Vaccines and Related Biological Products Advisory Committee Meeting
September 17, 2021

FDA Briefing Document

Application for licensure of a booster dose for COMIRNATY (COVID-19 Vaccine, mRNA)

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1. EXECUTIVE SUMMARY

On August 23, 2021, FDA approved COMIRNATY (COVID-19 Vaccine, mRNA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The vaccine is based on the SARS-CoV-2-spike glycoprotein antigen encoded by modified mRNA and formulated in lipid particles (LNPs). The approved regimen is a 2-dose primary vaccination series administered 3 weeks apart. During clinical development, the vaccine, containing 30 µg mRNA, was called BNT162b2.

On August 25, 2021, Pfizer submitted a supplement to their Biologics License Application (BLA) for COMIRNATY seeking approval for administration of a booster dose approximately 6 months after primary series. To support the need for a booster dose, the submission referenced several observational studies that suggest waning of protection in the setting of the current Delta variant surge among individuals who previously received a 2-dose series.

This BLA supplement includes safety and immunogenicity data assessed against the reference strain (wild-type) from approximately 300 immunocompetent adults 18 through 55 years of age enrolled in an ongoing Phase 2/3 study (C4591001) who completed the primary vaccination series consisting of two doses of BNT162b2 administered intramuscularly (IM) and who received a BNT162b2 booster dose approximately 6 months after completion of the 2-dose primary series. Efficacy was not evaluated for Phase 3 BNT162b2 booster group participants. Supportive data from the Phase 1 portion of this study in participants 18 through 55 years of age (N=11) and 65 through 85 years of age (N=12) who had received a 30 µg BNT162b2 prototype vaccine approximately 7 to 9 months after their second dose were also included and consisted of safety data and immunogenicity data evaluating neutralizing antibody titers elicited by the booster dose against the reference strain (wild-type) of SARS-CoV-2 and variants of concern (VOCs).

The effectiveness of the booster dose is based on immunobridging analyses from the Phase 3 group of participants 18 through 55 years of age comparing 50% neutralizing antibody titers against the reference strain at 1 month after the booster dose to those observed at 1 month post-primary series among participants without evidence of prior SARS-CoV-2 infection. Immunobridging analyses included hypothesis testing for:

- geometric mean titers (GMTs) of SARS-CoV-2 neutralizing antibodies at 1 month after the booster dose vs. those values 1 month after the primary series, using a 1.5-fold non-inferiority margin as the success criterion for the lower bound of the confidence interval around the GMT ratio, and
- percentage of participants with seroresponse (≥4-fold rise from baseline at 1 month after the booster dose vs. 1 month after primary series), using a -10% non-inferiority margin as the success criterion for the lower bound of the confidence interval around the difference between seroresponse rates.

Immunobridging analyses against the reference strain met the pre-specified success criteria for GMT ratio and difference in seroresponse rates for the booster dose compared to the 2-dose primary series. Additionally, the geometric mean-fold rise (GMFR) from before the booster dose to 1 month after the booster dose was analyzed descriptively. Pfizer proposes to infer effectiveness of the booster dose against the Delta variant from exploratory descriptive analyses of 50% neutralizing antibody titers against this variant evaluated among subjects from the Phase 1 portion of the study.

Solicited and unsolicited safety data from booster recipients (12 Phase 1 participants 65 through 85 years of age and 306 Phase 2 participants 18 through 55 years of age) were reviewed and compared to labeled safety data from the reactogenicity subset (N=~2700) of recipients of the 2-dose primary series. Safety following the booster dose was assessed for a median of 2.6 months among both Phase 1 and Phase 2/3 study participants. Reported frequencies and severities of local and systemic solicited adverse reactions following the booster dose were not substantially different from those following Dose 2 of the primary series. Reported frequencies and severities of solicited adverse reactions following the booster dose were lower among the 12 Phase 1 participants 65 through 85 years of age compared with the 306 Phase 3 participants 18 through 55 years of age, similar to age group-related differences in reactogenicity associated with the primary series. Lymphadenopathy (16/306; 5.2%) was the most common unsolicited adverse event (AE); all events of lymphadenopathy occurred within 3 days of vaccination. No other adverse events of clinical interest (i.e., myocarditis, pericarditis, Bell's Palsy, appendicitis) were reported following the booster dose. The incidence post-booster dose was substantially higher than the rate reported among adults after any of the 2 doses of the primary series (83/21,926; 0.4%). However, most (n=15) were mild to moderate in severity and lasted between 2 to 8 days. Two cases of mild lymphadenopathy were reported as ongoing and resolving at the time of last assessment. No deaths were reported following the booster dose, and one nonfatal serious adverse event (acute myocardial infarction 2 months after the booster dose, assessed as unrelated to study vaccination) was reported.

Pfizer is requesting approval of the booster dose for use in individuals 16 years of age and older; therefore, safety and effectiveness of the booster dose in individuals 16 and 17 years of age would be based on extrapolation from safety and effectiveness data in adults.

This September 17, 2021 VRBPAC meeting is being held to discuss whether the data Pfizer has submitted are sufficient to support licensure of a booster dose of COMIRNATY administered approximately 6 months after the primary series to individuals 16 years of age and older.

2. SARS-COV-2 VIRUS AND COVID-19 DISEASE

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus). SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV). SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of September 7, 2021, has caused approximately 222 million cases of COVID-19, including 4.5 million deaths worldwide. In the United States, more than 39 million cases have been reported to the Centers for Disease Control and Prevention (CDC), of which 90% have occurred in individuals 16 years of age or older. While the pandemic has caused morbidity and mortality on an individual level, the continuing spread of SARS-CoV-2, and emerging variants (such as the highly transmissible Delta variant that is now predominant in the US) have caused significant challenges and disruptions in worldwide healthcare systems, economies, and many aspects of human activity (travel, employment, education).

Following emergency use authorization of COVID-19 vaccines in December 2020, COVID-19 cases and deaths in the United States declined sharply during the first half of 2021. The emergence of the Delta variant, variable implementation of public health measures designed to control spread, and continued transmission among unvaccinated individuals are major factors in the recent resurgence of COVID-19. While recently reported cases appear to be declining relative to the Delta variant-associated peak globally and in the US, the future course of the pandemic is uncertain.

3. VACCINES FOR SARS-COV-2

3.1. COMIRNATY (COVID-19 Vaccine, mRNA)

On August 23, 2021, FDA approved COMIRNATY (COVID-19 Vaccine, mRNA) made by BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.). COMIRNATY is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The vaccine is administered IM as a series of two (30 µg mRNA) doses (0.3 mL each) 3 weeks apart. COMIRNATY contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein of SARS-CoV-2 that is formulated in lipid particles. During clinical development, the vaccine was called BNT162b2. COMIRNATY is the only vaccine or medical product that is FDA approved for prevention of COVID-19.

3.1.1. Efficacy of a 2-dose primary series of COMIRNATY

Efficacy of BNT162b2 for the prevention of COVID-19 occurring at least 7 days after the second dose of vaccine was evaluated in an ongoing Phase 3 study in approximately 44,000 participants randomized 1:1 to receive two doses of either BNT162b2 or placebo, 3 weeks apart. Participants were enrolled with stratification by age (younger adults: 18 through 55 years of age; older adults: over 55 years of age). The population for the vaccine efficacy analysis that supported approval of COMIRNATY included participants 16 years of age and older who had been enrolled from July 27, 2020, and who were followed for the development of COVID-19 during blinded placebo-controlled follow-up through as late as March 13, 2021. Overall, 60.8% of participants in the BNT162b2 group and 58.7% of participants in the placebo group had ≥4 months of follow-up time after the primary series in the blinded placebo-controlled follow-up period. The overall VE against COVID-19 in subjects without evidence of prior SARS-CoV-2 infection was 91.1% (95% CI: 88.8 to 93.1). The overall VE against COVID-19 in subjects with or without evidence of prior SARS-CoV-2 infection was 90.9% (95% CI: 88.5 to 92.8).

3.1.2. Safety of a 2-dose primary series of COMIRNATY

The most commonly reported solicited adverse reactions (occurring in ≥10% of participants) among BNT162b2 vaccine recipients 16 through 55 years of age following any dose were pain at the injection site (88.6%), fatigue (70.1%), headache (64.9%), muscle pain (45.5%), chills (41.5%), joint pain (27.5%), fever (17.8%), and injection site swelling (10.6%). The most commonly reported solicited adverse reactions in BNT162b2 vaccine recipients 56 years of age and older following any dose were pain at the injection site (78.2%), fatigue (56.9%), headache, (45.9%), muscle pain (32.5%), chills (24.8%), joint pain (21.5%), injection site swelling (11.8%), fever (11.5%), and injection site redness (10.4%).

Among participants 16 through 55 years of age, serious adverse events from Dose 1 up to the participant unblinding date in ongoing follow-up were reported by 0.8% of BNT162b2 recipients and 0.9% placebo recipients. In a similar analysis, in participants 56 years of age and older

serious adverse events were reported by 1.8% of BNT162b2 recipients and 1.7% of placebo recipients who received at least 1 dose of BNT162b2 or placebo, respectively. In these analyses, 58.2% of study participants had at least 4 months of follow-up after the primary series. There were no notable patterns between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2. From Dose 1 through the March 13, 2021 data cutoff date, there were a total of 38 deaths, 21 in the BNT162b2 group and 17 in the placebo group. None of the deaths were considered related to vaccination.

3.1.2.1. Myocarditis/pericarditis

During the time from Dose 1 to unblinding in Study C4591001, one report of pericarditis was identified in the vaccine group, occurring in a male participant ≥55 years of age, with no medical history, 28 days after a primary series of BNT162b2; the event was assessed by the investigator as not related to the study intervention and was ongoing at the time of the data cutoff. One report of myocarditis was identified in a male participant <55 years of age in the placebo group, occurring 5 days after his second placebo dose.

Post-EUA safety surveillance reports received by FDA and CDC identified serious risks for myocarditis and pericarditis following administration of the primary series (Dose 1 and Dose 2) of BNT162b2. Reporting rates for medical chart-confirmed myocarditis/pericarditis in VAERS have been higher among males under 40 years of age than among females and older males and have been highest in males 16-17 years of age (~75 cases per million doses administered as per CDC presentation to the ACIP on August 30, 2021), particularly following the second dose, with onset of symptoms occurring within 7 days following vaccination. Consistent findings were reported in an FDA analysis of the Optum database, which estimated an excess risk approaching 200 cases per million vaccinated males 16-17 years of age.[1] Although some cases of vaccine-associated myocarditis/pericarditis required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae and outcomes in affected individuals, or whether the vaccine might be associated with initially subclinical myocarditis (and if it is what are the long-term sequelae). A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established. FDA determined that the benefits of the two-dose primary series outweighed the risks of myocarditis and pericarditis, including for males ages 16-17 years of age, and the increased risk of myocarditis/pericarditis is described in section 5.2 Warnings and Precautions of the prescribing information for COMIRNATY.

3.2. Vaccines authorized under EUA for SARS-CoV-2

FDA has issued EUAs for three COVID-19 vaccines as shown in Table 1 below.

Table 1. Emergency Use Authorizations of COVID-19 Vaccines

Sponsor	Regimen	Indicated Population	Date of EUA
Pfizer	2 doses 3 weeks apart	• Individuals ≥16 years of age • Individuals ≥12 years of age • 3rd dose for individuals ≥12 years and who have undergone solid organ transplantation, or diagnosed with conditions considered to have an equivalent level of immunocompromise	December 11, 2020 May 10, 2021 August 12, 2021
Moderna	2 doses 1 month apart	• Individuals ≥18 years of age • 3rd dose for individuals ≥18 years of age who have undergone solid organ transplantation, or diagnosed with conditions considered to have an equivalent level of immunocompromise	December 18, 2020 August 12, 2021
Janssen	Single dose	• Adults ≥18 years of age	February 27, 2021

4. RATIONALE FOR BOOSTER DOSES FOR COVID-19 VACCINES

Concerns have been raised that declining neutralizing antibody titers or reduced effectiveness against symptomatic disease may herald significant declines in effectiveness against severe disease. The recent emergence of the highly transmissible Delta variant of SARS-CoV-2 resulted in a new wave of COVID-19 cases in many parts of the world and has led to considerations for administration of booster doses to individuals who received primary series of vaccines in an effort to enhance immunity, and thus sustain protection from COVID-19.

The expected benefit of booster vaccination will depend on the impact that booster vaccination has in reducing disease relative to the primary series. If the primary series of COMIRNATY is still effective in preventing important COVID-19-related outcomes, then the benefit of booster vaccination is likely to be more limited than if effectiveness following the primary series has waned substantially. Factors supporting licensure of a booster dose should consider the effectiveness of primary vaccination with COMIRNATY over time and against circulating variants, the effectiveness (and its duration) of booster vaccination in preventing important COVID-19-related outcomes in individuals who have already received a primary vaccination series, the dynamics of the pandemic in the United States, and the risks of booster vaccination in the general population or in certain subpopulations.

Some observational studies have suggested declining efficacy of COMIRNATY over time against symptomatic infection or against the Delta variant, while others have not. However, overall, data indicate that currently US-licensed or authorized COVID-19 vaccines still afford protection against severe COVID-19 disease and death in the United States. There are many potentially relevant studies, but FDA has not independently reviewed or verified the underlying data or their conclusions. Some of these studies, including data from the vaccination program in Israel, will be summarized during the September 17, 2021 VRBPAC meeting.

It should be recognized that while observational studies can enable understanding of real-world effectiveness, there are known and unknown biases that can affect their reliability. Due to these biases some studies may be more reliable than others. Furthermore, US-based studies of post-

authorization effectiveness of BNT162b2 may most accurately represent vaccine effectiveness in the US population.

5. APPROVAL REQUIREMENTS, GUIDANCE AND CONSIDERATIONS PERTAINING TO COVID-19 VACCINES

5.1. US approval requirements

A single set of regulatory requirements applies to all vaccines, regardless of the technology used to produce them. Section 351 of the Public Health Service Act (42 USC 262) states that a biologics license application (BLA) shall be approved based on a demonstration that "…(a) the biological product that is the subject of the application is safe, pure and potent; and (b) the facility in which the biological product is manufactured, processed, packed or held meets standards designed to assure that the biological product continues to be safe, pure, and potent...". Thus, regardless of indication or intended target population, only those COVID-19 vaccines that are demonstrated to be safe and effective and that can be manufactured in a consistent manner will be licensed by the FDA. For a licensed vaccine, a change in dosing regimen, such as inclusion of a booster dose, requires the approval of a supplemental BLA. This supplemental BLA must include data demonstrating the safety and effectiveness of the additional dose.

5.2. FDA guidance for industry related to COVID-19 vaccines

To facilitate the manufacturing, clinical development, and licensure of COVID-19 vaccines, FDA published the guidance for industry entitled Development and Licensure of Vaccines to Prevent COVID-19 (June 2020) describing FDA's current recommendations regarding the data needed to facilitate clinical development and licensure of vaccines to prevent COVID-19.[2] This guidance provides an overview of key considerations to satisfy regulatory requirements set forth in the investigational new drug application (IND) regulations in 21 CFR Part 312 and licensing regulations in 21 CFR Part 601 for chemistry, manufacturing, and controls (CMC), and nonclinical and clinical data through development and licensure, and for post-licensure safety evaluation of COVID-19 preventive vaccines. The guidance notes that the efficacy of COVID-19 vaccines should be demonstrated in adequate and well controlled clinical trials that directly evaluate the ability of the vaccine to protect humans from SARS-CoV-2 infection and/or disease. The guidance notes further that safety evaluations including the size of the database required to support licensure should be no different than for other preventive vaccines for infectious diseases. Of note, this guidance does not address immunogenicity studies to infer effectiveness of booster doses for COVID-19 vaccines. However, the guidance for industry document Emergency Use Authorization for Vaccines to Prevent COVID-19 (May 2021, February 2021, originally issued October 2020) describes data needed to support the effectiveness of a modified COVID-19 vaccine against VOCs.[3] FDA has applied these concepts to effectiveness evaluations of booster doses afforded by the prototype vaccine (refer to Section 5.4 below).

5.3. Regulatory considerations for a booster dose for COVID-19 vaccines

The benefit of a booster dose must be weighed against potential risk. Available data should support the effectiveness of the booster dose, particularly against currently circulating SARS-CoV-2 variants, and benefit should be considered relative to the benefit provided by completion of the primary series. Safety data should be available to identify the most frequently reported adverse reactions associated with the booster dose. Pre-licensure or pre-authorization clinical trials may not be adequately powered to characterize uncommon but potentially serious adverse

reactions, such as myocarditis/pericarditis (see Section 3.1.2.1). It is currently not known if there will be an increased risk of myocarditis/pericarditis or other adverse reactions after a booster dose of COMIRNATY. These risks and associated uncertainties have to be considered in when assessing benefit and risk.

5.4. Data to support safety and effectiveness of a booster dose of COVID-19 vaccines

As noted above, the Guidance for Industry Emergency Use Authorization for Vaccines to Prevent COVID-19 (May 2021) describes data that could support the effectiveness of modified COVID-19 vaccines directed against a VOC strain. While the current supplement is not for a booster dose targeted to a VOC, the intended use in the current pandemic situation is analogous, and corresponding recommendations have been conveyed to product sponsors seeking discussions on booster dosing with the prototype vaccine, as summarized below.

Effectiveness of a booster dose with a COVID-19 vaccine can be evaluated based on the efficacy of the manufacturer's authorized prototype vaccine made by the same manufacturing process and for which a clinical disease endpoint efficacy study has been conducted that met FDA's pre-specified success criteria. A determination of effectiveness of a booster dose should be supported by conducting clinical immunogenicity studies. The following considerations apply to homologous booster doses for COVID-19 vaccines that have already been licensed or received emergency use authorization for use in adults. As described in the EUA Guidance, a safety and immunogenicity study conducted in a single age group (e.g., adults 18-55 years of age) could potentially provide data to extrapolate safety and effectiveness of a booster dose for use in all age groups for which the primary series has been approved or authorized. As a scientific consideration, extrapolation of booster dose data across age groups presumes that no age group-specific safety or effectiveness considerations would preclude such extrapolation.

A favorable benefit-risk assessment to support authorization or approval of a booster dose would depend on evidence (e.g., longer term efficacy data and or data from post-authorization effectiveness studies) that a booster dose is needed and evidence (i.e., immunogenicity data) that the booster dose would be effective not only against the original reference or prototype SARS-CoV-2 strain but also against circulating variants. Furthermore, it is expected that justification for the interval chosen for the booster dose is provided taking into account both safety and effectiveness considerations. Clinical non-inferiority immunogenicity studies should be conducted in which the prototype COVID-19 vaccine is administered to persons who previously received the prototype COVID-19 vaccine according to the authorized or licensed dose and dose regimen. The immune response induced by the booster dose should be compared to the immune response induced by the primary series, as assessed by neutralizing antibody seroresponse rates and GMTs against the original virus (reference strain) upon which the prototype vaccine was based. It is expected that the booster would induce an immune response against the reference strain and clinically relevant variants of concern at levels that meet or exceed those elicited by the primary series against the reference strain. The study should be adequately powered for primary immunogenicity analyses to demonstrate statistical non-inferiority of seroresponse rate and GMT elicited by the booster dose compared to the primary series using non-inferiority margins of -10% for seroresponse rates and 1.5-fold for GMTs, respectively. Alternative non-inferiority margins may be considered, with adequate justification, on a case-by-case basis.

Conducting immunobridging analyses and evaluating neutralization against clinically relevant variant viruses will require development of the appropriate neutralization assays specific for the purpose. These assays would need to be sufficiently characterized (e.g., sensitivity, specificity)

as part of the qualification/validation process to understand and account for differences in behavior of the different input viruses (e.g., as a result of expressing different spike protein antigens) that could confound the ability to compare measured neutralization titers.

Safety assessments, including solicited and local and systemic adverse events assessed daily for at least 7 days after each study vaccination as well as serious and other unsolicited adverse events assessed during the immunogenicity evaluation period, may be sufficient to support emergency use authorization or licensure of a booster dose. Evaluation in a larger safety database than initially planned for immunogenicity analysis may be warranted if safety signals that can be reasonably evaluated in pre-licensure/pre-authorization studies arise during clinical evaluation of the booster dose. Post-licensure/post-authorization studies should be conducted to assess longer-term safety for serious and other medically important adverse events.

6. COMIRNATY (COVID-19 Vaccine, mRNA) manufactured by Pfizer Inc. FOR BIONTECH MANUFACTURING GMBH)

6.1. Vaccine indication and dosing regimen

COMIRNATY is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The vaccine is administered IM as a series of two 30 µg doses (0.3 mL each) 3 weeks apart.

6.2. Vaccine composition, dilution and storage

COMIRNATY contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein of SARS-CoV-2 that is formulated in lipid particles. It is supplied as a concentrated multi-dose liquid formulation (0.45 mL volume) stored frozen at -90°C to -60°C in a 2 mL Type 1 glass vial. A sterile diluent, 0.9% Sodium Chloride Injection, USP, is supplied separately and is stored at 20°C to 25°C. The COMIRNATY Multiple Dose Vial is thawed in a refrigerator (2°C to 8°C) for 2 to 3 hours or at room temperature (up to 25°C) for 30 minutes. Once at room temperature, the COMIRNATY Multiple Dose Vial is diluted with 1.8 mL of the diluent. After dilution, each vial of COMIRNATY contain six doses of 0.3 mL of vaccine. Each dose contains 30 µg mRNA. COMIRNATY does not contain preservative.

6.3. Proposed use of a COMIRNATY booster dose

The proposed use is for “booster administration of COMIRNATY approximately 6 months following a primary vaccination series.”

6.4. FDA review of clinical data from Study C4591001

6.4.1. Design

Study C4591001 is ongoing. The study was initially designed to evaluate two vaccine candidates and several dosages in healthy adults in the United States (Phase 1), of which 24 participants (n=12 per age group: 18-55 years and 65-85 years) received a 2-dose primary series of BNT162b2 (30 µg); the study population included healthy men and women and excluded participants at high risk of SARS-CoV-2 infection or with serological evidence of prior or current SARS-CoV-2 infection.

The Phase 2/3 portion of the study is being conducted in the United States, Argentina, Brazil, Germany, South Africa and Turkey. Please see the Summary Basis for Regulatory Action for the approval of a 2-dose primary series of COMIRNATY for study design details.[1] Enrolled Phase 2/3 participants were initially stratified by age (18-55 years and >55 years), with the goal of older adults (>55 years of age) comprising 40% of the total study population. The protocol was later amended to include adolescents 16 and 17 years of age. The study population included participants at higher risk for acquiring COVID-19 and at higher risk of severe COVID-19, such as health care workers, participants with autoimmune disease, and participants with chronic but stable medical conditions such as hypertension, asthma, diabetes, and infection with HIV, hepatitis B or hepatitis C. Participants were randomized 1:1 to receive two doses of either BNT162b2 or saline placebo 3 weeks apart. Per protocol, since December 14, 2020, following issuance of the Emergency Use Authorization for the Pfizer-BioNTech COVID-19 Vaccine, Phase 2/3 participants ≥16 years of age in the vaccine and placebo groups were progressively unblinded to their treatment assignment (when eligible for vaccination per local recommendations), and participants originally randomized to placebo were offered vaccination with BNT162b2 under the study protocol with continuing follow-up for safety and COVID-19-related outcomes.

In February and March 2021, the protocol was amended to evaluate the safety and immunogenicity of booster dose of BNT162b2 in Phase 1 participants (N=12 per age cohort: 18-55 years and 65-85 years) and a subset of Phase 2/3 adults (N=300, ages 18-55 years), who completed the 2-dose primary vaccination series with 30 µg BNT162b2. A booster dose of 30 µg BNT162b2 was administered approximately 7 to 9 months after a primary series for Phase 1 participants and approximately 6 months after a primary series for Phase 2/3 participants.

Immunogenicity evaluation

The effectiveness of the booster dose is based on an immunobridging analysis from the Phase 2/3 booster participants comparing 50% neutralizing antibody titers against the reference strain (recombinant USA-WA1/2020) at 1 month after the booster dose to those observed at 1 month post-primary series among subjects without evidence of prior SARS-CoV-2 infection. Immunobridging analyses included hypothesis testing for:

- GMTs of SARS-CoV-2 neutralizing antibodies at 1 month after the booster dose vs. those values 1 month after a primary series, using a 1.5-fold non-inferiority margin as the success criterion for the lower bound of the confidence interval around the geometric mean ratio (GMR), and
- percentage of participants with seroresponse (≥4-fold rise from baseline) at 1 month after the booster dose vs. 1 month after a primary series, using a -10% non-inferiority margin as the success criterion for the lower bound of the confidence interval around the difference between seroresponse rates.

In the protocol-specified analysis of seroresponse, the baseline neutralizing antibody titer for determining seroresponse to the booster dose was the pre-Dose 1 titer (same baseline titer as used for determining seroresponse to the primary series). However, FDA also asked Pfizer to conduct a post hoc seroresponse analysis using the pre-booster dose titer as the baseline for determining the booster dose seroresponse (defined as ≥4-fold increase from the pre-booster dose baseline titer).

Exploratory analyses of neutralizing antibody titers elicited by the BNT162b2 primary series and a 30 µg BNT162b2 booster dose against the reference strain (Wuhan) of SARS-CoV-2 and the

Beta and Delta variants were performed using samples from the Phase 1 study population. Discussion of these exploratory analyses in this briefing document is focused on the Delta variant, since it is currently the predominant circulating variant in the US.

Safety evaluation

Phase 1 participants and Phase 2/3 participants recorded reactogenicity assessments and antipyretic/pain medication use from Day 1 through Day 7 after booster in an e-diary. Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling) and systemic AEs (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain). Other safety assessments included: AEs occurring within 30 minutes after each dose, non-serious unsolicited AEs from Dose 1 through 1 month after the booster dose, and serious AEs (SAEs) from the booster dose to the data cut-off date of June 17, 2021 (Phase 2/3) or May 13, 2021 (Phase 1).

Analysis populations pertaining to the 30 µg BNT162b2 booster dose

- Safety: All randomized participants who received a booster dose of 30 µg BNT162b2. Analyses of reactogenicity endpoints were based on a subset of the safety population that included participants with any e-diary data reported after vaccination.
- All-available immunogenicity: All participants who received a primary series of 30 µg BNT162b2 at initial randomization, received a booster dose of 30 µg BNT162b2, and had at least 1 valid and determinate immunogenicity result after the booster dose.
- Evaluable immunogenicity: All eligible participants who received a primary series of 30 µg BNT162b2 as initially randomized, with Dose 2 received within 19-42 days after Dose 1, received a booster dose of 30 µg BNT162b2, had at least 1 valid and determinate immunogenicity result after the booster dose from a blood collection within 28-42 days after the booster dose, and had no other important protocol deviations as determined by the clinician.

6.4.2. Demographics and disposition

Demographic characteristics of the Phase 1 and Phase 2/3 study participants who received a BNT162b2 (30 µg) booster dose are summarized in Table 2 below. Booster recipients were predominantly White. Phase 1 excluded individuals with comorbidities that confer risk for severe COVID-19 (i.e., obesity, diabetes with or without complications, chronic pulmonary disease, cardiovascular conditions such as hypertension, congestive heart failure, ischemic heart disease, HIV). Approximately 20% of booster recipients in Phase 2/3 had such comorbidities.

Table 2. Demographics and Baseline Characteristics, Phase 1 and Phase 2/3 Recipients of BNT162b2 (30 µg) Booster Dose, Safety Population

Characteristic	Phase 1 18-55 Years N=11 n (%)	Phase 1 65-85 Years N=12 n (%)	Phase 2/3 18-55 Years N=306 n (%)
Sex: Female	9 (81.8)	6 (50.0)	166 (54.2)
Sex: Male	2 (18.2)	6 (50.0)	140 (45.8)
Age: Mean (years)	38.3	69.3	41.2
Age: Median (years)	39.0	69.0	42.0
Age: Min, max (years)	24, 55	65, 75	19, 55
Race: American Indian or Alaska Native	0	0	2 (0.7)
Race: Asian	2 (18.2)	0	16 (5.2)

Characteristic	Phase 1 18-55 Years N=11 n (%)	Phase 1 65-85 Years N=12 n (%)	Phase 2/3 18-55 Years N=306 n (%)
Race: Black or African American	1 (9.1)	0	28 (9.2)
Race: Native Hawaiian or other Pacific Islander	0	0	1 (0.3)
Race: White	8 (72.7)	12 (100.0)	249 (81.4)
Race: Multiracial	0	0	4 (1.3)
Race: Not reported	0	0	6 (2.0)
Ethnicity: Hispanic or Latino	0	0	85 (27.8)
Ethnicity: Not Hispanic or Latino	11 (100.0)	12 (100.0)	219 (71.6)
Ethnicity: Not reported	0	0	2 (0.7)
History of SARS-CoV-2 exposure pre-Dose 1[a]	0	0	11 (3.6)
Comorbidities[b]: Yes	0	0	56 (18.3)
Obese[c]	0	0	122 (39.9)

[a] Missing data for 7 of the 306 (2.3%) Phase 2/3 participants.
[b] Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease, characterized from medical conditions included in the Charlson comorbidity index. Phase 1: Co-morbidities that constituted risk factors for severe COVID-19 were exclusion criteria.
[c] Defined as BMI greater than 30 kg/m^2

Among the 24 Phase 1 study participants randomized to the BNT162b2 primary series, 23 participants received a BNT162b2 (30 µg) booster dose (11 adults ages 18-55 years and 12 adults ages 65-85 years). One participant in the 18-55 year-old cohort declined to receive a BNT162b2 booster dose. All 23 Phase 1 participants who received the booster dose were included in the safety analyses, and the booster dose evaluable immunogenicity population. The disposition of Phase 2/3 study participants who received a BNT162b2 (30 µg) booster dose is summarized in Table 3 below.

Table 3. Disposition of Phase 2/3 Recipients of BNT162b2 (30 µg) Booster Dose

Disposition	BNT162b2 (30 µg) n[a] (%)
Selected to receive BNT162b2	312 (100.0)
Safety population	306 (98.1)
Excluded because did not receive BNT162b2	6 (1.9)
Booster all-available immunogenicity population	306 (98.1)
Excluded because they did not have at least 1 valid and determinate immunogenicity result after booster vaccination	6 (1.9)
Booster evaluable immunogenicity population	268 (85.9)
Without evidence of infection up to 1 month after booster dose[c]	234 (75.0)
Subjects excluded from booster evaluable immunogenicity population	44 (14.1)

Disposition	BNT162b2 (30 µg) n[a] (%)
Reason for exclusion (subjects may have been excluded for >1 reason)	
Did not receive Dose 2 within 19 to 42 days after Dose 1	1 (0.3)
Did not receive BNT162b2	6 (1.9)
Did not have at least 1 valid and determinate immunogenicity result within 28 to 42 days after booster dose	15 (4.8)
Had protocol deviation(s) before the 1 month post-booster evaluation deemed to be important by the clinician[d]	30 (9.6)

[a] n = Number of subjects with specified characteristic
[b] Denominator for percentage calculations
[c] Subjects who had no serological or virological evidence (up to 1 month after receipt of booster vaccination) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1, 3, 301 (day of booster dose), and 303 (1 month after booster dose) and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1, 2, and 301) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster dose.
[d] Received booster dose outside protocol-specified window of 150 to 210 days after completing the primary series (n=15); had investigational product protocol deviations (n=13); received the booster dose outside the protocol-specified window of 150 to 210 days after a primary series & had an investigational product protocol deviation (n=1); had 6 months post-primary series/pre-booster blood draw after receiving booster dose (n=1).

6.4.3. Timing of BNT162b2 booster administration

The median interval between the booster dose and completion of a BNT162b2 primary series was 6.8 months (range 4.8-8.0) for Phase 2/3 participants and 8.3 months (range 7.9-8.5) for Phase 1 participants. Following the booster dose, the median follow-up time was 2.6 months (range: 2.1 to 2.9 months) for Phase 1 participants and 2.6 months (range: 1.1 to 2.8 months) for Phase 2/3 participants.

6.4.4. Immunogenicity evaluation

Primary immunogenicity objective - 30 µg BNT162b2 booster dose

Immunogenicity of a booster dose of BNT162b2 was assessed based on analyses of GMT ratio and seroresponse rates for neutralizing antibody titers to the reference strain.

GMTs of neutralizing antibody titers to the reference strain

Noninferiority was assessed based on the GMT of SARS-CoV-2 neutralizing titers 1 month after the booster dose compared to 1 month after completion of a primary vaccination series using a 1.5-fold margin. The GMT ratio was calculated as the mean of the difference of logarithmically transformed titers for each participant (i.e., later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 97.5% CIs were obtained by constructing CIs using Student's t-distribution for the mean difference on the logarithmic scale and exponentiating the confidence limits. For assessment of an adequate GMT booster response the criteria for success were met if the lower bound of the 2-sided 97.5% CI for the GMT ratio was >0.67 and the point estimate of the GMT ratio was ≥0.8.

Among Phase 2/3 participants in the booster evaluable immunogenicity population, the 50% neutralizing GMTs at 1 month after booster dose were approximately 3-fold higher than those observed at 1 month post-primary series and met the immunobridging success criteria for GMTs against the reference strain, as shown in Table 4 below.

Table 4. SARS-CoV-2 Neutralizing GMTs at 1 Month Post-Booster and 1 Month Post-Primary Series in Phase 2/3 BNT162b2 Participants[a] Without Evidence of SARS-CoV-2 Infection up to 1 Month After Booster, Based on SARS-CoV-2 Plaque Reduction Neutralization Assay-NT50 with Reference Strain

GMT (95% CI) 1 Month Post-Primary Series N[b] = 210	GMT (95% CI) 1 Month Post-Booster N[b] = 210	GMT Ratio (97.5% CI) Post-Booster/ Post-Primary Series
753.7 (658.2, 863.1)	2476.4 (2210.1, 2774.9)	3.3 (2.8, 3.9)

GMT: geometric mean titer. Assay: SARS-CoV-2 plaque reduction neutralization assay- NT50, reference strain: recombinant USA WA1/2020.
[a] Booster evaluable immunogenicity population pertaining to 30 µg BNT162b2. Participants were 18 through 55 years of age.
[b] N = Number of Phase 2/3 participants with valid and determinate assay results for the specified assay at the given dose/sampling time point within specified window.
[c] Noninferiority is declared if the lower limit of the 2-sided 97.5% CI for the GMT ratio is greater than 0.67 and the point estimate of the GMT ratio is ≥0.8.

Rates of neutralizing antibody seroresponse to the reference strain

Noninferiority was assessed based on the difference in percentages of participants with defined as a ≥4-fold rise from baseline (before Dose 1), at 1 month after booster dose and at 1 month after the primary series. If the baseline measurement was below the assay lower limit of quantification (LLOQ), a postvaccination titer of ≥4 × LLOQ was considered a seroresponse. Noninferiority was demonstrated if the lower limit of the 97.5% CI for the difference in percentages of participants with seroresponse (1 month post-booster minus 1 month post-primary series) was greater than -10%.

Based on booster seroresponse defined as at least 4-fold rise *relative to pre-Dose 1*, the difference in seroresponse rates was 1.5% (97.5% CI: -0.7%, 3.7%), which met the immunobridging success criterion for seroresponse rates against the reference strain. The percentage of Phase 2/3 participants 18 through 55 years of age with seroresponse was 99.5% at 1 month post-booster and 98.0% at 1 month post-primary series.

Additional analysis of rates of neutralizing antibody seroresponse to the reference strain

FDA requested that Pfizer perform a post hoc immunobridging analysis of seroresponse rates against the reference strain using the pre-booster titer as the baseline titer for determining booster dose seroresponse. As shown in Table 5 below, the booster dose seroresponse rate, with seroresponse defined as at least 4-fold rise relative to the *pre-booster* titer, was 93.9%. The difference in seroresponse rates in this post hoc analysis was -3.9% (95% CI: -8.2%, 0.4%).

Table 5. Seroresponse Rates at 1 Month Post-Booster Dose[a] and 1 Month Post-Primary Series[b] in Phase 2/3 BNT162b2 Participants[c] Without Evidence of SARS-CoV-2 Infection up to 1 Month After Booster, Based on SARS-CoV-2 Plaque Reduction Neutralization Assay-NT50 with Reference Strain

% with ≥4-fold Rise from Baseline to 1 Month After Primary Series[d] (95% CI) N=179	% with ≥4-fold Rise from Pre-Booster to 1 Month After Booster (95% CI) N=179	Difference in Seroresponse Rate (1 month post-booster minus 1 month post-primary series) (95% CI)
97.8 (94.4, 99.4)	93.9 (89.3, 96.9)	-3.9 (-8.2, 0.4)

Assay: SARS-CoV-2 plaque reduction neutralization assay-NT50, reference strain: recombinant USA WA1/2020.
[a] Seroresponse defined as at least 4-fold rise relative to pre-booster; if the baseline measurement was below LLOQ, a postvaccination titer of ≥4 × LLOQ was considered a seroresponse.
[b] Seroresponse defined as at least 4-fold rise relative to pre-Dose 1; if the baseline measurement was below LLOQ, a postvaccination titer of ≥4 × LLOQ was considered a seroresponse.
[c] Booster evaluable immunogenicity population pertaining to 30 µg BNT162b2
[d] %: n/N. n = number of Phase 2/3 participants with seroresponse for the given assay at the given dose/sampling time point.
N = number of subjects with valid and determinate assay results for the specified assay at baseline, pre-booster dose, 1 month after primary series and 1 month after the booster dose within the specified window.

Exploratory immunogenicity analyses against the Delta variant

In response to FDA's request for immunogenicity data to support effectiveness of a BNT162b2 booster dose against the Delta variant, Pfizer submitted exploratory descriptive analyses of data available to date from Phase 1 study participants who received a booster dose (11 adults ages 18-55 years and 12 adults ages 65-85 years). These data are summarized in Table 6 below. A very limited number of sera samples were available for this analysis. In addition, the data were generated using non-validated SARS-CoV-2 plaque reduction neutralization assays with the reference strain (USA-WA1/2020) and the Delta variant; the relative sensitivity of the two assays is not known.

Table 6. SARS-CoV-2 Neutralizing GMTs at 1 Month Post-Booster and 1 Month Post-Primary Series, Phase 1 Recipients of BNT162b2 (30 µg) Booster[a] Without Evidence of SARS-CoV-2 Infection Up to 1 Month After Booster, Based on SARS-CoV-2 Plaque Reduction Neutralization Assay with Reference and Delta Variant Strains

		18-55 Years of Age N=11	65-85 Years of Age N=12
Assay Target	**Time Point**	**GMT (95% CI)**	**GMT (95% CI)**
Reference strain	1 Month post-Primary Series	310.1 (203.3, 473.0)	195.8 (114.7, 334.4)
	1 Month post-Booster	1546.4 (896.9, 2666.0)	1612.7 (875.5, 2970.8)
Delta variant	1 Month post-Primary Series	241.0 (180.1, 322.4)	123.4 (70.2, 216.9)
	1 Month post-Booster	1321.0 (698.5, 2498.3)	1478.9 (734.9, 2975.8)

GMT = geometric mean titer. Assay: SARS-CoV-2 neutralization assay, SARS-CoV-2 strains: recombinant USA WA1/2020 (reference), B.1.617.2 (Delta).
[a] Booster all-available immunogenicity population pertaining to 30 µg BNT162b2
[b] N = number of Phase 1 participants with valid and determinate assay results for the specified assays at the given dose/sampling time point.

6.4.5. Safety evaluation

Overview of adverse events

Of the 306 Phase 2/3 participants 18 through 55 years of age in the booster safety population, 289 (94.4%) recorded local and systemic solicited adverse reactions (ARs) in an e-diary within 7 days following vaccination. Overall, 83.0% of participants reported any local reaction and 77.2% reported any systemic reaction. With respect to unsolicited adverse events, 44 (14.4%) reported at least 1 AE from booster to 1 month thereafter. Events considered by the study investigator to be related to study intervention were reported by 24 participants (7.8%). There was one serious adverse event (SAE) of an acute myocardial infarction that occurred 2 months after booster dose; this was characterized as unrelated to the booster dose. There were no events leading to withdrawal reported through 1 month after booster dose administration. No study participants in this Phase 2/3 booster group died.

Of the 23 Phase 1 booster recipients (i.e., 11 adults 18-55 years of age and 12 adults 65-85 years of age), 73.9% of participants reported any local reaction and 78.2% reported any systemic reaction. None of these 23 participants reported any AEs from booster to 1 month thereafter. There were no SAEs, events leading to withdrawal through 1 month after booster dose administration, and no deaths.

Immediate AEs

No participants reported immediate hypersensitivity or anaphylaxis after the BNT162b2 booster dose.

Solicited adverse reactions

The frequencies of local and systemic adverse reactions within 7 days of booster in the 289 Phase 2/3 participants with evaluable e-diary data are summarized in Table 7 and Table 8. These tables also include post-Dose 1 and post-Dose 2 data from the reactogenicity subset of the blinded Phase 2/3 portion of C4591001 and post-booster safety data from a small group of Phase 1 participants 65 through 85 years of age as points for comparison. Among the 289 Phase 2/3 booster recipients with evaluable e-diary data, injection site pain (83.0%) was the most frequent solicited adverse reaction, following by fatigue (63.7%) and headache (48.4%). The mean duration (not shown in tables) of pain at the injection site was 2.6 days (range 1 to 8 days), 2.2 days for redness (range 1 to 15 days), 2.2 days for swelling (range 1 to 8 days), 2.4 days for fatigue (range 1 to 30 days), and 2.1 days for headache (range 1 to 8 days). Severe solicited ARs were uncommon following the booster dose, with the most frequently reported severe solicited ARs being fatigue (4.5%) and muscle pain (1.4%) among participants 18 through 55 years of age. No Grade 4 local or systemic AR was reported after the booster dose. There were no notable differences in the frequency or duration of local and systemic ARs following the booster dose as compared to those reported following Dose 2 by the 2682 participants 16 through 55 years of age from the blinded Phase 2/3 portion of C4591001.

Table 7. Frequency of Solicited Local Reactions by Severity, Within 7 Days After Dose 2 Compared to After Booster Dose of BNT162b2 30 µg Among Participants in Phase 1/2/3 Study C4591001

	Dose 1 16-55 Years Blinded Phase 2/3 N=2899a n (%)	Dose 2 16-55 Years Blinded Phase 2/3 N=2682[a] n (%)	Booster 18-55 Years Phase 2/3 N=289[b] n (%)	Booster 65-85 Years Phase 1 N=12[c] n (%)
Injection Site Pain				
Any	2426 (83.7)	2101 (78.3)	240 (83.0)	8 (66.7)
Mild[d]	1464 (50.5)	1274 (47.5)	174 (60.2)	8 (66.7)
Moderate	923 (31.8)	788 (29.4)	65 (22.5)	0 (0.0)
Severe	39 (1.3)	39 (1.5)	1 (0.3)	0 (0.0)
Swelling				
Any (>2.0 cm)	184 (6.3)	183 (6.8)	23 (8.0)	0 (0.0)
Mild[e]	124 (4.3)	110 (4.1)	13 (4.5)	0 (0.0)
Moderate	54 (1.9)	66 (2.5)	9 (3.1)	0 (0.0)
Severe	6 (0.2)	7 (0.3)	1 (0.3)	0 (0.0)
Redness				
Any (>2.0 cm)	156 (5.4)	151 (5.6)	17 (5.9)	0 (0.0)
Mild[e]	113 (3.9)	90 (3.4)	10 (3.5)	0 (0.0)
Moderate	36 (1.2)	50 (1.9)	7 (2.4)	0 (0.0)
Severe	7 (0.2)	11 (0.4)	0 (0.0)	0 (0.0)

Adverse reactions were collected in the electronic diary (e-diary) from Day 1 through Day 7 after the booster dose.
N: Number of subjects reporting at least 1 yes or no response for the specified reaction after the specified dose.
n: number of subjects with the specified characteristic.
%: n/N.
[a] Reactogenicity subset of participants from the blinded, placebo-controlled Phase 2/3 portion of C4591001
[b] Recipients of booster dose of BNT162b2 (from P2/P3 portion of study after unblinding) with e-diary data
[c] Recipients of booster dose of BNT162b2 from Phase 1 vaccine candidate and dose-ranging portion of C4591001
[d] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[e] Mild: 2.0 to 5.0 cm; moderate: 5.0 to 10.0 cm; severe: >10.0 cm.

Table 8. Frequency of Solicited Systemic Reactions, by Severity, Within 7 Days After Dose 2 Compared to After Booster Dose of BNT162b2 30 µg Among Participants in Phase 1/2/3 Study C4591001

	Dose 1 16-55 Years Blinded Phase 2/3 N=2899 n (%)	Dose 2 16-55 Years Blinded Phase 2/3 N=2682 n (%)	Booster 18-55 Years Phase 2/3 N=289[*] n (%)	Booster 65-85 Years Phase 1 N=12 n (%)
Fatigue				
Any	1431 (49.4)	1649 (61.5)	185 (63.8)	5 (41.7)
Mild[a]	760 (26.2)	558 (20.8)	69 (23.8)	2 (16.7)
Moderate	630 (21.7)	949 (35.4)	103 (35.5)	3 (25.0)
Severe	41 (1.4)	142 (5.3)	13 (4.5)	0 (0.0)
Headache				
Any	1262 (43.5)	1448 (54.0)	140 (48.4)	5 (41.7)
Mild[a]	785 (27.1)	699 (26.1)	83 (28.7)	4 (33.3)
Moderate	444 (15.3)	469 (17.5)	54(18.7)	1 (8.3)
Severe	33 (1.1)	91 (3.4)	3 (1.0)	0 (0.0)
New/worsened muscle pain				
Any	664 (22.9)	1055 (39.3)	113 (39.1)	4 (33.3)
Mild[a]	353 (12.2)	441 (16.4)	52 (18.0)	2 (16.7)
Moderate	296 (10.2)	552 (20.6)	57 (19.7)	2 (16.7)
Severe	15 (0.5)	62 (2.3)	4 (1.4)	0 (0.0)

	Dose 1 16-55 Years Blinded Phase 2/3 N=2899 n (%)	Dose 2 16-55 Years Blinded Phase 2/3 N=2682 n (%)	Booster 18-55 Years Phase 2/3 N=289* n (%)	Booster 65-85 Years Phase 1 N=12 n (%)
Chills				
Any	479 (16.5)	1015 (37.8)	84 (29.1)	2 (16.7)
Mild[a]	338 (11.7)	477 (17.8)	37 (12.8)	0 (0.0)
Moderate	126 (4.3)	469 (17.5)	44 (15.2)	2 (16.7)
Severe	15 (0.5)	69 (2.6)	3 (1.0)	0 (0.0)
New/worsened joint pain				
Any	342 (11.8)	638 (23.8)	73 (25.3)	2 (16.7)
Mild[a]	200 (6.9)	291 (10.9)	36 (12.5)	0 (0.0)
Moderate	137 (4.7)	320 (11.9)	36 (12.5)	2 (16.7)
Severe	5 (0.2)	27 (1.0)	1 (0.3)	0 (0.0)
Diarrhea				
Any	309 (10.7)	269 (10.0)	25 (8.7)	0 (0.0)
Mild[b]	251 (8.7)	219 (8.2)	21 (7.3)	
Moderate	55 (1.9)	44 (1.6)	4 (1.4)	
Severe	3 (0.1)	6 (0.2)	0	
Vomiting	34 (1.2)	58 (2.2)	5 (1.7)	0 (0.0)
Mild[c]	29 (1.0)	42 (1.6)	5 (1.7)	
Moderate	5 (0.2)	12 (0.4)	0 (0.0)	
Severe	0 (0.0)	4 (0.1)	0 (0.0)	
Fever				
≥38.0°C	119 (4.1)	440 (16.4)	25 (8.7)	0 (0.0)
≥38.0 to 38.4°C	86 (3.0)	254 (9.5)	12 (4.2)	
>38.4 to 38.9°C	25 (0.9)	146 (5.4)	12 (4.2)	
>38.9 to 40.0°C	8 (0.3)	39 (1.5)	1 (0.3)	
>40.0°C	0 (0.0)	1 (0.0)	0 (0.0)	
Antipyretic or pain medication use[d]	805 (27.8)	1213 (45.2)	135 (46.7)	4(33.3)

N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
n = Number of participants with the specified reaction.
%: n/N
* For fatigue, n=290 due to one participant reporting it directly rather than through e-diary
[a] Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
[b] Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.
[c] Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration
[d] Severity was not collected for use of antipyretic or pain medication

Table 9 presents the unsolicited AEs obtained from the 306 Phase 2/3 booster recipients through 1 month after a booster dose. The most common unsolicited AE was lymphadenopathy (n=16; 5.2%), which was reported at a higher rate than following primary series doses (0.4%). Most events of lymphadenopathy following the booster dose (n=15) were mild to moderate in severity and lasted between 2 to 8 days. Two cases of mild lymphadenopathy were reported as ongoing and resolving at the time of last assessment. One severe event of lymphadenopathy was reported by one participant with an onset at 2 days post-Dose 3 and recovered/resolved 5 days from onset. Other unsolicited AEs occurring in more than one subject included nausea (0.7%), injection site pain (0.7%), pain (0.7%), back pain (0.7%), neck pain (0.7%), headache (0.7%), anxiety (0.7%), and contact dermatitis (0.7%). There were no reported AEs in the 1 month after the booster Dose in the Phase 1 subjects (n=23).

Table 9. Unsolicited Adverse Events Reported by ≥2 Phase 2/3 Participants from Booster Dose to 1 Month After Booster Dose, Phase 2/3 Booster Safety Population (N=306)

System Organ Class Preferred Term	n (%)
Blood and lymphatic system disorders	16 (5.2)
Lymphadenopathy	16 (5.2)
Gastrointestinal disorders	4 (1.3)
Nausea	2 (0.7)
General disorders and administration site conditions	8 (2.6)
Injection site pain	2 (0.7)
Pain	2 (0.7)
Musculoskeletal and connective tissue disorders	7 (2.3)
Back pain	2 (0.7)
Neck pain	2 (0.7)
Nervous system disorders	5 (1.6)
Headache	2 (0.7)
Psychiatric disorders	2 (0.7)
Anxiety	2 (0.7)
Skin and subcutaneous tissue disorders	3 (1.0)
Dermatitis contact	2 (0.7)

n = Number of Phase 2/3 participants reporting at least 1 occurrence of the specified event.
N = number of Phase 2/3 participants in the specified group. This value is the denominator for the percentage calculations.

After the 1-month post-booster monitoring period, one additional AE of acute myocardial infarction was reported as an unrelated serious AE on Day 62 post-booster dose that was recovered/resolved with sequelae. FDA reviewed the details of the serious AE and agrees with Pfizer's assessment that the event was unrelated to vaccination. No other serious AEs were reported during follow-up after the booster dose, and no participants were withdrawn due to AEs.

Aside from lymphadenopathy (described above), other adverse events of clinical interest identified from Study C4591001 and post-authorization use include myocarditis/pericarditis, anaphylaxis, appendicitis, and Bell's palsy. No cases of myocarditis, pericarditis, anaphylaxis, appendicitis, or Bell's Palsy were reported by Phase 1 or Phase 3 booster dose recipients through the data cutoff dates (May 13, 2021 and June 17, 2021, respectively).

6.4.6. COVID-19 cases among C4591001 study participants during the Delta variant surge

Responding to an FDA request, Pfizer performed a post hoc analysis of protocol-specified COVID-19 cases accrued during the period of July 1, 2021 through August 31, 2021 (corresponding to the Delta variant surge) among participants 16 years of age and older who completed the 2-dose primary series. The analysis compared rates of COVID-19 among participants who completed the 2-dose primary series early in the study (i.e., those who were originally randomized to BNT162b2) vs. those who completed the 2-dose primary series later in the study (i.e., those who were originally randomized to placebo and then crossed over to BNT162b2). Study participants included in the analysis were those who remained at risk for first occurrence of COVID-19 following the BNT162b2 primary series (i.e., participants who previously reported COVID-19 or who received additional study vaccinations after the primary series were excluded). The analysis used data extracted on September 2, 2021 from the study's live database; the datasets were not submitted to FDA.

Although not independently verified by FDA, the post hoc analysis appears to indicate that the incidence of SARS-CoV-2 during the analysis period among 18,727 study participants originally randomized to BNT162b2 (mean of 9.8 months post-Dose 2 at the beginning of the analysis period) was 70.3 cases per 1,000 person-years, compared with an incidence of 51.6 cases per 1,000 person-years among 17,748 study participants originally randomized to placebo and crossed over to BNT162b2 (mean of 4.7 months post-Dose 2 at the beginning of the analysis period). An additional analysis appears to indicate that incidence of COVID-19 generally increased in each group of study participants with increasing time post-Dose 2 at the start of the analysis period. Only 3 severe COVID-19 cases were reported during the analysis period, all of which occurred among study participants originally randomized to BNT162b2.

The reported incidence of COVID-19 among study participants who completed the primary series <4 months prior to the start of the analysis period was 43.4 cases per 1,000 person-years. In contrast, during the blinded, placebo-controlled follow-up period of the study with data cutoff of March 13, 2021 (prior to the Delta variant surge), the incidence of COVID-19 among BNT162b2 recipients in the Evaluable Efficacy Population (nearly 60% of whom had 4 months or more of blinded follow-up post-Dose 2) was 12.6 cases per 1,000 person-years.[1] This observation suggests that while waning immunity is one potential factor that may have contributed to the higher incidence breakthrough cases during the Delta variant surge, it is possible that other factors (e.g., dynamics of Delta variant transmission and potential differences in vaccine effectiveness against the Delta variant vs. strains circulating during the placebo-controlled portion of the trial) may also have contributed.

6.4.7. Summary of booster dose immunogenicity and safety data

The clinical data submitted to this BLA supplement come from an ongoing Phase 1/2/3 study (C4591001), which is also the source of clinical data supporting the original approval of the 2-dose primary series for use in individuals 16 years of age and older. The BNT162b2 30 µg booster dose was initially assessed in a cohort of 23 Phase 1 study participants (11 participants 18-55 years of age and 12 participants 65-85 years of age), and then in 306 Phase 2/3 study participants 18 through 55 years of age. Pfizer is requesting approval of the booster dose for use in individuals 16 years of age and older; therefore, safety and effectiveness of the booster dose in individuals 16 and 17 years of age would be based on extrapolation from safety and effectiveness data in adults. Effectiveness of the booster dose against the reference strain is being inferred based on immunobridging to the 2-dose primary series, as assessed by SARS-CoV-2 neutralizing antibody titers elicited by the vaccine. Immunobridging success criteria for the reference strain were met for both pre-specified co-primary immunogenicity endpoints of GMT ratio and difference in seroresponse rates among study participants with no evidence of SARS-CoV-2 infection prior to 1 month after the booster dose. The submission also includes exploratory descriptive analyses of immunogenicity against the SARS-CoV-2 Delta variant among adults 18 through 55 years of age and 65 through 85 years of age enrolled in the Phase 1 portion of the study. Safety data from 306 Phase 2/3 booster recipients do not show evidence of increased local or systemic reactogenicity relative to Dose 2. While evaluated in only 12 participants in the age cohort of 65 through 85 years, the booster dose was less reactogenic in this age cohort compared to younger adults 18 through 55 years of age. Most reactogenicity events after the booster dose were of mild to moderate severity and self-limited in duration. Lymphadenopathy was observed more frequently following the booster dose than after primary series doses (5.2% compared to 0.4%). No deaths, vaccine-related serious adverse events, or events of myocarditis, pericarditis, anaphylaxis, appendicitis, or Bell's palsy were reported among study participants who received the BNT162b2 booster dose.

7. TOPICS FOR VRBPAC DISCUSSION

The Vaccines and Related Biological Products Advisory Committee will convene on September 17, 2020, to discuss whether the data presented by Pfizer support the safety and effectiveness of a booster dose of COMIRNATY administered 6 months post primary vaccination series.

8. REFERENCES

[1] FDA. Vaccine approval package: COMIRNATY (COVID-19 Vaccine, mRNA) (Application No 125742). August 23, 2021. https://www.fda.gov/media/151733/download

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[3] FDA. Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19. February 2021. https://www.fda.gov/media/142749/download. 2021a.