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

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Vaccines and Related Biological Products Advisory Committee Meeting

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BNT162b2

[COMIRNATY (COVID-19 Vaccine, mRNA)]

Evaluation of a Booster Dose (Third Dose)

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE BRIEFING DOCUMENT

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ABBREVIATIONS

Abbreviations	Definition
ADR	adverse drug reaction
AE	adverse event
CDC	(US) Centers for Disease Control
CI	confidence interval
EUA	Emergency Use Authorization
FDA	(US) Food and Drug Administration
GMFR	geometric mean-fold rise
GMR	geometric mean ratio
GMT	geometric mean titers
HIV	human immunodeficieny virus
IM	intramuscular
KPSC	Kaiser Permanente Southern California
LLOQ	lower limit of quantitation
LNP	lipid nanoparticles
MI	myocardial infarction
MoH	Ministry of Health
mRNA	messanger ribonucleic acid
NATT	nucleic acid amplification test
PRNT	plaque-reduction neutralization tests
PVP	pharmacovigilance plan
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
sBLA	Supplemental Biologics License Application
SOC	system organ class
US	United States
VAED	vaccine associated enhanced disease
VE	vaccine effectiveness
VOC	variant of concern
WHO	World Health Organization

EXECUTIVE SUMMARY

The prophylactic, RNA-based SARS-CoV-2 vaccine BNT162b2 [COMIRNATY (COVID-19 Vaccine, mRNA)], developed by BioNTech SE and Pfizer Inc, received US FDA approval on 23 August 2021 for prevention of COVID-19 disease in individuals ≥16 years of age. BNT162b2 is currently administered intramuscularly (IM) as a series of two 30-µg doses (0.3 mL each) three weeks apart. Pfizer-BioNTech COVID-19 Vaccine has been available for prevention of COVID-19 disease in individuals ≥16 years of age since December 2020 under an Emergency Use Authorization (EUA 27034; 11 December 2020). On 27 August 2021, Pfizer and BioNTech Manufacturing GmbH submitted a supplemental Biologics License Application (sBLA) to seek approval of a booster dose (third dose) of BNT162b2 in individuals ≥16 years of age administered intramuscularly approximately 6 months after Dose 2.

COVID-19 is a serious and potentially fatal or life-threatening human infection. The data from the pivotal Phase 3 clinical study (C4591001) showed that 2 doses of BNT162b2 vaccine administered 3 weeks apart confers protection against both symptomatic and severe COVID-19.[1] The duration of such protection is currently unknown; however, an analysis of efficacy up to six months after Dose 2 shows that the initial vaccine efficacy (96.2% from 7 days after Dose 2 to <2 months after Dose 2) slightly wanes over time, to 90.1% from >2 months to <4 months after Dose 2; and to 83.7 % for >4 months after Dose 2.

Recent data from Israel and the United States (as described in Section 1.1 below) in the context of the delta Variant of Concern (VOC) predominant circulation suggest that vaccine protection against COVID-19 infection wanes approximately 6 to 8 months following the second dose. A retrospective cohort study conducted at Kaiser Permanente Southern California suggests that the observed erosion in vaccine effectiveness is likely primarily due to waning effectiveness rather than due to Delta escaping vaccine protection, given that (i) effectiveness against Delta infections was >90% early on; (ii) vaccine effectiveness decreases with increasing time since being fully vaccinated, irrespective of variant; and (iii) effectiveness against Delta variant hospitalizations remained high over the entire study period (see Section 1.1).

That vaccine effectiveness is waning over time is further supported by a recent FDA requested post-hoc analysis of breakthrough cases in the C4591001 pivotal Phase 3 clinical study. The analysis was performed for COVID-19 cases accrued during the current Delta variant surge (ie, during a defined time period beginning 01 July 2021 and through 31 August 2021). The analysis compared participants ≥16 years of age who were randomized to receive BNT162b2 and thus received the vaccine at the beginning of the study (original group) versus participants who were randomized to placebo and later crossed over to BNT162b2 (crossover group). The mean time from Dose 2 of BNT162b2 to 01 July 2021 was approximately 5 months for the crossover group and 10 months for the original group. Results showed that the incidence of breakthrough cases was higher among individuals who received Dose 2 at least 8 months before 01 July compared to those who received Dose 2 less than 4 months before 01 July 2021, confirming the waning of vaccine effectiveness over time.

The totality of the available data supports the public heath need for a booster (third) dose of BNT162b2 at approximately 6 months after the second dose of BNT162b2 for individuals 16 years of age and older.

To address the need for a booster (third) dose against COVID-19, Pfizer/BioNTech designed a substudy of the C4591001 pivotal study that complies with the 25 May 2021 FDA Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19 and supports the use of a booster dose in individuals 16 years of age and older.[2] The FDA guidance specifies that the booster study must be adequately powered to demonstrate that the immune responses induced by the booster dose (serum neutralizing titers against SARS-CoV-2, as measured by seroresponse rates and GMTs), are statistically non-inferior compared to those elicited by the vaccine in the primary series. The FDA-specified success criteria include demonstration of a non-inferiority margin of –10% for seroresponse rates and a 1.5-fold margin for GMTs. Based on consultations with CBER, these criteria are also considered sufficient to support licensure of a booster following full approval of the primary series.

Phase 1 of this substudy, conducted in 23 participants 24 to 75 years of age, demonstrated that a booster (third) dose of 30 µg BNT162b2 administered approximately 6 months after the second vaccination of BNT162b2 had an acceptable safety profile and elicited robust immune responses against the wild-type (reference strain), as well as against the Beta and Delta variants of concern. Phase 3 of the substudy, conducted in 306 participants ≥18 to 55 years of age, showed that the vaccine was as well tolerated as the second primary dose and elicited immune responses (SARS-CoV-2 50% neutralizing titers) against the wild-type 1 month after the third dose that were non-inferior to the immune responses observed 1 month after the second primary dose, meeting the protocol pre-specified success criteria for GMTs and seroresponse rates. Furthermore, in accordance with FDA guidance, the safety and effectiveness of the booster dose demonstrated in individuals ≥18 to 55 years of age has been extrapolated to individuals 16 and 17 years of age and to individuals older than 55 years of age.

Finally, data from a recently initiated booster (third dose) vaccination program in the entire eligible population of Israel indicate that, in the face of waning immunity and in the period when the delta is the dominant variant, a booster dose of BNT162b2 has a reactogenicity profile similar to that seen after receipt of the second primary series dose and restores high levels of protection against COVID-19 outcomes (ie, back to approximately 95% protection).

Based on the above and consultation with CBER, Pfizer/BioNTech is requesting licensure of a booster dose (third dose) of BNT162b2 administered intramuscularly approximately 6 months after Dose 2 in individuals ≥16 years of age.

1. BACKGROUND INFORMATION AND UNMET MEDICAL NEED

BNT162b2 has been shown to be effective in preventing COVID-19 and to elicit an immune response that confers this protection. However, the duration of that protection is currently unknown. Data from clinical trials show that SARS-CoV-2 50% neutralizing titers to the reference strain decline from 1 month after vaccination to 6 months after vaccination; however, the significance of that decline is not clear, as no agreed correlate of protection against breakthrough infection has been identified.[3] In the pivotal clinical trial, an analysis of efficacy up to six months after Dose 2 showed that the initial vaccine efficacy (96.2% from 7 days after Dose 2 to <2 months after Dose 2) slightly wanes over time, to 90.1% from >2 months to <4 months after Dose 2; and to 83.7% for >4 months after Dose 2.

Among vaccinated healthcare workers, decreased neutralizing antibody titers have been associated with vaccinees' breakthrough infections, along with increased viral load.[4] As described below, emerging data suggest that vaccine protection may wane approximately 6 to 8 months following the second dose, and evidence is building to suggest that administration of booster doses of COVID-19 mRNA vaccines is potentially an urgent emerging public health issue.

Note that in the context of the pivotal clinical study (C4591001), in which healthy, immunocompetent adult participants received a third dose of BNT162b2 (30 µg), the terms "booster" and "Dose 3" are used interchangeably, as these participants had an observed robust immune response to the two-dose regimen, and hence the third dose is effectively a boost. In the broader context of the general population, Dose 3 may not necessarily be a booster dose if an individual is immunosuppressed or did not mount an effective immune response following their second dose.

1.1. Real-World Effectiveness and Unmet Need Due to Breakthrough Infection

As the Delta variant has become widely disseminated, rates of COVID-19 are again on the rise in the United States and across the world. Although unvaccinated individuals continue to account for most SARS-CoV-2 infections and severe cases of COVID-19, real-world data suggest that rates of breakthrough infections may be on the rise and that vaccine effectiveness (VE) may be waning over time.

A recent real-world, retrospective cohort study conducted in Israel showed a correlation between time since vaccination and the incidence of breakthrough infections among fully-vaccinated individuals ≥16 years of age.[5] The analysis utilized healthcare records from an Israeli health maintenance organization that provides health coverage for 25% of the Israeli population and provides a representative sample. The study evaluated breakthrough infections between 01 June 2021 and 27 July 2021, a time when B.1.617.2 (Delta) was the predominant SARS-CoV-2 strain in circulation in Israel, using two logistic regression models that adjusted for demographic and clinical characteristics. The first model found the risk of breakthrough infection was 53% (95% CI: 40%, 68%) higher in early versus late vaccinees ($p<0.001$), with similar results across age strata. Correspondingly, the second model demonstrated higher risk for breakthrough infection in individuals who were vaccinated in early months. For example, individuals vaccinated in January 2021 had a 2.26-fold increased risk (95% CI: 1.80, 3.01) for breakthrough infection versus those vaccinated in April 2021.

Thus, the risk for breakthrough infection was significantly higher for individuals who were vaccinated early compared to those vaccinated later, suggesting waning of vaccine effectiveness.

The State of Israel Ministry of Health (Israel MoH) conducted an observational study to assess the effectiveness of BNT162b2 against various SARS-CoV-2 outcomes from 20 June 2021 through 17 July 2021. The study population consisted of residents of Israel (ie, the Census population) ≥16 years of age. Using previously-published methodology,[6] VE estimates were assessed against hierarchical laboratory-confirmed SARS-CoV-2 outcomes: all SARS-CoV-2 infections (symptomatic and asymptomatic), symptomatic COVID-19 cases, COVID-19-related hospitalizations, COVID-19-related severe or critical hospitalizations, and death. Individuals were defined as unvaccinated if they had never received a COVID-19 vaccine, and were defined as fully vaccinated if at least 7 days had passed since receiving the second dose of BNT162b2. Incidence rates were calculated for unvaccinated and fully vaccinated individuals for each SARS-CoV-2 outcome after excluding people with previous laboratory-confirmed SARS-CoV-2 infection. A negative binomial regression model was used to derive incidence rate ratios with 95% CIs for each outcome adjusted for age group, sex, and calendar week.

In this evaluation, among individuals ≥16 years of age, BNT162b2 effectiveness against SARS-CoV-2 infection was only 39.0% (95% CI: 9.0%, 59.0%) and against symptomatic COVID-19 was 40.5% (95% CI: 8.7%, 61.2%) between 20 June 2021 and 17 July 2021. This was considerably lower than published effectiveness estimates from an earlier time period. Specifically, between 24 January 2021 to 03 April 2021 VE against these same endpoints was ≥95% for all age groups.[6] Further, effectiveness estimates from 20 June 2021 to 17 July 2021 showed that VE against SARS-CoV-2 infections and against symptomatic COVID-19 progressively declined as time-from-vaccine increased, with individuals ≥16 years of age vaccinated in January having only 16% effectiveness against symptomatic COVID-19, which was not statistically significantly different from zero. By contrast, those who were fully vaccinated in April 2021 had 79% (60, 88) effectiveness against symptomatic COVID-19. These data were interpreted by MoH officials to suggest that waning of the vaccine, and not the introduction of the B.1.617.2 (Delta) variant (which became the predominant strain in July), was primarily driving declining VE estimates.[7] In addition, a subsequent Israel MoH evaluation showed that between 20 June 2021 and 07 August 2021 effectiveness among adults ≥65 years of age against severe COVID-19 dropped to approximately <60% for persons vaccinated early in the Israeli MoH vaccine campaign (ie, January or February) compared to those vaccinated in March, when effectiveness was >80%.[8]

Another, independent analysis of the Israel MoH data confirmed that individuals vaccinated earlier experienced higher rates of SARS-CoV-2 infections and severe COVID-19.[9] The study used data on all PCR (polymerase-chain reaction) positive test results among Israeli residents who were fully vaccinated before June 2021 and compared rates of SARS-CoV-2 infection and severe COVID-19 between individuals who were vaccinated in different time periods using a Poisson regression analysis to adjust for age group and other possible confounding factors. The rates of both documented SARS-CoV-2 infections and severe COVID-19 increased as more time after the second vaccine dose elapsed. Individuals

≥60 years of age who received their second dose in March 2021 were 1.6 (95% CI: 1.3, 2.0) times more protected against infection and 1.7 (1.0, 2.7) times more protected against severe COVID-19 compared to those who received their second dose in January 2021. Similar results were found for all age groups. The authors concluded that the study confirmed a strong effect of waning immunity in all age groups after six months.

On 18 August 2021, the CDC published two studies[10,11] showing similar reductions in effectiveness against SARS-CoV-2 infections. The first study[10] estimated the effectiveness of two doses of BNT162b2 between 01 March 2021 and 01 August 2021 among nursing home residents using data from the National Healthcare Safety Network, which included >3800 nursing homes in the United States. A generalized linear mixed effects model with a zero-inflated Poisson distribution was used to estimate the ratio of infection rates among fully vaccinated and unvaccinated residents after adjusting for calendar week, facility-level cumulative SARS-CoV-2 infection rates, weekly local county incidence of SARS-CoV-2 infections, and the CDC Social Vulnerability Index score for each facility's county. BNT162b2 effectiveness against SARS-CoV-2 infection (measured ≥14 days after the second dose) fell from 74.7% (95% CI: 70.0%, 78.8%) between 01 March 2021 and 09 May 2021 to 53.1% (95% CI: 49.1%,56.7%) between 21 June 2021 and 01 August 2021. The latter period corresponded to a time point at which many nursing home residents had been fully vaccinated roughly six months ago, and the B.1.617.2 (Delta) variant accounted for the vast majority of infections in the United States. A similar trend was observed for the Moderna COVID-19 mRNA-1273 vaccine. The authors determined that the effects of waning and the introduction of the B.1.617.2 (Delta) variant could not be fully teased apart, but that "an additional dose of COVID-19 vaccine might be considered for nursing home and long-term care facility residents to optimize a protective immune response."

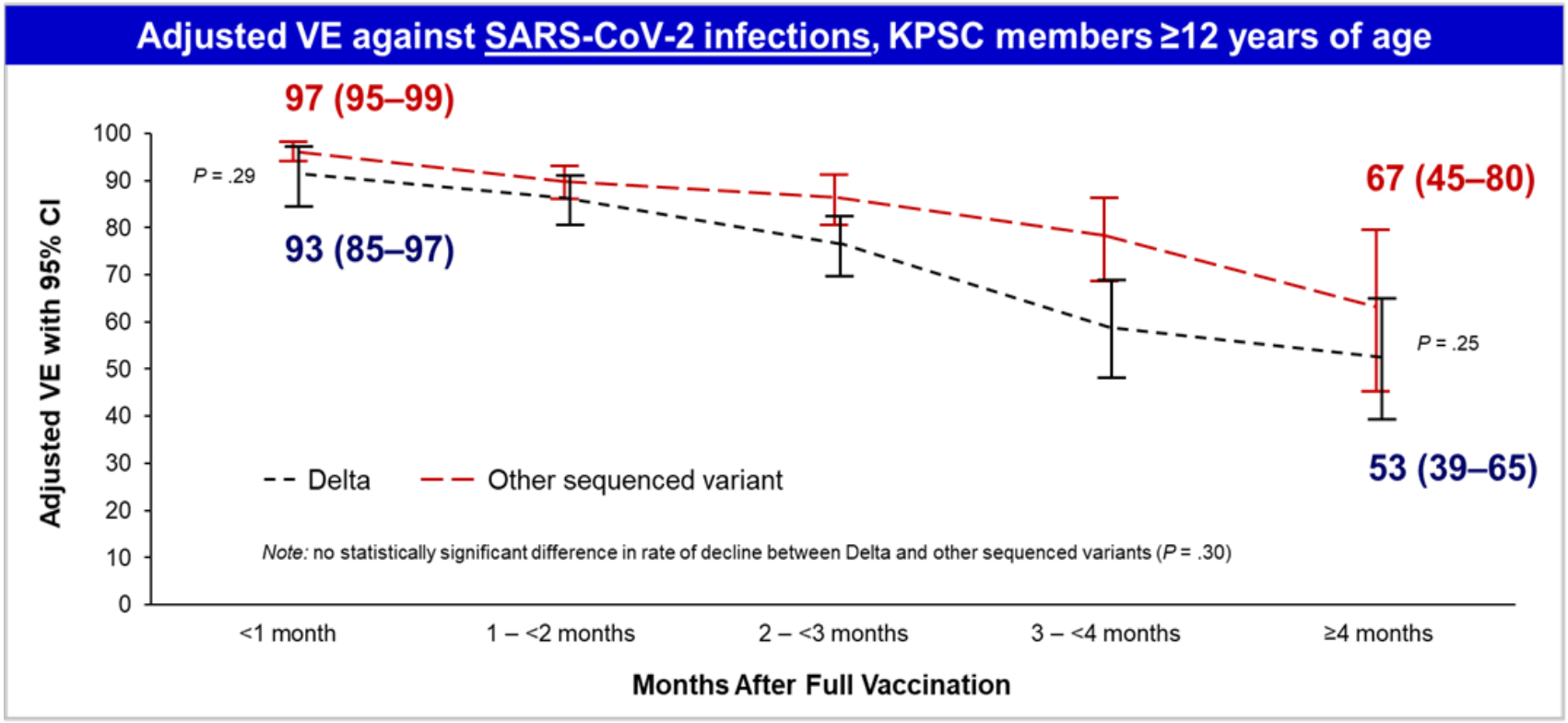
The second CDC study,[11] which was based on a retrospective analysis of four linked databases that included information about rates of reported SARS-CoV-2 infections and vaccination coverage for residents of the state of New York ≥18 years of age, showed similar findings. Among New York adult residents, VE against infection for fully vaccinated individuals declined from approximately 91% during May 2021 to <80% after 12 July 2021. The findings were not vaccine-specific; however, 91% of individuals in the study had received an mRNA vaccine. Again, the authors determined that the effects of waning and the introduction of the B.1.617.2 (Delta) variant could not be fully teased apart.

To better differentiate the impact of Delta from potential waning immunity on observed reductions in effectiveness against SARS-CoV-2 infections, another recent study conducted at the Kaiser Permanente Southern California (KPSC) integrated health system in the United States evaluated overall and variant-specific real-world effectiveness of BNT162b2 against SARS-CoV-2 infections and COVID-19-related hospitalizations by time since vaccination.[12] In the retrospective cohort study, electronic health records from KPSC between Dec 14, 2020 and Aug 8, 2021 were analyzed to assess BNT162b2 VE against SARS-CoV-2 infections and COVID-19-related hospitalization. Effectiveness calculations were based on hazard ratios from adjusted Cox models. In the KPSC study, effectiveness against infections declined from 88% (95% CI: 86, -89) during the first month after full vaccination to 47% (43–51) after ≥5 months. Among sequenced infections, VE estimates against both Delta and other (non-Delta) sequenced variants were high at <1 month after full vaccination (VE against Delta:

93% [85–97] *vs* other variants: 97% [95–99], p=.289). At ≥4 months after full vaccination, VE against Delta infections declined to 53% (39–65) and VE against other variants to 67% (45–80), p=.254. The difference in rate of decline in VE between Delta and other variants was not statistically significant (p=.303) (Figure 1). VE against hospitalization for Delta for all ages was high overall (93% [85-97]). Thus, the variant-specific analysis suggested that reductions in BNT162b2 effectiveness over time are likely primarily due to waning effectiveness rather than Delta escaping vaccine protection given that (i) effectiveness against Delta infections was >90% early on, (ii) reductions in effectiveness in infections by time since being fully vaccinated were observed irrespective of variant, and (iii) effectiveness against Delta hospitalizations remained high over the entire study period.

While the KPSC study and recent CDC studies have shown VE against hospitalization has remained high (mostly >90%) despite introduction of the B.1.617.2 (Delta) variant and potential for waning,[13] this should be carefully monitored, as data from Israel (as described above) suggest reduced effectiveness against severe disease could eventually follow observed reductions in effectiveness against SARS-CoV-2 infections.[13] Moreover, reductions in effectiveness against infections could lead to increased transmission, especially in the face of the highly transmissible B.1.617.2 (Delta) variant. Policymakers will need to continue to monitor VE over time and may need to consider recommendations for booster doses to restore initial high levels of protection observed early in the vaccination program, and to help control heightened transmission of B.1.617.2 (Delta) as we enter the upcoming fall/winter viral respiratory season.

Figure 1. Adjusted VE Against SARS-CoV-2 Infections: KPSC Members ≥12 Years of Age



*Whole genome sequencing was performed on all PCR+ samples collected Mar 4, 2021 – Jul 21, 2021.

1.2. Study C4591001 – Post Hoc Analysis of Cases by Time Since Vaccination

Using data from the pivotal clinical efficacy study (C4591001), a post-hoc analysis was performed for COVID-19 cases accrued during the current delta variant surge (ie, during a defined time period beginning 01 July 2021 and through 31 August 2021). The analysis included data for participants ≥16 years of age and compared incidence rates for confirmed COVID-19 cases among "early" versus "late" vaccinees: ie, incidence was compared between participants who were randomized to receive BNT162b2 and thus received the vaccine at the beginning of the study (original group) versus participants who were randomized to placebo and later crossed over to BNT162b2 (crossover group). The mean time from Dose 2 of BNT162b2 to 01 July 2021 was approximately 5 months for the crossover group and 10 months for the original group.

Overall, the post-hoc analysis of COVID-19 cases accrued during the current delta variant surge showed a 26.3% (95% CI: 7.4%, 41.4%) relative vaccine efficacy for the group vaccinated later (crossover group) compared to the group vaccinated earlier (original group), with a difference in incidence rates of -18.6 per 1000 person-years of follow-up. The magnitude of risk reduction, 26% higher for the more recently vaccinated compared to individuals vaccinated earlier, highlights the public health importance of time since immunization.

The impact of elapsed time since completion of Dose 2 on vaccine efficacy in those vaccinated more distant to the Delta variant wave cannot be determined from this analysis due to the lack of a placebo control, but longer-term vaccine efficacy for the original group relative to placebo can be derived based on an assumption of vaccine efficacy for the more recently vaccinated crossover group and the observed relative vaccine efficacy. If protection against COVID-19 falls below 70% at a mean exposure of 5 months, efficacy would be expected to be below 60% at a mean exposure of 10 months.

In addition, an increase in incidence rates was observed with increasing time since Dose 2 (Table 1), and these rates were substantially higher than those observed in prior analyses before the Delta variant was circulating (15.6 per 1000 person-years, which includes the period between Dose 1 and Dose 2 for which the vaccine effect was not fully established vs. 43.5 cases per 1000 person-years from 01 July 2021 to 31 August 2021 for those with less than 4 months between Dose 2 and 01 July 2021). This seems likely due to the Delta variant surge.

These results suggest that a booster (third) dose of BNT162b2 given approximately 6 months after the second dose of BNT162b2 should be considered to restore high levels of protection against SARS-CoV-2 infection.

Table 1. Incidence of First COVID-19 Occurrence From 01JUL2021 to 31AUG2021 by Time Since Dose 2 of BNT162b2 – Phase 2/3 Subjects ≥16 Years of Age and Older Who Received Two Doses of BNT162b2

	Vaccine Group								
	Placebo Crossover to BNT162b2 (30 µg)			Original BNT162b2 (30 µg)			Total		
Efficacy Endpoint	**n1[a]**	**Surveillance Time[b] (n2[c])**	**IR (/1000 PY)[d]**	**n1[a]**	**Surveillance Time[b] (n2[c])**	**IR (/1000 PY)[d]**	**n1[a]**	**Surveillance Time[b] (n2[c])**	**IR (/1000 PY)[d]**
First COVID-19 occurrence from 01JUL2021 to 31AUG2021	149	2.866 (17729)	51.989	163	2.310 (18713)	70.548	312	5.176 (36442)	60.273
Time from Dose 2 of BNT162b2 to 01JUL2021									
<4 Months	26	0.597 (3555)	43.522	0	0.000 (1)	0.000	26	0.598 (3556)	43.510
≥4-<6 Months	108	2.018 (12345)	53.515	0	0.001 (3)	0.000	108	2.019 (12348)	53.502
≥6-<8 Months	15	0.250 (1829)	59.883	4	0.076 (530)	52.330	19	0.327 (2359)	58.117
≥8-<10 Months	-	- (0)	-	73	0.951 (7690)	76.733	73	0.951 (7690)	76.733
≥10 Months	-	- (0)	-	86	1.282 (10489)	67.082	86	1.282 (10489)	67.082

Note: Subjects who received 2 planned doses of BNT162b2 and remained at risk till at least 01JUL2021 were included in the analysis. Subjects who were enrolled in Phase 3 boostability and VOC assessment of the study were excluded.

a. n1 = Number of subjects meeting the endpoint definition.

b. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 01JUL2021 to the earliest of confirmed case, death, withdrawn from the study, or 31AUG2021.

c. n2 = Number of subjects at risk for the endpoint.

d. Incidence rate (IR) is calculated as number of subjects meeting the endpoint definition/total surveillance time across all subjects at risk for the endpoint within the specific group.

PFIZER CONFIDENTIAL SDTM Creation: 09SEP2021 (07:36) Source Data: adc19efu Table Generation: 09SEP2021 (14:08)
(Data Cutoff Date: 31AUG2021, Database Snapshot Date: 08SEP2021) Output File: ./nda2_unblinded/C4591001_B_VRB/adc19ef_ve_covfup_bnt2d_vrb

2. OVERVIEW OF CLINICAL PHASE 1/2/3 STUDY C4591001

This section describes the evaluation of a third (booster) dose of BNT162b2 (30 µg) in clinical study C4591001. This is the ongoing, randomized, placebo-controlled study that demonstrated the efficacy, immunogenicity, and safety of a 2-dose series of 30 µg BNT162b2 for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. After the final efficacy analysis was completed, the protocol was amended to provide for evaluation of the safety and immunogenicity of a booster (third) dose of 30 µg BNT162b2 in both Phase 1 and Phase 2/3 participants.

2.1. Overview of Methods for Evaluation of a Booster (Third) Dose – Study C4591001

Phase 1 and Phase 3 participants who initially received BNT162b2 30 µg as a 2-dose series separated by 21 days were administered a booster (third) dose of BNT162b2 approximately 6 months after their second dose.

Information on reactogenicity events (local reactions and systemic events) and antipyretic/pain medication use was recorded by the study participants each evening for 7 days after Dose 3 using prompts from an electronic diary (e diary). Adverse events (AEs) were reported for 1 month after Dose 3 and serious adverse events (SAEs) are collected through 6 months after Dose 3.

Blood samples for determination of SARS-CoV-2 neutralizing titers had been collected from these participants before their first dose of BNT162b2 and at designated time points after Dose 1 and/or Dose 2; for the booster sub-study, blood samples were collected immediately before Dose 3 and at 7 days and 1 month after the booster dose.

Neutralizing titers were determined against wild-type (reference strain) in sera from both Phase 1 and Phase 3 participants; titers against the Beta and Delta variants were determined in sera from Phase 1 participants only.

The SARS-CoV-2 neutralization assays used for the analyses reported here are listed in Table 2. The plaque-reduction neutralization tests (PRNTs) used for Phase 1 data are exploratory assays and have been described previously[14,15] The reference strain SARS-CoV-2 neutralization assay (mNeonGreen microneutralization assay, SARS-CoV-2 mNG NT) is a validated assay used for the Phase 3 data to assess non-inferiority of the immune response after Dose 3 compared to after Dose 2.

PRNT titers were determined against:

- **Wild-type –** The designated wild-type (recombinant USA-WA1/2020; clinical strain isolated in January 2020);
- **Beta variant –** B.1.351 (recombinant USA-WA1/2020 bearing the full spike gene from Beta variant);[14,16]
- **Delta variant –** B.1.617.2 (recombinant USA-WA1/2020 with the full spike gene from the Delta variant).[14,16]

All samples from each time point were analyzed for this evaluation (ie, previously tested samples[16] were reanalyzed to ensure comparability of neutralization titers between the wild-type and Beta variant and between the wild-type and Delta variant) to ensure the most accurate assessments of persistence of neutralizing antibodies and response to Dose 3 (booster) of BNT162b2 30 µg.

Table 2. SARS-CoV-2 Neutralization Assays Supporting Pfizer & BioNTech COVID-19 Vaccine Program

Assay Name	Assay Platform	Strain/Variant	Status	Study Phase
SARS-CoV-2 mNG NT (WT)	mNeonGreen Microneutralization	Wildtype (USA-WA1/2020)	Qualified	C4591001 Phase 1
SARS-CoV-2 mNG NT (WT)	mNeonGreen Microneutralization	Wildtype (USA-WA1/2020)	Validated	C4591001 Phase 2/3 C4591001 WT booster
SARS-CoV-2 PRNT (WT)	Plaque reduction assay	Wildtype (USA-WA1/2020)	Exploratory	C4591001 Phase 1
SARS-CoV-2 PRNT (Beta)	Plaque reduction assay	Beta (B.1.351)	Exploratory	C4591001 Phase 1
SARS-CoV-2 PRNT (Delta)	Plaque reduction assay	Delta (B.1.617.2)	Exploratory	C4591001 Phase 1

NT= neutralization test; PRNT = plaque reduction neutralization test; WT = wild-type.

2.2. Immunogenicity Analysis Methods and Results

2.2.1. Phase 1

2.2.1.1. Statistical Methods

In Phase 1, PRNT geometric mean titers (GMTs) were determined at each time point for wild-type and Beta strains and at a subset of the time points for Delta strains. PRNT GMTs were calculated by exponentiating the mean of logarithmically transformed assay results; the associated 2-sided 95% CIs were obtained from the natural log scale of the results using the Student's *t* distribution and exponentiating the confidence limits. Geometric mean ratios (GMRs) for comparing strains and/or timepoints were calculated as the mean of the difference of logarithmically transformed neutralizing titers for each participant (ie, variant strain minus wild-type strain, 1 month after Dose 3 minus 1 month after Dose 2) and exponentiating the mean. Associated 2-sided CIs for GMRs were obtained using the Student's *t* distribution for the mean difference on the logarithm scale and exponentiating the confidence limits

2.2.1.2. Immunogenicity Results – Phase 1 Booster Substudy

Study Population – Phase 1

A total of 23 Phase 1 participants who had received 2 doses of BNT162b2 (30 µg) received a booster dose of 30 µg BNT162b2 (N=11 in the younger 18 to 55 years of age group and

N=12 in the older 65 to 85 years of age group). Most participants received the booster (third) dose approximately 8 months after their second vaccination (mean = 8.3 months). Approximately 87% of participants were white, and all were non-Hispanic/non-Latino; approximately 65% were female; and the median age was 39.0 years (range: 24 to 55 years) in the younger age group and was 69.0 years (range: 65 to 75 years) in the older age group.

Data presented here for Phase 1 booster dose participants are for the Dose 3 all-available immunogenicity population, which included all randomized participants who received 2 doses of BNT162b2 as initially randomized, received a third BNT162b2 dose, and had at least 1 valid and determinate immunogenicity result after Dose 3. Valid neutralization titers were obtained from all 23 participants.

Neutralization Titers Against Wild-Type

SARS-CoV-2 neutralization GMTs against the wild-type USA-WA1/2020 strain substantially increased after Dose 3. GMTs at 1 month after Dose 3 were 2119 (95% CI: 1229.1, 3653.4) for younger participants 18 to 55 years of age, and 2032 (95% CI: 1232.6, 3349.3) for older participants 65 to 85 years of age, which were >5-fold and >7-fold, respectively, the GMTs observed at 1 month after Dose 2 (Figure 2**,** left side). GMFRs against the wild-type strain from before Dose 3 to 1 month after Dose 3 were 25.7 (95% CI: 12.4, 53.3) for younger adults, and 49.4 (95% CI: 29.2, 83.3) for older adults. From 7 days to 1 month after the second dose, neutralizing GMTs decreased – in younger adults (from 497.4 to 386.6) and in older adults (from 538.2 to 261.4). In contrast, from 7 days to 1 month after the third dose, neutralizing GMTs increased – in younger adults (from 1754.0 to 2119.0) and in older adults (from 1317.5 to 2031.9).

Neutralization Titers Against the Beta Variant

A third dose also increased the neutralizing titers against recombinant SARS-CoV-2 with the Beta variant spike. At 1 month after Dose 3, GMTs were 1546 (95% CI: 888.1, 2692.4) for younger participants, and 1567 (95% CI: 875.2, 2804.7) for older participants, which were >15-fold and >20-fold, respectively, the GMTs observed at 1 month after Dose 2 (Figure 2, right side). GMFRs from before Dose 3 to 1 month after Dose 3 were 38.7 (95% CI: 19.8, 75.5) for younger adults, and 78.3 (95% CI: 40.7, 150.6) for older adults. From 7 days to 1 month after the second dose, neutralizing GMTs decreased – in younger adults (from 150.2 to 102.9) and in older adults (from 146.7 to 75.5). In contrast, from 7 days to 1 month after the third dose, neutralizing GMTs increased – in younger adults (from 1201.8 to 1546.4) and in older adults (from 879.3 to 1566.8).

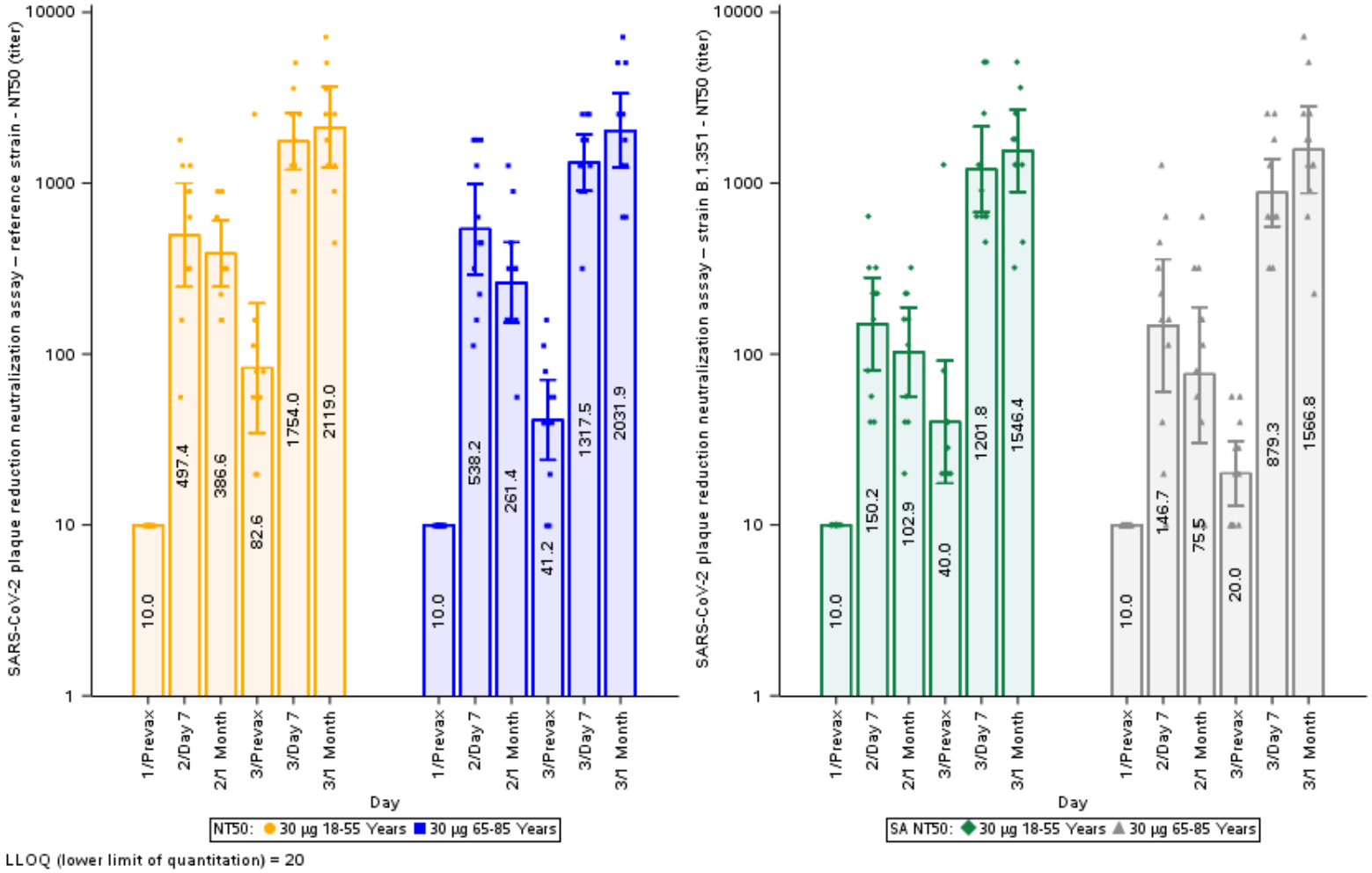
The difference between neutralizing titers against the wild-type virus and the Beta variant observed after Dose 2 narrowed after BNT162b2 Dose 3 (Figure 2). Specifically, at 1 month after Dose 2, the geometric mean ratios (GMRs) of neutralizing titers against the Beta variant to neutralizing titers against the wild-type virus were 0.27 (95% CI: 0.18, 0.39) for younger adults and 0.29 (95% CI: 0.17, 0.49) for older adults; at 1 month after Dose 3, the corresponding GMRs increased to 0.73 (95% CI: 0.52, 1.02) and 0.77 (95% CI: 0.51, 1.16).

Neutralization Titers Against the Delta Variant

A third dose of BNT162b2 also increased the neutralizing titers against recombinant SARS-CoV-2 with the Delta variant spike. At 1 month after Dose 3, GMTs were 1321 (95% CI: 698.5, 2498.3) for younger adults, and 1479 (95% CI: 734.9, 2975.8) for older adults, which were approximately 5-fold and 12-fold, respectively, the GMTs observed at 1 month after Dose 2 (Figure 3).

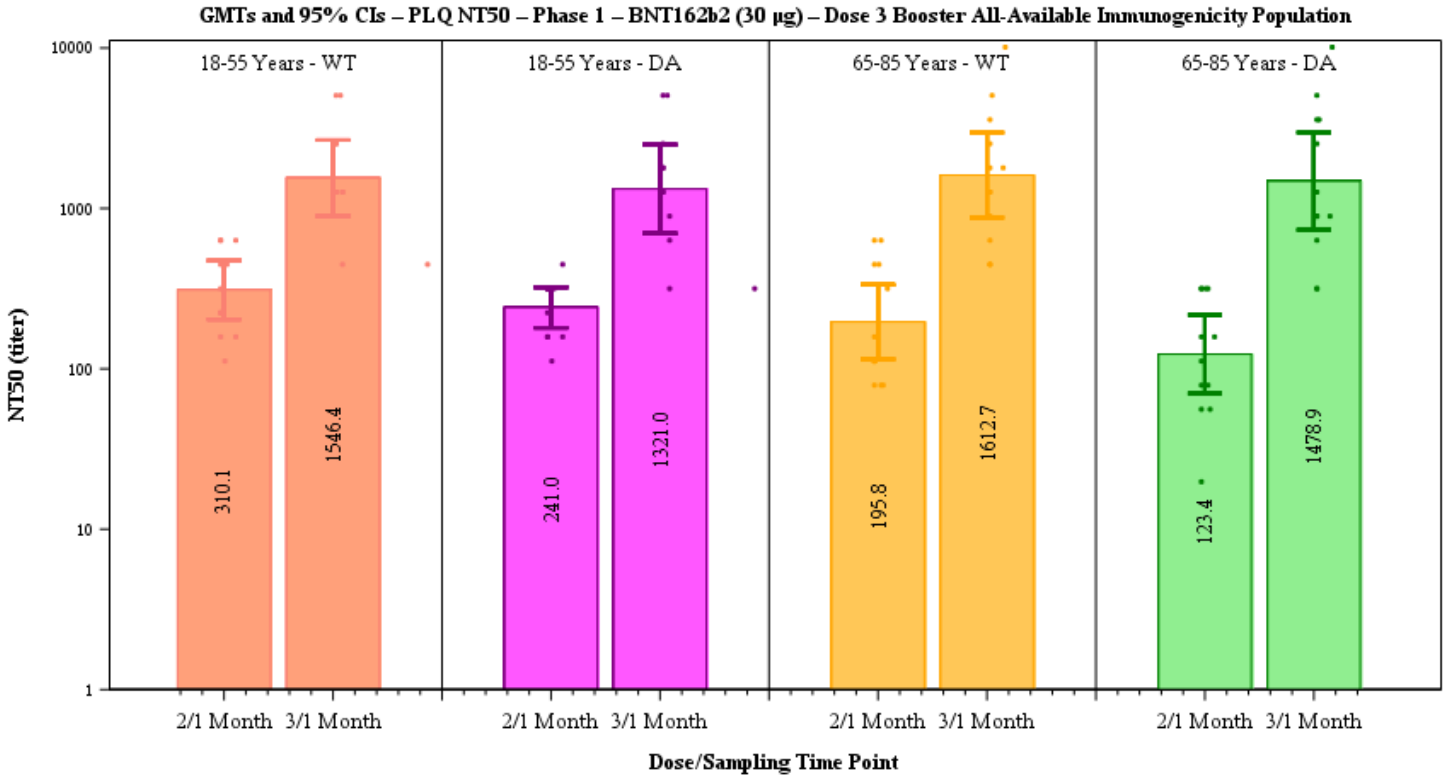
The difference between neutralizing titers against the wild-type virus and the Delta variant observed after Dose 2 narrowed after BNT162b2 Dose 3 (Figure 3). Specifically, at 1 month after Dose 2, the geometric mean ratios (GMRs) of neutralizing titers against the Delta variant to neutralizing titers against the wild-type virus were 0.78 (95% CI: 0.63, 0.96) for younger adults and 0.63 (95% CI: 0.46, 0.86) for older adults; at 1 month after Dose 3, the corresponding GMRs increased to 0.85 (95% CI: 0.71, 1.03) and 0.92 (95% CI: 0.71, 1.18), respectively.

Figure 2. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralizing Titers (NT50) for Wild-Type (Reference Strain) and B.1.351 (Beta) Variant – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster All-Available Immunogenicity Population (18-55 Years of Age and 65 to 85 Years of Age)



Wild-type (Reference Stain) **Beta variant (B.1.351)**

Figure 3. Geometric Mean Titers and 95% CIs for SARS-CoV-2 Plaque Reduction Neutralization Assay (NT50) for Wild-Type (Reference Strain) and B.1.617.2 (Delta) Variant – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster All-Available Immunogenicity Population (18-55 Years of Age and 65 to 85 Years of Age)



Abbreviations: DA = delta; GMT = geometric mean titer; NT50 = 50% neutralizing titer;
PLQ NT50 = SARS-CoV-2 plaque reduction neutralization assay – NT50 (titer); WT = wild type.
Note: Dots represent individual antibody levels.
Note: Number within each bar denotes geometric mean titer.
PFIZER CONFIDENTIAL SDTM Creation: 05AUG2021 (11:22) Source Data: adva Table Generation: 05AUG2021 (22:34)
(Data Cutoff Date: 13MAY2021, Database Snapshot Date: 08JUN2021) Output File: ./nda3/C4591001_P1_Booster_Delta/adva_f002_sars_50_b2_aai_da_p1

2.2.1.3. Phase 1 Booster Immunogenicity - Discussion and Conclusions

A third dose of BNT162b2 30 µg administered 7 to 9 months after the initial two-dose series in adults 18 to 55 and 65 to 85 years of age boosted serum neutralizing titers against the original SARS-CoV-2 wild-type strain, the Beta variant, and the Delta variant, resulting in an increase of neutralizing titers that were >5-fold , >15-fold, and >5-fold, respectively, those observed after Dose 2.

Furthermore, the difference in neutralizing titers between the wild-type and the variant viruses narrowed after the third dose compared with those after the second dose, showing that a booster dose increases the breadth of neutralizing response against SARS-CoV-2 variants. The kinetics of neutralizing titers changed from falling neutralizing titers during the month after the second dose to rising neutralizing titers during the month after the third dose. This phenomenon of increased magnitude and breadth and improved kinetics of the humoral response has also been observed when booster doses of pre-pandemic influenza vaccines were administered after a primary immunization series.[17]

Some SARS-CoV-2 variants have been associated with more rapid transmission, and potentially, greater pathogenicity,[18] leading to concerns about the potential for reduced vaccine-mediated protection. Studies of in vitro neutralization of a number of SARS-CoV-2 variants have found that the tested BNT162b2-immune sera neutralize all SARS-CoV-2 variants assayed to date, including the Beta and Delta variants.[14,19,20,21,22,23,24] Although the neutralization activity of BNT162b2-immune sera against recombinant SARS-CoV-2 with the B.1.351 lineage spike was lower, the efficacy and effectiveness of BNT162b2 against the Beta variant has remained very high, particularly for severe outcomes.[14,25,26] In the Phase 2/3 study, there was 100% observed vaccine efficacy of BNT162b2 against COVID-19 in the subgroup of participants from South Africa, with all 9 cases of COVID-19 in South Africa occurring in the placebo group. In 8 of these cases viral sequence could be obtained, and all 8 were confirmed as caused by the B.1.351 (Beta) variant.[25] Real-world data also indicate that two doses of BNT162b2 are 75%, 88%, and 90% effective against B.1.351 (Beta), B.1.617.2 (Delta), and B.1.1.7 (Alpha) variants, respectively.[26,27]

The high neutralizing titers against the Beta and Delta variants after a third dose, exceeding those after two doses, and the more comparable titers for the wild-type and variant strains after Dose 3 are encouraging. These data suggest that a third dose could re-establish the efficacy levels shown 1 month after two doses, prolong duration of protection, and further increase the breadth of protection.

2.2.2. Phase 3

Sera from Phase 3 booster substudy participants were analyzed using the reference strain SARS-CoV-2 neutralization assay (mNeonGreen microneutralization assay, SARS-CoV-2 mNG NT). Titers against the Beta and Delta variants were not determined for Phase 3 participants.

2.2.2.1. Immunogenicity Endpoints and Analysis Methods – Phase 3 Booster Substudy

Immunogenicity endpoints in Phase 3 were:

- GMT - geometric mean titer of SARS-CoV-2 neutralizing activity
- GMR - geometric mean ratio of SARS-CoV-2 neutralizing titer at 1 month after Dose 3 to the neutralizing titer at 1 month after Dose 2
- GMFR - geometric mean-fold rise in neutralizing titer from before Dose 3 to 1 month after Dose 3.
- Percentages of participants with seroresponse - Seroresponse was defined as a ≥4-fold rise in neutralizing titer from baseline (before Dose 1). For participants with a baseline titer less than the lower limit of quantitation (<LLOQ), seroresponse is defined as a postvaccination titer of ≥4 × LLOQ.

In the Phase 3 substudy of C4591001, the basis for demonstrating BNT162b2 booster (Dose 3) effectiveness is immunobridging: demonstration that the immune response to BNT162b2 30 µg at 1 month after Dose 3 is noninferior to that observed at 1 month after Dose 2 (when 95% efficacy was established in the primary analysis for this study), based on SARS-CoV-2 50% neutralizing titers to the reference strain in participants without prior evidence of SARS-CoV-2 infection up to 1 month following Dose 3.[a]

The immunobridging success criteria included prespecified margins for the geometric mean ratio (GMR) and seroresponse. Noninferiority was assessed based on the GMR of SARS-CoV-2 neutralizing titers at 1 month after Dose 3 to 1 month after Dose 2 using a 1.5-fold margin and comparison of the point estimate of the GMR to 0.8. Noninferiority was declared if the lower bound of the 2-sided 97.5% CI for the GMR was >0.67 and the point estimate of the GMR was ≥0.8.

Noninferiority was also assessed based on the difference in percentages of participants with seroresponse at 1 month after Dose 3 and 1 month after Dose 2 using a 10% margin. Noninferiority was declared if the lower limit of the 97.5% CI for the difference in percentages of participants with seroresponse was greater than -10%.

The statistical analyses of immunogenicity data from Study C4591001 were based on the evaluable immunogenicity populations and all-available immunogenicity populations.

[a] Prior serological or virological evidence of SARS-CoV-2 infection was determined by N-binding antibody or nucleic acid amplification test (NAAT), respectively.

Results from all-available population were similar to those for the evaluable immunogenicity population and are not included in this briefing document.

2.2.2.2. Immunogenicity Results – Phase 3 Booster Substudy

2.2.2.2.1. Study Population and Vaccine Administration Timing

In the Phase 3 booster substudy, a total of 312 participants who previously received the BNT162b2 30 µg two-dose regimen in Phase 3 of the study were rerandomized to receive a booster (Dose 3) of BNT162b2 30 µg. All received a third vaccination, and 309 completed the booster vaccination period from Dose 3 to the 1-month follow-up visit after Dose 3. Four participants withdrew from the study after receiving Dose 3, including 2 (0.6%) lost to follow-up and 2 (0.6%) who withdrew from the study.

Among these 312 participants, 6 received a prototype vaccine based upon the B.1.351 (Beta) variant that originated in South Africa (BNT162b2$_{SA}$) in error (this vaccine was being administered to a second randomized group). Safety and immunogenicity data are presented in this briefing document only for the 306 participants who received BNT162b2 30 µg.

Among the 312 randomized participants, most received Dose 3 between 6 and 8 months after Dose 2; the median duration between Dose 2 and Dose 3 was 6.8 months (range: 4.8 to 8.0 months) (Table 3).

Table 3. Vaccine Administration Timing – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg)

	Vaccine Group (as Randomized)
	BNT162b2 (30 µg) (N[a]=312) n[b] (%)
Rerandomized	312 (100.0)
Did not receive booster vaccination	0
Booster vaccination[c]	312 (100.0)
<5 Months	1 (0.3)
≥5-<6 Months	28 (9.0)
≥6-<7 Months	155 (49.7)
≥7 Months	128 (41.0)
Mean (SD)	6.8 (0.56)
Median	6.8
Min, max	(4.8, 8.0)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Months calculated since Dose 2.
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(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/advx_s002_time_p3_g1_rand

The demographic characteristics of the 306 participants who received BNT162b2 are shown in Table 4. This population was generally similar to the safety population and the efficacy populations analyzed for Phase 2/3 participants who had a median follow-up time of 2 months post-Dose 2 at the time of the prespecified final analysis of efficacy. Booster group participants had a diverse medical history profile consistent with that of individuals in the general population, as also noted in prior analyses of Phase 2/3 C4591001 participants. There were no participants with confirmed HIV in this Phase 3 booster population.

Table 4. Demographic Characteristics – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)
	BNT162b2 (30 µg) (N[a]=306) n[b] (%)
Sex	
Male	140 (45.8)
Female	166 (54.2)
Race	
White	249 (81.4)
Black or African American	28 (9.2)
American Indian or Alaska Native	2 (0.7)
Asian	16 (5.2)
Native Hawaiian or other Pacific Islander	1 (0.3)
Multiracial	4 (1.3)
Not reported	6 (2.0)
Ethnicity	
Hispanic/Latino	85 (27.8)
Non-Hispanic/non-Latino	219 (71.6)
Not reported	2 (0.7)
Country	
USA	306 (100.0)
Age at booster vaccination (years)	
Mean (SD)	41.3 (9.44)
Median	42.0
Min, max	(19, 55)
Body mass index (BMI)	
Underweight (<18.5 kg/m^2)	1 (0.3)
Normal weight (≥18.5-24.9 kg/m^2)	82 (26.8)
Overweight (≥25.0-29.9 kg/m^2)	101 (33.0)
Obese (≥30.0 kg/m^2)	122 (39.9)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
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(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adsl_s005_demo_p3_g1_1d30_saf

Evaluable Immunogenicity Population

Among the 312 participants who were rerandomized to receive a booster (Dose 3) of BNT162b2 30 µg, the Dose 3 booster evaluable immunogenicity population included 268 participants, and those without evidence of infection up to 1 month after Dose 3 included

234 participants (Table 5). The most common reason for exclusion (30 [9.6%] participants) from the evaluable immunogenicity population was that they had important protocol deviation(s) as determined by the clinician. The majority of these protocol deviations (16 participants, 53.3% of those with deviations leading to exclusion) had the Dose 3 vaccination visit outside the protocol-specified window.

Table 5. Immunogenicity Populations – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg)

	Vaccine Group (as Randomized)
	BNT162b2 (30 µg) n[a] (%)
Rerandomized[b]	312 (100.0)
Dose 3 booster all-available immunogenicity population	306 (98.1)
Subjects excluded from Dose 3 booster all-available immunogenicity population	6 (1.9)
Reason for exclusion	
Did not have at least 1 valid and determinate immunogenicity result after booster vaccination	6 (1.9)
Dose 3 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 Dose 3 booster evaluable immunogenicity population	44 (14.1)
Reason for exclusion[d]	
Did not receive Dose 2 within 19-42 days after Dose 1	1 (0.3)
Did not receive a booster vaccination of BNT162b2 or BNT162b2$_{SA}$ as rerandomized	6 (1.9)
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after booster vaccination	15 (4.8)
Had important protocol deviation(s) before 1 month post Dose 3 evaluation as determined by the clinician	30 (9.6)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. n = Number of subjects with the specified characteristic.
b. This value is the denominator for the 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, and 303 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 vaccination.
d. Subjects may have been excluded for more than 1 reason.
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2.2.2.2.2. Noninferiority of the Booster Response (Dose 3 Relative to Dose 2)

Geometric Mean Ratio (GMR) of Neutralization Titers (Dose 3 Relative to Dose 2)

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after the booster (Dose 3), the immune response to BNT162b2 30 µg at 1 month after the booster (Dose 3) was noninferior to that observed at 1 month after Dose 2 in the same participants, based on SARS-CoV-2 50% neutralizing titers (Table 6).

The SARS-CoV-2 neutralizing GMT ratio of 1 month after Dose 3 to 1 month after Dose 2 was 3.29 (2-sided 97.5% CI: 2.76, 3.91), which meets the 1.5-fold noninferiority criterion (ie, lower bound of the 2-sided 97.5% CI for GMR >0.67) and point estimate of GMR ≥0.8.

The lower bound of the 2-sided 97.5% CI for the GMR is >1, which indicates a statistically greater response following booster (Dose 3) administration than following Dose 2.

Difference in Seroresponse Rate (Dose 3 Relative to Dose 2)

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after the booster (Dose 3), a high proportion of participants (99.5%) had a seroresponse at 1 month after Dose 3, compared with 98.0% at 1 month after Dose 2 (Table 6).

The difference in proportions of participants with a seroresponse 1 month after the booster (Dose 3) and 1 month after Dose 2 (Dose 3 – Dose 2) was 1.5% (2-sided 97.5% CI: -0.7, 3.7%), which meets the 10% noninferiority margin (ie, lower bound of the 2-sided 97.5% CI was greater than -10%).

In addition, the US FDA requested that a post hoc analysis be performed using the prebooster (Dose 3) titer (rather than the pre-Dose 1 titer) as the baseline for determining booster dose seroresponse. Using this alternative definition, for the evaluable immunogenicity population, the seroresponse rate was 93.9% 1 month after the booster (Dose 3), compared with 97.8% 1 month after Dose 2. The difference in seroresponse rates was -3.9% (2-sided 95% CI: -8.2, 0.4%).

Table 6. Geometric Mean Ratio – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – BNT162b2-Experienced Subjects Without Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population

					Sampling Time Point		
					1 Month After Booster Dose	1 Month After Dose 2 (BNT162b2)	1 Month After Booster Dose/1 Month After Dose 2
Objective[a]	Assay at 1 Month After Booster Dose	Assay at 1 Month After Dose 2	Vaccine Group (as Randomized)	n[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (97.5% CI[e])
E1a	SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	BNT162b2 (30 µg)	210	2476.4 (2210.1, 2774.9)	753.7 (658.2, 863.1)	3.29 (2.76, 3.91)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: 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, and 303 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 vaccination were included in the analysis.
a. The first primary objective to be evaluated in Phase 3 booster portion of the study, where 'E' represents BNT162b2-experienced subjects and 'a' represents GMR estimands.
b. n = Number of subjects with valid and determinate assay results for both the specified assays at the given dose/sampling time point within specified window.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
e. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8.
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Table 7. Percentage Difference of Subjects Achieving Seroresponse – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – BNT162b2-Experienced Subjects Without Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population

					Sampling Time Point		Difference	
					1 Month After Booster Dose	1 Month After Dose 2 (BNT162b2)	(1 Month After Booster Dose – 1 Month After Dose 2)	
Objective[a]	Assay at 1 Month After Booster Dose	Assay at 1 Month After Dose 2	Vaccine Group (as Randomized)	N[b]	n[c] (%) (95% CI[d])	n[c] (%) (95% CI[d])	%[e]	(97.5% CI[f])[g]
E1b	SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	BNT162b2 (30 µg)	198	197 (99.5) (97.2, 100.0)	194 (98.0) (94.9, 99.4)	1.5	(-0.7, 3.7)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

Note: 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, and 303 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 vaccination were included in the analysis.

a. The first primary objective to be evaluated in Phase 3 booster portion of the study, where 'E' represents BNT162b2-experienced subjects and 'b' represents seroresponse rate estimands.

b. N = number of subjects with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.

c. n = Number of subjects with seroresponse for the given assay at the given dose/sampling time point.

d. Exact 2-sided CI based on the Clopper and Pearson method.

e. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).

f. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.

g. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is greater than -10.

PFIZER CONFIDENTIAL SDTM Creation: 16AUG2021 (09:19) Source Data: adva Table Generation: 18AUG2021 (11:35)
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2.2.2.2.3. SARS-CoV-2 Neutralizing Titers and Fold Rises

Geometric Mean Titers (GMTs)

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after the booster (third) dose, the SARS-CoV-2 50% neutralizing GMT increased substantially after the booster vaccination, from 136.2 before Dose 3 to 2374.2 1 month after Dose 3 (Figure 4). The GMT after the booster dose was 3 times those observed 1 month after Dose 2, showing a strong boost of the neutralizing antibody response.

From baseline (prior to receipt of Dose 1) to 1 month after Dose 2, the GMT substantially increased to 73-times the prevaccination GMT, from 10.4 (2-sided 95% CI: 10.0, 10.9) to 762.0 (2-sided 95% CI: 663.3, 875.5). The median duration between receipt of Dose 2 and the booster with Dose 3 was 6.8 months (Table 3). The GMT had declined by the time the booster (Dose 3) was administered: from 762.0 (2-sided 95% CI: 663.3, 875.5) 1 month after Dose 2 to 136.2 (2-sided 95% CI: 121.5, 152.6) at the time of booster administration. Following the booster (third) dose, the GMT increased to 1418.7 (95% CI: 1263.3, 1593.3) at 7 days post-Dose 3. By 1 month after Dose 3, the GMT increased further to 2374.2 (95% CI: 2134.1, 2641.3).

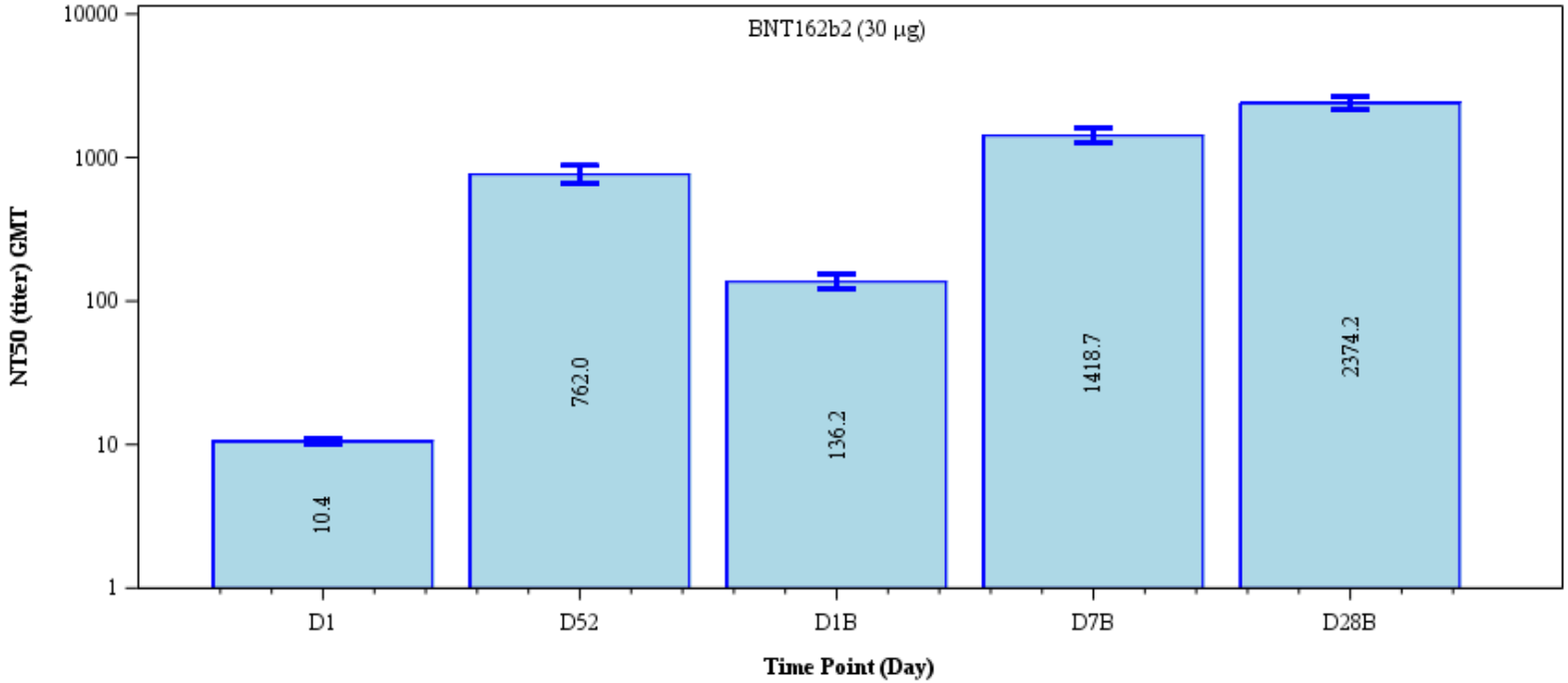
Geometric Mean Fold-Rise (GMFR) in Titers

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after the booster (Dose 3), the GMFR of SARS-CoV-2 50% serum neutralizing titers from before Dose 3 to 7 days after Dose 3 was 13.5 (2-sided 95% CI: 11.3, 16.3). At 1 month after Dose 3, the GMFR from before Dose 3 was 17.4 (2-sided 95% CI: 15.2, 20.0).

Seroresponse Rate

In the Dose 3 booster evaluable population, among participants without prior evidence of SARS-CoV-2 infection up to 1 month after the booster dose (Dose 3), the proportion of participants with seroresponse at 1 month after Dose 2 had been 98.0% (2-sided 95% CI: 95.0, 99.5). By the time of booster (Dose 3) administration (before booster vaccination), the proportion of participants with seroresponse had declined to 77.2% (2-sided 95% CI: 70.7, 82.8). At 7 days after Dose 3, the proportion of participants with seroresponse was 98.0% (2-sided 95% CI: 92.8, 99.8), and by 1 month after the booster (Dose 3) the seroresponse rate increased further to 99.5% (2-sided 95% CI: 97.4%, 100.0%).

Figure 4. Geometric Mean Titers and 95% Confidence Intervals, Reference Strain SARS-CoV-2 Neutralization Assay – NT50 – Phase 3 – BNT162b2-Experienced Subjects Without Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population



Abbreviations: B = booster vaccination; D = day; GMT = geometric mean titer; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: 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, and 303 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 vaccination were included in the analysis.
Note: Number within each bar denotes geometric mean titer.
PFIZER CONFIDENTIAL SDTM Creation: 16AUG2021 (09:19) Source Data: adva Table Generation: 18AUG2021 (22:21)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adva_f002_nt50_p3_g1

2.2.2.2.4. Immunogenicity Conclusions – Phase 3

SARS-CoV-2 reference strain 50% neutralizing titers following Dose 3 of BNT162b2 (30 µg) were noninferior to titers observed after Dose 2, and met the prespecified 1.5-fold noninferiority criterion for the GMR (ie, lower bound of the 2-sided 97.5% CI for GMR >0.67) and point estimate of GMR ≥0.8. The prespecified 10% noninferiority margin for the difference in seroresponse rates was also met (ie, lower bound of the 2-sided 97.5% CI was greater than -10%). Substantial increases over pre-boost levels for neutralizing GMTs and high seroresponse rates were observed at 1 month after Dose 3, demonstrating a robust effect of the third dose of BNT162b2 30 µg.

Phase 3 booster data showed that a third dose of BNT162b2 30 µg, administered between 4.8 and 8.0 months after completing the two-dose regimen, elicited neutralizing titers much higher than the neutralizing titers after Dose 2.

2.3. Safety and Tolerability Results

Safety data are presented in this briefing document for Phase 1 booster study participants from Dose 3 to 1 month after Dose 3; for Phase 3 participants, safety data include information collected from the booster (Dose 3) to 1 month after Dose 3, and from Dose 3 to the data cutoff date (17 June 2021), which accounts for at least 2 months post-Dose 3.

2.3.1. Phase 1

All 23 participants who received a booster (third) dose of BNT162b2 were included in the safety analysis. Overall, a third dose was well tolerated.

Local Reactions

Younger participants 18 to 55 years of age reported mild to moderate local reactions, which were primarily pain at the injection site after Dose 3 (Figure 5). In this age group, a higher percentage of participants reported local reactions after the first dose (91%) than after either the second (82%) or third dose (82%).

In older participants 65 to 85 years of age, mild to moderate pain at the injection site was the only local reaction reported (Figure 5). Again, a higher percentage of participants reported local reactions after the first BNT162b2 dose (75%) than after either the second (67%) or third dose (67%). A higher percentage of younger than older participants reported local reactions after each dose.

Systemic Events

A lower percentage of younger adults reported systemic events after the first BNT162b2 dose (73%) than after either the second (100%) or third dose (91%). In this age group, fatigue, headache, chills, and muscle pain were reported by more participants after both Doses 2 and 3 than after Dose 1 (Figure 6). Systemic events were predominantly mild to moderate in severity. Fever was more common after Dose 3 than after Doses 1 or 2.

As in the younger adult group, a lower percentage of participants in the older adult group reported systemic events after the first BNT162b2 dose (25%) than after the second (58%) or third dose (67%). In this older age group, fatigue, headache, chills, muscle pain, and joint pain were reported by more participants after Doses 2 and 3 than after Dose 1(Figure 6). No participant in this age group reported a severe systemic event. No fever was reported after the first or third dose. A lower percentage of older than younger participants reported systemic events after each dose.

Adverse Events

There were no adverse events reported in the 1 month after Dose 3 of BNT162b2 30 µg.

Figure 5. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population

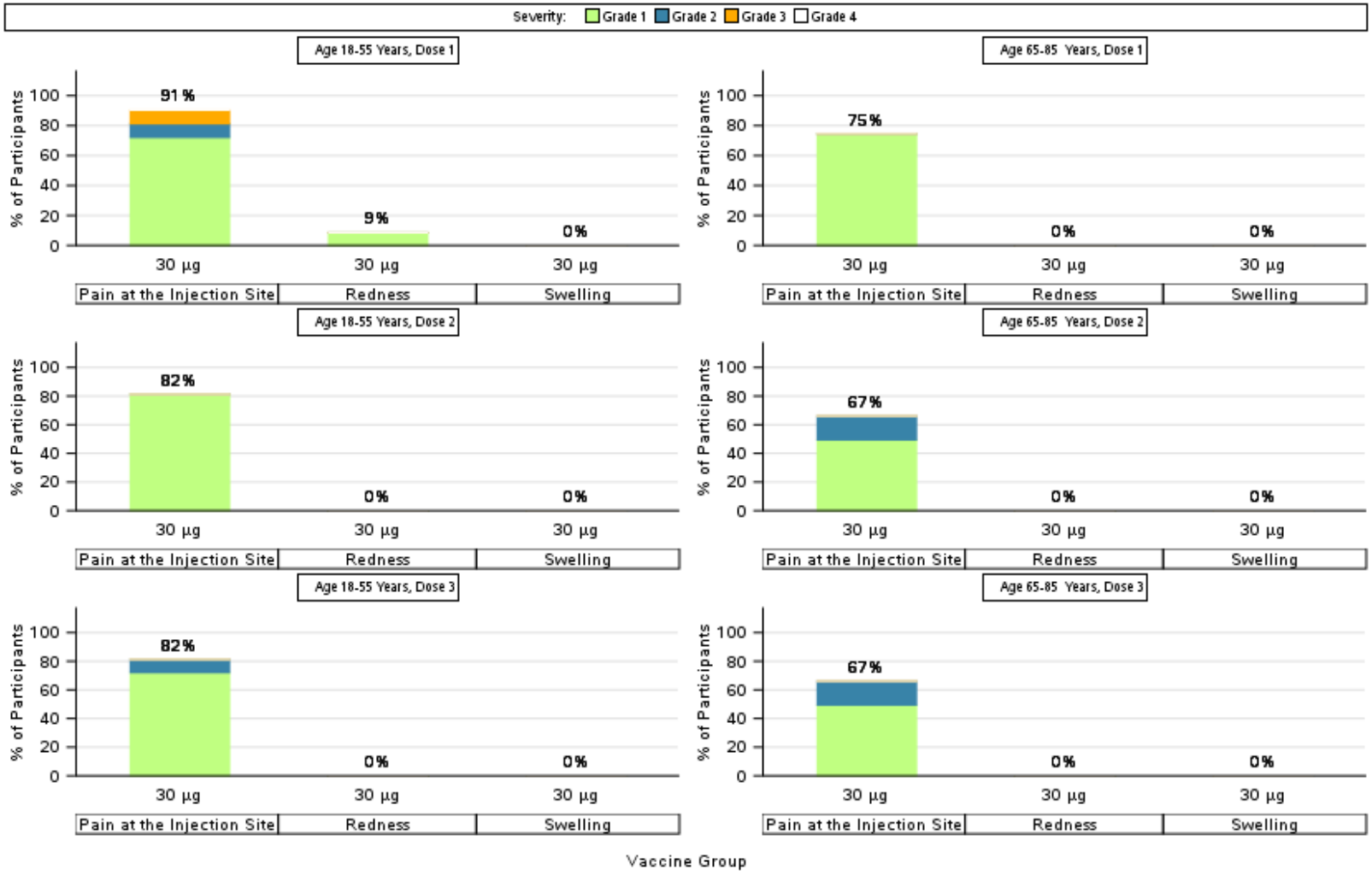
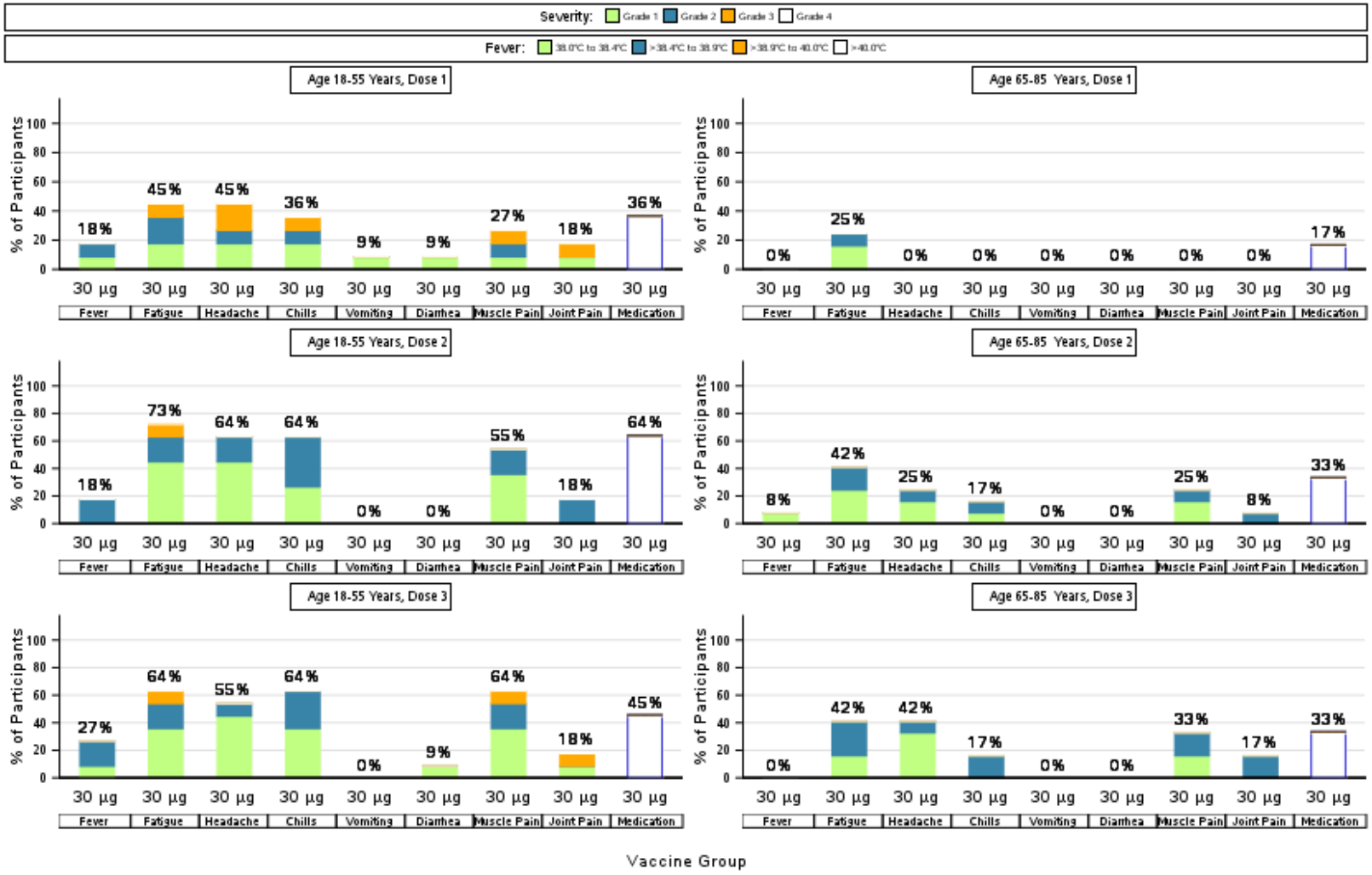


Figure 6. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population



2.3.2. Phase 3

2.3.2.1. Reactogenicity

A total of 289 participants had e-diary data reported after booster (Dose 3) administration.

Among these adults ≥18 to 55 years of age, the frequency and severity of local reactions and systemic events were generally similar to those previously reported in this study for the 16 to 55 years of age group after the second dose of BNT162b2.

Local Reactions

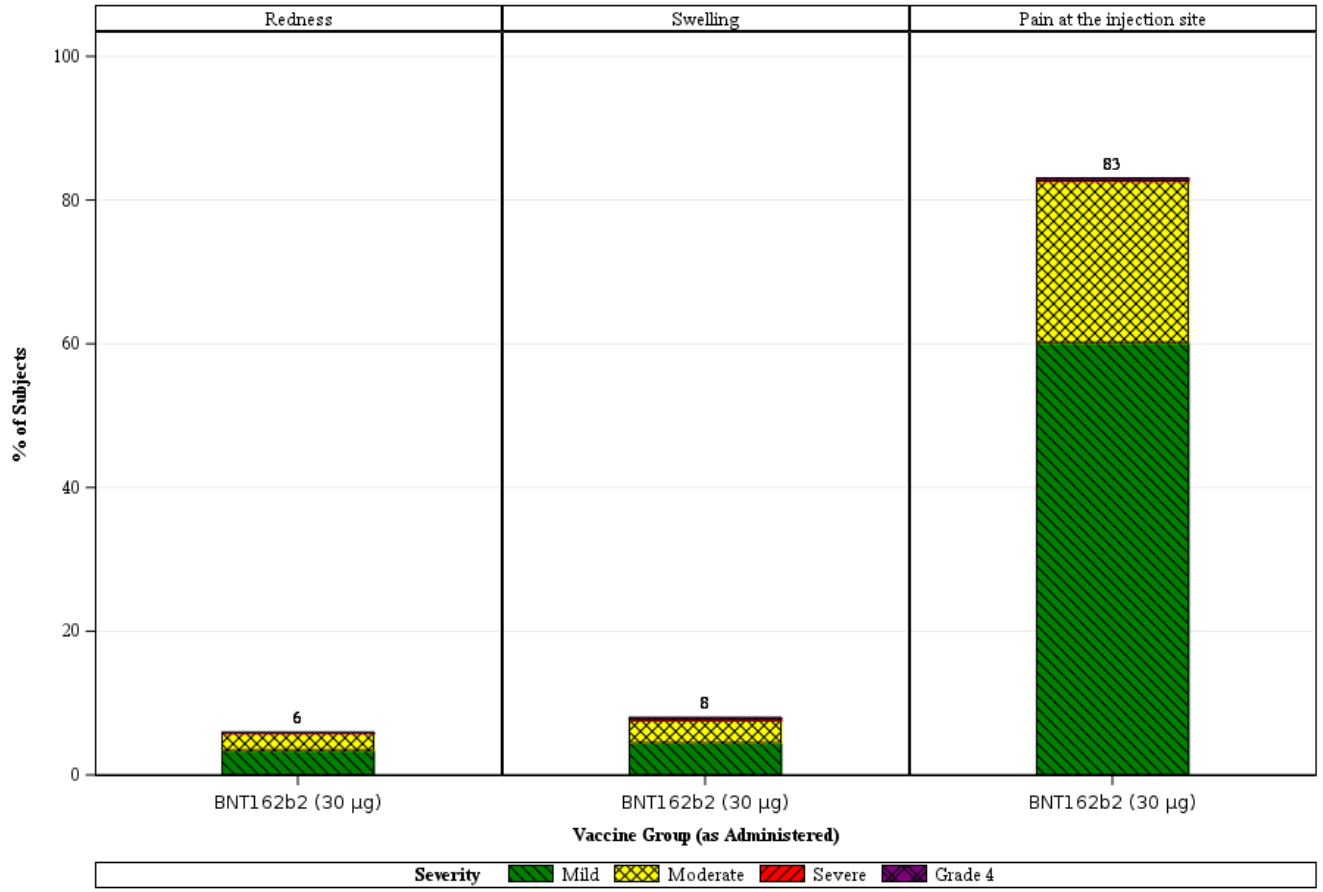
Local Reactions After the Booster (Third) Dose

Pain at the injection site was the most frequently reported local reaction after booster (Dose 3) administration, reported by 83.0% of participants; redness was reported by 5.9%, and swelling by 8.0% of participants (Figure 7). These frequencies are similar to the frequencies previously observed in this study after Dose 2 of BNT162b2 in the 16 to 55 years of age group (N=2682): pain at the injection site, 78.3%; redness, 5.6%; swelling, 6.8%.

After Dose 3, most local reactions were mild or moderate in severity. Severe local reactions were reported in 2 participants, including 1 (0.3%) with severe pain at the injection site and 1 (0.3%) with severe swelling at the injection site. No Grade 4 local reactions were reported after Dose 3.

The median onset for all local reactions after Dose 3 was Day 1 to Day 2 (Day 1 was the day of vaccination), and local reactions resolved within a median duration of 1 to 2 days.

Figure 7. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2 Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 ug) – Booster Safety Population



Note: Number above each bar denotes percentage of subjects reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (13:45) Source Data: adfacevd Table Generation: 18AUG2021 (22:21)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adce_f001_lr_max_p3_g1

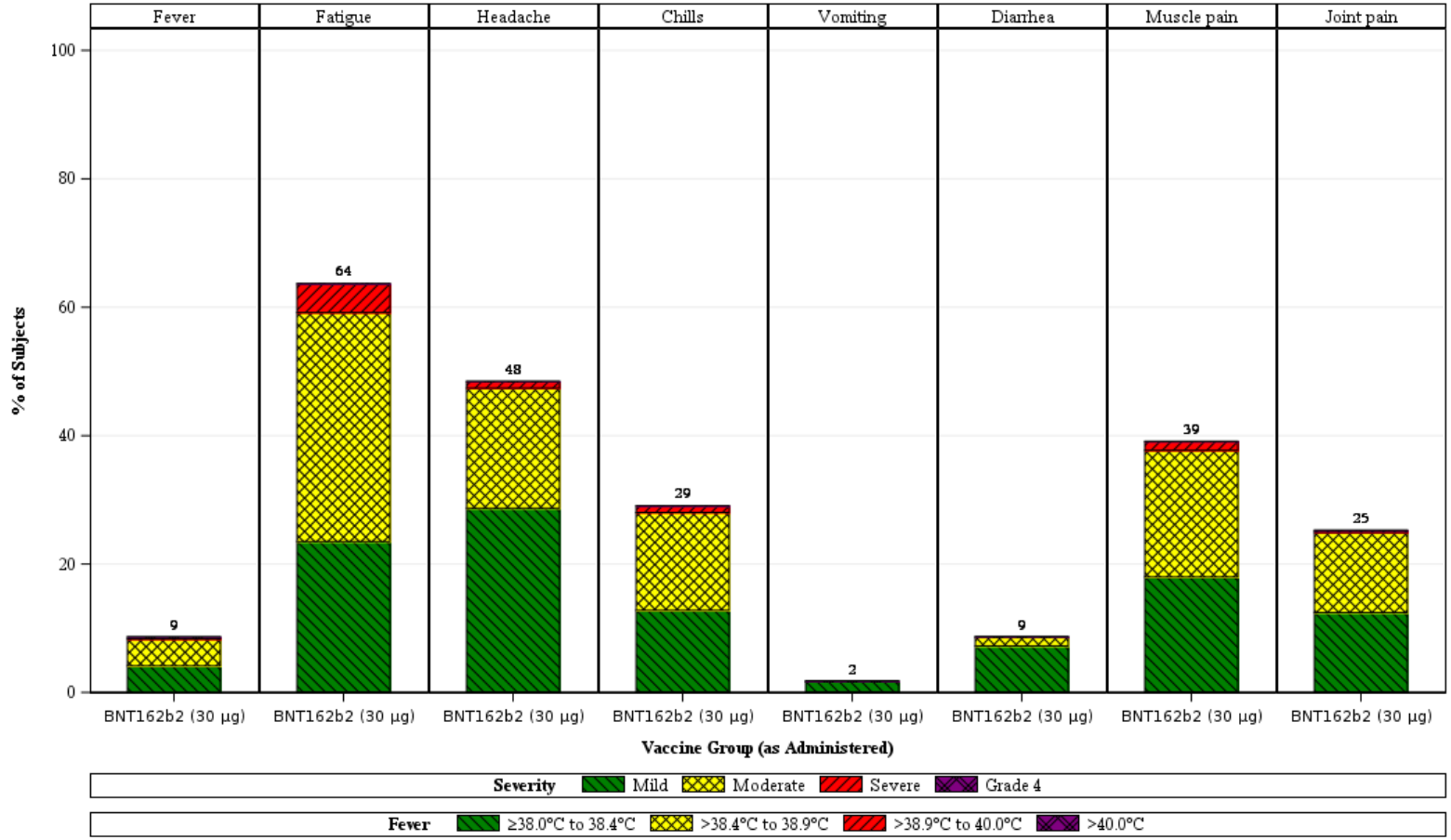
Systemic Events

The frequency of systemic events and use of antipyretic or pain medications reported by e-diary after booster (Dose 3) administration was generally similar to the frequency of systemic events previously reported in this study for the 16 to 55 years of age group after the second dose of BNT162b2 (Table 8). After Dose 3, most systemic events were mild or moderate in severity (Figure 8). Severe systemic events were reported infrequently (Table 8). A fever of >38.9 °C was reported in 1 participant; this individual had oral temperatures of 39.1 °C on Day 2 and 38.6 °C on Day 3 that returned to normal on Days 4 through 7. No Grade 4 systemic events were reported after Dose 3. The median onset for all systemic events after Dose 3 was Day 2 to Day 4 (Day 1 was the day of vaccination), and systemic events resolved within a median duration of 1 to 2 days.

Table 8. Frequency of Systemic Events Reported By E-Diary in Phase 3 of Study C4591001: Among Participants ≥18-55 Years Of Age After Booster (Dose 3) and After Dose 2 Among Participants 16-55 Years Of Age

	% of Participants Reporting the Event	
	(≥18 to 55 Years of Age)	(16 to 55 Years of Age)
Systemic Event	**After Booster (Dose 3) N = 289**	**After Dose 2 N = 2682**
Any Systemic Event		
Fatigue	63.7%	61.5%
Headache	48.4%	54.0%
Muscle Pain	39.1%	39.3%
Chills	29.1%	37.8%
Joint Pain	25.3%	23.8%
Fever (>38.0°C)	8.7%	16.4%
Diarrhea	8.7%	10.0%
Vomiting	1.7%	2.2%
Use of antipyretic or pain medication	46.7%	45.2%
Severe Systemic Events		
Fatigue	4.5%	5.3%
Headache	1.0%	3.4%
Muscle Pain	1.4%	2.3%
Chills	1.0%	2.6%
Joint Pain	0.3%	1.0%
Fever (>38.9°C)	0.3%	1.5%
Diarrhea	0.0%	0.2%
Vomiting	0.0%	0.1%

Figure 8. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 ug) – Booster Safety Population



Note: Number above each bar denotes percentage of subjects reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (13:45) Source Data: adfacevd Table Generation: 18AUG2021 (22:21)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adce_f001_se_max_p3_g1

2.3.2.2. Adverse Events

2.3.2.2.1. Overview of Adverse Events

The Phase 3 booster safety population included 306 participants, who had a median duration of 6.8 months between receiving the second and third doses (Table 3). The median follow-up time after receiving Dose 3 was 2.6 months (range: 1.1 to 2.8 months) (Table 9).

Table 9. Follow-up Time After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg)

	Vaccine Group (as Administered)
	BNT162b2 (30 µg) (N[a]=306) n[b] (%)
Total exposure from booster vaccination to cutoff date	
<2 Months	1 (0.3)
≥2-<4 Months	305 (99.7)
Mean (SD)	2.7 (0.15)
Median	2.6
Min, max	(1.1, 2.8)
Total exposure from Dose 2 to cutoff date	
≥6-<8 Months	4 (1.3)
≥8-<10 Months	248 (81.0)
≥10 Months	54 (17.6)
Mean (SD)	9.4 (0.57)
Median	9.5
Min, max	(7.5, 10.8)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (23:01) Source Data: adsl Table Generation: 16AUG2021 (23:05)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adsl_fu_d2_p3_g1

Summary of Adverse Events from Dose 3 to 1 Month After Dose 3

From Dose 3 to 1 month after Dose 3, among the 306 participants in the booster safety population, 44 (14.4%) reported at least one AE and 24 (7.8%) reported at least one AE considered by the investigator to be related to study intervention. One participant (0.3%) reported a severe AE (lymphadenopathy; onset at 2 days post-Dose 3 and recovered/resolved 5 days from onset). No immediate events were reported within 30 minutes after booster (Dose 3) administration. No deaths, SAEs or life-threatening (Grade 4) AEs were reported. No AEs leading to withdrawal were reported.

Most AEs reported during this period reflect reactogenicity events reported by the investigator as AEs. AE frequencies in SOCs for such reactogenicity terms were:

- general disorders and administration site conditions: 2.6%
- musculoskeletal and connective tissue disorders: 2.3%
- nervous system disorders: 1.6%
- gastrointestinal disorders: 1.3%.

The most commonly reported AE was lymphadenopathy, in 16/306 participants (5.2%). Lymphadenopathy is discussed below in Section 2.3.2.2.2, Adverse Events of Clinical Interest.

Lymphadenopathy was also the most frequently reported AE assessed by the investigator as related to study intervention (16/306 participants, 5.2%). Most of the other related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions, reported by 7/306 participants (2.3%).

Summary of Adverse Events from Dose 3 to Data Cutoff Date

From Dose 3 to the data cutoff date (17 June 2021), which represents at least 2 months of post-Dose 3 follow-up (median of 2.6 months), only 1 additional AE was reported beyond the 1-month post-Dose 3 period of follow-up.

The event was a severe SAE (acute myocardial infarction) reported 62 days after Dose 3 by an individual in their forties, and the event was considered unrelated to study intervention by the investigator. This participant had a medical history pertinent to the etiology of the MI. The MI was reported as recovered/resolved with sequelae within 1 day of onset following treatment.

As of the data cutoff date, no participants in the Phase 3 safety population had withdrawn from the study due to AEs, and none had died.

No AEs were reported that suggested any potential cases of severe COVID-19 among participants in the Phase 3 BNT162b2 booster group.

No pregnancies were reported in the Phase 3 BNT162b2 booster group from Dose 3 to the data cutoff date (17 June 2021).

2.3.2.2.2. Adverse Events of Clinical Interest

No cases of anaphylaxis, hypersensitivity, Bell's palsy, appendicitis, or myocarditis/pericarditis were reported in the Phase 3 BNT162b2 booster group from Dose 3 to the data cutoff date.

Overall, other than the unrelated SAE of acute myocardial infarction secondary to stimulant abuse, there were no AESIs reflecting the conditions targeted by the CDC list in this booster group as of the data cutoff date.

Adverse Drug Reactions

Adverse reactions (ADRs), defined as AEs for which there is reason to conclude that the vaccine caused the event, have been identified from clinical study safety data and are specified in the current product labeling. No new ADRs were identified from safety data associated with booster (Dose 3) administration of BNT162b2 30 µg in the Phase 3 BNT162b2 booster group.

One notable difference for this Phase 3 booster adult population was the higher frequency of lymphadenopathy after Dose 3 (5.2%) compared to the frequency of lymphadenopathy associated with the first two doses: 0.4% in individuals ≥16 years of age and 0.8% in adolescents 12 to 15 years of age.

Lymphadenopathy

In the Phase 3 booster safety population, 16/306 participants (5.2%) had cases of lymphadenopathy reported from Dose 3 to 1 month after Dose 3, of which all were considered by the investigator as related to study intervention. All cases of lymphadenopathy had an onset within 1 to 4 days after BNT162b2 booster (Dose 3) administration, and most were reported as recovered/resolved as of the data cutoff date, most within ≤5 days after onset. These cases predominantly occurred in female participants and were located in axillary nodes. Only 1 participant who had lymphadenopathy after receiving Dose 3 had also previously experienced lymphadenopathy during the blinded placebo-controlled period (with onset on the fourth day after Dose 2). No participants in the booster safety population reported a past medical history of lymphadenopathy at baseline (before Dose 1).

All lymphadenopathy cases occurring after Dose 3 were Grade 1, with one exception. One case of lymphadenopathy was graded as severe and judged by the investigator as related to study intervention: left axillary lymphadenopathy was reported in a participant in their early 40s, with onset at 2 days post-Dose 3, lasting for 5 days, and reported as recovered/resolved. The investigator-judged severity was based on the participant reporting that the lymphadenopathy prevented use of the affected arm.

Lymphadenopathy has been identified as an adverse reaction causally associated with the vaccine and is thought to be related to the development of the immune response to the vaccine. As Dose 3 is a booster, it is not surprising that stimulation of a lymph node reaction by vaccination would be present in the setting of a significant increase in neutralizing antibodies observed after Dose 3. While related to vaccination, this ADR is generally mild and self-limited and is unlikely to impede a booster vaccination program.

2.3.3. Safety Conclusions

Phase 1

Phase 1 data from 23 participants 24 to 75 years of age (11 in the younger 18 to 55 years of age group and 12 in the older 65 to 85 years of age group) who received a booster (Dose 3) of BNT162b2 30 µg showed that the third dose was safe and well-tolerated, based on the reactogenicity profile for 7 days after Dose 3 and the AE profile up to 1 month after Dose 3.

Phase 3

Phase 3 data from 306 participants ≥18 to 55 years of age who received a booster (Dose 3) of BNT162b2 30 µg showed that the third dose was safe and well-tolerated, based on the reactogenicity profile for 7 days after Dose 3 and the AE profile up to 1 month after Dose 3 and up to the data cutoff date of 17 June 2021 (which represents at least 2 months post-Dose 3).

Reactogenicity after Dose 3 was mostly mild to moderate and short-lived (ie, median onset of 1 to 4 days post-dose and resolved 1 to 2 days after onset). Local reactions after Dose 3 presented predominantly as injection site pain. Frequently reported systemic events were fatigue, headache, muscle/joint pain, and chills.

The AE profile after Dose 3 reflected mostly reactogenicity or lymphadenopathy events and did not suggest any serious short-term safety concerns for BNT162b2 booster (Dose 3) vaccination. Lymphadenopathy has been identified previously as a BNT162b2 adverse reaction and is also noted in the booster safety population but at a higher frequency with Dose 3.

After Dose 3, with the exception of the unrelated SAE of Grade 3 acute myocardial infarction, there were no AESIs reflecting the conditions targeted by the CDC list in this booster group as of the data cutoff date.

No related SAEs, withdrawals due to AEs, or deaths were reported following Dose 3 administration.

2.4. A Third Dose of BNT162b2 Administered in a Clinical Study To Describe Coadministration With Prevnar 20 (PCV20)

An additional study (NCT04887948) was conducted to describe the co-administration of Prevnar 20® (20-valent pneumococcal conjugate vaccine, PCV20) and a booster (third) dose of BNT162b2. Individuals ≥65 years of age who had received Dose 2 of BNT162b2 in Study C4591001 at least 6 months previously were randomized to receive (i) PCV20 and a third (booster) dose of BNT162b2; (ii) PCV20 and saline; or (iii) the third (booster) dose of BNT162b2 and saline (BNT162b2 control group), with approximately 190 participants randomized per group.

Safety data are available through approximately 1 month after vaccination in this ongoing study. Among the 372 participants who received the booster dose of BNT162b2, either with PCV20 (N=187) or with saline (N=185), the vaccine was generally well tolerated; reactogenicity events were mostly mild to moderate and were similar to what has been observed previously in clinical studies of the 2-dose regimen in older adults. These results provide additional data supporting a good tolerability profile for a third dose of BNT162b2 administered at least 6 months after the second dose in individuals ≥65 years of age.

These data are presented here for information only, as supportive safety data in individuals 65 years of age and older. These data are intended to complement the data submitted to support the booster dose but have not been submitted to CBER as part of the sBLA.

3. REAL-WORLD DATA ON THE PUBLIC HEALTH IMPACT OF BOOSTER DOSES OF mRNA VACCINES

As a result of emerging evidence of waning immunity and increasing rates of transmission and infection following the introduction of the Delta variant, the Israel MoH initiated a BNT162b2 booster (third dose) program for older adults and immunocompromised individuals who were previously fully immunized, a program that has since been expanded to the entire vaccine-eligible population. Early unpublished data from an Israeli health maintenance organization suggest that a third booster dose is highly effective in a setting where B.1.617.2 (Delta) accounts for nearly all cases. These initial booster data show that giving of a third dose of BNT162b2 to individuals >60 years of age was associated with 86% effectiveness against testing positive for SARS-CoV-2 infection from at least 7 days after Dose 3.

A recent Israel MoH study also confirmed that a third (booster) dose of BNT162b2 restored very high levels of protection against COVID-19 even in a period when Delta was the dominant strain.[28] The study included 1,144,690 individuals age 60 years and older who were eligible for a booster dose between July 30, 2021 and August 22, 2021.Vaccine status was defined using dynamic cohorts in which individuals initially belonged to the 'non-booster' cohort and entered the 'booster' cohort 12 days after receiving a third dose of BNT162b2. Rates of infection and severe COVID-19 outcomes per person-days at risk were compared between individuals who did and did not receive a third dose, using Poisson regression and adjusting for possible confounding factors, including age, sex, sector, and calendar day. Individuals who received the booster dose were 11.4-fold (95% CI: 10.0, 12.9) less likely to develop a confirmed infection and 15.5-fold (95% CI: 10.5, 22.8) less likely to develop severe illness compared to those who were previously fully vaccinated but did not receive a booster dose. The authors highlight that this additional protection after receiving a booster translated to roughly 95% effectiveness against COVID-19 endpoints in the Delta era—which is comparable to levels of BNT162b2 effectiveness seen early in the vaccine rollout, when the Alpha variant was predominant.

Since the rollout of the booster (third) dose program in Israel, 2.7 million Israelis ≥12 years of age have received a third dose of BNT162b2, the great majority over 60 years of age. No new safety signals or adverse events have been identified; the reactogenicity profile has appeared similar to the profile seen after the receipt of the second dose; and rates of adverse events reported after the third dose are lower than those observed after Dose 1 or Dose 2.

Thus, Israel has clearly demonstrated that, in the face of waning immunity, a booster (third dose) program can be implemented safely at a national level and that a booster dose of BNT162b2 is an effective strategy to restore high levels of protection against COVID-19 outcomes (ie, back to roughly 95%) in a period when Delta is the dominant strain.

4. PHARMACOVIGILANCE

Upon approval, Pfizer/BioNTech will include the booster dose into the ongoing pharmacovigilance activities previously agreed with the FDA for the primary two-dose schedule. These activities are succinctly summarized in Table 10.

Table 10. Studies Contributing to Pharmacovigilance

Study Title	Summary of Objectives
Ongoing Studies	
C4591001: Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals.	To evaluate the safety, tolerability, immunogenicity, and efficacy of BNT162b2. An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of VAED/VAERD. Surveillance is planned for 2 years following Dose 2.
C4591007 substudy: A Phase 3 substudy of 750 participants 5 to <12 years of age (randomized 2:1 to receive BNT162b2 10 µg or placebo) and 500 participants 12-15 years of age (open label receipt of BNT162b2 30 µg).	To obtain serum samples within the first ~4 days after vaccination for potential Troponin I testing, in order to evaluate the frequency of subclinical myocarditis amongst individuals 5 to 15 years of age.
C4591008: HERO Together: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 Vaccine in US healthcare workers, their families, and their communities.	To characterize the real-world incidence of safety events of interest, including events indicative of severe or atypical COVID-19 disease, among individuals vaccinated with the BNT162b2 since EUA
C4591012: Post-emergency use authorization active safety surveillance study among individuals in the Veteran's Affairs Health System receiving Pfizer-BioNTech COVID-19 Vaccine.	To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, including anaphylaxis, myocarditis and pericarditis, following receipt of the Pfizer-BioNTech COVID-19 Vaccine
C4591021: Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine	To assess the potential increased risk of adverse events of special interest (AESI), including myocarditis/pericarditis after being vaccinated with COVID 19 mRNA vaccine.
C4591031 substudy: A Phase 3 substudy of 1000 participants with documented receipt of 2 prior 30 µg doses of BNT162b2 (the second dose received at least 6 months ago), 16 to 30 years of age (randomized 1:1 in a crossover design to receive 30 µg BNT162b2 or placebo at baseline and the alternative 4 weeks later).	To obtain serum samples within the first ~4 days after vaccination for potential Troponin I testing, in order to evaluate the frequency of subclinical myocarditis amongst individuals 16 to 30 years of age.

Table 10. Studies Contributing to Pharmacovigilance

Study Title	Summary of Objectives
Planned Studies	
C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA vaccine in the United States.	To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general US population of all ages, pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System
C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the US Department of Defense population following Emergency Use Authorization	To assess whether individuals in the US DoD Military Health System (MHS) experience increased risk of safety events of interest, including myocarditis and pericarditis, following receipt of the Pfizer-BioNTech COVID-19 Vaccine.
C4591021 substudy: Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine. Substudy to investigate natural history of post-vaccination myocarditis and pericarditis.	To describe the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine.
C4591036: Pediatric Heart Network Study: Working title: *Myocarditis/pericarditis follow-up study within the Pediatric Heart Network.*	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.

5. BENEFIT/RISK ASSESSMENT

Booster Vaccination – An Unmet Public Health Need

As the Delta variant has spread widely, rates of COVID-19 are again on the rise in the United States and in many other countries around the world. Although unvaccinated individuals continue to account for most SARS-CoV-2 infections and severe cases of COVID-19, real-world data from Israel and the United States suggest that rates of breakthrough infections are rising faster in individuals who were vaccinated earlier in the vaccination campaigns compared to those who have been vaccinated more recently. Evidence gathered in studies conducted both in Israel and in the United States by Kaiser Permanente Southern California and the CDC indicate that the observed decrease of vaccine effectiveness against COVID-19 infections is primarily due to waning of vaccine immune responses over time rather than a result of the Delta variant escaping vaccine protection. While the waning is slightly more pronounced against the Delta variant, it does occur irrespective of the VOC. In addition, the short-term vaccine effectiveness (VE) against the delta VOC is very high in all age groups and is comparable to that induced by the vaccine against the wild type strain in the pivotal Phase 3 study.

Although VE against hospitalizations and other severe COVID-19 outcomes remain high in all age groups in the United States, reports from Israel have shown that sustained VE reductions against infections may be followed by VE decreases against hospitalizations and other severe outcomes, especially among those most vulnerable (eg, over 65 years of age) who were vaccinated earlier in the vaccination campaign (eg, January-February 2021). Based on these epidemiological trends, the Government of Israel launched a third dose (booster) roll out campaign that started with the population >60 years of age and health care workers and immediately expanded to the entire eligible population of 12 years of age and older in an attempt to prevent a potential exponential upsurge of infections and hospitalizations.

Given that an epidemiological pattern similar to the one observed in Israel may be occurring in the United States and elsewhere, consideration of the approval of a booster dose of BNT162b2 approximately 6 months after of the second primary dose is warranted.

Immunogenicity of a Booster (Third) Dose of BNT162b2 in Study C4591001

The immunogenicity of a booster dose of BNT162b2 was measured in a substudy of the C4591001 pivotal study that is in compliance with the 25 May 2021 FDA Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19.

Phase 1 data were evaluated for younger (18 to 55 years of age) and older (65 to 85 years of age) participants who were given Dose 3 of 30 µg BNT162b2 7 to 9 months after completing the two-dose series of BNT162b2 30 µg. The results demonstrate that serum neutralizing titers at 1 month after Dose 3 were higher than the responses observed 1 month after Dose 2. Specifically, titers against the original SARS-CoV-2 wild-type strain, the B.1.351 (Beta) variant, and the B.1.617.2 (Delta) variant at 1 month after Dose 3 were 5-times, 15-times, and from 4.76- to 7.51-times those attained at 1 month after Dose 2.

While titers against the wild-type were higher than those against the Beta and Delta variants, importantly, the difference in neutralizing titers between wild-type and variant strains narrowed after the third dose compared to after the second dose, showing that a booster dose reduces the gap between wild-type and variant strain neutralization and results in increased magnitude and breadth of the humoral response. These results suggest that, by eliciting strong booster responses against major VOCs, BNT162b2 may reasonably be expected to provide the breadth of protection needed during a period where the Delta variant is highly prevalent.

Additionally, the Phase 3 booster substudy data show that, in adults ≥18 to 55 years of age who were without evidence of SARS-CoV-2 infection through 1 month after Dose 3, administration of a third dose of BNT162b2 30 µg approximately 6 months after completion of the 2-dose regimen met the protocol prespecified 1.5-fold noninferiority success criterion for the GMR (ie, lower bound of the 2-sided 97.5% CI >0.67 and point estimate ≥0.8), and the immune response after Dose 3 was statistically higher than the response after Dose 2 (the lower bound of the 2-sided 97.5% CI for the GMR is >1). Furthermore, the prespecified 10% noninferiority margin for the difference in seroresponse rates was also met (ie, lower bound of the 2-sided 97.5% CI was greater than -10%). Finally, in accordance with US FDA's May 2021 Guidance for Industry,[2] the use of a booster dose in individuals 16 and 17 years of age

and in individuals older than 55 years of age is based on extrapolation of the safety and effectiveness demonstrated in adults at least 18 to 55 years of age in the Phase 2 booster study.

Overall, the present Phase 1 and Phase 3 booster data show that a third dose of BNT162b2 administered approximately 6 months after completing the two-dose regimen induces a strong and broad immune response that is expected to confer extended protection against COVID-19, including variants of concern.

Safety and Tolerability of a Booster (Third) Dose of BNT162b2 in Study C4591001

The safety and tolerability of a booster (third) dose of 30 µg BNT162b2 (administered approximately 6 months after completion of the two-dose regimen) have been evaluated in:

- 306 Phase 3 participants ≥18 to 55 years of age who had a median duration of 6.8 months between receiving the second and third doses, and a median follow-up time of 2.6 months after the booster (Dose 3); and in
- 23 Phase 1 participants (11 in the younger 18 to 55 years of age group and 12 in the older 65 to 85 years of age group) who had a mean of 8.3 months between receiving the second and third doses and were followed for safety through 1 month after Dose 3.

The reactogenicity and adverse event profile observed after the booster (Dose 3) was generally similar to that observed following Dose 2 of the initial two-dose regimen, which suggests no potentiation of reactogenicity or any new safety concern arising from administration of a third dose.

The reactogenicity events during the 7-day period after booster (Dose 3) were typically mild to moderate, arose within the first 1 to 2 days after dosing, and were short-lived. Reactogenicity after Dose 3 administration was generally similar to that observed following Dose 2 in the 16 to 55 years of age group participants who received the initial two-dose regimen.

As of the data cutoff date of 17 June 2021, the AE profile up to at least 2 months after Dose 3 mostly reflects reactogenicity events, with low incidences of related and/or severe events and no serious events within 1 month after Dose 3. Review of AEs, SAEs, and events of clinical interest suggested no short-term safety concerns after Dose 3 administration. One exception was the increase in frequency of lymphadenopathy after Dose 3 (5.2%) in adults compared with the first two doses: (0.4%) in individuals ≥16 years of age and 0.8% in adolescents. Lymphadenopathy has been observed after vaccination and is thought to be related to the development of the immune response to the vaccine.

Overall, the safety profile associated with a third dose of BNT162b2 at 30 µg administered approximately 6 months after completing the two-dose regimen is highly similar to the safety profile of the initial regimen itself, with no new safety concerns identified in the booster population and no increased reactogenicity or unusual AEs or other safety findings. The consistency of the safety profile for BNT162b2 through at least 6 months of follow-up after Dose 2, and the similarities of safety profiles across adolescent and adult age groups,

reasonably suggest that the booster (Dose 3) safety profile for Phase 3 adults at least 18 to 55 years of age may be extrapolated to individuals 16 and 17 years of age and >55 years of age.

Initial Confirmatory Safety and Effectiveness Evidence of BNT162b2 Booster (Third Dose) in the Israel National Immunization Program

As a result of emerging evidence of waning immunity and increasing rates of infection and hospitalization following the introduction of the Delta variant, the Israel Ministry of Health launched a BNT162b2 booster (third dose) program covering the entire vaccine-eligible population from 12 years of age and older. Data reported publicly by the Ministry of Health (but not yet peer reviewed) clearly demonstrated that, in the face of waning immunity, a booster (third dose) program can be implemented safely at a national level and that a booster dose of BNT162b2 is an effective strategy to restore high levels of protection against COVID-19 outcomes in a period when Delta is the dominant strain.

Overall Benefit/Risk Conclusions

The potential risks and benefits as assessed by the safety profile and by the efficacy and immunogenicity of BNT162b2 demonstrated in the pivotal clinical study are balanced in favor of the potential benefits of adding a booster dose (third dose) to the vaccination schedule.

Based on the data summarized in this briefing document and in consultation with CBER, Pfizer/BNT is requesting licensure of a booster dose (third dose) of BNT162b2 administered intramuscularly approximately 6 months after Dose 2 in individuals ≥16 years of age.

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