

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

### Identifying Information

Application Type	EUA Amendment
Application Number	EUA 27034, Amendment 617
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Review Completion Date	August 31, 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 0.3 mL suspension for intramuscular injection
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)  Use: A single booster dose administered at least 2 months after completion of primary vaccination or receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 Vaccine
Intended Population	Individuals 12 year of age and older

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## 1 Executive Summary

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to be an ongoing global health challenge, and as of August 26, 2022, has led to over 599 million cases of coronavirus disease 2019 (COVID-19), including 6.4 million deaths worldwide.<sup>1</sup> 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/reference) Wuhan-Hu-1 SARS-CoV-2 strain. The Pfizer-BioNTech COVID-19 Vaccine was authorized under Emergency Use Authorization (EUA) on December 10, 2020, and approved under the trade name Comirnaty on August 23, 2021, as a 2-dose primary series for active immunization to prevent COVID-19 due to SARS-CoV-2 in individuals 16 years of age and older. Since its initial approval in August 2021, Comirnaty has subsequently been approved for use as a 2-dose primary series in adolescents 12 through 15 years of age. Since the initial authorization in December 2020, the EUA has been amended to extend the age indication for the primary series down to 6 months of age and to include use of Pfizer-BioNTech COVID-19 Vaccine as a first booster dose in individuals 5 years of age and older and as a second booster dose in certain populations.

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, a June 28, 2022, meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) was held to discuss potential changes to COVID-19 vaccine strain composition for use in future vaccination campaigns. Following this VRBPAC meeting and discussions with World Health Organization (WHO) and other global regulatory authorities, FDA recommended that manufacturers develop bivalent COVID-19 vaccines that include a component based on the original strain and a component based on Omicron BA.4/BA.5 for use as a booster dose potentially beginning in fall 2022.

On August 22, 2022, Pfizer submitted a request to FDA to amend its EUA to allow for the use of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in individuals 12 years of age and older as a single booster dose after either completion of primary vaccination or after the most recent booster dose with an authorized or approved monovalent COVID-19 Vaccine. Each 30 µg booster dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) contains 15 µg of mRNA encoding the S-protein of the original strain and 15 µg mRNA encoding the S-protein of Omicron BA.4/BA.5.

In consideration of this EUA request, the totality of data evaluated by the FDA to support the safety and effectiveness of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) include:

- clinical safety and immunogenicity data from a study which evaluated a second booster dose of another bivalent vaccine, Bivalent BA.1, which contains original and Omicron BA.1 mRNA components and is manufactured by the same process as the original Pfizer-BioNTech COVID-19 Vaccine and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5),

- safety and effectiveness data from clinical trials and observational studies which evaluated primary and booster (homologous and heterologous) vaccination with the original Pfizer-BioNTech COVID-19 Vaccine (previously reviewed by FDA),
- post-marketing safety surveillance data with primary series and booster doses of the original Pfizer-BioNTech COVID-19 Vaccine, and
- supportive non-clinical immunogenicity data from a study with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

While clinical data for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are not yet available, FDA determined that for purposes of this EUA it is reasonable to assess the effectiveness and the known and potential benefits and risks of this bivalent vaccine based primarily on extrapolation of data from another bivalent vaccine, Bivalent BA.1, manufactured by the same process and containing original and Omicron BA.1 components, and extensive experience to date with the original Pfizer-BioNTech COVID-19 Vaccine. This extensive experience with the original vaccine also provides a basis for extrapolation to assess known and potential benefits and risks of the bivalent (Original and Omicron BA.4/BA.5) vaccine as a booster dose administered at least 2 months after completion of primary vaccination or receipt of the most recent booster dose of any authorized or approved monovalent COVID-19 vaccine, even though clinical evaluation of Bivalent BA.1 was limited to use as a second booster dose administered at an interval range of 4.7 to 11.5 months since the previous COVID-19 vaccination. Furthermore, extensive experience with the original Pfizer-BioNTech COVID-19 Vaccine primary series and booster doses supports extrapolation of clinical data with the Bivalent BA.1 vaccine in adults >55 years of age to inform the effectiveness and benefits and risks of the bivalent (Original and Omicron BA.4/BA.5) vaccine for use as a booster dose in younger age groups.

Pfizer's EUA request includes safety data from a total of 610 participants >55 years of age who received either the original Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) or the Bivalent BA.1 vaccine as a second booster dose (Dose 4) following primary vaccination and first booster dose with BNT162b2. Almost all of these study participants had at least 1 month of safety follow-up after the study intervention, and the median duration of safety follow-up was 1.7 months through a data cut-off March 22, 2022. A majority of the 610 participants (76.7% of BNT162b2 recipients and 75.4% Bivalent BA.1 recipients) received the second booster dose study intervention between 5 and 7 months after their first booster dose (range 5.3 to 13.1 months for BNT162b2 recipients and 4.7 to 11.5 months for Bivalent BA.1 recipients).

Vaccine effectiveness of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is extrapolated and inferred, in part, based on the evaluation of the SARS-CoV-2 50% neutralizing antibody titers at 1 month after a second booster dose of Bivalent BA.1 vaccine. The analyses included evaluations of SARS-CoV-2 GMTs and seroresponse rates against the B.1.1.529 (Omicron BA.1) and USA\_WA1/2020 reference strains elicited by the Bivalent BA.1 vaccine as compared to BNT162b2. Co-primary endpoints and secondary endpoints were evaluated in participants in the evaluable immunogenicity population without evidence of SARS CoV-2 infection through 1 month post study intervention. The success criteria for co-primary objectives were met as the geometric mean ratio (GMR; Bivalent BA.1 / BNT162b2) of neutralizing antibody titers against Omicron BA.1 was 1.56 (95% CI: 1.17, 2.08), demonstrating statistical superiority based on a lower bound of the 95% CI >1.0, and the seroresponse rate difference (Bivalent BA.1 minus BNT162b2) evaluating seroresponse from pre-study intervention to 1 month after study intervention against Omicron BA.1 was 14.6% (4.0%, 24.9%), demonstrating statistical non-inferiority based on a lower bound of the 95% CI >-5% (and also demonstrating statistical superiority in a post-hoc analysis). The success

criteria for the secondary objective were also met as the GMR against the reference strain was 0.99 (0.82, 1.20), demonstrating statistical non-inferiority based on a lower bound of the 95% CI >0.67 and a point estimate  $\geq 0.8$ . A post-hoc analysis also demonstrated statistical non-inferiority of seroresponse rates against the reference strain.

Solicited local and systemic adverse reactions (ARs) were mostly mild to moderate in severity, generally of short duration, and reported with similar frequency among BNT162b2 and Bivalent BA.1 recipients. The most common solicited adverse reactions following Bivalent BA.1 as a second booster dose were injection site pain (58.1%), fatigue (49.2%), headache (33.6%), muscle pain (22.3%), chills (13.0%), joint pain (11.3%), injection site redness (7.0%), injection site swelling (6.6%), and fever (5.0%). There were no substantial differences in the frequencies or severities of solicited local or systemic ARs based on participant baseline SARS-CoV-2 status. The unsolicited AE reports were consistent with reactogenicity events, with axillary lymphadenopathy reported in 1 participant in each treatment group and related events of nausea and malaise. No related SAEs, withdrawals due to AEs, myocarditis/pericarditis, anaphylaxis or deaths were reported among participants in the safety population.

The post-marketing safety data for the original Pfizer-BioNTech COVID-19 Vaccine are relevant to the safety evaluation of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) because the vaccines are manufactured using the same process. As of July 27, 2022, more than 356 million doses of the original Pfizer-BioNTech COVID-19 Vaccine have been administered in the U.S., including 60,773,376 first booster doses and 11,032,234 second booster doses. In recipients of any age and all doses, the most frequently reported preferred terms (PTs) in Vaccine Adverse Event Reporting System (VAERS) were headache, fatigue, pyrexia, dizziness, pain, nausea, pain in extremity. For important risks identified in the pharmacovigilance plan for Pfizer-BioNTech COVID-19 Vaccine, anaphylaxis and myocarditis/pericarditis remain 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 will also conduct 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 AESIs in the general US population.

The immunogenicity of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was evaluated in mice, and data from this study suggest that formulations of BNT162b2 containing an Omicron BA.4/BA.5 component could provide a greater breadth of response against antigenically diverse SARS-CoV-2 spikes, including those from Omicron sublineages.

The totality of scientific evidence available at this time supports the conclusion that a booster dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in individuals 12 years of age and older, when administered at least 2 months after either completion of a primary series or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine, may be effective and that the known and potential benefits outweigh the known and potential risks. Therefore, the review team recommends authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) under EUA for use in individuals 12 years of age and older as a single booster dose administered at least 2 months after either completion of a primary series or previous booster dose with an authorized or approved monovalent COVID-19 Vaccine. The review team also recommends a revision to the existing EUA for Pfizer-BioNTech COVID-19 Vaccine to remove

the use of the monovalent vaccine as a first or second booster dose in individuals 12 years of age and older.

## **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. 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<sup>2</sup>, 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.<sup>3</sup> 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.<sup>4,5</sup> Other symptoms in children include nausea and vomiting, diarrhea, dyspnea, nasal symptoms, rashes, fatigue and abdominal pain.<sup>4</sup> Most children with COVID-19 recover within 1 to 2 weeks. Estimates of asymptomatic infection in children vary from 15 to 50% of infections.<sup>6,7</sup> However, COVID-19-associated hospitalizations and deaths have occurred in adolescents, and for some children, COVID-19 symptoms may continue for weeks to months after their initial illness.

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of August 26, 2022, has led to over 599 million cases of COVID-19 and 6.4 million deaths worldwide.<sup>8</sup> In the US, more than 93 million cases and 1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC).<sup>9</sup> Over 89% of cases occurred in adults greater than 12 years of age. Individuals 50 years of age and older accounted for 93.2% of deaths due COVID-19, and <0.1% of deaths occurred in adolescents 12 through 17 years of age.<sup>10</sup>

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 (B.1.1.529). The Omicron 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 most recently BA.4 and BA.5, which account for nearly all reported COVID-19 cases in the US currently, that have been associated with recent increases in COVID-19 case rates.<sup>11</sup> 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.<sup>12</sup> 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). Consequently, a booster vaccine that is able to elicit improved protection against the Omicron BA.4/BA.5 sublineages is an important public health need.

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

## **2.2 Authorized and Approved Vaccines and Therapies for COVID-19**

### **2.2.1 Comirnaty and Pfizer-BioNTech COVID-19 Vaccine**

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: three-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, a third primary series dose for individuals 5 years of age and older with certain types of immunocompromise. The Pfizer-BioNTech COVID-19 vaccine is also authorized as: a first booster dose in individuals 5-17 years of age and older to be administered at least 5 months after completion of a primary series, a first booster dose in individuals 18 years of age and older after completion of primary vaccination with any authorized or approved COVID-19 vaccine (with the same interval as authorized for a booster dose with the vaccine used for primary vaccination), and a second booster dose at least four months after a first booster dose of any authorized or approved COVID-19 vaccine in individuals 50 years of age and older and individuals 12-49 years of age with certain types of immunocompromise. Each of the authorized and approved primary series and booster doses are administered according to the age group: 3 µg in 0.2 mL (primary series only) 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 efficacy data supporting approval of Comirnaty and authorization of the Pfizer-BioNTech COVID-19 Vaccine are detailed in the decision memoranda available on the [FDA website](#).

### **2.2.2 Spikevax and Moderna COVID-19 Vaccine**

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, third primary series dose for individuals 6 months of age and older with certain types of immunocompromise, homologous or heterologous first booster dose administered after completion of primary vaccination to individuals 18 years of age and older (the authorized dosing interval for a homologous booster is at least 5 months after completion of a primary series, and the authorized interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination), and homologous or heterologous second booster dose administered at least 4 months after the first booster dose to individuals 50 years of age and older and individuals 18-49 years of age with certain types of immunocompromise. Each of the authorized and approved primary series doses are administered according to the age group: 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. When used as a first or second booster dose, the vaccine is administered as a dose of 50 µg in 0.5 mL or 0.25 mL. Safety and efficacy 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 single homologous or heterologous booster dose (the dosing interval for a homologous booster is at least 2 months after the single primary vaccination dose, and the dosing interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination). 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. 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 approved by the FDA for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

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

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

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

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

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

### **3 Rationale for Bivalent Booster Doses**

#### **3.1 Post-authorization Effectiveness Data Against Clinically Relevant SARS CoV-2 Variants**

While the currently authorized and approved 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.<sup>13,14,15,16,17,18,19,20,21,22,23</sup>

Results from observational studies that have investigated the effectiveness of primary vaccination with authorized and approved vaccines have shown decreased effectiveness against certain variants (notably Omicron, for which neutralizing antibody titers are decreased compared with the original strain) and waning effectiveness over time.<sup>13,14,15</sup> Although first booster doses have restored waning vaccine effectiveness (VE), including against severe disease and hospitalization associated with Omicron,<sup>13,14,15,16</sup> 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<sup>13,17,18,19</sup> and lower effectiveness among the immunocompromised individuals.<sup>20</sup> In Israeli experience with a second 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.<sup>21,22</sup>

#### **3.2 June 28<sup>th</sup> VRBPAC and Subsequent Regulatory Discussions**

On June 28, 2022, the 175<sup>th</sup> meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened in open session to discuss whether and how the SARS-CoV-2 strain composition of COVID-19 vaccines should be modified (see [FDA website](#) for background materials). The committee heard presentations on the current epidemiology of the COVID-19

Pandemic and SARS-CoV-2 variants in the United States and COVID-19 vaccine effectiveness (CDC) and future COVID-19 Pandemic epidemiology modeling (J. Lessler, University of North Carolina). In addition, available clinical data on modified COVID-19 vaccines were presented by COVID-19 vaccine manufacturers (Pfizer Inc., ModernaTX, and Novavax Inc.) and considerations for vaccine strain composition from the WHO Technical Advisory Group on COVID-19 Vaccine Composition (K. Subbarao, WHO). FDA perspective on considerations for strain composition for modifications of COVID-19 vaccines was also provided. After these presentations and committee discussions, the VRBPAC voted 19-2 in favor of the inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines in the US. Although there was no vote on a more specific strain composition, there was general preference among committee members for a bivalent vaccine with an ancestral strain component and an Omicron variant component and a preference for vaccine coverage of Omicron sublineages BA.4 and BA.5. Several members stressed the need to continue to accumulate additional data on this complex issue.

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

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

## **4 Regulatory Considerations for an Omicron Booster EUA**

### **4.1 U.S. Requirements to Support Issuance of an EUA for a Biological Product**

Based on the declaration by the Secretary of the U.S. Department of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met [section 564 of the FD&C Act (21 U.S.C. 360bbb-3)].

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can authorize unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's known and potential benefits outweigh its known and potential risks. This includes demonstrating that manufacturing information ensures product quality and consistency.

#### **4.2 FDA Guidance on 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, the approach and associated immunogenicity endpoints and analyses for supporting vaccine effectiveness are relevant to bivalent modified vaccines. In discussions with COVID-19 vaccine manufacturers, FDA has advised that effectiveness of a bivalent (original and Omicron variant) vaccine should be supported by immunobridging analyses demonstrating: 1) statistically superior neutralizing geometric mean titers (GMTs) against the Omicron variant elicited by the bivalent vaccine as compared to the previously authorized original vaccine; 2) statistically non-inferior neutralizing antibody seroresponse rates against the Omicron variant elicited by the bivalent vaccine as compared to the previously authorized original vaccine; 3) statistically non-inferior neutralizing antibody GMTs against the original strain elicited by the bivalent vaccine as compared to the previously authorized original vaccine; and 4) statistically non-inferior neutralizing antibody seroresponse rates against the original strain elicited by the bivalent vaccine as compared to the previously authorized original vaccine. FDA also advised vaccine manufacturers that, as discussed in the guidance document for monovalent modified vaccines, safety data to support EUA of a modified bivalent vaccine should include analyses of adverse events collected during the immunogenicity evaluation period. While the guidance encouraged clinical evaluation of modified vaccines across different age groups, the guidance also indicates that extrapolation of data accrued in one age group to support EUA of a modified vaccine in other age groups could be considered.

## **5 EUA Amendment Request for the Bivalent Pfizer-BioNTech COVID-19 Vaccine Booster Dose For Individuals 12 Years of age and older**

### **5.1 Summary of the EUA Request**

On August 22, 2022, Pfizer and BioNTech submitted a request to amend the EUA to include use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in individuals 12 years of age and older as a single booster dose after either completion of primary vaccination or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine. Each 30 µg dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is formulated to contain 15 µg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of the original SARS-CoV-2 strain and 15 µg of modRNA encoding the S glycoprotein of SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 (Omicron BA.4/BA.5). The S-proteins of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical.

The EUA amendment request included data from a clinical trial (C4591031 Substudy E) that enrolled participants >55 years of age who were previously vaccinated with a 2-dose primary series and a first booster dose of BNT162b2 (monovalent vaccine based on the original reference strain). In this substudy, 305 participants received a second booster dose with 30 µg BNT162b2 and 305 participants received a second booster dose of 30 µg Bivalent BA.1 (containing 15 µg each of mRNA encoding the S protein from the original reference strain and mRNA encoding the S protein from Omicron variant sublineage BA.1). The median duration of safety follow-up for BNT162b2 recipients was 1.8 months and for Bivalent BA.1 recipients was 1.7 months. The submission includes immunobridging analyses comparing neutralizing antibody responses between Bivalent BA.1 second booster dose recipients and BNT162b2 second booster dose recipients. Additionally, the EUA amendment submission included supportive non-clinical studies evaluating the immunogenicity of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

### **5.2 FDA Approach to Extrapolation from Available Clinical Data**

Due to the rapid evolution of SARS-CoV-2 virus variants, including the currently predominant circulating Omicron sublineages, improved protection for the upcoming winter season could be achieved with expedient authorization and deployment of modified COVID-19 vaccines, for use as booster doses, that are more closely antigenically matched to currently circulating SARS-CoV-2 than the currently authorized COVID-19 vaccines. This approach is supported by evidence, as summarized below and reviewed in detail in [Section 6](#), indicating that an improved booster dose antibody response to SARS-CoV-2 Omicron sublineages, and therefore the potential for improved vaccine effectiveness results from inclusion of an Omicron component in the vaccine, together with the original (ancestral/reference) component, as a bivalent formulation.

Authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine is being considered based on extrapolation of available immunogenicity and safety data from the Bivalent BA.1 (Original and Omicron BA.1) vaccine formulation to meet the urgent public health need due to the currently circulating Omicron sublineages. This extrapolation is being considered in the context of the totality of available evidence, which includes:

- 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 this memorandum 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 this 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 inform 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).

As described in [Section 6.1.4](#), neutralizing antibody responses against Omicron BA.1 elicited by the Bivalent BA.1 (Original and Omicron BA.1) formulation were statistically superior compared to those elicited by the original (monovalent) BNT162b2 vaccine, and neutralizing antibody responses against the reference strain (D614G) elicited by the Bivalent BA.1 (Original and Omicron BA.1) formulation were statistically non-inferior to those elicited by the original (monovalent) BNT162b2 vaccine. In exploratory analyses using a non-validated fluorescent focus reduction neutralization test (FFRNT), booster vaccination with Bivalent BA.1 (Original and Omicron BA.1) elicited neutralizing antibody GMTs against Omicron BA.4/BA.5 that were not meaningfully higher compared to vaccination with BNT162b2 monovalent (Original). Analysis of similarities and differences between Omicron BA.1 and BA.4/BA.5 Spike protein sequences reveal that Omicron BA.4/BA.5 shares 21 of the 30 mutations and 2 of the amino acid deletions; there are 10 additional amino acid changes in BA.4/BA.5. Looking only at the receptor binding domain (RBD) region, BA.1 has 15 amino acid changes relative to the original strain. BA.4/BA.5 shares 12 of these 15 amino acid changes and has an additional 7 changes in the RBD region, one of which is a reversion to the original strain sequence, for a total of 10 amino acid changes relative to BA.1. These data suggest that Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) could provide improved neutralizing antibody responses against BA.4/BA.5 as compared to both the original (monovalent) and Bivalent BA.1 (Original and Omicron BA.1) formulations of the vaccine.

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, as further detailed in [Section 7](#), it is 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 booster dose (including for individuals who previously received primary vaccination and two booster doses) at least 2 months after either completion of primary vaccination or the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine. While the available clinical safety and immunogenicity data with the Bivalent BA.1 (Original and Omicron BA.1) booster dose reflect a median interval of 6.3 months (range: 4.7-11.5 months) after the previous COVID-19 vaccine dose, authorization of a minimum interval of 2 months for booster vaccination with Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is based on extrapolation of data from a published study with BNT162b2 boosters evaluating shorter intervals between the primary series and

booster doses, along with clinical experience in immunocompromised individuals who received third primary series doses within one to two months of the second primary series dose.<sup>24,25</sup>

As mentioned in [Section 4.2](#) above, 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, the relationship between safety profile of and neutralizing antibody response to primary series doses as compared to booster doses has been very similar across age groups. FDA therefore considers that it is reasonable to extrapolate safety and effectiveness data for a bivalent COVID-19 vaccine booster dose to any age group for which available evidence has supported (or would support) emergency use authorization of a booster dose of any COVID-19 vaccine manufactured by the same process as the bivalent vaccine. In the case of the Pfizer-BioNTech COVID-19 Vaccine, the monovalent (original) vaccine has been authorized under EUA for use as a booster dose in individuals 5 years of age and older. Thus, FDA considers that it is reasonable to extrapolate safety and effectiveness data with Bivalent BA.1 (Original and Omicron BA.1) accrued in individuals >55 years of age to support EUA of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in individuals 5 years of age and older. However, at the time of this review, manufacturing and product quality information sufficient to support an EUA is not yet available for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) formulation intended for use in individuals 5 through 11 years of age. Consequently, this EUA amendment request, and FDA assessment of the evidence, is limited to use in individuals 12 years of age and older.

Finally, it is reasonable to extrapolate the totality of clinical experience with administration heterologous booster doses to support authorization of a bivalent mRNA COVID-19 vaccine booster dose following primary vaccination with the Novavax COVID-19 Vaccine, Adjuvanted. Published literature and data submitted to the agency by the respective sponsors regarding the safety and immunogenicity of the heterologous boosting with various COVID-19 vaccines<sup>24</sup> indicate: 1) heterologous primary series or booster doses provide similar vaccine effectiveness to homologous regimens; 2) heterologous schedules with mRNA and vectored vaccines show similar or more robust immunogenicity compared with homologous schedules; and 3) limited safety data for heterologous schedules have generally shown similar to transiently increased reactogenicity compared with homologous regimens.<sup>25</sup>

### **5.3 Basis for EUA Revision to Remove Authorization of the Original Pfizer-BioNTech COVID-19 Vaccine as a Booster Dose**

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 a 2- or 3-dose primary series (depending on the age group), as a homologous booster dose in individuals 5 years of age and older, as a homologous or heterologous booster dose in individuals 18 years of age and older, and as a homologous or heterologous second booster dose in certain populations. Authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use

as a booster dose following completion of primary vaccination or most recent booster dose with any authorized or approved COVID-19 vaccine is being considered for the express purpose of improving protection conferred by COVID-19 booster doses 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. Consequently, at this time, revising the Pfizer-BioNTech COVID-19 Vaccine EUA to remove the authorization of BNT162b2 as booster doses is appropriate to protect the public health.

Accordingly, authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use as a booster dose in individuals 12 years and older, would be accompanied by the revision of the authorization for the monovalent Pfizer COVID-19 Vaccine (BNT162b2) such that the monovalent vaccine would no longer be authorized for use as a first or second booster dose for individuals 12 years of age and older.

## 6 FDA Review of Clinical Safety and Effectiveness Data

### 6.1 Substudy E of Study C4591031

The EUA amendment request contains safety and immunogenicity analyses of data collected from adults >55 years of age enrolled in Substudy E of the ongoing Phase 3 master protocol, C4591031, designed to evaluate BNT162b2 boosting strategies across different age groups. C4591031 Substudy E is a randomized, observer-blinded substudy to evaluate the safety and immunogenicity of booster doses of various BNT162b2 vaccine candidates in participants >18 years of age who received 3 prior doses of 30 µg BNT162b2 at least 5 months prior to randomization at 35 US sites.

Only safety and effectiveness data in individuals >55 years of age, who received the 30 µg bivalent (15 µg BNT162b2 + 15 µg BNT162b2 Omicron BA.1) vaccine candidate (Bivalent BA.1, hereafter) and 30 µg BNT612b2 vaccine (BNT162b2, hereafter) as a booster dose, are presented in this clinical memorandum because data from participants 18-55 years of age who received the Bivalent BA.1 vaccine in the substudy are not yet available.

#### Supporting data from study C4591031

- Safety data from 305 BNT162b2 recipients and 305 Bivalent BA.1 booster dose (Dose 4) recipients >55 years of age with a median duration of follow-up after Dose 4 of 1.8 months (range: 0.3 to 2.0 months) and 1.7 months (range: 1.0 to 2.0 months), respectively.
- Immunogenicity data from 186 evaluable Bivalent BA.1 booster dose (Dose 4) recipients and 182 BNT162b2 second booster dose (Dose 4) recipients with data available and no evidence of prior SARS-CoV-2 infection up to 1 month after Dose 4.

**Table 1. Data Submitted in Support of Safety and Immunogenicity of a Bivalent Pfizer-BioNTech COVID-19 Vaccine Booster Dose, Study C4591031<sup>a</sup>**

<b>Data Type</b>	<b>BNT162b2<sup>b</sup> Recipients N=305</b>	<b>Bivalent BA.1<sup>c</sup> Recipients N=305</b>	<b>Total</b>
Safety data, n	305	305	610
Evaluable immunogenicity data following Dose 4 without	182	186	368



<b>Data Type</b>	<b>BNT162b2<sup>b</sup> Recipients N=305</b>	<b>Bivalent BA.1<sup>c</sup> Recipients N=305</b>	<b>Total</b>
evidence of prior SARS-CoV-2 infection <sup>d</sup> , n			

N= total number of participants in analysis set

n = number of participants with specified characteristics

a. Data analysis cut-off date: May 16, 2022.

b. Participants >55 years of age who received 30 µg BNT612b2 vaccine as a 4<sup>th</sup> dose.

c. Participants >55 years of age who received 30 µg Bivalent BA.1 (15 µg BNT162b2 + 15 µg BNT162b2 Omicron BA.1) vaccine as a 4<sup>th</sup> dose.

d. No evidence of prior SARS-CoV-2 infection as defined in Section 4.1.1 of this memo.

### 6.1.1 Study Design

Participants >55 years of age were randomized into different booster dose treatment groups, including one group which received 30 µg BNT162b2 and another group which received 30 µg Bivalent BA.1, as a second booster (fourth dose). Sentinel cohorts of 20 participants per group were initially enrolled with review of safety data by an internal review committee prior to enrollment into the expanded cohort of an additional 300 participants per group. A random sample of 230 participants was selected from each group in the expanded-enrollment cohort as an immunogenicity subset to evaluate the immunogenicity objectives. Participants were surveilled for potential COVID-19 illness from the first study dose visit onwards.

#### Immunogenicity evaluation

The SARS-CoV-2 50% neutralizing antibody (NT50) geometric mean titers (GMT) against Omicron B.1.1.529 (sublineage BA.1) and the reference strain (USA\_WA1/2020) in BNT162b2 and Bivalent BA.1 recipients were compared, as follows:

- GMTs and geometric mean ratio (GMR) of GMTs between Bivalent BA.1 vs. BNT162b2 groups
- Percentages of participants with seroresponse at 1 month post-Dose 4 (seroresponse rates, SRR) and difference in seroresponse rates between Bivalent BA.1 and BNT162b2 groups

Sera were tested using a 384-well SARS-CoV-2 virus microneutralization (SARS-CoV-2\_NT) assay. SARS-CoV-2 NT50 titers against Omicron sublineages BA.4/BA.5 were also evaluated in a subset of participants in the expanded cohort (n=200) using a non-validated fluorescence focus reduction neutralization test (FFRNT) assay.

#### Primary Immunogenicity Objective:

- To demonstrate superiority with respect to level of neutralizing GMT and non-inferiority with respect to seroresponse rate of anti-Omicron BA.1 immune response after 1 dose of Bivalent BA.1 compared to 1 dose of BNT162b2 given as a fourth dose in BNT162b2-experienced participants >55 years of age

#### Secondary Immunogenicity Objectives:

- To demonstrate non-inferiority of anti-reference strain GMT after 1 dose of Bivalent BA.1 compared to after 1 dose of BNT162b2 given as a fourth dose in BNT162b2-experienced participants >55 years of age
- To demonstrate “super” superiority of anti-Omicron GMTs (with a superiority margin of 1.5) after 1 dose of Bivalent BA.1 compared to after 1 dose of BNT162b2 given as a fourth dose in BNT162b2-experienced participants >55 years of age

Of note, additional primary and secondary objectives to evaluate immunogenicity of other vaccine formulations were specified in the protocol but are not listed in this memo as only relevant objectives within the scope of this review are presented.

#### Primary Endpoints and Criteria for Study Success:

The co-primary immunogenicity endpoints were Omicron BA.1-neutralizing titer and seroresponse rate 1 month after second booster vaccination, defined as:

- a change from a baseline (pre-study vaccination) titer below the LLOQ to  $\geq 4 \times \text{LLOQ}$  28 days after vaccination, or
- at least a four-fold rise in titer from baseline when the baseline titer is  $\geq \text{LLOQ}$ .

The primary immunogenicity objective was evaluated by testing the following hypotheses in the immunogenicity subset of the expanded cohort:

1.  $H_0: \ln(\mu_1) - \ln(\mu_2) \leq \ln(1)$  vs.  $H_A: \ln(\mu_1) - \ln(\mu_2) > \ln(1)$
2.  $H_0: p_1 - p_2 \leq -5\%$  vs.  $H_A: p_1 - p_2 > -5\%$

where  $\ln(\mu_1)$  and  $\ln(\mu_2)$  are the natural logs of the Omicron-neutralizing GMTs and  $p_1$  and  $p_2$  are the percentages of participants with seroresponse to the Omicron BA.1 variant at 1 month after second booster vaccination with Bivalent BA.1 and BNT162b2, respectively. The objective would be met if both hypotheses are rejected at a one-sided  $\alpha$  of 0.025.

The secondary objective of non-inferiority of anti-reference strain GMTs was evaluated by testing Hypothesis 1 using anti-reference strain titers at 1 month post vaccination and a non-inferiority margin of  $\ln(0.67)$  instead of  $\ln(1)$ , in addition to requiring a point estimate of the GMR to be  $\geq 0.8$ . The secondary objective of “super” superiority of anti-Omicron BA.1 GMTs was evaluated by testing Hypothesis 1 using anti-Omicron titers at 1 month post vaccination and a superiority margin of  $\ln(1.5)$  instead of  $\ln(1)$ .

GMRs and the 95% CIs were obtained by exponentiating the mean and associated 95% CIs of the log-transformed titers based on the t-distribution. The confidence interval for the SRR difference was estimated via the Miettinen-Nurminen method. Analyses were based on the Evaluable Immunogenicity Population, defined as participants in the immunogenicity subset who: 1) received the randomized vaccine, 2) had at least one valid and determinate immunogenicity result collected within 28 to 42 days after vaccination, and 3) had no other important protocol deviations. In addition, for the primary analysis, participants must not have any evidence of SARS-CoV-2 infection up to 1 month after vaccination. Additional analyses were performed on the All-Available Immunogenicity Population, consisting of randomized participants who received at least 1 dose of the study intervention and had at least 1 valid and determinate immunogenicity result after vaccination.

Prior SARS-CoV-2 infection was determined by virological testing via nucleic acid amplification test (NAAT) on anterior nares swab and serological testing (N-binding assay) for IgG to the SARS-CoV-2 N-antigen at study baseline.

Participants who had no serological or virological evidence (prior to the 1-month post-study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] result negative at the study vaccination and the 1--month post-study vaccination visits,

negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post-study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis populations.

No statistical hypothesis testing was performed for analysis of SARS-CoV-2 NT50 titers against Omicron sublineages BA.4/BA.5; these analyses were descriptive.

### **Efficacy evaluation**

C4591031 Substudy E did not include a formal assessment of vaccine efficacy. However, participants were instructed to contact the site if they developed acute respiratory illness so they could be evaluated for potential symptomatic COVID-19. See the [Appendix](#) for the case definitions of confirmed COVID-19 and severe COVID-19.

### **Safety evaluation**

#### Reactogenicity (solicited local and systemic adverse reactions)

The participants recorded in an e-diary reactogenicity assessments and antipyretic/pain medication use from Day 1 through Day 7 following each dose. Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling) and systemic adverse events (AEs), which were fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain.

#### Unsolicited adverse events

Other safety assessments included: AEs occurring within 30 minutes after each dose, non-serious unsolicited AEs through 1 month after study vaccination, and SAEs from Day 1 to 6 months after Dose 4, or the data cut-off date. AEs are categorized by frequency and maximum severity according to MedDRA System Organ Class and Preferred Term (PT), and relationship to the study intervention was assessed. Deaths are recorded through the end of the study.

#### Adverse events of clinical interest

The occurrence of certain AEs including lymphadenopathy and myocarditis/pericarditis were assessed as part of the safety review, as well as additional AEs requested by FDA (including anaphylaxis, Bell's palsy, appendicitis, autoimmune and neuroinflammatory disorders).

### **Analysis populations**

In the context of this EUA amendment request, the safety database was comprised of 305 participants >55 years old who received the Bivalent BA.1 vaccine candidate during C4591031 Substudy E. The all-available immunogenicity population includes 225 participants who completed the 1-month post-Dose 4 visit. The data analysis cut-off date was May 16, 2022.

- Safety population: All participants who received a study intervention.
- All-available immunogenicity population: All participants who received the study intervention with at least 1 valid and determinate immunogenicity result.
- Evaluable immunogenicity population: All eligible randomized/assigned participants who receive the study intervention to which they are randomized or assigned, have a valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.

### 6.1.2 Disposition

Of the 306 participants enrolled in each group, 305 (99.7%) per group received study vaccine, and 296 (96.7%) BNT162b2 recipients and 300 (98.0%) Bivalent BA.1 recipients completed the 1-month post-study vaccination visit. A total of 4 participants, (3 BNT162b2, 1 Bivalent BA.1) withdrew from the study, mainly due to voluntary withdrawal of informed consent.

#### Safety population

**Table 2. Disposition of Safety Population, Expanded Cohort, Participants >55 Years of Age, Immunogenicity Subset, C4591031 Substudy E**

<b>Disposition</b>	<b>BNT162b2 n<sup>a</sup> (%)</b>	<b>Bivalent BA.1 n<sup>a</sup> (%)</b>
Randomized <sup>b</sup>	306 (100.0)	306 (100.0)
Not vaccinated	1 (0.3)	1 (0.3)
Vaccinated	305 (99.7)	305 (99.7)
Completed 1-month post-study vaccination visit	296 (96.7)	300 (98.0)
Withdrawn from the study	3 (1.0)	1 (0.3)
Reason for withdrawal: withdrawal by participant	2 (0.7)	1 (0.3)
Reason for withdrawal: other	1 (0.3)	0

Source: IND 19736.882 c4591031-sse-interim-mth1-report-body.pdf. Table 4, p 39-40.

a. n = Number of participants with the specified characteristic, or the total sample.

b. These values are the denominators for the percentage calculations.

Median duration of safety follow-up for BNT162b2 recipients was 1.8 months (range: 0.3-2.0 months) and 1.7 months for Bivalent BA.1 recipients (range: 1.0-2.0 months).

#### Immunogenicity populations

Immunogenicity analyses for the primary objectives were based on evaluable participants >55 years of age without evidence of prior SARS-CoV-2 infection through 1 month after study vaccine.

**Table 3. Disposition of Immunogenicity Populations, Expanded Cohort, Participants >55 Years of Age, Immunogenicity Subset, C4591031 Substudy E**

<b>Disposition</b>	<b>BNT162b2 n<sup>a</sup> (%)</b>	<b>Bivalent BA.1 n<sup>a</sup> (%)</b>
Randomized <sup>b</sup>	230 (100.0)	230 (100.0)
All-available immunogenicity population	225 (97.8)	225 (97.8)
Excluded because participant did not have a valid and determinate immunogenicity result after study vaccination	5 (2.2)	5 (2.2)
Evaluable immunogenicity population	221 (96.1)	216 (93.9)
Without evidence of infection up to 1 month after study vaccination <sup>c</sup>	182 (79.1)	186 (80.9)
Excluded from evaluable immunogenicity population <sup>d</sup>	9 (3.9)	14 (6.1)
Did not have a valid and determinate immunogenicity result within 28-42 days after study intervention	9 (3.9)	11 (4.8)
Had other important protocol deviation	0	3 (1.3)

Source: IND 19736.882 c4591031-sse-interim-mth1-report-body.pdf. Table 6, p 42.

a. n = Number of participants with the specified characteristic, or the total sample.

b. These values are the denominators for the percentage calculations.

c. No evidence of prior SARS-CoV-2 infection as defined in Section 5.1.1 of this memo

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

### 6.1.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the C4591031 Substudy E safety population are summarized in [Table 4](#) below. Overall, participants were predominately White, with mean ages of 66.4 and 67.4 years, respectively, in the BNT162b2 and Bivalent BA.1 groups, respectively. Demographic and other baseline characteristics were generally well balanced between the BNT162b2 and Bivalent BA.1 groups. Of the Bivalent BA.1 recipients, 34.1% were obese and 12.5% had evidence of prior SARS-CoV-2 infection. All participants were enrolled in the United States.

**Table 4. Demographic and Other Baseline Characteristics, Participants >55 Years of Age, Safety Population, C4591031 Substudy E**

<b>Characteristic</b>	<b>BNT162b2 (N<sup>a</sup>=305) n<sup>b</sup> (%)</b>	<b>Bivalent BA.1 (N<sup>a</sup>=305) n<sup>b</sup> (%)</b>
<b>Sex</b>	--	--
Female	160 (52.5)	143 (46.9)
Male	145 (47.5)	162 (53.1)
<b>Race</b>	--	--
White	268 (87.9)	274 (89.8)
Black or African American	19 (6.2)	13 (4.3)
American Indian or Alaska Native	13 (4.3)	16 (5.2)
Asian	2 (0.7)	0
Native Hawaiian or other Pacific Islander	3 (1.0)	1 (0.3)
Multiracial	0	1 (0.3)
Not reported	268 (87.9)	274 (89.8)
<b>Ethnicity</b>	--	--
Hispanic or Latino	57 (18.7)	45 (14.8)
Not Hispanic or Latino	248 (81.3)	260 (85.2)
Not reported	0	0
<b>Age at Study Vaccination</b>	--	--
Mean years (SD)	66.4	67.4
Median (years)	66.0	67.0
Min, max	(56, 87)	(56, 85)
<b>Body Mass Index (BMI)</b>	--	--
Underweight (<18.5 kg/m <sup>2</sup> )	4 (1.3)	1 (0.3)
Normal weight (≥18.5-24.9 kg/m <sup>2</sup> )	85 (27.9)	71 (23.3)
Overweight (≥25.0-29.9 kg/m <sup>2</sup> )	108 (35.4)	129 (42.3)
Obese (≥30.0 kg/m <sup>2</sup> )	108 (35.4)	104 (34.1)
<b>Baseline Evidence of Prior SARS-CoV-2 Infection</b>	--	--
Negative <sup>c</sup>	262 (85.9)	267 (87.5)
Positive <sup>d</sup>	41 (13.4)	38 (12.5)
Missing	2 (0.7)	0

Characteristic	BNT162b2 (N <sup>a</sup> =305) n <sup>b</sup> (%)	Bivalent BA.1 (N <sup>a</sup> =305) n <sup>b</sup> (%)
<b>Time (months) from Dose 3 to study vaccination</b>	--	
Mean (SD)	6.8 (1.44)	6.8 (1.39)
Median	6.3	6.3
Min, Max	5.3, 13.1	4.7, 11.5
<5 Months	0	1 (0.3)
≥5 to <7 Months	234 (76.7)	230 (75.4)
≥7 to <9 Months	40 (13.1)	43 (14.1)
≥9 to <11 Months	28 (9.2)	26 (8.5)
≥11 Months	3 (1.0)	5 (1.6)

Source: IND 19736.882 c4591031-sse-interim-mth1-report-body.pdf. Table 7, p 45-47.

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.

b. n = Number of participants with the specified characteristic.

c. Negative N-binding antibody result at Dose 1, negative NAAT result at Dose 1, and no medical history of COVID-19.

d. Positive N-binding antibody result at Dose 1, positive NAAT result at Dose 1, or medical history of COVID-19.

The demographic and baseline characteristics of the evaluable immunogenicity population with and without evidence of infection prior to 1 month after study vaccination were similar to the overall characteristics of the safety population described above; 14.0% of BNT162b2 recipients and 12.9% of Bivalent BA.1 vaccine recipients had baseline evidence of prior SARS-CoV-2 infection.

The BNT162b2 second booster dose was administered 5.3 to 13.1 months (median 6.3 months) after the first booster dose, and the Bivalent BA.1 second booster dose was administered 4.7 to 11.5 months (median 6.3 months) after the first booster dose.

A total of 2 participants in the Bivalent BA.1 group received a concomitant vaccine after study vaccination, both of which were tetanus containing vaccines.

## 6.1.4 Vaccine Effectiveness Results

### 6.1.4.1 Primary Immunogenicity

Vaccine effectiveness was inferred based on the evaluation of SARS-CoV-2 50% neutralizing antibody titers (NT50) at 1 month after a second booster dose. The analyses 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.

#### GMTs of neutralizing antibody titers against Omicron BA.1 and the reference strain

Among evaluable participants >55 years of age without prior evidence of SARS-CoV-2 infection up to 1-month post-booster (Dose 4), 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) (Table 5, below). The primary objective of superiority was met as the lower bound of the 95% CI around the GMT ratio 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  $\geq 0.8$ .

**Table 5. SARS-CoV-2 NT50 GMTs<sup>a</sup> against Omicron BA.1 and Reference Strain at 1 Month Post-Dose 4, Participants >55 Years of Age Without Evidence of SARS-CoV-2 Infection, Evaluable Immunogenicity Population, C4591031 Substudy E**

Variant	BNT162b2 GMT (95% CI)	Bivalent BA.1 GMT (95% CI)	GMR <sup>c</sup> (95% CI)	Success Criterion Met
Omicron BA.1	N <sup>b</sup> = 163 455.8 (365.9, 567.6)	N <sup>b</sup> = 178 711.0 (588.3, 859.2)	1.56 (1.17, 2.08)	Yes <sup>d</sup>
Reference Strain	N <sup>b</sup> = 182 5998.1 (5223.6, 6887.4)	N <sup>b</sup> = 186 5933.2 (5188.2, 6785.2)	0.99 (0.82, 1.20)	Yes <sup>e</sup>

Source: IND 19736.882 c4591031-sse-interim-mth1-report-body.pdf. Table 12, p 58-59.

a. 384-well SARS-CoV-2 virus microneutralization assay-NT50, Omicron BA.1: B.1.1.529 (sublineage BA.1) and reference strain: recombinant USA\_WA1/2020

b. N = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point within specified window.

c. GMR= Geometric Mean Ratios and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (vaccine group in the corresponding row - BNT162b2 [30 µg]) and the corresponding CI (based on the Student t distribution).

d. Success criterion: Superiority of bivalent BA.1 to BNT162b2 was met, as the lower bound of the 2-sided 95% CI for GMR was > 1.

e. Success criterion: Non-inferiority of bivalent BA.1 to BNT162b2 was met, as the lower bound of the 2-sided 95% CI for GMR was > 0.67 and the point estimate is  $\geq 0.8$ .

Analyses of NT50 GMTs in the all-available immunogenicity populations were generally comparable to the results in the evaluable immunogenicity populations. Pre- and post-study vaccination GMTs were higher in the all-available population, due to inclusion of participants with prior SARS-CoV-2 infection.

#### Seroresponse rates against Omicron BA.1 and the reference strain

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%.

Seroresponse rates among participants without evidence of prior SARS-CoV-2 infection are presented in [Table 6](#). The anti-reference strain seroresponse rates are also displayed, although there was no hypothesis testing with pre-specified success criteria for this analysis; however, this post-hoc analysis indicates that the FDA-recommended success criterion for non-inferiority of seroresponse rates (lower bound of the 95% CI >-10%) would have been met.

**Table 6. SARS-CoV-2 Seroreponse Rates at 1 Month Post-Booster Dose (Dose 4), Participants >55 Years of Age Without Evidence of SARS-CoV-2 Infection, Evaluable Immunogenicity Population, C4591031 Substudy E**

Variant	BNT162b2 Seroresponders <sup>a</sup> n (%) (95% CI)	Bivalent BA.1 Seroresponders <sup>b</sup> n (%) (95% CI)	Difference <sup>c</sup> (95% CI)	Success Criterion Met
Omicron BA.1	N=149 85 (57.0) (48.7, 65.1)	N=169 121 (71.6) (64.2, 78.3)	14.6 (4.0, 24.9)	Yes <sup>d</sup>
Reference Strain	N=179 88 (49.2) (41.6, 56.7)	N=186 93 (50.0) (42.6, 57.4)	0.8 (-9.4, 11.1)	N/A

Source: IND 19736.882 c4591031-sse-interim-mth1-report-body.pdf. Table 14, p 64-65.  
384-well SARS-CoV-2 virus microneutralization assay-NT50, Omicron BA.1: B.1.1.529 (sublineage BA.1) and reference strain: recombinant USA\_WA1/2020.

a. Proportion of participants with a  $\geq 4$ -fold rise in NT50 GMT from pre-study vaccination to 1-month post-study vaccination

b. Proportion of participants with a  $\geq 4$ -fold rise in NT50 GMT from indicated baseline to 1-month post-booster.

c. Difference in proportion of participants with  $\geq 4$ -fold rise from pre-dose 4 to post- Dose 4.

d. Non-inferiority was met as the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroreponse is  $> -5\%$ .

%, n/N. n = number of participants with seroreponse for the given assay at the given dose/sampling time point. N = Number of subjects with valid and determinate assay results for the specified assay within the specified window for blood samples collected at indicated baseline and 1 month after study vaccination.

### Subgroup analyses of immunogenicity

Overall, there were no clinically meaningful differences between subgroups for neutralizing GMTs and seroreponse rates against the Omicron BA.1 variant or the reference strain, except for differences between subgroups stratified by baseline SARS-CoV-2 status, due to higher baseline GMTs in the subgroup with evidence of prior infection. As several subgroups (e.g., Black or African American, Asian, Hispanic/Latino, SARS-CoV-2 baseline positive or NAAT positive participants) included a limited number of participants, their results should be interpreted with caution.

- GMTs at 1 month-post-Dose were higher for participants who were baseline positive compared to those who were baseline negative for SARS-CoV-2.
- Seroreponse rates at 1 month-post-Dose were generally lower for participants who were baseline positive compared to those who were baseline negative for SARS-CoV-2.

### **6.1.4.2 Exploratory Immunogenicity Analyses**

#### GMTs against the Omicron BA.4/BA.5 sublineages

Pfizer submitted exploratory descriptive analyses of data from 100 randomly selected participants from the evaluable immunogenicity population of each treatment group. GMTs were determined using a non-validated SARS-CoV-2 fluorescence focus reduction neutralization test (FFRNT) assay with the Omicron BA.4/BA.5 variant. The post-second booster GMTs in the Bivalent BA.1 group were slightly higher than in the BNT162b2 group (though with overlapping CIs), regardless of baseline SARS-CoV-2 status. Additionally, participants in the BNT162b2 group had higher baseline GMTs than participants in the Bivalent BA.1 group, so the geometric mean fold-rise from pre-second booster to post-second booster would be expected to be slightly lower in the BNT162b2 group than in the Bivalent BA.1 group.



**Table 7. Anti-Omicron BA.4/BA.5 SARS-CoV-2 Neutralizing GMTs<sup>a</sup> at 1 Month Post- Vaccination, Participants >55 Years of Age Without Evidence of SARS-CoV-2 Infection, Subset of the Evaluable Immunogenicity Population<sup>b</sup>, C4591031 Substudy E**

Baseline Status	n per Group	Time Point	BNT162b2 GMT (95% CI)	Bivalent BA.1 GMT (95% CI)
All	100	Baseline	46.8 (34.5, 63.4)	37.3 (28.0, 49.7)
All	100	1 Month	155.1 (122.2, 196.8)	167.4 (128.0, 218.9)
Positive	20	Baseline	355.1 (179.8, 701.0)	211.1 (92.5, 481.6)
Positive	20	1 Month	607.6 (380.3, 970.7)	774.4 (410.5, 1460.9)
Negative	80	Baseline	28.2 (22.2, 35.7)	24.2 (19.5, 30.0)
Negative	80	1 Month	110.2 (88.5, 137.3)	114.1 (90.3, 144.3)

Source: Adapted from IND 19736.882. C4591031 Substudy E Interim Clinical Study Report, Table 7.

a. SARS-CoV-2 fluorescence focus reduction neutralization test (FFRNT), SARS-CoV-2 strain: B.1.1.529 (sublineage BA.4/BA.5).

b. N = number of participants with valid and determinate assay results for the specified assays at the given dose/sampling time point.

c. GMT= geometric mean neutralizing antibody titers to Omicron variant in each study group

## Surveillance of COVID-19 Cases

A total of 8/610 participants (7/305 BNT162b2 recipients and 1/305 Bivalent BA.1 recipient) had confirmed COVID-19 as of the May 16, 2022, data cutoff date. There were no severe COVID-19 cases. The median duration of follow-up for Bivalent BA.1 recipients was 1.7 months post vaccination.

The clinical study report did not provide estimates of the relative vaccine efficacy. Based on FDA statistical reviewer’s calculations, the relative vaccine efficacy comparing Bivalent BA.1 vs. BNT162b2 was approximately 85.8% (95% CI: –10.7% to 99.7%), adjusted for surveillance time, starting after study vaccination among participants who received any study vaccination. All cases observed in these two treatment groups occurred beyond 7 days post vaccination. Interpretation of the COVID-19 incidence rates in the two groups is limited by the small number of cases accrued during the short follow-up period as the wide confidence intervals demonstrate.

## 6.1.5 Safety Results

### Overview of Adverse Events

In the C4591031 Substudy E expanded cohort, e-diary data on reactogenicity (local and systemic reactions) were collected from 298 and 301 BNT162b2 and Bivalent BA.1 booster dose recipients, respectively. There were no immediate unsolicited AEs in the study. Overall, injection site reactions occurring within 7 days of vaccination with the study intervention were common, occurring in 59.5% of Bivalent BA.1 recipients. Systemic AEs occurred in 60.5% of Bivalent BA.1 recipients. Other unsolicited non-serious AEs occurred in 5.9% of participants. No participants in the safety population withdrew because of AEs, and there were no deaths or related SAEs reported. See [Table 8](#) below.

**Table 8. Safety Overview, Phase 2/3 Participants >55 Years of Age, Safety Population, C4591031 Substudy E**

Event	BNT162b2 n <sup>b</sup> /N <sup>a</sup> (%)	Bivalent BA.1 n <sup>b</sup> /N <sup>a</sup> (%)
Immediate unsolicited AE within 30 minutes	0/305	0/305
Solicited injection site reaction within 7 days <sup>c</sup>	182/298 (61.1)	179/301 (59.5)
Solicited systemic AE within 7 days <sup>c</sup>	167/298 (56.0)	182/301 (60.5)
From study vaccination through 1 month after study vaccination	--	--
Any AE	18/305 (5.9)	19/305 (6.2)
Unsolicited non-serious AE	18/305 (5.9)	18/305 (5.9)
Related non-serious AE	4/305 (1.3)	7/305 (2.3)
SAE <sup>d</sup>	2/305 (0.7)	1/305 (0.3)
Related SAE	0/305	0/305
Deaths <sup>d</sup>	0/305	0/305
AE leading to discontinuation <sup>d</sup>	0/305	0/305

Source: IND 19736.882: c4591031-sse.interim-mth1-report-body.pdf. Table 19, p 92 and IND 19736.909. c4591031-508-compliant-tables-sse-expan-55up.pdf. Table Q, page 7.

Note: MedDRA (v25.0) coding dictionary applied.

Note: Immediate AE refers to an AE reported in the 30-minute observation period after vaccination.

a. N = number of administered participants in the specified group. This value is the denominator for the percentage calculations.

b. n = Number of participants with the specified characteristic.

c. There were no Grade 4 ARs reported in either group

d. Reported through data cutoff: May 16, 2022

### 6.1.5.1 Solicited adverse reactions

The most commonly reported reactions were pain at the injection site (60.1% for BNT162b2 and 58.1% for Bivalent BA.1), fatigue (45.3% for BNT162b2 and 49.2% for Bivalent BA.1), and headache (26.5% for BNT162b2 and 33.6% for Bivalent BA.1). Most solicited reactions were mild or moderate in severity, with a median onset at Day 2 or Day 3 after vaccination and a median duration of 1 to 2 days.

[Table 9](#) and [Table 10](#) summarize the frequency by severity of Adverse Reactions reported within 7 days after study vaccination.

**Table 9. Frequency of Solicited Local Reactions Within 7 Days After Vaccination, Participants >55 Years of Age, Safety Population<sup>a</sup>, C4591031 Substudy E**

Event	BNT162b2 N=298 n <sup>b</sup> (%)	Bivalent BA.1 N=301 n <sup>b</sup> (%)
Redness <sup>c</sup>	--	--
Any	19 (6.4)	21 (7.0)
Mild	12 (4.0)	13 (4.3)
Moderate	6 (2.0)	8 (2.7)
Severe	1 (0.3)	0
Swelling <sup>c</sup>	--	--
Any	18 (6.0)	20 (6.6)
Mild	10 (3.4)	14 (4.7)
Moderate	8 (2.7)	6 (2.0)
Severe	0	0

<b>Event</b>	<b>BNT162b2 N=298 n<sup>b</sup> (%)</b>	<b>Bivalent BA.1 N=301 n<sup>b</sup> (%)</b>
Pain at the injection site <sup>d</sup>	--	--
Any	179 (60.1)	175 (58.1)
Mild	154 (51.7)	159 (52.8)
Moderate	24 (8.1)	15 (5.0)
Severe	1 (0.3)	1 (0.3)
Any local reaction <sup>e</sup>	182 (61.1)	179 (59.5)

Source: IND 19736.909. c4591031-508-compliant-tables-sse-expan-55up.pdf. Table R, page 8-9.

Note: Reactions were collected in the electronic diary (e-diary) and unscheduled clinical assessments from Day 1 through Day 7 after each vaccination.

Note: No Grade 4 reactions were reported

Note: All randomized participants who received at least 1 dose of the study intervention.

a. N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.

b. n = Number of participants with the specified characteristic.

c. Mild (Grade 1):  $\geq 0.5$  to 2.0 cm; moderate (Grade 2):  $> 2.0$  to 7.0 cm; severe (Grade 3):  $> 7.0$  cm; Grade 4: necrosis (redness and swelling categories) or exfoliative dermatitis (redness category only).

d. Mild (Grade 1): does not interfere with activity; moderate (Grade 2): interferes with activity; severe (Grade 3): prevents daily activity; Grade 4: emergency room visit or hospitalization for severe pain at the injection site.

e. Any local reaction: any redness  $\geq 0.5$  cm, any swelling  $\geq 0.5$  cm, or any pain at the injection site.

**Table 10. Frequency of Solicited Systemic Adverse Events Within 7 Days After Vaccination, Participants >55 Years of Age, Safety Population<sup>a</sup>, C4591031 Substudy E**

<b>Event</b>	<b>BNT162b2 N=298 n<sup>b</sup>(%)</b>	<b>Bivalent BA.1 N=301 n<sup>b</sup>(%)</b>
Fever	--	--
$\geq 38.0^\circ\text{C}$	11 (3.7)	15 (5.0)
$\geq 38.0^\circ\text{C}$ to $38.4^\circ\text{C}$	6 (2.0)	11 (3.7)
$> 38.4^\circ\text{C}$ to $38.9^\circ\text{C}$	5 (1.7)	0
$> 38.9^\circ\text{C}$ to $40.0^\circ\text{C}$	0	4 (1.3)
$> 40.0^\circ\text{C}$	0	0
Fatigue <sup>c</sup>	--	--
Any	135 (45.3)	148 (49.2)
Mild	70 (23.5)	88 (29.2)
Moderate	64 (21.5)	55 (18.3)
Severe	1 (0.3)	5 (1.7)
Headache <sup>c</sup>	--	--
Any	79 (26.5)	101 (33.6)
Mild	47 (15.8)	71 (23.6)
Moderate	31 (10.4)	29 (9.6)
Severe	1 (0.3)	1 (0.3)
Chills <sup>c</sup>	--	--
Any	49 (16.4)	39 (13.0)
Mild	32 (10.7)	25 (8.3)
Moderate	17 (5.7)	14 (4.7)
Severe	0	0
Vomiting <sup>d</sup>	--	--
Any	4 (1.3)	5 (1.7)
Mild	2 (0.7)	5 (1.7)
Moderate	2 (0.7)	0
Severe	0	0

Event	BNT162b2 N=298 n <sup>b</sup> (%)	Bivalent BA.1 N=301 n <sup>b</sup> (%)
Diarrhea <sup>e</sup>	--	--
Any	13 (4.4)	27 (9.0)
Mild	10 (3.4)	18 (6.0)
Moderate	3 (1.0)	5 (1.7)
Severe	0	4 (1.3)
New or worsened muscle pain <sup>c</sup>	--	--
Any	59 (19.8)	67 (22.3)
Mild	35 (11.7)	40 (13.3)
Moderate	24 (8.1)	27 (9.0)
Severe	0	0
New or worsened joint pain <sup>c</sup>	--	--
Any	27 (9.1)	34 (11.3)
Mild	16 (5.4)	23 (7.6)
Moderate	11 (3.7)	11 (3.7)
Severe	0	0
Any systemic event <sup>f</sup>	167 (56.0)	182 (60.5)
Use of antipyretic or pain medication <sup>g</sup>	80 (26.8)	88 (29.2)

Source: IND 19736.909. c4591031-508-compliant-tables-sse-expan-55up.pdf. Table S, page 10-13.

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) and unscheduled clinical assessments from Day 1 through Day 7 after each dose. Grade 4 events were classified by the investigator or medically qualified person.

Note: All randomized participants who received at least 1 dose of the study intervention.

a. N = number of participants reporting at least 1 yes or no response for the specified event after the specified dose.

b. n = Number of participants with the specified characteristic.

c. Mild (Grade 1): does not interfere with activity; moderate (Grade 2): some interference with activity; severe (Grade 3): prevents daily activity; Grade 4: emergency room visit or hospitalization for severe fatigue, severe headache, severe chills, severe muscle pain, or severe joint pain.

d. Mild (Grade 1): 1 to 2 times in 24 hours; moderate (Grade 2): >2 times in 24 hours; severe (Grade 3): requires intravenous hydration; Grade 4: emergency room visit or hospitalization for severe vomiting.

e. Mild (Grade 1): 2 to 3 loose stools in 24 hours; moderate (Grade 2): 4 to 5 loose stools in 24 hours; severe (Grade 3): 6 or more loose stools in 24 hours; Grade 4: emergency room visit or hospitalization for severe diarrhea.

f. Any systemic event: any fever ≥38.0°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.

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

Among Bivalent BA.1 recipients, a higher percentage of female than male recipients reported solicited ARs, such as injection site pain: 78.5% vs. 56.4%, injection site redness: 11.0% vs. 3.4%, fatigue: 66.3% vs. 47.7%, headache: 45.4% vs. 26.8%, and muscle pain: 31.9% vs. 22.1%. A similar pattern was also observed among BNT162b2 recipients.

There were no substantial differences in the frequencies or severities of reported local or systemic solicited ARs based on participant baseline SARS-CoV-2 status. Overall, ~88% of the study population was White, and ~83% were not Hispanic or Latino; the number of non-White participants and Hispanic or Latino participants was too small to make definitive conclusions about differences in reactogenicity based on race or ethnicity.

### 6.1.5.2 Unsolicited Adverse Events

As of the data cutoff date of May 16, 2022, the median duration of safety follow-up for the Bivalent BA.1 group was 1.7 months, and 98% of the Bivalent BA.1 recipients had at least one month of follow up after study vaccination. For the BNT162b2 group, the median duration of safety follow-up was 1.8 months, and 96.7% of the BNT162b2 recipients had at least one month of follow up after study vaccination.

Unsolicited AEs that occurred within 1 month of study vaccination at rates  $\geq 1\%$  in either treatment group were limited to 4 (1.3%) participants reporting headache in the Bivalent BA.1 group. Unsolicited AEs that were considered related to the study vaccine were reported by 4 (1.3%) of BNT162b2 recipients and 7 (2.3%) of Bivalent BA.1 recipients. The majority of these events were consistent with events assessed as solicited adverse reactions. By Preferred Term (PT), *Headache* (1.0%), *Myalgia* (0.7%), and *Injection site pain* (0.7%) were the most commonly reported AEs considered related to study vaccine.

Overall, frequencies of any AEs reported after study vaccination up the data cutoff date were generally similar between vaccine groups. Many of the AEs were consistent with reactogenicity events (arthralgia, myalgia, headache and fatigue) and reports of nausea and malaise were also considered related to vaccination. The additional AEs reported after 1-month post-study vaccination through the data cutoff date consisted of unrelated events.

One (0.3%) participant in the BNT162b2 group reported a non-serious AE of chest discomfort on Day 2 after study vaccination, which resolved within 28 days with no other symptoms. The investigator considered the event as related to study intervention. The participant had no other reported AEs. Troponin levels reported at the cardiac illness visit were  $<3$  ng/L (Reference range: 0-47 ng/L), and ECG was reported as normal. The participant had a medical history of type 2 diabetes, diabetic neuropathy, hypertension and hyperlipidemia.

Lymphadenopathy was reported by 1 participant in each treatment group, both of which were considered related to study vaccination by the study investigator. Both cases occurred with 1-4 days post study vaccine, were located in the axillae and resolved within 2-8 days.

### **6.1.5.3 Serious Adverse Events**

The one serious adverse event reported in the Bivalent BA.1 group was considered unrelated to vaccine by the investigator and FDA (worsening gastroesophageal reflux which occurred 27 days post vaccine). The 2 serious adverse events reported in BNT162b2 recipients occurred between the 1-month post study vaccination visit and the data cutoff, and they were both considered unrelated to vaccine by the investigator and FDA (pneumonia which occurred 46 days post vaccine and ischemic stroke which occurred 33 days post vaccine with a concurrent unrelated AE of hypertension).

There were no deaths reported in either treatment group through the data cutoff date of May 16, 2022.

### **6.1.5.4 AEs of Clinical Interest**

Standardized MedDRA Queries (SMQs) were conducted to evaluate for constellations of unsolicited AEs among BNT162b2 and Bivalent BA.1 recipients  $>55$  years of age, through the data cut-off date of May 16, 2022. SMQs (narrow and broad in scope) were conducted on adverse event PTs that could represent various conditions, including but not limited to angioedema, arthritis, cardiomyopathy, ischemic heart disease, cardiac arrhythmia, cardiac failure, central nervous system vascular disorders, convulsions, demyelination, embolic and thrombotic events, hearing and vestibular disorders, hematopoietic cytopenias, hypersensitivity, peripheral neuropathy, thrombophlebitis, and vasculitis. For example, the cardiomyopathy SMQ includes PTs that may be related to myocarditis and pericarditis, such as chest pain, palpitations, dyspnea, syncope, troponin elevation, ECG with ST elevation or PR depression, pericardiac rub, or echocardiographic findings.

This search identified the following:

- One BNT162b2 recipient who reported an AE within the hypersensitivity SMQ, which was contact dermatitis.
- Two BNT162b2 recipients who reported AEs within the arthritis SMQ, one of which was gout and the other of which was arthritis, considered related to recent outdoor activities the participant reported.
- One Bivalent BA.1 recipient who reported an AE within the arthritis SMQ, which was ankylosing spondylitis.

There were no cases reported of myocarditis/pericarditis, Bell's palsy, appendicitis or vaccine-related anaphylaxis.

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

### **6.1.6 Summary of Findings from Study C4591031 Substudy E**

The clinical data submitted with this EUA request come from the ongoing Substudy E from Study C4591031. Immunogenicity of the Bivalent BA.1 vaccine as a booster dose was assessed in a subset of 178 participants >55 years of age who had previously received 3 doses of BNT162b2 and who had no evidence of prior SARS-CoV-2 infection up to 1 month after the study vaccination. Vaccine effectiveness was inferred based on the evaluation of the neutralizing antibody titers (GMTs) and the seroresponse rates against the Omicron BA.1 and reference strains elicited by the Bivalent BA.1 vaccine as compared to BNT162b2, 1 month after a second booster dose. Statistical success criteria for the co-primary objectives (superiority with respect to level of neutralizing GMT and non-inferiority with respect to seroresponse rate of anti-Omicron BA.1 immune response) were met as the GMT ratio (Bivalent BA.1 / BNT162b2) against Omicron BA.1 was 1.56 (95% CI: 1.17, 2.08), and the difference in seroresponse rates (Bivalent BA.1 minus BNT162b2) against Omicron BA.1 was 14.6 (95% CI: 4.0, 24.9). The statistical success criteria for the secondary objective to demonstrate non-inferiority of anti-reference strain GMT and point estimate for GMT  $\geq 0.8$  were met as the GMT ratio (Bivalent BA.1 / BNT162b2) against the reference strain was 0.99 (95% CI: 0.82, 1.20). The statistical the super-superiority success criterion for the secondary objective (anti-Omicron GMT/BNT162b2 GMT) was not met as the lower bound of the 95% CI was <1.5.

Descriptive immunogenicity analyses against the Omicron BA.4/BA.5 variant were evaluated in randomly selected participants from the evaluable immunogenicity population of each treatment group, using a non-validated SARS-CoV-2 fluorescence focus reduction neutralization test (FFRNT) assay with the Omicron BA.4/BA.5 variant. The anti-Omicron BA.4/BA.5 GMTs at 1 month post vaccination were similar between treatment groups, regardless of baseline serostatus, although the BNT162b2 group had slightly higher baseline GMTs than the Bivalent BA.1 group.

Solicited local and systemic adverse reactions (ARs) were mostly mild to moderate in severity, generally of short duration, and reported with similar frequency among BNT162b2 and Bivalent BA.1 recipients. The most common solicited adverse reactions following Bivalent BA.1 as a second booster dose were injection site pain (58.1%), fatigue (49.2%), headache (33.6%), muscle pain (22.3%), chills (13.0%), joint pain (11.3%), injection site redness (7.0%), injection site swelling (6.6%), and fever (5.0%). There were no substantial differences in the frequencies or severities of solicited local or systemic ARs based on participant baseline SARS-CoV-2 status. The unsolicited AE reports were consistent with reactogenicity events, with axillary

lymphadenopathy reported in 1 participant in each treatment group and related events of nausea and malaise. No related SAEs, withdrawals due to AEs, myocarditis/pericarditis, anaphylaxis or deaths were reported among participants in the safety population.

## 6.2 FDA Review of Post-authorization Safety Data from Booster Doses

As of July 27, 2022, more than 356 million doses of the original Pfizer-BioNTech COVID-19 Vaccine have been administered in the U.S., including 60,773,376 first booster doses and 11,032,234 second booster doses ([CDC COVID Data Tracker](#), accessed on August 3, 2022). It is not known what proportions of these numbers represent unauthorized use of the vaccine. The Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) has not been previously authorized for use and as such, post-authorization safety data are not available. However, post-authorization data for the original Pfizer-BioNTech COVID-19 Vaccine are relevant for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), as these vaccines are manufactured using the same process and both vaccines contain an original SARS-CoV-2 component.

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event (AE) reports following administration of the original Pfizer-BioNTech COVID-19 Vaccine, and the results are briefly summarized below. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, stimulated reporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported event was actually due to the vaccine. A 3<sup>rd</sup>, 4<sup>th</sup>, or 5<sup>th</sup> COVID-19 vaccine dose as recorded in VAERS might not represent a dose given as an authorized booster dose.

As of August 3, 2022, VAERS cumulatively received 826,382 reports (404,482 U.S. reports) following vaccination with the original Pfizer-BioNTech COVID-19 Vaccine among all ages, including 67,147 reports (45,816 U.S.) following a 3<sup>rd</sup>, 4<sup>th</sup>, or 5<sup>th</sup> dose (i.e., booster dose) among individuals  $\geq 12$  years of age. The majority of U.S. VAERS reports for the original Pfizer-BioNTech COVID-19 Vaccine were non-serious (82.2% for any dose among all ages, and 78.6% for booster doses among those aged  $\geq 12$  years). The top ten most frequently reported MedDRA PTs (U.S. and foreign) include:

- Most frequent PTs among all ages and all doses: SARS-CoV-2 test, COVID-19, headache, fatigue, pyrexia, dizziness, pain, nausea, pain in extremity, vaccination failure.
- Most frequent PTs among persons  $\geq 12$  years of age receiving a booster dose: immunization, SARS-CoV-2 test, COVID-19, headache, fatigue, pyrexia, off label use, interchange of vaccine products, pain, chills.

Note that a report may have one or more PTs.

Safety concerns previously identified from post-authorization safety surveillance data in VAERS for the original Pfizer-BioNTech COVID-19 Vaccine are summarized below. Anaphylaxis, myocarditis, and pericarditis are existing safety concerns that have been added to the product Fact Sheets.

## **Anaphylaxis**

Post-authorization surveillance for the original Pfizer-BioNTech COVID-19 Vaccine identified a risk of anaphylaxis, occurring at a rate similar to reported rates of anaphylaxis following licensed preventive vaccines, primarily in individuals with history of prior severe allergic reactions to other medications or foods.<sup>26,27</sup> Anaphylaxis is an important identified risk in the PVP and included in the Warnings sections of the vaccine Fact Sheets and Prescribing Information. As of August 3, 2022, there have been 1,701 U.S. reports of anaphylaxis/anaphylactoid reaction following the original Pfizer-BioNTech COVID-19 Vaccine among individuals of all ages (based on an automated search). PTs included in the automated VAERS query were as follows: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and anaphylactoid shock. The estimated crude reporting rate for anaphylaxis following the original Pfizer-BioNTech COVID-19 Vaccine for all ages in the U.S. is 4.8 cases per million doses administered which is similar to estimated rates for other vaccines.<sup>28</sup>

## **Myocarditis and pericarditis**

Post-EUA safety surveillance reports received by FDA and CDC identified increased rates of myocarditis and pericarditis, particularly 0-7-days following administration of the second primary series dose or first booster dose of the original Pfizer-BioNTech COVID-19 Vaccine. Reporting rates for reports verified to meet the CDC case definition of myocarditis and pericarditis in VAERS have been generally higher among males under 40 years of age than among females and older males. The highest reporting rates have been in males 12 through 17 years of age (rates of verified cases per million doses 0-7-days following dose 2 administration of the original Pfizer-BioNTech COVID-19 Vaccine were 75.9 cases among males ages 16-17 years and 46.4 cases among males ages 12-15 years).<sup>4</sup> VAERS monitoring has also shown that reporting rates of myocarditis among individuals ages 12-29 years following a first booster dose of original Pfizer-BioNTech COVID-19 Vaccine exceeded background rates (rates of verified cases per million doses 0-7-days following first booster dose administration were 24.1 cases among males ages 16-17 years and 15.3 cases among males ages 12-15 years).<sup>29</sup>

Although some cases of vaccine-associated myocarditis/pericarditis following the original Pfizer-BioNTech COVID-19 Vaccine have required intensive care support, available data from short-term follow-up suggests that most individuals have had resolution of symptoms with conservative management. CDC is conducting enhanced surveillance for VAERS case reports using patient and healthcare provider surveys to assess functional status and clinical outcomes among individuals reported to have developed myocarditis after mRNA COVID-19 vaccination. Among individuals aged 12-29 years, available data from follow-up with cardiologists/healthcare providers at least 90 days after onset of myocarditis symptoms suggests most individuals fully recover from myocarditis following mRNA vaccination.<sup>4</sup> Information is not yet available about potential longer-term sequelae and outcomes in affected individuals, or whether the vaccine might be associated initially with subclinical myocarditis (and if so, what are the long-term sequelae). A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established.

Myocarditis and pericarditis were added as important identified risks in the PVP and included in the vaccine Fact Sheets and Prescribing Information (Section 5 Warnings and Precautions, 5.2 Myocarditis and Pericarditis, Section 6.2 Post Authorization Experience) for the original Pfizer-BioNTech COVID-19 Vaccine. The Sponsor is conducting additional post-authorization/post-marketing studies to assess known serious risks of myocarditis and pericarditis as well as to identify an unexpected serious risk of subclinical myocarditis for the original Pfizer-BioNTech COVID-19 Vaccine. To help ensure appropriate monitoring of such risks and protect public



health, the Sponsor and vaccination providers will be required, under the conditions of authorization, to report all cases of myocarditis and pericarditis (regardless of seriousness) to VAERS. Because some cases of myocarditis or pericarditis following vaccine administration are conservatively managed and may not meet the definition of serious adverse events, this will help ensure that all cases are reported by the Sponsor and vaccination providers.

Review of the above VAERS data, as well as ongoing review of VAERS data and the Sponsor's periodic safety reports, did not identify new safety concerns for the original Pfizer-BioNTech COVID-19 Vaccine. Most AEs are labeled events, including anaphylaxis and myocarditis/pericarditis, and consistent with the known safety profile for the original vaccine. No unusual frequency, clusters, or other trends for AEs were identified that would suggest new safety concerns for the original vaccine.

## **7 FDA Review of Other Information Submitted in support of the EUA Amendment**

### **7.1 Nonclinical Data for the Bivalent (Original + Omicron BA.4/BA.5) Vaccine**

The immunogenicity of BNT162b2 vaccine formulations containing an Omicron (BA.4/BA.5) component was evaluated in mice. The vaccine candidates were tested in both naïve and BNT162b2-experienced mice as either monovalent (Omicron BA.4/BA.5) or bivalent [1:1 mixture of BNT162b2 monovalent (Original) and monovalent (Omicron BA.4/BA.5)] formulations. For studies in naïve mice, monovalent (Omicron BA.4/BA.5) or bivalent (Original and Omicron BA.4/BA.5) vaccines were evaluated as a two-dose primary series. To assess the vaccine candidates as boosters in BNT162b2-experienced mice, test animals were immunized with 2 prior doses of the BNT162b2 monovalent (Original) vaccine (at Days 0 and 21) followed by a 3rd boosting dose of the monovalent (Omicron BA.4/BA.5) or bivalent (Original and Omicron BA.4/BA.5) vaccines on Day 49. Immunogenicity data for serum collected 7 days following the 3rd dose booster show that the Omicron (BA.4/BA.5) vaccine enhanced neutralizing antibody responses against the SARS-CoV-2 original strain as well as Omicron sublineages. In the monovalent group, neutralizing titers increased by 2-, 4-, 17-, and 45-fold against the original strain, Omicron BA.1, Omicron BA.2, and Omicron BA.4/BA.5, respectively, at 7 days post booster compared with 1-month post-BNT162b2 Dose 2. In the bivalent group, neutralizing titers increased by 3-, 5-, 11-, and 22-fold against the original strain, BA.1, BA.2, and BA.4/BA.5, respectively, at 7 days post booster compared with 1-month post-BNT162b2 Dose 2. These data suggest that a modified vaccine containing an Omicron BA.4/BA.5 component could provide a greater breadth of response against antigenically diverse SARS-CoV-2 spikes, including those from Omicron sublineages. The nonclinical study is still ongoing; additional time points at 1-month post boost and following a 2-dose primary series of the monovalent (Omicron BA.4/BA.5) and bivalent (Original and Omicron BA.4/BA.5) vaccines will be evaluated as samples become available. Additionally, spleen and lymph nodes will be harvested from the test animals at the end of study and collected samples will be subjected for B- and T-cell analysis.

### **7.2 Clinical Assay Information**

A 384-well SARS-CoV-2 virus microneutralization (SARS-CoV-2\_NT) assay was developed and validated to measure neutralizing antibodies against the original SARS-CoV-2 strain and Omicron BA.1 sublineage using Vero cell monolayers in a 384-well plate format. In this assay, productive viral infection is detected using a SARS-CoV-2 Nucleocapsid (N) protein monoclonal antibody followed by an (b) (4). Viral foci are enumerated on a (b) (4). A 50% neutralizing titer (NT50) is determined as the reciprocal serum dilution at which a 50% reduction of virus infection is observed. Each

sample is tested in duplicate, and the final sample titer is determined as the geometric mean titer (GMT) of the two replicate results.

Validation of the 384-well SARS-CoV-2\_NT assay has been completed for the USA\_WA1/2020 reference strain and for the Omicron BA.1 sublineage at Pfizer's Vaccine Research & Development laboratory at Pearl River, NY. The validation studies included assessment of assay precision, intermediate precision, dilutional linearity, limit of quantification (LOQ), limit of detection, and extravariability of replicates using serum samples from BNT162b2-vaccinated subjects as well as convalescent serum samples with known Omicron infection. The results demonstrate that the 384-well SARS-CoV-2\_NT assay is suitable for its intended use for testing of clinical trial immunogenicity samples.

In addition, a fluorescent focus reduction neutralization test (FFRNT) was used to determine neutralizing titers against the USA\_WA1/2020 reference strain, Omicron BA.1 sublineage, and Omicron BA.4/BA.5 sublineage. The FFRNT is a non-validated assay and was used for exploratory purposes only.

### 7.3 Chemistry, Manufacturing, and Control (CMC) Information

The Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) contains two mRNA constructs, one encoding the spike protein from the original SARS-CoV-2 strain (Original; Wuhan-Hu-1) and the other encoding the spike protein from the SARS-CoV-2 Omicron BA.4/BA.5 variant. The bivalent vaccine is formulated in Tris/Sucrose buffer as a 30-µg mRNA dose (15 µg of each mRNA construct). Each bivalent dose also contains the following ingredients: a total lipid content of 0.76 mg (ALC-0315, ALC-0159, DSPC, and cholesterol), 0.06 mg tromethamine (Tris base), 0.4 mg tromethamine hydrochloride (Tris-HCl), and 31 mg sucrose.

The 30-µg mRNA dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is supplied as either a multi-dose vial filled at 2.25 mL fill volume, providing a total of 6 doses per vial, or a single-dose vial filled at 0.48 mL fill volume. For both the multi-dose and single-dose presentations, no dilution is needed prior to administration, and each dose contains 30-µg mRNA in a 0.3 mL injection volume. The shelf life of the bivalent vaccine is set to be 12 months when stored frozen at -90°C to -60°C in vials. The established shelf life also includes an allowance for short-term storage at 2°C to 8°C for up to 10 weeks at the point of use, counted within the 12-month shelf life.

The Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for emergency supply material is manufactured based on the original Pfizer-BioNTech COVID-19 Vaccine platform, with the same product composition, a highly similar manufacturing process, and the use of the same manufacturing sites and facilities previously authorized/approved for the original Pfizer-BioNTech COVID-19 Vaccine. The only difference in the bivalent manufacturing process is to include a (b) (4) step for the two mRNA drug substances in a 1:1 ratio (b) (4). Additional process development and characterization studies on the bivalent mixing were performed, and the study results confirmed suitability of the existing monovalent processing parameters for the manufacture of the bivalent vaccine.

Specifications for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) drug product remain the same as the original Pfizer-BioNTech COVID-19 Vaccine drug product except for strain- and valency-specific quality attributes, which include the identity and ratio of the two mRNA constructs, (b) (4). A new identity test method (b) (4)

(b) (4) has been developed. The assay specificity was evaluated, and the results support its intended use for distinguishing the Omicron BA.4/BA.5 mRNA vaccine sequence from the sequence of the original mRNA vaccine. (b) (4) is also used for mRNA ratio determination in the final bivalent DP. A validation of the (b) (4) assay for measuring the mRNA ratio has been successfully executed and all acceptance criteria were met. In addition, a modified (b) (4) method was developed and has been validated for the determination of (b) (4) in the bivalent vaccine.

The manufacture of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is performed at existing facilities that were previously authorized under EUA for the manufacture of the original Pfizer-BioNTech COVID-19 Vaccine. No changes were made to the facilities, equipment, container closure systems, quality systems and controls. The Sponsor appears to conduct manufacturing operations and controls as previously authorized for the original Pfizer-BioNTech COVID-19 Vaccine. We find that all facilities within the scope of this authorization are adequate to support the use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) under an Emergency Use Authorization.

#### **7.4 Inspection of Clinical Study Sites**

The review team decided that Bioresearch Monitoring (BIMO) inspections are not needed to support the review of this EUA amendment because clinical study sites participating in study C4591031 Substudy E also participated in studies that supported previous authorizations, and FDA is not aware of any new issues that would raise concerns about clinical trial conduct.

#### **7.5 Pharmacovigilance Activities**

Pfizer is conducting safety-related post-authorization/post-marketing studies for the monovalent vaccine, including post-marketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. Pfizer submitted a revised 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 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 should be conducted in large scale databases with an active comparator. This condition of authorization under the EUA, to conduct post-authorization observational studies, will encompass the evaluation of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in the following studies:
  - C4591021: Post-Authorization/Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine
 

Objective: To assess the potential increased risk of prespecified AESIs, including myocarditis/pericarditis, after being vaccinated with COVID-19 vaccine, including the Bivalent Omicron modified vaccine, if feasible.
  - C4591036: Pediatric Heart Network [PHN] 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, if feasible.
  - C4591012: Post-emergency use authorization active safety surveillance study among individuals in the Veteran’s Affairs Health System receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) vaccine
 

Objective: To assess whether individuals in the U.S. Veteran’s Affairs Health System experience increased risk of safety events of interest, including myocarditis and pericarditis, following receipt of the Pfizer-BioNTech COVID-19 Vaccine, including the Bivalent Omicron modified vaccine, if feasible.

In addition, the Sponsor will conduct a new stand-alone post-authorization observational study 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 AESIs in the general U.S. population for individuals ≥12 years of age who will receive a bivalent booster dose in the U.S. The protocol synopsis for this study will be submitted by 10/31/2022. The Sponsor also plans to include vaccine effectiveness analyses among individuals who received Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in Study C4591014 entitled “Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study Kaiser Permanente Southern California” and study WI255886 entitled “Avon Community Acquired Pneumonia Surveillance Study”.

## 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.

## **7.6 EUA Prescribing Information and Fact Sheets**

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

## **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 Dose in Individuals 12 Years 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 nearly 94 million cases of COVID-19 and over 1.04 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. Current treatment options for COVID-19 include antiviral medications and monoclonal antibodies approved or authorized for the management of individuals with COVID-19. 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. There are currently 4 approved or authorized COVID-19 vaccines for disease prevention. These include two mRNA-based vaccines, one from Moderna and one from Pfizer-BioNTech, one non-replicating viral vectored vaccine from Janssen/Johnson & Johnson, and one protein-based adjuvanted vaccine from Novavax. These monovalent vaccines are 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 transmission and symptomatic disease declines more rapidly than that against serious disease, as has been illustrated by studies conducted in the United States,<sup>30,31</sup> Israel,<sup>17</sup> Qatar,<sup>14</sup> Portugal,<sup>32</sup> and England.<sup>9</sup>

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 indicate that a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose will provoke an antibody response to current predominantly circulating BA.4 and BA.5 variants which is several-fold higher than the response provoked by the original (monovalent) vaccine.

Based on previous experience and available evidence, vaccination with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster dose is expected to provoke a stronger immune response to the currently circulating BA.4 and BA.5 variants. That noted, it is uncertain exactly how the magnitude of the increase in antibody response to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster dose will translate into effectiveness against specific COVID-19 outcomes in humans, including symptomatic and serious disease with currently circulating variants, and this uncertainty is even greater for potential variants that may emerge in the future.

Additional booster doses may be associated with transient local and systemic symptoms like those seen with primary series and booster doses given previously. The most notable uncommon side effect of the mRNA COVID-19 vaccines has been myocarditis. Based on the data from BEST, 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.<sup>33</sup> 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.<sup>28</sup> The myocarditis associated with the administration of mRNA COVID-19 vaccines has been mild and transient in most cases (>95%). Limited clinical evaluation of bivalent mRNA COVID-19 vaccine formulations has not suggested any new safety concerns 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 COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster doses will likely increase the immune response against SARS-CoV-2 variants and may particularly help target the currently predominant BA.5 variant. Administration of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster is appropriate for all individuals 12 years of age and older at least two months after previous primary or booster vaccination regardless of the number of prior COVID-19 vaccinations they have had, but is particularly important in those individuals who have never been previously boosted since protection against symptomatic and serious COVID-19 may have waned over time since administration of the primary series. Limited clinical evaluation of bivalent mRNA COVID-19 vaccine formulations has not suggested any 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 utilized to assess whether any new safety concerns emerge. [Table 19](#) provides a summary of the benefit risk considerations in a standard FDA format.

**Table 11. Summary of Benefit-Risk Assessment**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<ul style="list-style-type: none"> <li>• COVID caused by SARS-CoV-2 has been responsible for nearly 94 million cases and 1.04 million deaths in the US</li> <li>• There has been a succession of variants (Delta, Omicron BA.1 and most recently BA.5) that have led to a reduction in vaccine effectiveness</li> <li>• 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</li> </ul>	<ul style="list-style-type: none"> <li>• 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</li> <li>• 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</li> </ul>
<b>Current Treatment Options</b>	<ul style="list-style-type: none"> <li>• Antiviral medications and monoclonal antibodies 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</li> <li>• There are four approved or authorized COVID-19 vaccines (two mRNA-based, one non-replicating viral vector, and one protein-based, adjuvanted); these are all effective as primary series, and the mRNA-based and non-replicating viral vector vaccines are effective as boosters</li> </ul>	<ul style="list-style-type: none"> <li>• 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)</li> <li>• Vaccines play an important role in pandemic control and provide important protection.</li> </ul>
<b>Benefit</b>	<ul style="list-style-type: none"> <li>• 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</li> <li>• Non-clinical studies indicate that a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose will provoke an antibody response against BA.4 and BA.5 that is many-fold higher than the Original booster</li> <li>• Uncertain how the magnitude of the increase in antibody response in humans will translate into effectiveness against COVID-19 outcomes, including symptomatic and serious disease</li> </ul>	<ul style="list-style-type: none"> <li>• The totality of the available evidence indicates that bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster doses will likely increase the broad immune response against SARS-CoV-2 variants and may particularly help target the currently predominant BA.5 variant</li> <li>• Administration of bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster doses is appropriate for all previously vaccinated individuals 12 years of age and older, regardless of the number of prior COVID-19 vaccinations, but especially those who have never been previously boosted since protection against serious disease may have waned over time since administration of the primary series</li> </ul>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<b>Risk and Risk Management</b>	<ul style="list-style-type: none"> <li>Additional booster doses may be associated with transient local and systemic symptoms like those seen with primary series and prior booster doses</li> <li>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.<sup>28</sup></li> </ul>	<ul style="list-style-type: none"> <li>Limited clinical evaluation of bivalent mRNA COVID-19 vaccine formulations has not suggested any new safety concerns additional to the extensively characterized safety profile of original mRNA COVID-19 vaccines</li> <li>Post-deployment monitoring for adverse events using both passive and active surveillance systems will be utilized to assess whether any new safety concerns emerge</li> </ul>

## 8.2 Conclusions Regarding Benefit-Risk

The known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster dose outweigh the known and potential risks of the bivalent booster 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 current wave of COVID-19 caused in large part by the BA.5 sublineage, administration of a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose is expected to have a favorable benefit-risk profile, potentially not only restoring protection against serious outcomes from COVID-19, but also by reducing symptomatic disease that may be followed by debilitating post-acute COVID-19 syndrome. Broader protection against COVID-19 variants potentially elicited by the bivalent vaccine may also help protect against future emerging variants.

## 9 Overall Summary and Recommendations

Following review of information submitted in support of the EUA request, and VRBPAC recommendations from the June 28, 2022, meeting, the review team considered the following in its assessment of the Pfizer-BioNTech COVID-19 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 was as follows:
  - clinical safety and immunogenicity data from a study which evaluated a second booster dose with the Bivalent BA.1(Original and Omicron BA.1) vaccine following a primary series and first booster with the original Pfizer-BioNTech COVID-19 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,
  - post-marketing safety surveillance data with primary series and booster doses of the original Pfizer-BioNTech COVID-19 Vaccine, and



- non-clinical immunogenicity data from a study of BNT162b2 formulations containing an Omicron BA.4/BA.5 component.
- 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), when administered as a single booster dose to individuals 12 years of age and older who have completed primary vaccination or a booster dose of an authorized or approved COVID-19 vaccine at least 2 months prior, 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. Vaccine effectiveness was inferred based on extrapolation of clinical immunogenicity data from a related bivalent COVID-19 vaccine (Bivalent BA.1) manufactured using the same process and also containing original and Omicron variant (BA.1 sublineage) components. Effectiveness of the Bivalent BA.1 vaccine was based on the evaluation of the SARS-CoV-2 50% neutralizing antibody titers at 1 month after a second booster dose. The analyses included evaluations of SARS-CoV-2 GMTs and seroresponse rates elicited by a second booster dose of Bivalent BA.1 vaccine against the Omicron BA.1 and reference strains as compared to a second booster dose of the original Pfizer-BioNTech COVID-19 Vaccine. The statistical success criteria were met for the co-primary objectives of demonstrating superiority of the SARS CoV-2 neutralizing antibody GMTs and non-inferiority of the seroresponse rates against Omicron BA.1. Additionally, statistical success criteria were met for a secondary objective to demonstrate non-inferiority of the SARS-CoV-2 neutralizing antibody GMTs against the reference strain, and a post-hoc analysis would have met the FDA-recommended statistical success criterion for demonstrating non-inferiority of the SARS-CoV-2 neutralizing antibody seroresponse rates against the reference strain.
- 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 a booster dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) outweigh the known and potential risks when used as a booster dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. Known and potential benefits 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 related to benefits include that effectiveness of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to prevent COVID-19 is inferred and extrapolated from immunogenicity data with a different Omicron-containing bivalent vaccine (Original and Omicron BA.1) manufactured by the same process. It is also uncertain how any given magnitude of the increase in antibody response to a bivalent (Original and BA.4/BA.5) booster vaccine, relative to the original (monovalent) vaccine, will translate into effectiveness against COVID-19 outcomes, including symptomatic disease. However, this uncertainty is considered against available evidence demonstrating waning protection from COVID-19 vaccine primary series and booster doses, decreased effectiveness of currently available COVID-19 vaccines against Omicron BA.5 (the predominant SARS-CoV-2 sublineage in the US) compared to previous strains, and the time that would be needed to accrue clinical trial data with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to more directly assess effectiveness. Additional uncertainties include effectiveness against future SARS-CoV-2 variants, effectiveness against asymptomatic SARS-CoV-2 infection and SARS-CoV-2 transmission, and effectiveness in certain high-risk populations such as severely immunocompromised individuals. Known and potential risks include generally self-limited common local and systemic adverse reactions (notably injection site reactions, fatigue,

headache, muscle pain, chills, fever and joint pain), lymphadenopathy, and rarely anaphylaxis and myocarditis/pericarditis based on experience in original Pfizer-BioNTech COVID-19 Vaccine recipients 12 years of age and older. Risks that should be further evaluated include quantifying the rate of vaccine-associated myocarditis/pericarditis in this age group and surveillance for other adverse reactions that may become apparent with widespread use of the vaccine and with longer duration of follow-up.

- The Pfizer-BioNTech COVID-19 Vaccine and the Moderna COVID-19 Vaccine are currently authorized for use under EUA as a first booster dose in individuals 5 years of age and older and individuals 18 years of age and older, respectively, and as a second booster dose in certain populations. The Janssen COVID-19 vaccine is also authorized for limited use under EUA as a first booster dose in individuals 18 years of age and older. These vaccines are monovalent vaccines based on the original (ancestral) SARS-CoV-2 strain. COVID-19 vaccines based on currently circulating variants of concern are not currently approved or available.

Based on the considerations outlined above, the review team recommends authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) under EUA for use as a single booster dose administered at least 2 months after either completion of primary vaccination or the most recent booster dose in individuals 12 years of age and older. The review team also recommends a revision to the existing EUA for Pfizer-BioNTech COVID-19 Vaccine to remove the use of the monovalent vaccine as a first or second booster dose for individuals 12 years of age and older because the benefit/risk profile for this currently-authorized booster dose use is expected to be inferior against the currently circulating Omicron variant compared to Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

## 10 Appendix: COVID-19 Surveillance and Case Definitions

If, at any time, a participant develops acute respiratory illness, they will be considered to potentially have COVID-19 illness and the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the protocol Schedule of Activities. The assessments will include collection of a nasal (midturbinate) swab, which will be tested at a central laboratory using an RT-PCR test (Cepheid Xpert Xpress SARS-CoV-2; authorized by the FDA under EUA and Pfizer-validated), or other equivalent nucleic acid amplification–based test (i.e., NAAT) to detect SARS-CoV-2. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche Cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

Definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered as follows (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
  - Fever;
  - New or increased cough;

- New or increased shortness of breath;
  - Chills;
  - New or increased muscle pain;
  - New loss of taste or smell;
  - Sore throat;
  - Diarrhea;
  - Vomiting.
- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:
    - Clinical signs at rest indicative of severe systemic illness (RR  $\geq$ 30 breaths per minute, HR  $\geq$ 125 beats per minute, SpO<sub>2</sub>  $\leq$ 93% on room air at sea level, or PaO<sub>2</sub>/FiO<sub>2</sub>  $<$ 300 mm Hg);
    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
    - Evidence of shock (SBP  $<$ 90 mm Hg, DBP  $<$ 60 mm Hg, or requiring vasopressors);
    - Significant acute renal, hepatic, or neurologic dysfunction;
    - Admission to an ICU;
    - Death.
  - Confirmed severe COVID-19 (CDC definition): confirmed COVID-19 and presence of at least 1 of the following:
    - Hospitalization;
    - Admission to the ICU;
    - Intubation or mechanical ventilation;
    - Death.

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