexisting immunity generated through infection alone or a combination of mRNA vaccination (two or three doses) and previous infection (hybrid immunity) was effective in preventing Omicron infection. Immunization with three doses of mRNA vaccine was associated with the highest protection compared to two doses, even in previously infected individuals.
- Andeweg et al. 2022[23] reported that a combination of previous infection and primary vaccination provided better protection against Omicron infection than either one alone. Boosting offered highest protection even in previously infected individuals. Protection was found to be similar in individuals who were infected first followed by vaccination or who were vaccinated first followed by infection, indicating that order of infection or vaccination did not influence protection offered by hybrid immunity.
- Bates et al. 2022[25] found that individuals who had breakthrough infections after vaccination and those who were vaccinated after a natural infection neutralized SARS-CoV-2 infections to a similar degree. Hybrid immunity was observed irrespective of the order of infection and vaccination and broadly neutralized SARS-CoV-2 variants to a similar degree.

Although all the above studies generally support a simplified immunization schedule based upon two or more exposures to S protein through vaccination and/or infection, interpreting the data from these studies is complicated because of the diversity of study designs, populations studied, and clinical endpoints used. Of note, some other studies highlight evidentiary inconsistencies regarding the need for a periodic (e.g., annual) dose of an approved or authorized COVID-19 vaccine to restore protective immunity in immunocompetent individuals. High-level summaries of two such published studies are provided as follows:

- Carazo et al. 2023[30] reported that health-care workers who acquired hybrid immunity through the receipt of two doses of mRNA vaccine and a previous BA.1 infection were subsequently well protected for a prolonged period against BA.2 reinfection and a third vaccine dose did not offer improvement to the protection conferred by “pre-existing hybrid immunity.” The authors of this study noted that if the protection from pre-existing hybrid immunity also pertains to future variants, there might be limited benefit from additional vaccine doses for people with hybrid immunity, depending on timing and variant.

- Carazo et al. 2022 reported that a third vaccine dose in twice-vaccinated individuals who had had a non-Omicron SARS-CoV-2 infection offered limited protection against Omicron-associated hospitalization.[31]

At this time, the totality of the evidence, including population-based seroprevalence and COVID-19 incidence rates, along with data from real world studies, support administration of a single dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent for most of the US population 5 years of age and older.

5.3 Basis for EUA Revision to Remove Authorization for Use of the Original Pfizer-BioNTech COVID-19 Vaccine in the US and Clarify Export Conditions

FDA may revise or revoke an EUA if the circumstances justifying its issuance (under section 564(b)(1) of the FD&C Act) no longer exist, the criteria for its issuance are no longer met, or other circumstances make a revision or revocation appropriate to protect the public health or safety (see section 564(g)(2) of the FD&C Act).

Currently, circumstances exist that make it appropriate to revise the Pfizer-BioNTech COVID-19 Vaccine EUA to protect the public health. As outlined in Section 2.2, the monovalent Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) is authorized for use as part of a 3-dose primary series for individuals 6 months through 4 years of age, a two-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. FDA's revisions to the EUA for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to authorize its use in individuals 6 months of age and older, as described in the EUA request, is being considered for the express purpose of improving protection against the currently circulating Omicron variant of SARS-CoV-2, resulting in a more favorable anticipated benefit-risk balance for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) as compared to BNT162b2. In addition, the revision is being considered to help simplify COVID-19 vaccine composition and dosing schedules in the United States, which should reduce complexity, decrease vaccine administration errors due to the complexity of the number of different vial presentations, and potentially increase vaccine uptake. Consequently, at this time, revising the Pfizer-BioNTech COVID-19 Vaccine EUA to remove its authorization for use in the United States is appropriate to protect the public health.

That said, the considerations about simplifying the US vaccination schedule are not applicable when the vaccine is used in other countries, and existing supplies of the monovalent Pfizer-BioNTech COVID-19 Vaccine may continue to be available for export. FDA continues to conclude that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks, when used in accordance with the current authorization. In addition, all other requirements in section 564(c) of the FD&C Act continue to be met with respect to the uses for which the Pfizer-BioNTech COVID-19 Vaccine is currently authorized. Therefore, it is appropriate to continue to authorize the Pfizer-BioNTech COVID-19 Vaccine for export.

Accordingly, authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in individuals 6 months of age and older as described in the EUA request, would be accompanied by the revision of the authorization for the monovalent Pfizer COVID-19 Vaccine to remove its authorization for use in the United States but permit its continued export under the EUA, subject to specific conditions. These conditions include, among other things, that the regulatory authorities of the countries in which the vaccine will be

used are informed that the Pfizer-BioNTech COVID-19 Vaccine and associated Fact Sheets are no longer authorized for use in the United States and that FDA is no longer revising those Fact Sheets with updated information. These conditions also include a requirement to provide the regulatory authorities, upon request, with the currently authorized Fact Sheets. These conditions will ensure that the regulatory authorities in destination countries have relevant information with respect to the vaccine.

6 FDA Review of Clinical Effectiveness and Safety Data

6.1 Overview of Clinical Studies

Please refer to prior FDA review memoranda for detailed review of the data supporting authorization the Original Pfizer-BioNTech COVID-19 Vaccine and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). A high-level summary of prior data reviewed and additional evidence relevant to the change to use of one vaccine composition [i.e., Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)] and material supporting the updated vaccination schedule described in the EUA request are provided here.

6.2 Effectiveness of a Single Dose of Pfizer BioNTech COVID-19 Vaccine, Bivalent for 5 Years of Age and Older

6.2.1 Establishing Efficacy of Pfizer BioNTech COVID-19 Vaccine (Monovalent)

6.2.1.1 Efficacy of 2-Dose Primary Series of Pfizer-BioNTech COVID-19 Vaccine in Participants 16 Years of Age and Older

Study C4591001 (Study 2), a Phase 1/2/3, multicenter, multinational, randomized, saline placebo-controlled, observer-blind, dose-finding, vaccine candidate selection (Phase 1) and efficacy (Phase 2/3) study, enrolled approximately 46,000 participants, 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19.

In the Phase 2/3 portion of Study 2, based on data accrued through November 14, 2020, approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of Pfizer-BioNTech COVID-19 Vaccine (30 µg modRNA) or placebo separated by 21 days. The study specified 24-month follow-up to assess safety and efficacy against COVID-19. The population for the analysis of the primary efficacy endpoint included 36,523 participants 16 years of age and older (18,198 in the Pfizer-BioNTech COVID-19 Vaccine group and 18,325 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.

In the planned final primary efficacy analysis, vaccine efficacy after 7 days post Dose 2 was 95% (95% CI 90.3; 97.6) in participants without prior evidence of SARS-CoV-2 infection and 94.6% (95% CI: 89.9%; 97.3%) in the larger group of participants with or without prior infection. Efficacy outcomes were consistently robust (≥93%) across demographic subgroups. Secondary and post-hoc efficacy analyses also suggested efficacy against severe COVID-19, efficacy against COVID-19 in the period between Dose 1 and Dose 2, and against COVID-19 in subjects with evidence of SARS-CoV-2 infection prior to vaccination.

Based on adequate and well-controlled trials in participants 16 years of age and older, the vaccine efficacy data of the Pfizer-BioNTech COVID-19 Vaccine provided compelling direct evidence of clinical benefit and an efficacy foundation for immunobridging.

Please refer to section 4.2 of the EUA Memorandum dated December 11, 2020 for a detailed review of this study.

6.2.1.2 Efficacy of 2-Dose Primary Series of Pfizer-BioNTech COVID-19 Vaccine in Participants 12 Through 15 Years of Age

A descriptive efficacy analysis of Study 2 was performed in approximately 2,200 participants 12 through 15 years of age, evaluating confirmed COVID-19 cases accrued up to a data cutoff date of March 13, 2021. In this supplemental efficacy analyses, VE after 7 days post Dose 2 was 100%, (95% CI 75.3; 100.0) in participants 12-15 years of age without prior evidence of SARS-CoV-2 infection and 100% (95% CI 78.1; 100.0) in the group of participants with or without prior infection. VE between Dose 1 and Dose 2 was 75.0 (95% CI 7.4; 95.5), with divergence of cumulative incidence of COVID-19 cases in BNT162b2 vs. placebo groups beginning at approximately 14 days after Dose 1.

Although based on a small number of cases, the supplementary VE data of the Pfizer-BioNTech COVID-19 Vaccine provided compelling direct evidence of clinical benefit in addition to the vaccine effectiveness inferred by immunobridging data in the study.

Please refer to section 3.2 of the EUA Memorandum dated May 10, 2021 for a detailed review of this study.

6.2.1.3 Efficacy of 2-Dose Primary Series of Pfizer-BioNTech COVID-19 Vaccine in Participants 5 Through 11 Years of Age

Study C4591007 (Study 3) is a Phase 1/2/3 multicenter, randomized, dose-finding, open label (Phase 1) and multinational, saline placebo-controlled, observer-blind, immunogenicity and efficacy (Phase 2/3) study that has enrolled 4,695 participants 5 through 11 years of age, of whom 3,109 participants received Pfizer-BioNTech COVID-19 Vaccine (10 µg modRNA) and 1,538 participants received placebo in Phase 2/3. A descriptive efficacy analysis of confirmed symptomatic COVID-19 cases accrued up to a data cutoff date of October 8, 2021, in Study 3 was performed in 1,968 participants 5 through 11 years of age without evidence of infection prior to 7 days after Dose 2. Vaccine efficacy (VE) after 7 days post-Dose 2 was 90.7% (95% CI: 67.7%; 98.3%).

Although based on a small number of cases and descriptive analysis, the supplemental Pfizer-BioNTech COVID-19 Vaccine VE data provided compelling direct evidence of clinical benefit in addition to the immunobridging data in the study.

Please refer to section 4.2 of the EUA Memorandum dated October 29, 2021 for a detailed review of this study.

The totality of the vaccine efficacy data from clinical trials in participants 5 through 11 years of age, 12 through 15 years of age, and 16 years of age and older provided compelling direct evidence of clinical benefit of the Pfizer BioNTech COVID-19 Vaccine in individuals 5 years of age and older and established an efficacy foundation for immunobridging.

6.2.2 Inferring Effectiveness Through Immunogenicity of Pfizer BioNTech COVID-19 Vaccine

6.2.2.1 Immunogenicity of 2-Dose Primary Series of Pfizer-BioNTech COVID-19 Vaccine in Participants 5 Through 11 Years of Age

SARS-CoV-2 50% neutralizing antibody titers (NT50) 1 month after the primary series were compared between randomly selected subsets of Phase 2/3 participants 5 through 11 years of age from study C4591007 and the efficacy study C4591001 Phase 2/3 participants 16 through 25 years of age, using a microneutralization assay against the reference strain (USA_WA1/2020). The primary immunobridging analyses compared the geometric mean titers (using a geometric mean ratio [GMR]) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 2 in each group.

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the ratio of SARS-CoV-2 50% neutralizing GMT in children 5-11 years of age (10 µg each dose) compared to individuals 16-25 years of age (30 µg each dose) was 1.04 (95% CI: 0.93; 1.18). The lower bound of the 2-sided 95%CI for GMR was >0.67 and the point estimate was ≥1. The prespecified immunobridging criteria were met for both the GMR and the seroresponse difference, supporting the inference of Pfizer-BioNTech COVID-19 Vaccine effectiveness in children 5-11 years of age.

Please refer to section 4.2 of the EUA Memorandum dated October 29, 2021 for a detailed review of this study.

6.2.2.2 Immunogenicity of Pfizer-BioNTech COVID-19 Vaccine Administered as a First Booster Dose Following a Primary Series of Pfizer-BioNTech COVID-19 Vaccine in Participants 18 Through 55 Years of Age

Effectiveness of a booster dose of Pfizer-BioNTech COVID-19 Vaccine (30 µg modRNA) was based on an assessment of 50% neutralizing titers (NT50) against SARS-CoV-2 (USA_WA1/2020). In Study 2, NT50 1 month after the booster dose was compared to 1 month after the primary series in individuals 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster vaccination. Seroresponse for a participant was defined as achieving a ≥4-fold rise in NT50 from baseline (before primary series).

Among Study 2 Phase 2/3 participants in the booster evaluable immunogenicity population, the NT50 GMTs at 1 month after booster dose were 3.29-fold (97.5% CI: 2.77; 3.90) higher than those observed at 1-month post-primary series and met the immunobridging success criteria for GMTs against the reference strain. The percentage of Phase 2/3 participants 18 through 55 years of age with seroresponse was 99.5% at 1-month post-booster and 98.0% at 1-month post-primary series. The difference in seroresponse rates was 1.5% (97.5% CI: -0.7%, 3.7%), which met the immunobridging success criterion for seroresponse rates against the reference strain. Demonstration of noninferiority for both GMR and difference in seroresponse rates allowed for inference of vaccine effectiveness in individuals 18 through 55 years of age.

Please refer to section 5.4 of the EUA Memorandum dated September 22, 2021 for detailed review of this study.

6.2.2.3 Immunogenicity of Pfizer-BioNTech COVID-19 Vaccine Booster Dose Following Pfizer-BioNTech COVID-19 Vaccine Primary Series in Participants 5 Through 11 Years of Age

In Study 3, immunogenicity of a booster dose administered at 7 to 9 months after the second primary series dose was evaluated in 67 study participants 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose. Using a microneutralization assay against the reference strain of SARS-CoV-2 (USA_WA1/2020), the NT50 GMT at 1 month after the booster dose [2720.9 (95% CI: 2280.1; 3247.0)] was increased compared to before the booster dose [271.0 (95% CI: 229.1; 320.6)]. Using a non-validated fluorescence focus reduction neutralization test assay against the Omicron variant of SARS-CoV-2 (B.1.1.529), the NT50 GMT at 1 month after the booster dose among a subset of 17 study participants [614.4 (95% CI: 410.7; 919.2)] was increased compared to the NT50 GMT at 1 month after dose 2 among a subset of 29 study participants [27.6 (95% CI: 22.1; 34.5)].

This observation of higher neutralizing antibody titers against SARS-CoV-2, including against the Omicron variant, in children 5-11 years of age who received a booster dose of BNT162b2 as compared to children 5-11 years old who received the Pfizer-BioNTech COVID-19 Vaccine primary series is similar to the neutralizing antibody responses observed in adults following a booster dose. These neutralizing antibody responses, considered in the context of real-world evidence of increased effectiveness of BNT162b2 against COVID-19 and associated serious outcomes following a booster dose in adults when compared to following a 2-dose primary series in adults and adolescents,[33] supported the extrapolation of similar benefit in children 5-11 years of age.

Please refer to section 7.2 of the EUA Memorandum dated May 21, 2022 for detailed review of this study.

6.2.2.4 Immunogenicity of the Pfizer-BioNTech COVID-19 Vaccine Booster Dose Following Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine

Effectiveness of a Pfizer-BioNTech COVID-19 Vaccine booster dose (30 µg modRNA) in individuals who completed primary vaccination with another authorized or approved COVID-19 Vaccine (heterologous booster dose) is inferred from immunogenicity data supporting effectiveness of a Pfizer-BioNTech COVID-19 Vaccine booster dose administered following completion of Pfizer BioNTech COVID-19 Vaccine primary series and from immunogenicity data from an independent NIH study Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine.

In this study, participants who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of 1 of 3 vaccines: Moderna COVID 19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine (30 µg modRNA). Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the booster dose and on Day 15 after the booster dose. A booster response to the Pfizer BioNTech COVID-19 Vaccine was demonstrated regardless of the vaccine used for primary vaccination supporting

the inference of vaccine effectiveness of a heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine.

Please refer to the EUA Memorandum dated October 20, 2021 for detailed review of this study.

6.2.2.5 Immunogenicity of the Bivalent Vaccine (Original and Omicron BA.1) Administered as a Second Booster Dose

Vaccine effectiveness of the Bivalent Vaccine (Original and Omicron BA.1) was inferred based on the evaluation of SARS-CoV-2 50% neutralizing antibody titers (NT50) at 1 month after a second booster dose compared to a second booster dose of BNT162b2. The analyses were conducted on a subset of participants from Study 4 and included evaluations of SARS-CoV-2 GMTs and the seroresponse rates elicited by the Bivalent BA.1 vaccine as compared to BNT162b2 against the B.1.1.529 (Omicron sublineage BA.1) and USA_WA1/2020 reference strains. Co-primary endpoints and secondary endpoints were evaluated in participants in the evaluable immunogenicity population without evidence of prior SARS CoV-2 infection through 1-month post-study intervention.

A total of 610 participants greater than 55 years of age who had previously received a 2-dose primary series and 1 booster dose with Pfizer BioNTech COVID-19 Vaccine received one of the following as a second booster dose: Pfizer BioNTech COVID-19 Vaccine or bivalent vaccine (Original and Omicron BA.1). GMRs and seroresponse rates were evaluated at 1 month after vaccination with the bivalent vaccine (Original and Omicron BA.1) (Dose 4). The bivalent vaccine (Original and Omicron BA.1) booster dose was administered 4.7 to 11.5 months (median 6.3 months) after the first booster dose. The Pfizer-BioNTech COVID-19 Vaccine booster dose was administered 5.3 to 13.1 months (median 6.3 months) after the first booster dose.

The ratio (Bivalent BA.1 / BNT162b2) of SARS-CoV-2 50% anti-Omicron BA.1 neutralizing GMTs 1-month post-booster was 1.56 (95% CI: 1.17; 2.08). The primary objective of superiority was met as the lower bound of the 95% CI was 1.17, and the statistical success criterion for simple superiority was a lower bound of the 95% CI >1.0; the super-superiority success criterion was not met as the lower bound of the 95% CI was <1.5. The secondary objective's success criteria of non-inferiority for anti-reference strain GMTs were also met as the lower bound of the 95% CI around the GMT ratio was 0.82 and the statistical success criteria were a lower bound of the 95% CI >0.67 and a point estimate of ≥0.8.

The difference in the seroresponse rates (Bivalent BA.1 minus BNT162b2) against Omicron BA.1 was 14.6%, with a lower bound of the 95% CI of 4.0%. The primary objective of non-inferiority was met as the lower limit of the 2-sided 95% CI for the difference in seroresponse rates was >−5%.

Vaccine effectiveness of a second dose in older adults of a bivalent vaccine with an Omicron variant component (Original and Omicron BA.1) was inferred based on the totality of relative immunogenicity data when compared to a second booster dose of BNT162b2.

Please refer to section 6.14 of the EUA memorandum dated August 31, 2022 for a detailed review of this study.

Based on the totality of the immunogenicity data from clinical trials of the Pfizer BioNTech COVID-19 Vaccine and Bivalent Vaccine (Original and Omicron BA.1), it is

reasonable to infer the effectiveness of Pfizer BioNTech COVID-19 Vaccine, Bivalent in individuals 5 years of age and older.

6.2.3 Inferring the Effectiveness of a Single Dose of Pfizer-BioNTech COVID 19 Vaccine, Bivalent in Individuals with Evidence of Prior SARS-CoV-2 Infection

Recent evidence suggests that a combination of SARS-CoV-2 infection and vaccination, termed hybrid immunity, confers significant protection against COVID-19 and that immunity acquired by infection should be considered in determining the immunization schedule (Pilz et al 2022). With "sufficient preexisting immunity," through prior infection, vaccination, or combination thereof, administration of a single dose of an authorized bivalent COVID-19 vaccine would likely induce or restore the expected protective immunity for a desired duration. Given recent seroprevalence surveys[32] and the clinical data generated with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent Vaccine (Original and Omicron BA.1) and Pfizer BioNTech COVID-19 Vaccine, Bivalent that is available for different age groups, it is appropriate to simplify the immunization schedule for the Pfizer BioNTech COVID-19 Vaccine, Bivalent to a single dose for most individuals 5 years of age and older.

The evidence to support inference of the effectiveness of a single dose of Pfizer-BioNTech COVID 19 Vaccine, Bivalent in individuals previously vaccinated and/or with prior SARS-CoV-2 infection includes real-world data or observational studies. A real-world study calculated vaccine effectiveness against symptomatic COVID-19 for participants who received one dose of the Pfizer-BioNTech COVID-19 Vaccine after previous SARS-CoV-2 infection.[28]

A large observational test-negative study conducted by Powell et al. in England from August 9, 2021 to March 31, 2022 included symptomatic individuals 12 to 17 years of age with SARS-CoV-2 polymerase-chain-reaction (PCR) testing results.[28] Among 1,161,704 SARS-CoV-2 PCR tests linked to COVID-19 vaccination status, there were 390,467 SARS-CoV-2 PCR confirmed positive tests during Delta variant predominance and 212,433 SARS-CoV-2 positive tests during Omicron variants BA.1 and BA.2 predominance. At 2 to 14 weeks following 1 dose of Pfizer-BioNTech COVID-19 Vaccine, the estimated vaccine effectiveness was 18.8% (95% CI: 17.2%; 20.3%), 81.5% (95% CI: 80.0%; 82.9%), 78.8% (95% CI: 77.9; 79.5%), and 79.6% (95% CI: 44.9%; 92.4%) for individuals with no evidence of prior infection, and evidence of prior Alpha, Delta, and Omicron infection, respectively.

Vaccine effectiveness of a single dose of Pfizer COVID-19 Vaccine, Bivalent in individuals 5 to 11 years of age who have been previously infected and/or vaccinated have been extrapolated from adolescent and adult data. Little real-world evidence for the effectiveness of a bivalent booster dose in this age group has been reported, largely because the bivalent booster was authorized later than for older age groups and the vaccine uptake has been lower. Given the real world and immunogenicity studies described above and the well understood safety profile of the vaccines in this age group, it is reasonable to expect that a single dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals 5 to 11 years of age will improve protection against severe COVID-19.

Based on the totality of evidence, including from seroprevalence surveys and real-world studies (see also Section 5.2.2), it is reasonable to expect that in most of the US population 5 years of age and older, a single dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent may induce or restore protective immunity against severe COVID-19 caused by currently circulating sublineages of Omicron.

6.3 Effectiveness of Pfizer BioNTech COVID-19 Vaccine, Bivalent in Individuals 6 Months Through 4 Years of Age

6.3.1 Establishing Efficacy of Pfizer BioNTech COVID-19 Vaccine (Monovalent)

6.3.1.1 Efficacy of 3-Dose Primary Series of Pfizer-BioNTech COVID-19 Vaccine in Participants 6 Months Through 4 Years of Age

In the Phase 2/3 portion of Study C4591007 at the time of the data cutoff on June 17, 2022, 3793 BNT162b2 recipients and 1891 placebo recipients 6 months through 4 years of age (6m-4y) [1444 BNT162b2 recipients and 718 placebo recipients 6 months through 23 months of age (6-23m) and 2349 BNT162b2 recipients and 1173 placebo recipients 2 years through 4 years of age (2-4y)] had received at least one dose of the study product. A descriptive vaccine efficacy (VE) analysis was performed across the combined population of participants 6mo-4y based on PCR-confirmed COVID-19 cases among 873 participants in the Pfizer BioNTech COVID-19 Vaccine group and 381 participants in the placebo group (2:1 randomization) who were included in the VE analysis population (i.e., the Dose 3 evaluable efficacy population of 554 BNT162b2 and 224 placebo recipients 2-4y and 319 BNT162b2 and 157 placebo recipients 6-23 m without evidence of infection prior to 7 days after Dose 3). The median dose interval between Dose 2 and Dose 3 was 13.4 weeks (range 8 to 33 weeks) among participants 6-23 m and 10 weeks (range 8 to 34 weeks) among participants 2-4 y who received Pfizer-BioNTech COVID-19 Vaccine. The median length of blinded efficacy follow-up post-Dose 3 was 1.9 months for 6-23m participants and 2.4 months for 2-4y participants. The Omicron variant of SARS CoV-2 (BA.2) was the predominant variant in circulation.

As of the data cutoff, VE was 73.2% (95% CI: 43.8%, 87.6%) against protocol-defined COVID-19 in participants 6m-4y without evidence of infection up to 7 days post-Dose 3. Similar VEs were observed within each age group [in 6-23m, 75,8% (95% CI: 9.7%; 94.7%); and in 2-4y, 71.8% (95% CI: 28.6%; 89.4%)] and among participants with or without evidence of infection [in 6m-4y, 72.5% (95% CI:44.3%; 86.9%)]. Although based on a small number of cases and descriptive analysis, the supplemental VE data provided compelling direct evidence of clinical benefit in addition to the immunobridging data in the study.

Please refer to EUA memorandum dated September 8, 2022 for a detailed review.

The totality of the vaccine efficacy data from clinical trials in participants 6 months and older provided compelling direct evidence of clinical benefit of the Pfizer BioNTech COVID-19 Vaccine in individuals 6 months through 4 years of age and establishes an efficacy foundation for immunobridging.

6.3.2 Inferring Effectiveness Through Immunogenicity of Pfizer-BioNTech COVID-19 Vaccine

6.3.2.1 Immunogenicity of 3-Dose Primary Series of Pfizer-BioNTech COVID-19 Vaccine in Participants 6 Months Through 4 Years of Age

Effectiveness in individuals 6 months through 4 years of age is based on a comparison of immune responses in this age group to individuals 16 through 25 years of age. The immunogenicity analyses in Study 3 were performed with the immunobridging subset of 143 participants 2 through 4 years of age without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 based on a data cutoff date of April 29, 2022. The median age was 3.0 years and 44.1% of participants were male. The primary immunobridging analyses compared the SARS-CoV-2 NT50 geometric mean titers (using a GMR) and the seroresponse

(defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population to a randomly selected subset from Study 2 Phase 2/3 participants 16 through 25 years of age at 1 month after the 2-dose primary series, using a microneutralization assay against the reference strain (USA_WA1/2020). In addition, a non-validated fluorescence focus reduction neutralization test assay was used to assess immune responses against the Omicron variant of SARS-CoV-2 (BA.1).

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

Seroresponse rates were similar among participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 2 (comparator group 16-25 years of age) or Dose 3 (2-4 years of age). The difference between the two age groups was 1.2% (95% CI: −1.5; 4.2). The LL of the 95% CI for the difference in seroresponse rate was −1.5%, which was greater than the prespecified margin of −10%, and thus the immunobridging criterion based on seroresponse rate was met.

The NT50 GMT against the Omicron variant of SARS-CoV-2 (BA.1) at 1 month after Dose 3 among a subset of 34 study participants without evidence of prior SARS-CoV-2 infection [82.5 (95% CI: 55.4; 122.9)] was increased compared to the NT50 GMT before Dose 3 [14.0 (95% CI: 10.6; 18.5)].

Vaccine effectiveness of Pfizer-BioNTech COVID-19 Vaccine in individuals 6 months through 4 years of age was inferred by immunobridging based on a comparison with young adults 16 to 25 years of age, the most clinically relevant subgroup of the study population in whom VE has been demonstrated.

Please refer to section 4.2.6 of the EUA memorandum dated June 16, 2022 for a detailed review of this study.

6.3.2.2 Immunogenicity in Participants 6 Through 23 Months of Age After a 3-Dose Primary Series

Effectiveness in individuals 6 months through 23 months was assessed through immunogenicity analyses in the immunobridging subset of 82 Study 3 participants 6 through 23 months of age without evidence of infection up to 1 month after Dose 3 based on a data cutoff date of April 29, 2022. The median age was 16.0 months and 62.2% of participants were male. The primary immunobridging analyses compared the SARS-CoV-2 NT50 geometric mean titers (using a GMR) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 6 through 23 months of age to a randomly selected subset from Study 2 Phase 2/3 participants 16 through 25 years of age at 1 month after the 2 dose primary series, using a microneutralization assay against the reference strain (USA_WA1/2020). In addition, a non-validated fluorescence focus reduction neutralization test assay was used to assess immune responses against the Omicron variant of SARS-CoV-2 (BA.1).

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

Seroresponse rates were similar among participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 2 (comparator group 16-25 years of age) or Dose 3 (participants 6-23 months of age). The difference in seroresponse rates between the two age groups was 1.2% (95% CI: -3.4; 4.2). The LL of the 95% CI for the difference in seroresponse rate was −3.4%, which was greater than the prespecified margin of −10%, and thus the immunobridging criterion based on seroresponse rate was met.

The NT50 GMT against the Omicron variant of SARS-CoV-2 (BA.1) at 1 month after Dose 3 among a subset of 32 study participants without evidence of prior SARS-CoV-2 infection [127.5 (95% CI: 90.2; 180.1)] was increased compared to the NT50 GMT before Dose 3 [16.3 (95% CI: 12.8; 20.8)].

Vaccine effectiveness of Pfizer-BioNTech COVID-19 Vaccine in individuals 6 through 23 months of age was inferred by immunobridging based on a comparison with young adults 16 to 25 years of age, the most clinically relevant subgroup of the study population in whom VE has been demonstrated.

Please refer to section 4.2.6 of the EUA memorandum dated June 16, 2022 for a detailed review of this study.

6.3.2.3 Immunogenicity of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) Administered as a Booster (Fourth Dose) in Individuals 6 Months Through 4 Years of Age

In Study 6, a subset of 60 participants 6 months through 4 years of age received a booster dose (fourth dose) of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (3 µg modRNA) after receiving 3 prior doses of Pfizer-BioNTech COVID-19 Vaccine (3 µg modRNA). A subset of 60 participants 6 months-4 years of age from Study 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 6 participants served as a reference group. Regardless of age, prior SARS-CoV-2 infection, or sampling time point, the neutralizing antibody 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 reference subset of participants 6 months through 4 years of age in Study 3 who received 3 doses of Pfizer-BioNTech COVID-19 Vaccine (3 µg modRNA). 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). No formal statistical comparisons of the immune response between subsets from the two studies were conducted. Based on the totality of evidence, including the immunogenicity data above, it is reasonable to expect vaccine effectiveness of Pfizer-BioNTech COVID-19 Vaccine, Bivalent and a fourth dose in individuals 6 months through 4 years of age.

Please refer to section 6 of the EUA memorandum dated March 14, 2023 for a detailed review of this study.

Based on the totality of the immunogenicity data from clinical trials of the Pfizer-BioNTech COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine, Bivalent, it is reasonable to infer the effectiveness of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals 6 months through 4 years of age.

6.3.3 Extrapolation of Effectiveness of Pfizer BioNTech COVID-19 Vaccine, Bivalent Through Immunogenicity

6.3.3.1 Immunogenicity of Pfizer-BioNTech COVID-19 Vaccine Booster Dose Following Pfizer-BioNTech COVID-19 Vaccine Primary Series in Participants 5 Through 11 Years of Age

As noted in Section 6.2.2.1 above, neutralizing antibody responses in children 5-11 years of age, considered in the context of real-world evidence of increased effectiveness of BNT162b2 against COVID-19 and associated serious outcomes following a booster dose when compared to following a 2-dose primary series in adults and adolescents,[33] supported the extrapolation of similar benefit of a third vaccine dose to children 5-11 years of age. Similarly, the totality of evidence supports the extrapolation of a similar benefit of completing a 3-dose regimen in individuals 6 months to 4 years of age.

Please refer to Section 6.2.2.1 above and section 7.2 of the EUA Memorandum dated May 17, 2022, for detailed review for a detailed review of this study.

6.3.3.2 Immunogenicity of the Bivalent Vaccine (Original and Omicron BA.1) Administered as a Second Booster Dose

As noted in Section 6.2.2.5 above, vaccine effectiveness of a second booster dose of a bivalent vaccine with an Omicron variant component (Original and Omicron BA.1) was inferred based on the totality of relative immunogenicity data when compared to a second booster dose of BNT162b2. The vaccine effectiveness of a fourth dose and of a bivalent vaccine with an Omicron variant component in individuals 6 months through 4 years of age was extrapolated from effectiveness in adults (55 years and older).

Please refer to the Section 6.2.2.5 above and section 6.1.4.1 of the EUA memorandum dated August 31, 2022 for detailed review.

Based on the totality of the evidence from clinical trials, including efficacy data of the Pfizer BioNTech COVID-19 Vaccine and immunogenicity data of the Pfizer BioNTech COVID-19 Vaccine, Bivalent Vaccine (Original and Omicron BA.1), and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), it is reasonable to extrapolate from immunogenicity in individuals 5 years of age and older and infer from efficacy and immunogenicity in individuals 6 months through 4 years of age the effectiveness of Pfizer BioNTech COVID-19 Vaccine, Bivalent in individuals 6 months through 4 years of age.

6.4 Effectiveness of Additional Doses Pfizer-BioNTech COVID-19 Vaccine, Bivalent in Individuals 65 Years of Age and Older

Waning of vaccine-induced protection against symptomatic disease after an mRNA vaccine booster dose, more modest waning of protection against hospitalization, and additional

protection, at least in the short-term, against COVID-19 and COVID-19-associated hospitalization conferred by an additional dose of an mRNA vaccine led to authorization of a second booster dose of the Pfizer-BioNTech COVID-19 Vaccine administered following a first booster dose of any FDA authorized or approved COVID-19 vaccine in certain individuals.

Please see EUA memorandum dated March 28, 2022 for detailed review.

Based on the totality of the evidence, including evidence described in Sections 6.2.2.4 and 6.2.2.5 above, it is reasonable to extrapolate from immunogenicity and real-world studies the effectiveness of an additional dose of Pfizer BioNTech COVID-19 Vaccine, Bivalent in individuals 65 years of age and older at least 4 four months after their first dose of a bivalent COVID-19 vaccine.

6.5 Effectiveness of Additional Doses Pfizer BioNTech COVID-19 Vaccine, Bivalent in Immunocompromised Individuals

Additional doses of Pfizer BioNTech COVID-19 Vaccine have previously been authorized in individuals 5 years and older with certain kinds of immunocompromise (i.e., those who have undergone solid organ transplant or who are diagnosed with conditions considered to have an equivalent level of immunocompromise).

Please refer to the EUA Memorandum dated August 12, 2021.

6.5.1 Immunogenicity of a Third Primary Series Dose in Individuals with Certain Kinds of Immunocompromise

Immunogenicity of third primary series dose Pfizer-BioNTech COVID-19 vaccine was evaluated in a single-arm study of 101 individuals who had undergone various solid organ transplant procedures (heart, kidney, liver, lung, pancreas) 97±8 months previously (Kamar N, Abravanel F, Marion O, et al. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. N Engl J Med). A third dose of the Pfizer-BioNTech COVID-19 vaccine was administered to 99 of these individuals approximately 2 months after they had received a second dose. Of 59 transplant recipients who had been seronegative before the third dose, 26 (44%) were seropositive at 4 weeks after the third dose. All 40 patients who had been seropositive before the third dose were still seropositive 4 weeks later. The prevalence of anti-SARS-CoV-2 antibodies was 68% (67 of 99 patients) 4 weeks after the third dose.

Please refer to the EUA Review Memorandum dated August 12, 2021 for detailed review.

Based on the totality of evidence, vaccine effectiveness of additional doses of a Pfizer-BioNTech COVID-19 Vaccine, Bivalent in certain immunocompromised individuals is extrapolated from Pfizer-BioNTech COVID-19 Vaccine effectiveness inferred from immunogenicity evidence in those immunocompromised individuals. Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent in severely immunocompromised individuals 6 months of age to 17 years of age are extrapolated from adult data.

6.6 Safety Data

Please refer to prior FDA review memoranda for detailed review of the safety data from clinical studies used to authorize the Pfizer-BioNTech COVID-19 Vaccine and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).
The safety of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals 6 months of age and older is based on:

- safety data from clinical studies which evaluated primary and booster vaccination with Pfizer-BioNTech COVID-19 Vaccine. Please refer to Section 6 of EUA Memorandum dated May 17, 2022, for detailed review.
- safety data from clinical studies which evaluated booster vaccination with Pfizer-BioNTech COVID-19 Vaccine, Bivalent. Please refer to Section 6 of the EUA memorandum dated March 14, 2023 for detailed review.
- safety data from a clinical study which evaluated a booster dose of bivalent vaccine (Original and Omicron BA.1). Please refer to Section 6 of EUA memorandum dated August 31, 2022, for detailed review.

The safety data accrued with the Pfizer-BioNTech COVID-19 Vaccine and Pfizer-BioNTech's bivalent COVID-19 vaccine (Original and Omicron BA.1) are relevant to Pfizer-BioNTech COVID-19 Vaccine, Bivalent because these vaccines are manufactured using the same process.

A high-level summary of post marketing safety data is provided below.

Postmarketing Safety Data
Review of Postmarketing safety data indicate a similar safety profile of the Original Pfizer-BioNTech COVID-19 Vaccine and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). As of April 5, 2023, more than 366 million doses of the original Pfizer-BioNTech COVID-19 Vaccine have been administered in the US, and 35,690,430 booster doses of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Of the total doses of either the Original or Bivalent formulation given in the US, 2,792,884 have been administered to individuals 6 months through 5 years of age and 63,145,813 have been administered to individuals 6 through 17 years of age, and 332,754,043 doses administered to adults 18 years of age and older (data lock point Apr 5, 2023). In recipients of any age and all doses, the most frequently reported preferred terms (PTs) in the Vaccine Adverse Event Reporting System (VAERS) were headache, pyrexia, fatigue, chills, pain, pain in extremity, nausea, dizziness, myalgia, and injection site pain. For important risks identified in the pharmacovigilance plan for Pfizer-BioNTech COVID-19 Vaccine, anaphylaxis and myocarditis/pericarditis are identified risks that are included in product labeling. The Sponsor is conducting additional safety-related post-authorization/post-marketing studies for the Original Pfizer-BioNTech COVID-19 Vaccine, including post-marketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. The Sponsor is also conducting planned post-authorization studies to evaluate the association between the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and a pre-specified list of adverse events of special interest (AESIs) in all authorized ages in the general US population (refer to Section 7 for details).

Taken together, these data informed FDA's assessment of the known and potential benefits and risks of the Pfizer BioNTech COVID-19 Vaccine, and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Based upon the accumulated experience with primary series, first booster doses, and second booster doses (homologous and heterologous) of the Pfizer-BioNTech COVID-19 Vaccine and booster doses of Pfizer BioNTech COVID-19 Vaccine, Bivalent, FDA determined that it was reasonable to extrapolate the available safety data, supporting a favorable benefit-risk balance for use of one vaccine composition (i.e., Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)) and an updated vaccination schedule as: a three dose series in individuals 6 months through 4 years of age; as a single dose in individuals 5 years of age and older administered at least 2 months after receipt

of a monovalent COVID-19 vaccine; an additional dose at least 4 months following administration of a first bivalent COVID-19 vaccine in individuals >65 years of age; and an additional vaccine dose at least 2 months following administration of an initial bivalent COVID-19 vaccine and subsequent doses at the discretion of the healthcare provider in individuals 5 years of age and older with certain kinds of immunocompromise (solid organ transplant recipients and those determined to have a similar level of immunocompromise).

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

7.1 Chemistry Manufacturing and Control (CMC) Information:

The three presentations of Pfizer BioNTech COVID-19 Vaccine, Bivalent are noted below. The Sponsor did not submit any new CMC/facilities information with this EUA as there are no changes to CMC or facilities.

Multiple Dose Vials with Maroon Caps and Labels with Maroon Borders
The Pfizer-BioNTech COVID-19 Vaccine, Bivalent in multiple dose vials with maroon caps and labels with maroon borders is supplied as a frozen suspension; each vial must be diluted with 2.2 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine.

For CMC review, please refer to Section 7 of the EUA Memorandum dated December 8, 2022

Multiple Dose Vials with Orange Caps and Labels with Orange Borders
The Pfizer-BioNTech COVID-19 Vaccine, Bivalent in multiple dose vials with orange caps and labels with orange borders is supplied as a frozen suspension; each vial must be diluted with 1.3 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine.

For CMC review, please refer to Section 7 of the EUA memorandum dated October 11, 2022

Multiple Dose Vials and Single Dose Vials with Gray Caps and Labels with Gray Borders
The Pfizer-BioNTech COVID-19 Vaccine, Bivalent in multiple dose vials and single dose vials with gray caps and labels with gray borders is supplied as a sterile, frozen suspension. This presentation does not need to be diluted.

For CMC review, please refer to Section 7.3 of the of EUA memorandum dated August 31, 2022,

7.2 Clinical Assay Information

Assays used in clinical studies described in Section 6 have been reviewed in previous EUA memoranda. Please refer to Section 6 for the reference to the review memoranda (see also prior FDA review memoranda) for detailed review.

7.3 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 has a pharmacovigilance plan to monitor safety concerns that could be associated with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). 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 Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/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 the Pfizer-BioNTech COVID-19 Vaccine and/or the Pfizer-BioNTech COVID-19 Vaccine, Bivalent 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 below are being conducted for Pfizer-BioNTech Covid-19 Vaccine, Original monovalent in large scale databases with an active comparator and will include a sub-analysis for Pfizer-BioNTech COVID-19 Vaccine, Bivalent. This condition of authorization under the EUA, to conduct post-authorization observational studies, will encompass the evaluation of Pfizer-BioNTech COVID-19 Vaccine and/or Pfizer-BioNTech COVID-19 Vaccine, Bivalent in all age groups in safety studies:
- **C4591008** - HERO Together: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 Vaccine in US healthcare workers, their families, and their communities.

  Objective: To characterize the real-world incidence of safety events of interest, including events indicative of severe or atypical COVID-19 disease, among individuals vaccinated with the BNT162b2 since EUA.
- **C4591009** - A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 vaccine in the United States.

  Objective: To assess the occurrence of safety events of interest, including myocarditis, among individuals in the general US population of all ages, and in subcohorts of interest within selected data sources participating in the US Sentinel System.
- **C4591011** - Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the US Department of Defense population following Emergency Use Authorization.

  Objective: To assess whether individuals in the US DoD Military Health System (MHS) experience increased risk of safety events of interest, following receipt of

the COVID-19 mRNA Vaccine.

- **C4591012** - Post-emergency use authorization active safety surveillance study among individuals in the Veteran's Affairs Health System receiving Pfizer-BioNTech COVID-19 Vaccine.

  Objective: To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine, including the Bivalent Omicron-modified vaccine.

- **C4591021** - Post-authorization approval active surveillance study among individuals in Europe receiving the Pfizer-BioNTech Coronavirus Disease (COVID-19) vaccine.

  Objective: To assess the potential increased risk of adverse events of special interest (AESI), after being vaccinated with COVID-19 mRNA vaccine, in all authorized age groups, including individuals less than 12 years of age.

- **C4591036** - Pediatric Heart Network Study: Low interventional cohort study of myocarditis/pericarditis associated with Comirnaty in persons less than 21 years of age.

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

- **C4591038** - (former, C4591021 substudy): Post-authorization active surveillance study of myocarditis and pericarditis among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine.

  Objective: To describe the clinical course (treatment, survival, hospitalization, long-term cardiac outcome) of myocarditis and pericarditis among individuals diagnosed with myocarditis and/or pericarditis after receiving at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine and among individuals diagnosed with myocarditis and/or pericarditis who had no prior COVID-19 vaccination, using a cohort study design.

- **C4591049** - HERO-Together Boost: A post-Emergency Use Authorization (EUA) observational cohort study to evaluate the safety of the Pfizer-BioNTech Bivalent Coronavirus Disease 2019 (COVID-19) vaccine.

  Objective: To characterize the real-world incidence of safety events of interest, including events indicative of severe or atypical COVID-19 disease, among individuals vaccinated with the Bivalent Omicron-modified vaccine, since EUA.

- **C4591051** - A non-interventional post-approval safety study of Pfizer- BioNTech COVID-19 vaccine in the United States.

  Objective: To assess the occurrence of safety events of interest following receipt of the COVID-19 bivalent Omicron-modified vaccine in the general US population of all ages.

- **C4591052** - Post-Authorization Safety Study of Comirnaty Original/Omicron BA.1 and Comirnaty Original/Omicron BA.4-5 in Europe.

  Objective: To assess the potential increased risk of adverse events of special interest (AESI), including myocarditis/pericarditis, after being vaccinated with COVID-19 bivalent Omicron-modified vaccine, in all authorized age groups.

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.

7.4 EUA Prescribing Information and Fact Sheets

The Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), and 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. Note that in the consolidated Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), the Dosage and Administration section no longer refers to “primary series” and “booster” doses.

8 Benefit/Risk in the Context of the Proposed EUA For Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) Booster in Individuals 6 Months of Age and Older

8.1 Discussion of Benefits, Risks, and Uncertainties

COVID-19 is caused by SARS-CoV-2 and the virus has been responsible for over 104 million cases of COVID-19 and over 1.1 million deaths in the US. Since the start of the pandemic, there has been a succession of COVID-19 variants including Beta, Delta, Omicron BA.1 and most recently Omicron BA.5, BQ.1.1, XBB.1.5, and Omicron sublineages. Current treatment options for COVID-19 include antiviral medications, immune modulators, and convalescent plasma. These interventions are generally most effective in disease of mild to moderate severity. Although treatments exist for those infected with SARS-CoV-2 they are usually not effective in severe disease. Additionally, 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. Currently authorized COVID-19 vaccines for disease prevention in individuals 6 months of age and older include the mRNA-based vaccines from Moderna and Pfizer-BioNTech, an adjuvanted, protein subunit vaccine from Novavax (in individuals 12 years of age and older only), and the non-replicating viral vector vaccine from Janssen (in certain individual 18 years of age and older only).

The monovalent vaccines were based on the original (ancestral) strain of SARS-CoV-2, and some vaccines initially had effectiveness of up to 90 to 95% against symptomatic disease. 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,[34,35] Israel,[21] Qatar,[18] Portugal,[36] and England.[13]

The immunogenicity and safety of mRNA booster vaccines developed against the Beta, Delta, and Omicron BA.1 variants have previously been evaluated by both Moderna and Pfizer-BioNTech. However, these booster vaccines were not deployed in the United States due to the rapid evolution of the SARS-CoV-2 variants. In addition to those clinical data, nonclinical studies indicated that a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose induces antibody responses to BA.4 and BA.5 variants that was several-fold higher than the response induced by the original (monovalent) vaccine. Indeed, based on previous experience and available evidence, vaccination with the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) booster doses were expected to induce a stronger immune response and provide better protection against hospitalization to the more recent Omicron subvariants, and evidence from several studies now indicate this to be the case.[22,23,24,25,26,27,28]

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 FDA Biologics Effectiveness and Safety (BEST) System, within a week after second dose of mRNA-based COVID-19 vaccine primary series, the crude observed rate (without adjustment for delay of reporting and other factors) of myocarditis or pericarditis events was 2.1 per 100,000 doses for individuals aged 18–64 years (unpublished data), and 12.5 per 100,000 doses for males aged 18–25 years.[37] Within a week after a second dose of vaccine, the adjusted observed rate of myocarditis or pericarditis for individuals aged 18–64 years who received mRNA-based COVID-19 vaccines was 1.8 per 100,000 doses (unpublished data), and 13.0 per 100,000 doses for males aged 18–25 years.[35] The meta-analysis of BEST data for the Pfizer COVID-19 Vaccine reports excess cases per one million second doses for 12–15-year-old males as 132.2 (95%CI: 92.0-189.6), for 16-17-year-old males as 159.9 (95%CI: 59.9-414.3), and for 18-25- year-old males as 95.6 (95%CI: 61.0-147.4). Based on the data from BEST, within a week after the second dose of the 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 aged 5-11 years, and 0.95 cases per 100,000 vaccine doses among male individuals aged 5-11 years (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 new safety concerns 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 totality of the available evidence indicates that Pfizer-BioNTech Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine doses will likely increase the immune response and clinical protection against SARS-CoV-2 variants and may particularly help target the currently predominant Omicron subvariants related to BA.4/BA.5.

Clinical evaluation of bivalent mRNA COVID-19 vaccine formulations has not suggested new safety concerns additional to the extensively characterized safety profile of originally authorized and approved mRNA COVID-19 vaccines, and post-deployment monitoring for adverse events using both passive and active surveillance systems will be used to assess whether any new safety concerns emerge. Table 4 provides a summary of the benefit-risk considerations in a standard FDA format.

Table 4. 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 nearly 104 million cases and 1.1 million deaths in the US. • There has been a succession of variants (Delta, Omicron BA.1, BA.5. and more recently XBB.1.5, among others) 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 recent 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Options for Treatment or Prevention of COVID-19 Disease	• Antiviral medications, immune modulators, and convalescent plasma have been approved or authorized for the management of individuals with COVID-19; they are generally most effective in disease of mild to moderate severity. • There are two authorized mRNA COVID-19 vaccines for use as a primary series in individuals 6 months of age and older and bivalent forms of those vaccines are available for use as single booster doses or third primary series dose in individuals 6 months of age and older. • An adjuvanted, protein subunit COVID-19 vaccine is authorized for use as a primary series in individuals 12 years of age and older and as a single booster dose for certain individuals 18 years of age and older. • A non-replicating viral vector COVID-19 vaccine authorized for primary vaccination and as a single booster dose in certain individuals 18 years of age and older.	• Although treatments exist for those infected with SARS-CoV-2, they are usually not effective in severe disease; additionally, treatments may not prevent complications from COVID-19, including post-acute sequelae of COVID-19 (long COVID) • Vaccines play an important role in pandemic control and provide important protection.
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 US because of SARS-CoV-2 variant evolution. • Studies indicate that a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose provides better protection compared to the monovalent (Original) against symptomatic disease, hospitalization, and death caused by more recently circulating Omicron subvariants.	• The totality of the available evidence indicates that bivalent (Original and BA.4/BA.5) vaccines provide benefit and may particularly help target the currently circulating Omicron variants. • Administration of bivalent (Original and BA.4/BA.5) COVID-19 vaccine doses is appropriate for all authorized mRNA COVID-19 vaccine doses to be given in the United States, given the protection compared to the monovalent (Original) that it provides against both original and more recent variant SARS-CoV-2 strains. • Given the prior exposure of most individuals to the virus, the vaccine, or both (hybrid immunity), a single vaccination is appropriate for otherwise healthy individual 5 years of age and older and for those 6 months through 4 years of age who have completed an initial COVID-19 vaccination series. • Such simplification of the vaccination regimen may help facilitate further vaccination efforts and reduce vaccine administration errors in support of public health.

8.2 Conclusions Regarding Benefit-Risk

For individuals 6 months of age and older, the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine administered for all doses appropriate to age and any immunocompromise, outweigh the known and potential risks of the vaccine 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 demonstrated that the benefits of available COVID-19 vaccines outweigh their risks. During the recent past when COVID-19 cases have been caused in large part by the BA.5 sublineage and other Omicron subvariants such as XBB.1.5, administration of the bivalent (Original and BA.4/BA.5) COVID-19 vaccine has been demonstrated to have a favorable benefit-risk profile, reducing symptomatic disease, hospitalization, and death, the latter two outcomes being most relevant at this time.

9 Overall Summary and Recommendations

Following review of the EUA request, and VRBPAC recommendations from the January 26, 2023, meeting, the review team considered the following in its assessment of the Pfizer-BioNTech Vaccine, Bivalent (Original and Omicron BA.4/BA.5):

- 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:
    - Clinical safety and effectiveness data following administration of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.1) vaccine,
    - Clinical safety, immunogenicity, efficacy, and observational effectiveness data from studies which evaluated primary and booster vaccination with the original Pfizer BioNTech COVID-19 Vaccine and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.1),
    - Post-marketing safety surveillance data of the original Pfizer-BioNTech COVID-19 Vaccine and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.1) and,
    - Literature evidence, including population-based seroprevalence and COVID-19 incidence rates, along with data from real world studies.

- Although available evidence suggests that the Original Pfizer-BioNTech COVID-19 Vaccine continues to provide protection against serious disease from COVID-19, based on the totality of available scientific evidence, it is reasonable to conclude that the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), administered as a single dose to all individuals (unvaccinated or vaccinated) in the United States 5 years of age and older at least 2 months following any prior monovalent COVID-19 vaccine dose, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages BA.4/BA.5 and other Omicron subvariants such as XBB.1.5.
- Based on the totality of available scientific evidence, in previously unvaccinated individuals 6 months through 4 years of age, it is reasonable to conclude that the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5),

administered as three doses may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages BA.4/BA.5 and other Omicron subvariants such as XBB.1.5.

- Based on the totality of available scientific evidence, in individuals 6 months through 4 years of age who have already received one dose of Pfizer-BioNTech COVID-19 Vaccine, it is reasonable to conclude that the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), administered as two doses, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages BA.4/BA.5 and other Omicron subvariants such as XBB.1.5.
- Based on the totality of available scientific evidence, it is reasonable to conclude that a dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), administered at least 4 months following a prior bivalent COVID-19 vaccine dose, to individuals 65 years of age and older may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages BA.4/BA.5 and other Omicron subvariants such as XBB.1.5.
- Based on the totality of available scientific evidence, it is reasonable to conclude that an additional dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), administered at least 2 months following a prior bivalent dose to individuals 5 years of age and older who are immunocompromised, and subsequent additional doses administered at the discretion of the healthcare provider, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages BA.4/BA.5 and other Omicron subvariants such as XBB.1.5.
- As summarized in Section 6, effectiveness of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is derived from a combination of clinical studies and real-world evidence.
- 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 Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) outweigh the known and potential risks when used appropriate to age and immune status for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older.
- Known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) include reduction in the risk of symptomatic COVID-19 and associated serious sequelae, including from COVID-19 due to Omicron variant sublineages BA.4 and BA.5. Uncertainties include those around the level of effectiveness against future SARS-CoV-2 variants, effectiveness against asymptomatic SARS-CoV-2 infection and SARS-CoV-2 transmission, especially in children, 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 injection site reactions, fatigue, headache, muscle pain, and axillary swelling/tenderness) and rarely anaphylaxis and myocarditis/pericarditis based on experience in original Pfizer-BioNTech COVID-19 Vaccine recipients. Risks that should be further evaluated include quantifying the rate of vaccine-associated myocarditis/pericarditis and surveillance for other adverse reactions that may become apparent with widespread use of the vaccine and with longer duration of follow-up.

Based on the considerations outlined above, the review team recommends removing authorization for emergency use of the monovalent Pfizer-BioNTech COVID-19 in the United States and revision of the EUA to provide for use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) administered in an appropriate schedule based on age and immune status, as reflected in the fact sheets.

10 Appendix A. Adverse Events of Special Interest

Table 5. Adverse Events of Special Interest

Body System/Classification Adverse Event of Special Interest	Estimated Risk Window (Days)
Autoimmune diseases	--
Guillain-Barré syndrome[1]	1-42
Acute disseminated encephalomyelitis	1-42
Narcolepsy[1]	1-42[2]
Acute aseptic arthritis	1-42[4]
Diabetes (type 1 and broader)	Any
(Idiopathic) thrombocytopenia[1]	1-42
Heparin-induced thrombocytopenia (HIT)–like event[1]	1-15
Cardiovascular system	--
Acute cardiovascular injury including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia	Any[5]
Myocarditis[1], Pericarditis[1], Myocarditis and pericarditis[1]	1-14 after each dose 1-7 after each dose
Circulatory system	--
Coagulation disorders: thromboembolism, hemorrhage	1-28
Single organ cutaneous vasculitis	1-286
Hepato- gastrointestinal and renal system	--
Acute liver injury	1-42[8]
Acute kidney injury	1-42[8]
Acute pancreatitis	1-42[8]
Rhabdomyolysis	Any
Nerves and central nervous system	--
Generalized convulsion	1-42
Meningoencephalitis	1-42
Transverse myelitis[1]	1-42
Bell's palsy	1-42
Respiratory system	--
Acute respiratory distress syndrome	Any
Skin and mucous membrane, bone and joints system	--
Erythema multiforme	1-42[7]
Chilblain-like lesions	1-42[6]
Other system	
Anosmia, ageusia	1-42
Anaphylaxis[1]	1
Multisystem inflammatory syndrome	1-42[3]
Death (any causes)	Any
Subacute thyroiditis	1-42[4]
Sudden death	Any
Gestational diabetes	Any time pregnancy
Pregnancy outcome, maternal	--
Preeclampsia	Any time pregnancy
Maternal death	Any time pregnancy
Foetal growth restriction	Any time pregnancy

Body System/Classification Adverse Event of Special Interest	Estimated Risk Window (Days)
Pregnancy outcome, neonates. Define design taking trimester into account	--
Spontaneous abortions	After vaccination
Stillbirth	After vaccination
Preterm birth	At preterm birth
Major congenital anomaliesa	1 year after birth
Microcephaly	At birth
Neonatal death	At birth
Termination of pregnancy for fetal anomaly	At termination
COVID-19 Disease	Any
Any	--
Vaccine-associated enhanced disease (VAED)[1]	Any

Source: Sponsors Clinical Study Protocol C4591021

1. For this AESI clinical validation will occur.
2. Published risk and control intervals for demyelinating diseases and cranial disorders were applied to TM and narcolepsy/cataplexy.
3. As severe COVID-19 ranges from severe pneumonia, acute respiratory distress syndrome, and multisystem organ failure/MIS-A, a 1-42 day risk interval was applied in order to capture the 14-day incubation period of the disease and 4-5 day period from exposure to symptom onset.
4. Published risk and control intervals for autoimmune disorders were applied to similar autoimmune rheumatic conditions (i.e., fibromyalgia and autoimmune thyroiditis).
5. Published risk and control intervals for myocarditis and pericarditis were applied to other cardiovascular conditions (i.e., heart failure and cardiogenic shock, stress cardiomyopathy, coronary artery disease, arrhythmia, acute myocardial infarction).
6. Similar risk and control intervals were applied to all cardiovascular and hematological disorders characterized by damage to the blood vessels and/or arteries and clotting (i.e., microangiopathy, deep venous thrombosis, pulmonary embolus, limb ischemia, hemorrhagic disease, disseminated intravascular coagulation , chilblain-l ke lesions). The published risk and control intervals for KD were applied to vasculitides given that KD is a type of medium and small-vessel vasculitis.
7. Published risk and control intervals for non-anaphylactic allergic reactions were applied to hypersensitivity disorders (i.e., erythema multiforme).
8. Risk intervals of 42 days were applied for acute kidney injury and liver injury to be consistent with other COVID-19 related safety events of interest.

11 Appendix B. List of Preferred Terms Used in the Enhanced Analysis for Potential Cases of Myocarditis or Pericarditis, Based on CDC Case Definition

The following PTs were used in the enhanced analysis to identify potential cases of myocarditis or pericarditis based on the CDC case definition (for adults).

- acute chest syndrome
- angina pectoris
- autoimmune myocarditis
- autoimmune pericarditis
- cardiac dysfunction
- cardiac function test abnormal
- cardiomyopathy
- cardiovascular function test abnormal
- chest discomfort
- chest pain
- conduction disorder
- defect conduction intraventricular
- dyspnoea
- dyspnoea at rest
- dyspnoea exertional
- ECG electrically inactive area
- ECG P wave inverted
- ECG signs of myocardial infarction
- ECG signs of myocardial ischemia
- ECG signs of ventricular hypertrophy
- electrocardiogram abnormal
- electrocardiogram ST segment
- electrocardiogram ST segment abnormal
- electrocardiogram ST segment depression
- electrocardiogram ST segment elevation
- electrocardiogram ST-T segment depression
- electrocardiogram ST-T segment abnormal
- electrocardiogram ST-T segment elevation
- eosinophilic myocarditis
- giant cell myocarditis
- hypersensitivity myocarditis
- immune-mediated myocarditis
- magnetic resonance imaging heart
- musculoskeletal chest pain
- myocardial edema
- myocarditis
- painful respiration
- palpitations
- pericardial effusion
- pericardial effusion malignant
- pericardial rub
- pericarditis
- pericarditis constructive
- pleuropericarditis
- syncope
- troponin
- troponin C
- troponin I
- troponin I increased
- troponin I normal
- troponin T increased

Table 66. CDC Working Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

Condition	Probable Case Definition	Confirmed Case Definition
Acute myocarditis	Presence of ≥1 new or worsening of the following clinical symptoms:[a] • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope **OR,** infants and children aged <12 years might instead have ≥2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy **AND** ≥1 new finding of • troponin level above upper limit of normal (any type of troponin) • abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis[c] • abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI findings consistent with myocarditis[c] **AND** • No other identifiable cause of the symptoms and findings	Presence of ≥1 new or worsening of the following clinical symptoms:[a] • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope **OR,** infants and children aged <12 years might instead have ≥2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy **AND** ≥1 new finding of • histopathologic confirmation of myocarditis[b] • cMRI findings consistent with myocarditis[c] in the presence of troponin level above upper limit of normal (any type of troponin) **AND** • No other identifiable cause of the symptoms and findings
Acute pericarditis[d]	Presence of ≥2 new or worsening of the following clinical features: • acute chest pain[e] • pericardial rub on exam • new ST-elevation or PR-depression on EKG • new or worsening pericardial effusion on echocardiogram or MRI	
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.	

Source: Sponsor's Clinical Overview, mRNA-1273-P203, Section 7.5.5.
Abbreviations: AV = atrioventricular; cMRI = cardiac magnetic resonance imaging; ECG/EKG = electrocardiogram.
Note: An independent CEAC comprising medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events (Gargano et al 2021) and provide the assessment to the Sponsor. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.
a. Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).
b. Using the Dallas criteria (Aretz 1987). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.
c. To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects. Using either the original or the revised Lake Louise criteria (Ferreira et al. 2018).
d. Adler et al 2015.
e. Typically descr bed as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.

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