2.5 CLINICAL OVERVIEW

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ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
ADR	adverse reaction
AE	adverse event
AESI	adverse event of special interest
BLA	(US FDA) Biologics License Application
BMI	body mass index
CBER	(US FDA) Center for Biologics Evaluation and Research
CDC	(US) Centers for Disease Control and Prevention
CDS	Core Data Sheet
CFR	case fatality rate
CHMP	Committee for Human Products for Medicinal Use
CMC	chemistry, manufacturing, and controls
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CTA	Clinical Trial Application
DART	developmental and reproductive toxicity
DMC	(US Study C4591001) Data Monitoring Committee
EMA	European Medicines Agency
EU	European Union
EUA	Emergency Use Authorization
FDA	(US) Food and Drug Administration
FIH	first-in-human
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GMFR	geometric mean-fold rise
GMT/GMC	geometric mean titer/concentration
HIV	human immunodeficiency virus
ICH	International Council on Harmonisation
ICU	intensive care unit
IFNγ	interferon-gamma
IM	intramuscular(ly)
IND	Investigational New Drug application
LLN	lower limit of normal
LNP	lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
modRNA	nucleoside-modified messenger RNA
MoH	Ministry of Health
mRNA	messenger RNA
NAAT	nucleic acid amplification testing
NHP	non-human primate
P2 S	SARS-CoV-2 full-length, P2 mutant, “heads up,” prefusion spike glycoprotein
PaO_2	arterial oxygen partial pressure

Abbreviation	Definition
PCR	polymerase chain reaction
PT	Preferred Term
RBD	receptor binding domain
RNA-LNP	RNA lipid nanoparticle
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
S glycoprotein, S	spike glycoprotein
SMSR	Summary Monthly Safety Report
SOC	System Organ Class
UK	United Kingdom
US	United States
VE	vaccine effectiveness/efficacy
WHO	World Health Organization

2.5. CLINICAL OVERVIEW

This Clinical Overview (CO) describes clinical data for a prophylactic, RNA-based SARS-CoV-2 vaccine BNT162b2 (COMIRNATY), developed by BioNTech and Pfizer. BNT162b2 is currently administered intramuscularly (IM) as a series of two doses (0.3 mL each) three weeks apart.

A Marketing Authorization Application (MAA) was submitted to the European Medicines Agency (EMA) via a rolling review procedure that completed on 07 December 2020. Conditional marketing authorization was granted by EMA on 21 December 2020 for individuals ≥16 years of age and was subsequently expanded based on a Type II Variation approved on 28 May 2021 to include individuals ≥12 years of age.

A Biologics License Application (BLA) was submitted to the FDA on 18 May 2021. Licensure was granted on 23 August 2021 for individuals ≥16 years of age.

The present submission is intended to support approval for booster (Dose 3) administration of BNT162b2.

This CO summarizes the data on immunogenicity and safety for a group of Phase 3 participants in Study C4591001 who received a booster (Dose 3) of BNT162b2 (30 µg). This group is comprised of approximately 300 adults at least 18 to 55 years of age who were in the originally randomized Phase 3 study and completed the original BNT162b2 (30 µg) two-dose series, and then received a third dose of BNT162b2 (30 µg) approximately 6 months after receipt of Dose 2, with safety and immune response evaluations at 1 month after Dose 3. Supportive data are also provided from Phase 1 participants in the younger (18 to 55 years of age) and older (65 to 85 years of age) groups who received three doses of BNT162b2 (30 µg), including neutralizing sera titers against wild-type (reference) and VOC strains of SARS-CoV-2. Altogether, a robust BNT162b2-induced immune response has been observed after the two-dose regimen across individuals in the 12 to 15, 16 to 55, and ≥56 years of age strata in C4591001 and it is therefore reasonable to expect a substantial increase in the immune response with a third dose for individuals who are <18 years of age (ie, older adolescents 16 and 17 years of age) and adults who are >55 years of age.

Based on the strength of the C4591001 booster data, real-world effectiveness data, and in accordance with health authority guidance as well as in line with the approved indication and usage of BNT162b2 (30 µg) for individuals ≥16 years of age, Pfizer/BioNTech propose to revise the currently approved dosing regimen to include that a booster dose (third dose) may be administered from approximately 6 months after Dose 2.

Note that in the context of healthy, immunocompetent adult Phase 3 participants in Study C4591001 who received a third dose of BNT162b2 30 µg, the applied terms used in this CO are “booster” and “Dose 3” which are used interchangeably, as these participants had an observed robust immune response to the two-dose regimen, 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 the individual is immunosuppressed or did not mount an effective immune response following their second dose.

2.5.1. Product Development Rationale

2.5.1.1. Therapeutic Context

2.5.1.1.1. Disease or Condition

COVID-19 is caused by SARS-CoV-2, a zoonotic virus that first emerged as a human pathogen in China and has rapidly spread around the world by human to human transmission.

At the time of this submission, the ongoing pandemic remains a significant challenge to public health and economic stability worldwide, for which for a licensed prophylactic vaccine is a necessary and critical mitigation.

2.5.1.1.2. Clinical Features and Epidemiology of COVID-19

COVID-19 presentation is generally with cough and fever, with chest radiography showing ground-glass opacities or patchy shadowing.[1] However, many patients present without fever or radiographic changes, and infections may be asymptomatic which is relevant to controlling transmission. For symptomatic patients, disease progression may lead to acute respiratory distress syndrome requiring ventilation, subsequent multi-organ failure, and death.[1]

Common symptoms in hospitalized patients (in order of highest to lowest frequency) include fever, dry cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhea, headache, weakness, and rhinorrhea.[1] Anosmia (loss of smell) or ageusia (loss of taste) may be the sole presenting symptom in approximately 3% of individuals who have COVID-19.[1]

The US Centers for Disease Control and Prevention (CDC) defined COVID-19 symptoms as including 1 or more of the following:[2] fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, vomiting, fatigue, headache, nasal congestion or runny nose, or nausea.

All ages may present with the disease, but notably, case fatality rates (CFR) are elevated in persons >60 years of age.[3] Comorbidities are also associated with increased CFR, including cardiovascular disease, diabetes, hypertension, and chronic respiratory disease.[4] Healthcare workers are over-represented among COVID-19 patients due to occupational exposure to infected patients.[4]

2.5.1.2. Vaccine Clinical Development Program

2.5.1.2.1. Rationale for Development

2.5.1.2.1.1. Current Therapies

Currently available therapies have different benefit-risk considerations depending on the stage of illness and disease manifestations.[1,5] While care for individuals who have COVID-19 has improved with clinical experience, vaccination is the most effective medical countermeasure to decrease risk and mitigate spread of the SARS-CoV-2 virus during the ongoing pandemic.

Booster vaccine dosing may be necessary to ensure persistence of immunity and protection from COVID-19 illness caused by SARS-CoV-2. BNT162b2 has demonstrated high efficacy

and a robust elicited immune response, but the total duration of protection against COVID-19 remains unknown at this time. Clinical study and real-world data have shown that breakthrough COVID-19 cases do occur in some individuals after full vaccination with BNT162b2, which has been concurrent with predominant circulation of the highly transmissive B.1.617.2 (Delta) variant of SARS-CoV-2.[6,7] This has been shown in some cases, for other vaccines and for BNT162b2, to be due to waning or poor immune response following an initial vaccine regimen that could be addressed with booster vaccination to either prevent breakthrough infection and/or augment immune responsiveness in individuals with weakened immune systems.[8,9,10] Booster dose evaluation in C4591001 was conducted in accordance with health authority guidance.[11,12]

2.5.1.2.1.2. BNT162b2 Development

Pfizer and BioNTech developed an investigational vaccine that targets SARS-CoV-2, intended to prevent COVID-19, for which BioNTech initiated a FIH study in April 2020 in Germany (BNT162-01) and Pfizer initiated a Phase 1/2/3 study (C4591001) shortly afterwards in the US which expanded to include global sites upon initiation of the Phase 2/3 part of the study. Additional information on Study BNT162-01 is provided in Section 2.5.1.2.3.2.1, and on Study C4591001 is provided in Section 2.5.1.2.3.2.2.

The vaccine is based on SARS-CoV-2 spike glycoprotein (S) antigens encoded in RNA formulated in lipid nanoparticles (LNPs) and is referred to as BNT162b2 (BioNTech code number BNT162, Pfizer code number PF-07302048). The structural elements of the vector backbones of BNT162 vaccines are optimized for prolonged and strong translation of the antigen-encoding RNA. The potency of RNA vaccines is further optimized by encapsulation of the RNA into LNPs, which protect the RNA from degradation by RNAses and enable transfection of host cells after IM delivery.

2.5.1.2.2. Vaccine Product Information

BioNTech has developed multiple RNA-LNP platforms, including nucleoside-modified RNA (modRNA) which has blunted innate immune sensor activating capacity and thus augmented antigen expression. Each modRNA candidate encodes either a P2 mutant S (P2 S) or the trimerized receptor binding domain (RBD) of S. Each candidate is given a V number to indicate the specific version of the optimized insert genomic sequence.

The licensed vaccine is BNT162b2 (RBP020.2) modRNA encoding P2 S (V9). Vaccine candidates based on other RNA platforms are not discussed further herein.

2.5.1.2.3. Vaccine Development Program

2.5.1.2.3.1. Nonclinical Studies

Key nonclinical evaluations of BNT162b2 included pharmacology (mouse immunogenicity studies, non-human primate [NHP] immunogenicity and challenge studies) and toxicity (two Good Laboratory Practice [GLP] rat repeat-dose toxicity studies) in vitro and in vivo. A developmental and reproductive toxicity (DART) study was completed in rats.

These data supported the further clinical development of BNT162b2 and were previously submitted. Additional details of nonclinical studies were provided in Module 2.4.

2.5.1.2.3.2. Clinical Studies

2.5.1.2.3.2.1. Phase 1/2 Study BNT162-01

Study BNT162-01 is the ongoing, FIH, Phase 1 dose level-finding study, in which healthy younger adults (18 to 55 years of age) and older adults (56 to 85 years of age) all receive active vaccine. This study is evaluating the safety and immunogenicity of several different candidate vaccines at various dose levels.

Multiple vaccine candidates are being evaluated in this study. For each candidate, participants receive escalating dose levels (N=12 per dose level) with progression to subsequent dose levels based on recommendation from a Sponsor Safety Review Committee.

The study design is detailed in the Module 5.3.5.1 BNT162-01 Protocol. Available data from both age groups the Phase 1 part of this study have been previously submitted, and there are no new or additional data from this study presented in this CO.

2.5.1.2.3.2.2. Phase 1/2/3 Study C4591001

Study C4591001 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 registration study. It was started as a Phase 1/2 study in adults in the US, was then amended to expand the study to a global Phase 2/3 study planning to enroll enough participants to accrue sufficient COVID-19 cases to conduct a timely efficacy assessment; amended to include older adolescents 16 to 17 years of age, then later amended to include younger adolescents 12 to 15 years of age. Booster groups were subsequently added to evaluate boostability and protection against variant virus strains.

The study design is detailed in Module 5.3.5.1 C4591001 Protocol and summarized below.

Study Eligibility Criteria

In Phase 1, two age groups were studied separately, younger participants (18 to 55 years of age) and older participants (65 to 85 years of age). The study population includes male and female participants deemed healthy as determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study. Exclusions included screened individuals with high risk of exposure to SARS-CoV-2 infection due to exposure in the workplace and/or medical conditions that represent risk factors, clinically important prior illness or laboratory abnormalities, serological evidence of prior SARS-CoV-2 infection or current SARS-CoV-2 infection as measured by polymerase chain reaction (PCR).

In Phase 2/3, participants were enrolled with stratification of younger adults (18 to 55 years of age) and older adults (>55 years of age) to achieve approximately 40% enrollment in the older adult group. Adolescents were added later by a protocol amendment: older adolescents 16 to 17 years of age are included in the younger adult stratum (ie, 16 to 55 years of age), and younger adolescents 12 to 15 years of age were analyzed as a separate age stratum. Eligibility in Phase 2/3 included higher risk for acquiring COVID-19 in the investigator's judgment, due to medical conditions or exposure.

Phase 1

The Phase 1 part of the study, randomized participants 4:1 to receive active vaccine or placebo. The vaccines candidates, administered IM in the upper arm in a two-dose regimen separated by approximately 21 days, were:

- BNT162b1 (dose levels: 10, 20, 30, 100 µg)
- BNT162b2 (dose levels: 10, 20, 30 µg)

Phase 1 of Study C4591001 was conducted in the US. For each of the two vaccine candidates evaluated, younger participants received escalating dose levels (N=15 per dose level, 4:1 randomization ratio between vaccine and placebo) with progression to subsequent dose levels and the older age group (N=15 per dose level, 4:1 randomization ratio between vaccine and placebo) based on recommendation from an Internal Review Committee. Note: it was recommended that a second dose of BNT162b1 at 100 µg not be administered and discontinued due to reactogenicity after the first dose in the younger age group. Participants in this group of younger adults instead received a second dose of BNT162b1 at the 10-µg dose level approximately 3 months after Dose 1, and the 100 µg dose level was discontinued (ie, not administered to older adults receiving BNT162b1).

The Sponsor/agent study team was not blinded in this part of the study. Participants who enrolled in Phase 1 are followed for cases of COVID-19 but do not contribute to the efficacy assessment. Safety follow-up will continue for at least 2 years and/or end of study. Based upon review of safety and immunogenicity from the Phase 1 part of the study, the final candidate and dose level was selected as BNT162b2 at 30 µg given twice 21 days apart. Details are provided in Section 2.5.1.2.5.

Booster Evaluation

Phase 1 participants who were randomized to either BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg were offered booster vaccination (Dose 3) with BNT162b2 at 30 µg, approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This provided an early assessment of the safety and immunogenicity associated with a third vaccine dose.

Preliminary data from Phase 1 booster study participants who previously received BNT162b2 30 µg and then received a third dose of BNT162b2 30 µg, comprised of safety and immunogenicity data including neutralization of the B.1.351 (Beta) variant of SARS-CoV-2 from are provided separately in a Module 5.3.5.1 C4591001 Phase 1 Booster Beta Report. Additional immunogenicity data from this Phase 1 group including neutralization of the B.1.617.2 (Delta) variant of SARS-CoV-2 are provided separately in a Module 5.3.5.1 C4591001 Phase 1 Booster Delta Report.

Phase 2/3

Phase 2/3 of Study C4591001 commenced with the selected vaccine candidate and dose level (BNT162b2 at 30 µg) administered to participants randomized 1:1 to vaccine or placebo.

Phase 2 was conducted in the US. The Phase 2 portion of the study evaluated reactogenicity and immunogenicity for 360 participants 18 to 85 years of age enrolled into the study when the Phase 2/3 part commenced, balancing younger (≤55 years of age) and older (>55 years of age) strata within each group. Phase 2 participants in this blinded part of the study also contribute to the overall efficacy and safety assessments in the Phase 3 portion of the study.

Phase 3 (which is ongoing) included planned interim analyses of the first primary efficacy endpoint, ongoing efficacy and safety evaluations including reactogenicity assessment in a subset of participants, and exploratory vaccine immunogenicity evaluation in a subset of participants. Phase 3 is being conducted at sites in the US, Brazil, Argentina, Turkey, South Africa, and Germany. Participants were stratified by age group as previously described. The final efficacy analysis was conducted when at least the prespecified total number of 164 efficacy events accrued. Safety and long-term persistence of efficacy follow-up will continue for at least 2 years and/or end of study. Safety and efficacy analyses included the 360 participants who were analyzed for Phase 2.

Booster and Variant Strain Evaluation

For further evaluation of booster effects and/or protection against emerging SARS-CoV-2 variants of concern, approximately 600 existing Phase 3 participants 18 to 55 years of age were randomized 1:1 to receive either receive a booster (Dose 3) at 30 µg of either BNT162b2 or a prototype based upon the B.1.351 (Beta) variant that originated in South Africa, BNT162b2$_{SA}$, approximately 6 months after their second dose of BNT162b2.

Additional Phase 3 booster and/or VOC vaccine groups (not reported in this CO; to be reported at a later time) include:

- Additional subset of approximately 30 existing Phase 3 participants 18 to 55 years of age enrolled to receive a third and fourth dose of BNT162b2$_{SA}$.
- New cohort recruited who were COVID-19 vaccine-naïve (ie, had not received BNT162b2) and had not experienced COVID-19 to receive BNT162b2$_{SA}$ as a two-dose series 21 days apart.
- Further group of approximately 144 existing Phase 3 participants ≥18 years of age to receive a third, lower, dose of BNT162b2 of either 5 or 10 µg, with approximately 24 participants 18 to 55 years of age and 48 participants >55 years of age to be enrolled in each dose group.

This CO reports the results for Phase 3 "BNT162b2-experienced" BNT162b2-booster group (ie, participants who were previously randomized to and received the two-dose series of BNT162b2 in Study C4591001), including Phase 3 participants at least 18 to 55 years of age who were re-randomized to receive a third dose of BNT162b2 at 30 µg.

Unblinding Considerations

Starting 14 December 2020, individuals ≥16 years of age have been progressively unblinded in the study to receive BNT162b2 vaccination when eligible per protocol (refer to Section 2.5.1.3). Since 10 May 2021, adolescents 12 to 15 years of age have been unblinded in the study to receive BNT162b2 as they became eligible. Unblinded participants continue in study follow-up in an open-label manner.

Participants randomized into Phase 3 booster and variant strain vaccine groups remain blinded to their randomization assignment at this time. Sponsor and site personnel responsible for the ongoing conduct of the study remain blinded to individual participants' randomization information for any who have not been unblinded. Safety evaluation for such participants by the study team remains blinded until a decision is made to unblind the entire study. A separate (from study conduct) unblinded submissions team is responsible for regulatory submissions.

All participants continue to be expected to remain in study follow-up for a maximum of approximately 2 years after Dose 2 of randomized study intervention.

2.5.1.2.3.2.3. Planned Studies

Further studies (or additional groups/analyses from ongoing studies) are planned or ongoing, including pediatric populations, maternal immunization, concomitant use with adult pneumococcal and influenza vaccines, booster efficacy evaluation, and obtaining blood samples for potential evaluation for subclinical myocarditis.

2.5.1.2.4. Proposed Indication

The current indication for BNT162b2 (30 µg) is active immunization to prevent COVID-19 caused by SARS-CoV-2 virus in individuals ≥12 years of age, or in individuals ≥16 years of age (depending on the country/market and authorization/approval type). Refer to Section 2.5.1.3 for details of regulatory authorizations and approvals.

This submission is intended to support approval for booster (Dose 3) administration of BNT162b2 (30 µg) approximately 6 months following the two-dose series.

Supplemental applications are planned for pediatric populations, maternal immunization, and use in immunocompromised individuals, pending conclusion of the appropriate studies/analyses and Agency feedback.

2.5.1.2.5. Rationale for Candidate and Dose Selection

The final candidate and dose level (BNT162b2 at 30 µg) was selected following review of immunogenicity and safety data from Phase 1 of Study C4591001 and nonclinical data. The final vaccine candidate selection for clinical development in Phase 2/3 was based on:

- NHP challenge data; BNT162b2 led to earlier virus clearance, no evidence of virus in lung
- Favorable reactogenicity for BNT162b2 in both younger and older Phase 1 participants
- Robust immunogenicity in both younger and older Phase 1 participants at 30 µg dose level.

BNT162b2 at 30 µg proceeded into the Phase 2/3 portion of Study C4591001 because this dose and construct provided the optimum combination of a favorable reactogenicity profile and a robust immune response, likely to afford protection against COVID-19 in younger and older age groups. This dose was used for a boostability assessment of administering Dose 3.

2.5.1.3. Regulatory Status

As of July 2021, BNT162b2 has received temporary authorization for emergency use in 43 countries and conditional marketing authorization approval in 45 countries globally. The name of the product supplied under emergency/temporary use authorization for all applicable regions is Pfizer-BioNTech COVID-19 Vaccine. The tradename of the product for all applicable regions is COMIRNATY.

European Union

Conditional marketing approval was granted by the EMA on 21 December 2020 for individuals ≥16 years of age. A Type II Variation to support use individuals ≥12 years of age was submitted to EMA on 30 April 2021, which was approved on 28 May 2021. A Type II Variation to provide 6-month follow-up for individuals ≥16 years of age was submitted to EMA on 18 May 2021.

United States

In the US, the vaccine is in clinical development under an Investigative New Drug (IND) application, BB-IND 19736. Fast Track Designation was granted on 07 July 2020 for individuals ≥18 years of age. An Emergency Use Authorization (EUA) application was filed to the US Food and Drug Administration (FDA) on 20 November 2020 and the product was authorized for emergency use in the US on 11 December 2020 for individuals ≥16 years of age (EUA 27034). An amendment to the EUA was submitted to the FDA on 09 April 2021 and was authorized on 10 May 2021 to support emergency use in individuals ≥12 years of age. An amendment to the EUA was submitted to the FDA on 14 May 2021 to provide 6-month follow-up for individuals ≥16 years of age. Authorization for a third dose of BNT162b2 30 µg for individuals ≥12 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise was granted on 13 August 2021.

A BLA was submitted to US FDA on 18 May 2021 and licensure (via the traditional approval pathway) was approved on 23 August 2021 for individuals ≥16 years of age.

Rest of World

Marketing Authorization Applications were initiated beginning in October 2020 and Conditional Marketing Authorizations have been granted in many countries globally including Switzerland, Japan, Australia, New Zealand, and Brazil. Requests for temporary authorization for emergency supply have also been filed and approved in many countries globally under emergency or temporary use authorization procedures or special import procedures beginning in November 2020, including UK and Canada. The World Health Organization (WHO) issued a positive opinion on the Emergency Use Listing of COMIRNATY on 31 December 2021.

2.5.1.4. Ethical Considerations

All studies in the clinical development program were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. They were designed, performed, and analyzed in accordance with all applicable regulations, laws, and guidelines in effect at the time they were conducted from the US FDA, EU Directive 2001/20/EC, and local regulatory agencies in countries where the study was conducted. The study design reflects recommendations from local review boards/committees, and other local regulatory authorities.

The pivotal Phase 1/2/3 Study C4591001 was conducted at sites in the US, Brazil, Argentina, Turkey, South Africa, and Germany; the majority of participants were enrolled at sites in the US. The supporting Phase 1/2 Study BNT162-01 was conducted at sites in Germany.

2.5.2. Overview of Biopharmaceutics

2.5.2.1. Formulation Development

The vaccine is administered IM as a series of two 30-µg doses of the diluted vaccine solution (0.3 mL each) according to the following schedule: a single 0.3-mL dose followed by a second 0.3-mL dose 21 days later.

Details of formulation development and storage conditions are provided in Module 3.

2.5.2.2. Biopharmaceutical Studies

Bioavailability and bioequivalence assessments are not relevant to vaccine antigenicity and have not been measured.

2.5.2.3. Bioanalytical and Analytical Methods Used in Human Studies

Information on assays used to assess SARS-CoV-2 infection and immune response is in Module 2.7.1. Only validated (PCR and neutralization immunoassay) methods were used.

2.5.3. Overview of Clinical Pharmacology

Pharmacokinetic studies are not usually required for vaccines. Measurement of the plasma concentration of the vaccine over time is not feasible.

2.5.4. Overview of Efficacy (Including Immunogenicity)

Efficacy

Efficacy was previously evaluated in Phase 2/3 of pivotal Study C4591001. The prespecified interim analysis of efficacy in Study C4591001 was conducted after accrual of 94 confirmed COVID-19 cases (data cutoff date: 04 November 2020), and the prespecified final analysis of efficacy was conducted after accrual of 170 confirmed COVID-19 cases (data cutoff date: 14 November 2020), based on cases reported in participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen. These analysis results were reported in the initial MAA and BLA, and updated efficacy analyses of cases accrued up to

6 months after Dose 2 have been submitted[13] (refer to Section 2.5.1.3). Ongoing surveillance for potential cases of COVID-19 required participants who experienced symptoms of COVID-19 (as specified in the protocol) to contact the site immediately for assessment and case confirmation based on protocol-specified criteria in the Module 5.3.5.1 C4591001 Protocol.

Efficacy was not evaluated for Phase 3 BNT162b2 booster group participants.

Immunogenicity

Immunogenicity associated with the vaccine two-dose regimen has been described previously and was submitted previously.[14,15] Details of analysis methods in Study C4591001 are located in the Module 5.3.5.1 C4591001 Protocol and SAP.

The basis of 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 has been 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. The immunobridging success criteria included prespecified margins for the geometric mean ratio (GMR) and seroresponse (≥4-fold rise from baseline, before Dose 1) as detailed in Section 2.5.4.1.1 (endpoints) and Section 2.5.4.1.2 (analysis methods).

2.5.4.1. Immunogenicity Endpoints and Analysis Methods

Assay validation reports were provided in Module 2.7.1. Only a validated SARS-CoV-2 neutralization assay was used for Phase 3 immunogenicity data. Immunogenicity endpoints are summarized in Section 2.5.4.1.1 and immunogenicity analysis methods are summarized below in Section 2.5.4.1.2.

2.5.4.1.1. Immunogenicity Endpoints in Study C4591001

BNT162b2 booster (Dose 3) effectiveness is based on immunobridging to the immune response after Dose 2 in participants. SARS-CoV-2 50% neutralizing titers were compared at 1 month post-Dose 3 to those observed at 1 month post-Dose 2, for the same participants for the SARS-CoV-2 reference strain.

Immunogenicity endpoints were:

- geometric mean titers (GMT) and geometric mean ratio (GMR) of SARS-CoV-2 neutralizing titer at 1 month after Dose 3 to 1 month after Dose 2
- percentages and difference in percentages of participants with seroresponse at 1 month after Dose 3 and 1 month after Dose 2, where seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1); for baseline measurement <LLOQ, postvaccination measure ≥4 × LLOQ is considered seroresponse
- geometric mean-fold rise (GMFR) from before Dose 3 to 1 month after Dose 3.

2.5.4.1.2. Immunogenicity Analysis Methods in Study C4591001

The statistical analyses of immunogenicity data from Study C4591001 were based on the evaluable immunogenicity populations and all-available immunogenicity populations (described in the C4591001 protocol and SAP).

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. The GMR was calculated as the mean of the difference of logarithmically transformed titers for each participant (eg, 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 logarithm scale and exponentiating the confidence limits. 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 a seroresponse defined as a ≥4-fold rise from baseline (before Dose 1) at 1 month after Dose 3 and 1 month after Dose 2 using a 10% margin. If the baseline measurement is below LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse. The difference in percentages (1 month after Dose 3 – 1 month after Dose 2) and the associated 2-sided 97.5% CI calculated using the adjusted Wald interval as described by Agresti and Min were provided. 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%.

Noninferiority analyses were conducted for participants without prior serological or virological evidence, by N-binding antibody or nucleic acid amplification test (NAAT), respectively, of SARS-CoV-2 infection up to 1 month after Dose 3.

GMTs and GMFRs were provided with associated 2-sided 95% CIs calculated with reference to Student's t-distribution. Titers/concentrations below the LLOQ or denoted as BLQ were set to 0.5 × LLOQ for all analyses except for seroresponse.

Assuming a 20% nonevaluable rate, approximately 240 evaluable participants in the BNT162b2 booster group were planned to contribute to immunogenicity evaluation, to provide sufficient power for noninferiority evaluation with appropriate multiplicity adjustment for type I error control. The study had >99.9% power to demonstrate noninferiority based on GMR for the objectives in vaccine-experienced individuals using a 1.5-fold margin, and 99% power or 89% power to show noninferiority based on seroresponse rate under the assumption of moderate or high discordance in response status at 2 comparative timepoints for the objectives in vaccine-experienced individuals using a 10% margin.

Note that blood samples collected at Visit 1 (before Dose 1), Visit 3 (1 month post Dose 2), Visit 301 (before booster dose), Visit 302 (1 week after booster dose), and Visit 303 (1 month post booster dose) were planned to be tested for the immunogenicity assessment. During clinical testing, due to higher repeating rate, the viral reagent for the assay was not sufficient to complete testing of all samples. Testing was reprioritized for samples from critical time points for hypothesis testing, which resulted smaller number of sample size for the 1 week after booster dose visit.

2.5.4.2. Immunogenicity Results

Additional results details are provided in the Module 5.3.5.1 C4591001 Phase 3 Booster (Dose 3) Interim CSR Section 10 (study participants) and Section 11 (immunogenicity evaluation).

2.5.4.2.1. C4591001 Phase 3 Booster (Dose 3) Immunogenicity Results

Phase 3 BNT162b2 booster group immunogenicity population characteristics are summarized in Section 2.5.4.2.1.1.

Immunogenicity results are summarized in Section 2.5.4.2.1.2 (noninferiority analyses) and Section 2.5.4.2.1.3 (SARS-CoV-2 neutralizing titers and fold rises).

2.5.4.2.1.1. Immunogenicity Populations

2.5.4.2.1.1.1. Disposition and Data Sets Analyzed

Disposition

Disposition of Phase 3 participants rerandomized to receive a third dose is shown in Table 4.

Immunogenicity Populations

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 1). 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 included 16 (53.3%) participants with Visit 301 (booster [Dose 3] vaccination) conducted outside the protocol-specified window.

Table 1. 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)

Table 1. 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] (%)[b]
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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2.5.4.2.1.1.2. Demographics

Within the Phase 3 BNT162b2 booster group, most participants in the Dose 3 booster evaluable immunogenicity population were White (81.3%), with 10.4% Black or African American participants, 4.1% Asian participants, and other racial groups comprising ≤1.5%. There were 30.2% Hispanic/Latino participants. The median age at the time of booster (Dose 3) vaccination was 42.0 years, and 46.3% of participants were male. Obese participants made up 40.7% of the Dose 3 booster evaluable immunogenicity population.

Demographics in the Dose 3 booster evaluable immunogenicity population were generally similar to those without evidence of infection up to 1 month after the booster dose in the same population, similar to those in the Dose 3 booster all-available immunogenicity population, and similar to the booster safety population (Section 2.5.5.2.1.1.4).

2.5.4.2.1.2. Noninferiority of Booster Response to Initial Regimen Response

Geometric Mean Ratio (GMR) of Neutralization Titers to Reference Strain

Among participants 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 2).

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 that observed following Dose 2.

The GMR result for the Dose 3 booster all-available immunogenicity population was similar to those observed for the Dose 3 booster evaluable immunogenicity population.

Difference in Seroresponse Rate to Reference Strain

Among participants 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 seroresponse (defined in Section 2.5.4.1) at 1 month after Dose 3 compared with 98.0% at 1 month after Dose 2 (Table 3).

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%) (Table 3), which meets the 10% noninferiority margin (ie, lower bound of the 2-sided 97.5% CI was greater than -10%).

The seroresponse result for the Dose 3 booster all-available immunogenicity population was similar to those observed for the Dose 3 booster evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection.

Table 2. 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 3. 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.

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2.5.4.2.1.3. SARS-CoV-2 Neutralizing Titers and Fold Rises

Geometric Mean Titers (GMTs) to Reference Strain

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after the booster (Dose 3), at 1 month after the booster (Dose 3) of BNT162b2 30 µg, SARS-CoV-2 50% neutralizing GMTs increased substantially relative to GMTs observed prior to receipt of Dose 3 (Figure 1).

From baseline (prior to receipt of Dose 1) to 1 month after Dose 2, GMTs were substantially increased to 73-fold that of the prevaccination titers, 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 7). GMTs had declined by the time the booster (Dose 3) was administered. From Dose 2 up to the day of Dose 3 administration (before booster vaccination), GMTs were 136.2 (2-sided 95% CI: 121.5, 152.6), which represents a 5.59-fold reduction compared to that observed at 1 month after Dose 2.

Following booster (Dose 3) vaccination, GMTs were increased by 7 days post-Dose 3 to 1418.7 (95% CI: 1263.3, 1593.3). By 1 month after Dose 3, GMTs were further elevated to 2374.2 (95% CI: 2134.1, 2641.3), a level 1.74-fold that observed on the day of booster vaccination (prior to receipt of Dose 3).

Overall, among participants in the Dose 3 booster evaluable immunogenicity population, the neutralizing GMTs at 1 month after Dose 3 were substantially greater than that observed at 1 month after Dose 2 (ie, 3-fold), showing a strong boost to the neutralizing antibody response.

The SARS-CoV-2 50% neutralizing GMTs for all participants in the Dose 3 booster evaluable immunogenicity population regardless of prior infection status and the Dose 3 booster all-available immunogenicity population were similar to those observed for the Dose 3 booster evaluable immunogenicity population without evidence of SARS-CoV-2 infection up to 1 month after the booster (Dose 3).

Geometric Mean Fold-Rise (GMFR) in Titers to Reference Strain

Among participants 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)

By 1 month after Dose 3, the GMFR from before Dose 3 was 17.4 (2-sided 95% CI: 15.2, 20.0).

The GMFRs for all participants in the Dose 3 booster evaluable immunogenicity population regardless of prior infection status and the Dose 3 booster all-available immunogenicity population were similar to those observed for the Dose 3 booster evaluable immunogenicity population without evidence of SARS-CoV-2 infection up to 1 month after the booster (Dose 3).

Seroresponse Rate to Reference Strain

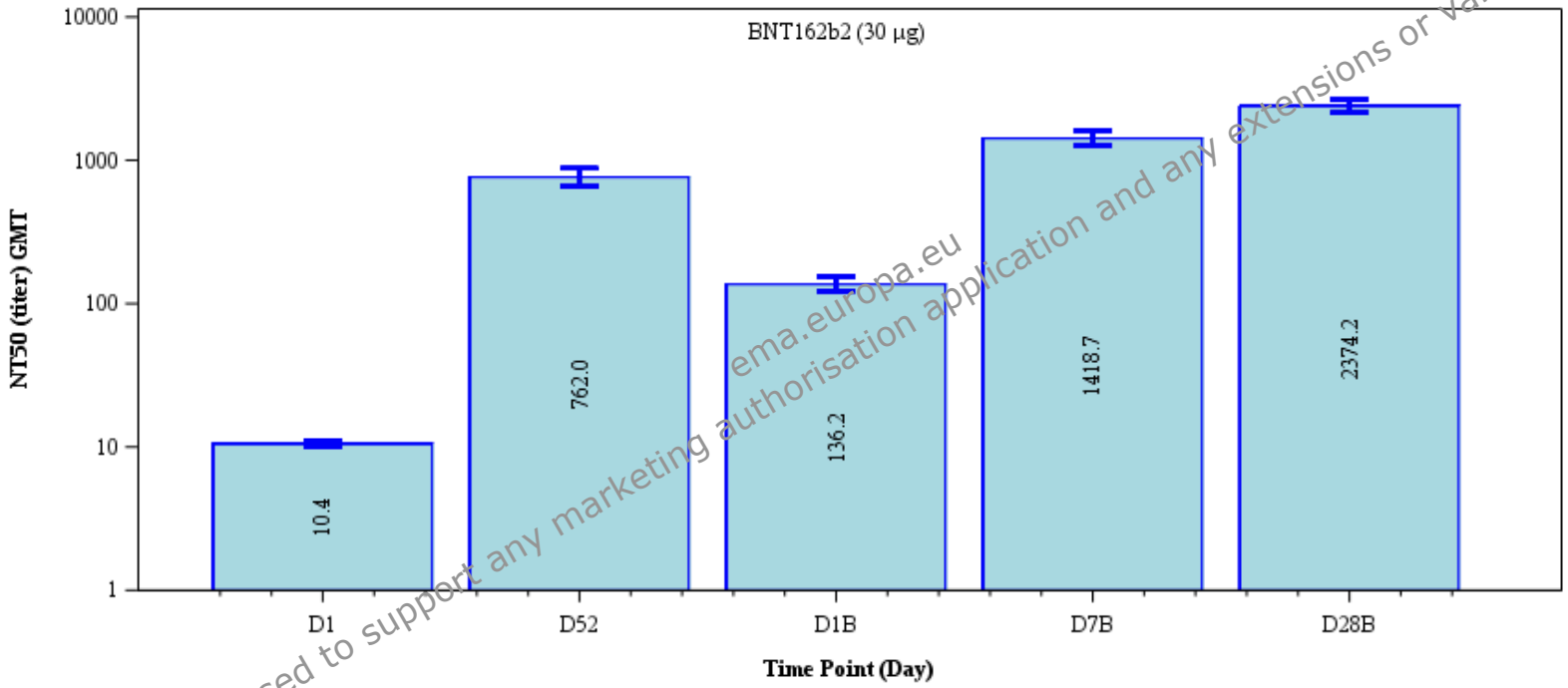
At 1 month after Dose 2, the proportion of participants without prior evidence of SARS-CoV-2 infection up to 1 month after the booster (Dose 3) with seroresponse (defined in Section 2.5.4.1) in the Dose 3 booster evaluable population was 98.0% (2-sided 95% CI: 95.0, 99.5).

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). The proportion with seroresponse at 1 month after the booster (Dose 3) (ie, seroresponse rate) increased further to 99.5% (2-sided 95% CI: 97.4%, 100.0%).

The seroresponse results for all participants in the Dose 3 booster evaluable immunogenicity population regardless of prior infection status and the Dose 3 booster all-available immunogenicity population were similar to those observed for the Dose 3 booster evaluable immunogenicity population without evidence of SARS-CoV-2 infection up to 1 month after the booster (Dose 3).

Figure 1. 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.
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2.5.4.2.2. Immunogenicity Conclusions

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 a boosted immune response to levels greatly increased over those previously observed following Dose 2.

2.5.5. Overview of Safety

Safety analyses from the pivotal study (C4591001) up to 6 months after Dose 2, and for the supporting study (BNT162-01), were previously submitted[13] (refer to Section 2.5.1.3).

Safety presented in this CO corresponds to the C4591001 Phase 3 BNT162b2 booster group from 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.

2.5.5.1. Safety Endpoints and Analysis Methods

Details of safety methods and analyses in Study C4591001 are located in the Module 5.3.5.1 C4591001 Protocol and SAP and summarized below. Statistical analyses are provided in Section 2.5.5.1.2.

2.5.5.1.1. Safety Endpoints

In accordance with FDA guidance issued in May 2021, safety evaluation of BNT162b2 30 µg booster (Dose 3) administration included reactogenicity assessed daily for at least 7 days after each study vaccination, and serious and non-serious adverse events (AEs) reported during the immunogenicity evaluation period (refer to Section 2.5.4.1.1 for immunogenicity evaluation).

Reactogenicity

All booster group participants were to record reactogenicity for 7 days post-boost (Dose 3):[16]

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

Participants were also to record antipyretic/pain medication usage. Reactogenicity and antipyretic use was recorded each evening for 7 days after Dose 3 administration using prompts from an electronic diary (e-diary). This allowed recording only within a fixed time window to provide an accurate representation of the participant's experience.

Adverse Events

AEs were collected from the time the participant provided informed consent for participation in the booster group up to 1 month after the last BNT162b2 administration (Dose 3). Serious AEs (SAEs) were collected from the time the participant provided informed consent for participation in the booster group up to 6 months after the last administration (Dose 3) of BNT162b2. AEs were categorized by frequency, maximum severity, seriousness, and relationship to study intervention using system organ class (SOC) and preferred term (PT) according to MedDRA. Deaths are recorded to the end of study.

AEs of special interest (AESIs) were not prespecified in the protocol. Instead, Pfizer utilizes a list of Targeted Medical Events (TMEs) of clinical interest that are highlighted during clinical safety data review and signal detection. TMEs are a dynamic list of MedDRA AE terms that are reviewed on an ongoing basis throughout the clinical study; the TMEs are based on review of known pharmacology, toxicology findings, possible class effects, published literature, and potential signals arising from safety data assessments. The list of TMEs includes events of interest due to their association with COVID-19 and terms of interest for vaccines in general; it takes into consideration the CDC list of AESIs for COVID-19 that include events potentially indicative of severe COVID-19 or autoimmune and neuroinflammatory disorders.

Any pregnancies (if applicable) were reported for participants in any phase of the study.

Narratives

Narratives for safety events are located in Module 5.3.5.1, and were prepared for participants if they had the following events:

- Deaths
- Vaccine-related SAEs
- Safety-related participant withdrawals
- Events of specific clinical interest requested by FDA*: anaphylaxis, appendicitis, Bell's palsy, pregnancy exposures, myocarditis/pericarditis

* Note that lymphadenopathy is described in summary rather than individual narratives, since the information available for these cases is typically very limited; summary case information provided includes severity, timing of onset and duration, and resolution of the event.

2.5.5.1.2. Safety Analysis Methods

Safety data were analyzed and reported using descriptive summary statistics for the safety population for each study phase. Analyses were performed for endpoints described in Section 2.5.5.1.1.

Reactogenicity

Descriptive statistics were provided for each reactogenicity endpoint after the boost (Dose 3) of BNT162b2 30 µg, for the booster safety population. Local reactions and systemic events from Day 1 through Day 7 after vaccination are presented by severity and cumulatively across severity levels. Descriptive summary statistics included counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% confidence intervals (CIs). Missing reactogenicity e-diary data were not imputed.

Adverse Events

AE data were summarized descriptively for the booster safety population. Descriptive summary statistics including counts, percentages, and associated Clopper-Pearson 2-sided 95% CIs were provided for AEs reported from Dose 3 through 1 month after Dose 3.

2.5.5.2. Safety Results

Additional results details are provided in the Module 5.3.5.1 C4591001 Phase 3 Booster (Dose 3) Interim CSR Section 10 (study participants) and Section 12 (safety evaluation).

2.5.5.2.1. C4591001 Phase 3 Booster (Dose 3) Safety Results

Phase 3 BNT162b2 booster group safety population characteristics are summarized in Section 2.5.5.2.1.1.

Reactogenicity is summarized in Section 2.5.5.2.1.2.

AE data overview and analyses are summarized in Section 2.5.5.2.1.3, which include data from 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.

2.5.5.2.1.1. Safety Population

2.5.5.2.1.1.1. Disposition and Data Sets Analyzed

Disposition

Among the 312 participants who were rerandomized to receive a booster (Dose 3) of BNT162b2 in Phase 3, 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 (Table 4).

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.

Table 4. Disposition of All Randomized Subjects – 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
Vaccinated	312 (100.0)
Booster vaccination	312 (100.0)
Completed booster vaccination period[c]	309 (99.0)
Discontinued from booster vaccination period but continued in the study	0
Discontinued after booster vaccination	0
Withdrawn from the study	4 (1.3)
Withdrawn after booster vaccination	4 (1.3)
Reason for withdrawal	
Lost to follow-up	2 (0.6)
Withdrawal by subject	2 (0.6)

a. N = number of randomized subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Booster vaccination period: from booster vaccination to the 1-month follow-up visit after the booster vaccination.
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Safety Population

The BNT162b2 booster safety population included 312 adult participants who previously received the BNT162b2 30 µg two-dose regimen in Phase 3 of the study and were rerandomized to receive a booster (Dose 3) of BNT162b2 30 µg (Table 5). Among those, 306 were included in the BNT162b2 30 µg group, and 6 were in the BNT162b2$_{SA}$ 30 µg group due to medication error (refer to Section 2.5.5.2.1.1.2 for details of vaccine administration and timing).

All safety analyses in this CO present data from the 306 participants in the BNT162b2 30 µg group.

Table 5. Booster Safety Population – 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
Received booster vaccination	312 (100.0)
BNT162b2 (30 µg)	306 (98.1)
BNT162b2$_{SA}$ (30 µg)[c]	6 (1.9)
Booster safety population	312 (100.0)
BNT162b2 (30 µg) Group	306 (98.1)
BNT162b2$_{SA}$ (30 µg) Group[c]	6 (1.9)

a. n = Number of subjects with the specified characteristic, or the total sample.
b. This value is the denominator for the percentage calculations.
c. Subjects who were rerandomized to BNT162b2 (30 µg) but received BNT162b2$_{SA}$ (30 µg).
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(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adsl_s003_pop_p3_g1_1d30

2.5.5.2.1.1.2. Vaccine Administration and Timing

Vaccine Administration

Among all participants who were administered the booster vaccination, 98.1% received Dose 3 of BNT162b2 as randomized (Table 6).

Of the 312 participants who received a third dose, 6 participants who were rerandomized to receive a third dose of BNT162b2 30 µg were instead administered BNT162b2$_{SA}$ by error. These 6 participants are identified in the rerandomization listing. These participants are not included in the Dose 3 booster evaluable immunogenicity population analyses or safety analyses of the BNT162b2 booster group, to avoid confounding the BNT162b2 booster results interpretation. Immunogenicity data from these participants, if available, are included in the Dose 3 all-available immunogenicity population analyses (in accordance with the definition of all-available immunogenicity population which follows the modified intent-to-treat principle). Any AEs reported for these participants are provided in the safety listings.

Table 6. Vaccine as Administered – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg)

Vaccine (as Administered)	Vaccine Group (as Randomized)
	BNT162b2 (30 µg) (N[a]=312) n[b] (%)
Received booster vaccination	312 (100.0)
Did not receive booster vaccination	0
Booster vaccination	
BNT162b2 (30 µg)	306 (98.1)
BNT162b2$_{SA}$ (30 µg)	6 (1.9)

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/advx_s002_adm_p3_g1_rand

Vaccine Timing

The median duration between Dose 2 and Dose 3 was 6.8 months (range: 4.8 to 8.0 months) (Table 7). There were 49.7% of participants who received booster (Dose 3) administration between 6 and <7 months after receiving Dose 2. Fewer than 10% of participants received Dose 3 at <6 months following Dose 2. Dose 3 was administered ≥7 months after Dose 2 for 41.0% of participants; this included 16 participants who received Dose 3 outside of the protocol defined window (ie, <150 days or >210 days after Dose 2).

Table 7. 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

2.5.5.2.1.1.3. Duration of Follow-Up

There were 99.7% of booster group participants who had follow-up time between ≥2 to <4 months after Dose 3 of BNT162b2 30 µg, and 81.0% had follow-up time between ≥8 to <10 months after Dose 2 of BNT162b2 30 µg (Table 8). The median follow-up time after Dose 3 was 2.6 months (range: 1.1 to 2.8 months). The median follow-up time since completion of the two-dose regimen was 9.5 months (range: 7.5 to 10.8 months).

Table 8. 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.
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(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adsl_fu_d2_p3_g1

2.5.5.2.1.1.4. Demographics

Most participants in the Phase 3 BNT162b2 booster safety population were White (81.4%), with 9.2% Black or African American participants, 5.2% Asian participants, and other racial groups comprising ≤2.0% (Table 9). There were 27.8% Hispanic/Latino participants. The median age at the time of Dose 3 administration was 42.0 years, and 45.8% of participants were male. Obese participants made up 39.9% of the booster safety population.

The demographics of the booster safety population (Table 9) were generally similar to the demographics of 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, as reported in the Module 5.3.5.1 C4591001 Final Analysis Interim CSR.

Table 9. 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

Medical History

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. In the BNT162b2 group, conditions in the surgical and medical procedures (125 [40.8%]), psychiatric disorders (80 [26.1%), metabolism and nutrition disorders (69 [22.5%]), and immune system disorders (114 [37.3%]; all of which were participants with a history of allergic disease) SOCs were most frequently reported. There were no participants with confirmed HIV in this Phase 3 booster population.

Concomitant Vaccine Administration

No participants received any concomitant vaccines after the booster (Dose 3).

2.5.5.2.1.2. Reactogenicity

2.5.5.2.1.2.1. Local Reactions

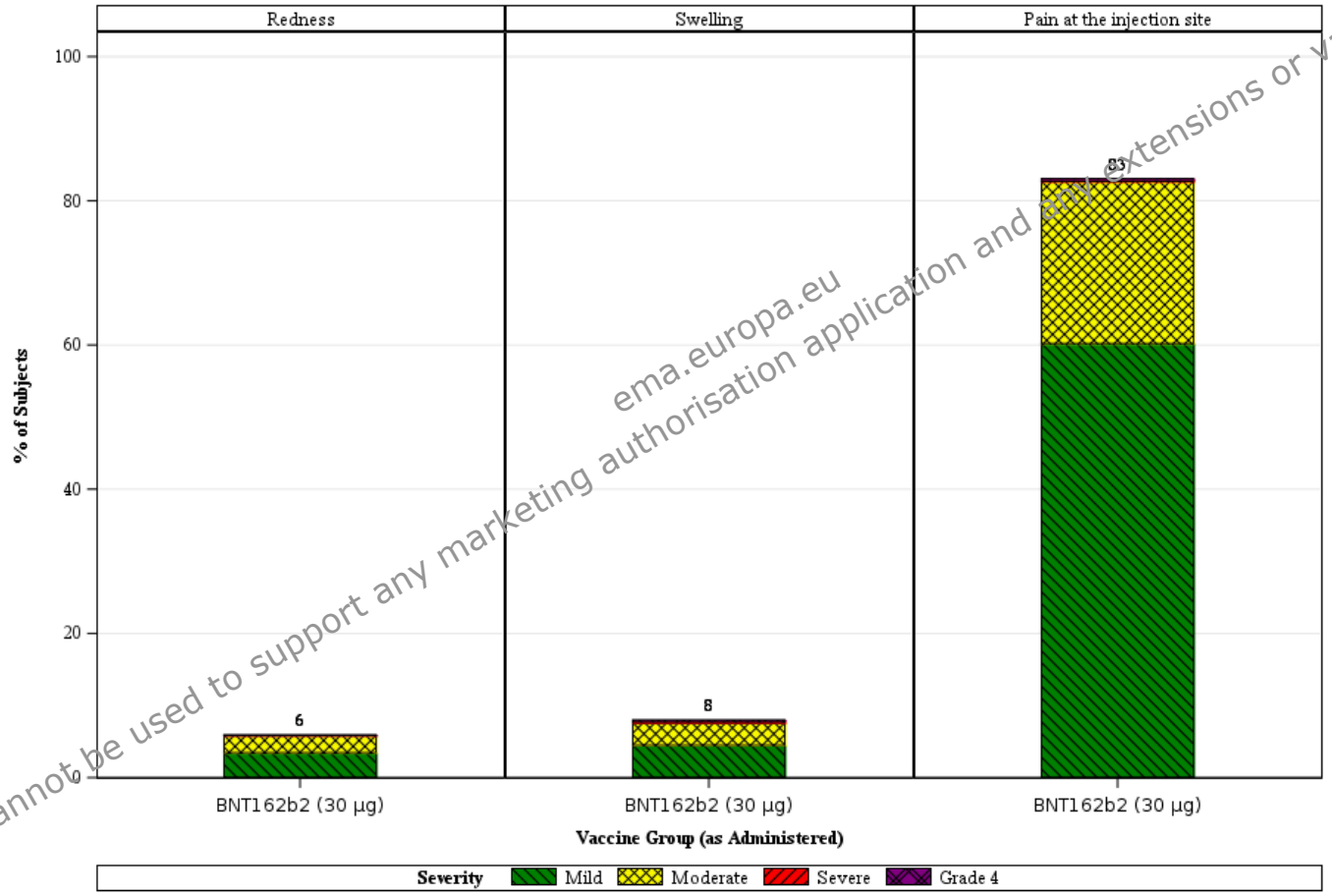
Pain at the injection site was the most frequently reported local reaction after booster (Dose 3) administration, reported by 83.0% of participants out of N=289 with e-diary data (Figure 2). Frequencies of redness and swelling after Dose 3 were lower, reported by 5.9% and 8.0% of participants, respectively.

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.

Overall, the pattern of local reactions reported in this Phase 3 booster group after Dose 3 was generally similar to that observed in prior analyses of Phase 2/3 participants after Dose 2 (refer to Module 5.3.5.1 C4591001 6-Month Update Interim CSR, dated 29 April 2021). Further details are provided in the CO conclusions (Section 2.5.6.2).

Figure 2. 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

2.5.5.2.1.2.2. Systemic Events

Systemic events reported after booster (Dose 3) administration out of N=289 participants with e-diary data, of any severity and in decreasing order of frequency, were (Figure 3):

- fatigue: 63.7%
- headache: 48.4%
- muscle pain: 39.1%
- chills: 29.1%
- joint pain: 25.3%
- fever: 8.7%
- diarrhea: 8.7%
- vomiting: 1.7%.

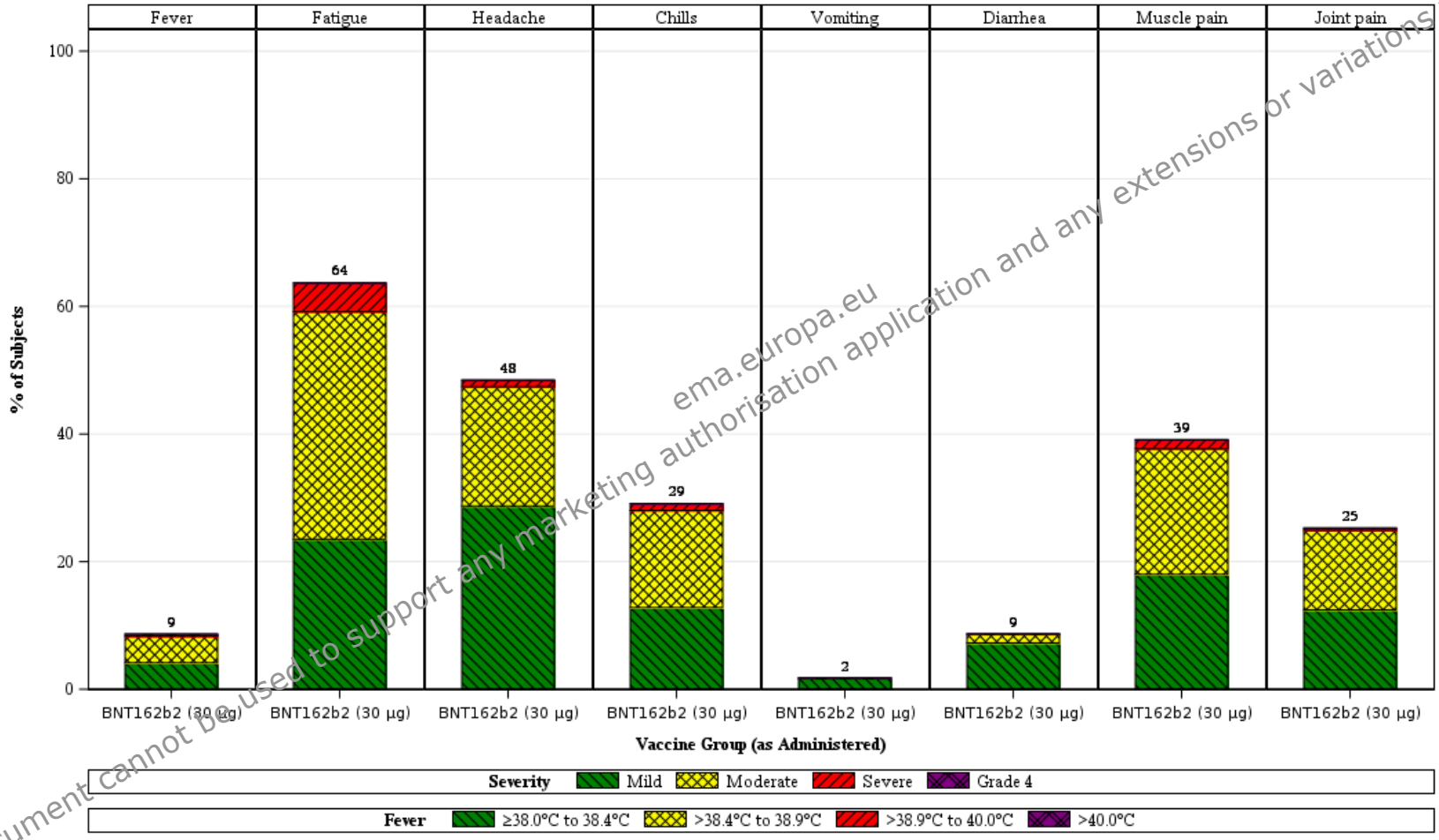
After Dose 3, use of antipyretic/pain medication was reported by 46.7% of participants.

After Dose 3, most systemic events were mild or moderate in severity. Severe systemic events were reported infrequently, in <2% of participants for all systemic events except for severe fatigue (4.5%). Severe muscle pain was reported in 4 participants (1.4%), and severe headache or severe chills were reported in 3 participants each (1.0%). Severe joint pain was reported in 1 participant (0.3%). A fever of >38.9 °C to 40 °C was reported in 1 participant (0.3%); 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.

Overall, the pattern of systemic events reported in this Phase 3 booster group after Dose 3 was generally similar to that observed in prior analyses of Phase 2/3 participants after Dose 2 (refer to Module 5.3.5.1 C4591001 6-Month Update Interim CSR, dated 29 April 2021). Further details are provided in the CO conclusions (Section 2.5.6.2).

Figure 3. 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.
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(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adce_f001_se_max_p3_g1

2.5.5.2.1.3. Adverse Events

2.5.5.2.1.3.1. Overview of Adverse Events

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

A summary of AEs from Dose 3 to 1 month after Dose 3 is shown in Table 10.

From Dose 3 to 1 month after Dose 3, the number of participants with any AE was 44/306 (14.4%). Events considered by the investigator as related to study intervention were reported by 24/306 participants (7.8%). One participant reported a severe AE of lymphadenopathy (see details in Section 2.5.5.2.2.1).

No SAEs or events leading to withdrawal were reported from Dose 3 to 1 month after Dose 3, and no study participants in this Phase 3 booster group died.

Table 10. Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)
Adverse Event	BNT162b2 (30 µg) (N[a]=306) n[b] (%)
Any adverse event	44 (14.4)
Related[c]	24 (7.8)
Severe	1 (0.3)
Life-threatening	0
Any serious adverse event	0
Related[c]	0
Severe	0
Life-threatening	0
Any nonserious adverse event	44 (14.4)
Related[c]	24 (7.8)
Severe	1 (0.3)
Life-threatening	0
Any adverse event leading to withdrawal	0
Related[c]	0
Severe	0
Life-threatening	0
Death	0

Table 10. Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)
Adverse Event	BNT162b2 (30 µg) (N[a]=306) n[b] (%)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any adverse event," n = number of subjects reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to investigational product.
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(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adae_s091_all_pd2_p3_g1_1d30

Summary of Adverse Events from Dose 3 to Data Cutoff Date

A summary of AEs from Dose 3 to the data cutoff date is shown in Table 11.

From Dose 3 to the data cutoff date (17 June 2021), in addition to the participants who reported AEs up to 1 month after Dose 3, 1 additional participant reported an AE, for a cumulative number of participants with any AE of 45/306 (14.7%). As of the cutoff date, events considered by the investigator as related to study intervention remained the same as at 1 month after Dose 3, reported by 24/306 participants (7.8%). In addition to the participant with a severe AE of lymphadenopathy that was reported up to 1 month after Dose 3 (see details in Section 2.5.5.2.2.1), as of the data cutoff date there was 1 additional participant who reported a severe AE; this event was considered an unrelated SAE (acute myocardial infarction) (see details in Section 2.5.5.2.1.3.3).

As of the data cutoff date, no events leading to withdrawal were reported and no study participants in this Phase 3 booster group died.

Table 11. Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to Cutoff Date – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)
Adverse Event	**BNT162b2 (30 µg) (N[a]=306) n[b] (%)**
Any adverse event	45 (14.7)
Related[c]	24 (7.8)
Severe	2 (0.7)
Life-threatening	0
Any serious adverse event	1 (0.3)
Related[c]	0
Severe	1 (0.3)
Life-threatening	0
Any nonserious adverse event	44 (14.4)
Related[c]	24 (7.8)
Severe	1 (0.3)
Life-threatening	0
Any adverse event leading to withdrawal	0
Related[c]	0
Severe	0
Life-threatening	0
Death	0

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any adverse event," n = number of subjects reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to investigational product.
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(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adae_s091_all_pd2_p3_g1_1dcut

2.5.5.2.1.3.2. Analysis of Adverse Events

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

AEs reported from Dose 3 to 1 month after Dose 3 are presented by SOC and PT in Table 12.

The most commonly reported AE was lymphadenopathy, in 16/306 participants (5.2%); see other significant AEs in Section 2.5.5.2.2.1 for details. 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%.

Overall, many AEs observed during the reporting period up to 1 month after Dose 3 were largely attributable to reactogenicity and lymphadenopathy (5.2%).

One event of dysgeusia (Grade 1, related to study intervention) is discussed further in Section 2.5.5.2.2.1.

Table 12. Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 (30 µg) (N[a]=306) n[b] (%)	(95% CI[c])
Any event	44 (14.4)	(10.6, 18.8)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	16 (5.2)	(3.0, 8.4)
Lymphadenopathy	16 (5.2)	(3.0, 8.4)
EAR AND LABYRINTH DISORDERS	1 (0.3)	(0.0, 1.8)
Cerumen impaction	1 (0.3)	(0.0, 1.8)
Ear pain	1 (0.3)	(0.0, 1.8)
GASTROINTESTINAL DISORDERS	4 (1.3)	(0.4, 3.3)
Nausea	2 (0.7)	(0.1, 2.3)
Eructation	1 (0.3)	(0.0, 1.8)
Irritable bowel syndrome	1 (0.3)	(0.0, 1.8)
Salivary duct obstruction	1 (0.3)	(0.0, 1.8)

Table 12. Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – 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)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8 (2.6)	(1.1, 5.1)
Injection site pain	2 (0.7)	(0.1, 2.3)
Pain	2 (0.7)	(0.1, 2.3)
Chills	1 (0.3)	(0.0, 1.8)
Facial pain	1 (0.3)	(0.0, 1.8)
Fatigue	1 (0.3)	(0.0, 1.8)
Swelling	1 (0.3)	(0.0, 1.8)
Swelling face	1 (0.3)	(0.0, 1.8)
INFECTIONS AND INFESTATIONS	1 (0.3)	(0.0, 1.8)
Diverticulitis	1 (0.3)	(0.0, 1.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4 (1.3)	(0.4, 3.3)
Arthropod bite	1 (0.3)	(0.0, 1.8)
Contusion	1 (0.3)	(0.0, 1.8)
Procedural pain	1 (0.3)	(0.0, 1.8)
Skin laceration	1 (0.3)	(0.0, 1.8)
INVESTIGATIONS	3 (1.0)	(0.2, 2.8)
Vitamin D decreased	1 (0.3)	(0.0, 1.8)
Weight decreased	1 (0.3)	(0.0, 1.8)
White blood cell count decreased	1 (0.3)	(0.0, 1.8)
METABOLISM AND NUTRITION DISORDERS	2 (0.7)	(0.1, 2.3)
Decreased appetite	1 (0.3)	(0.0, 1.8)
Dyslipidaemia	1 (0.3)	(0.0, 1.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	7 (2.3)	(0.9, 4.7)
Back pain	2 (0.7)	(0.1, 2.3)
Neck pain	2 (0.7)	(0.1, 2.3)
Exostosis	1 (0.3)	(0.0, 1.8)
Pain in extremity	1 (0.3)	(0.0, 1.8)
Plantar fasciitis	1 (0.3)	(0.0, 1.8)
NERVOUS SYSTEM DISORDERS	5 (1.6)	(0.5, 3.8)
Headache	2 (0.7)	(0.1, 2.3)
Dizziness	1 (0.3)	(0.0, 1.8)
Dysgeusia	1 (0.3)	(0.0, 1.8)
Migraine	1 (0.3)	(0.0, 1.8)
Syncope	1 (0.3)	(0.0, 1.8)
PSYCHIATRIC DISORDERS	2 (0.7)	(0.1, 2.3)

Table 12. Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – 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)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])
Anxiety	2 (0.7)	(0.1, 2.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (1.0)	(0.2, 2.8)
Dermatitis contact	2 (0.7)	(0.1, 2.3)
Rash	1 (0.3)	(0.0, 1.8)

Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
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(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adae_s130_1mdl_p3_g1

Related Adverse Events

From Dose 3 to 1 month after Dose 3, 24/306 participants (7.8%) had AEs assessed by the investigator as related to study intervention. The most common related events were lymphadenopathy cases, in 16/306 participants (5.2%); see other significant AEs in Section 2.5.5.2.2.1 for details. 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%).

One event of dysgeusia (Grade 1, related to study intervention) is discussed further in Section 2.5.5.2.2.1.

Immediate Adverse Events

No immediate events were reported within 30 minutes after booster (Dose 3) vaccination.

Severe or Life-Threatening Events

From Dose 3 to 1 month after Dose 3, one severe event (lymphadenopathy) was reported by 1 participant with an onset at 2 days post-Dose 3 and recovered/resolved 5 days from onset (see Section 2.5.5.2.2.1 for details). No life-threatening (Grade 4) events were reported.

Analysis 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, the cumulative number of participants with any AE included only 1 additional AE beyond the 1-month post-Dose 3 period of follow-up.

The additional event was acute myocardial infarction, reported as an unrelated SAE of Grade 3 severity that was recovered/resolved with sequelae (see details in Section 2.5.5.2.1.3.3).

2.5.5.2.1.3.3. Serious Adverse Events

Serious Adverse Events from Dose 3 to 1 Month After Dose 3

No SAEs were reported in the Phase 3 BNT162b2 booster safety population up to 1 month after Dose 3.

Serious Adverse Events from Dose 3 to Data Cutoff Date

From Dose 3 to the data cutoff date (17 June 2021), 1 SAE was reported, as summarized below.

The participant was a PPD 40 years of age with a BMI of PPD kg/m^3 who received BNT162b2 30 µg Dose 1 on PPD Dose 2 on PPD , and Dose 3 on PPD . This participant had a pertinent medical history of PPD . On PPD (which was 62 days after receiving Dose 3) PPD presented to the emergency department with excruciating pain radiating from PPD chest to the left jaw area; an electrocardiogram was unremarkable with no significant changes, troponin was elevated at 1.4 ng/mL (normal range not reported), a chest x-ray was normal except for mild hyperinflation, and a computerized tomography angiogram showed minimal atherosclerotic calcification and a calcified granuloma in the caudate lobe of the liver. PPD was diagnosed as having acute myocardial infarction (non-ST elevated) and was hospitalized for cardiac catheterization placement upon cardiac consultation. The event was reported as Grade 3 SAE considered by the investigator as not related to study intervention and was reported as recovered/resolved with sequelae within 1 day of onset, following treatment with drug (PPD) and non-drug (cardiac catheterization, angioplasty, and stent) interventions. During this hospitalization, the participant reported that PPD had visited the emergency department 3 to 4 months prior due of PPD . PPD was discharged from the hospital for this episode on PPD . PPD was readmitted to the hospital on PPD with dizziness, blurred vision, diaphoresis, chest pain, fatigue, and heartburn. PPD reported that PPD "PPD ," and PPD heart rate was noted to be 51 beats per minute. The troponin levels on PPD were elevated but declining (values not provided). The predisposing factors of PPD were considered, and the participant confirmed PPD 1 hour prior to onset of these symptoms.

A narrative for the participant with a reported SAE is located in the Module 5.3.5.1 C4591001 Phase 3 Booster (Dose 3) Interim CSR Section 14.

2.5.5.2.1.3.4. Deaths

No deaths were reported in the Phase 3 BNT162b2 booster safety population as of the data cutoff date (17 June 2021).

2.5.5.2.1.3.5. Adverse Events Leading to Withdrawal

No participants in the Phase 3 BNT162b2 booster safety population were withdrawn due to AEs from Dose 3 to the data cutoff date (17 June 2021).

2.5.5.2.2. C4591001 Other Safety Assessments

2.5.5.2.2.1. 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 (detailed in Section 2.5.5.2.1.3.3), there were no AESIs reflecting the conditions targeted by the CDC list in this booster group as of the data cutoff date.

One event of dysgeusia "PPD" (verbatim reporting) was reported in a PPD participant ≤24 years of age with onset at 2 days after Dose 3, that was reported as recovered/resolved 72 days from onset. The event was Grade 1 in severity and considered by the investigator to be related to study intervention. This participant also reported nausea "PPD" (verbatim reporting) at 2 days after Dose 3 that was recovered/resolved by 7 days after onset. At 3 days after Dose 3, PPD again reported nausea along with headache and injection site pain that were all reported as recovered/resolved 6 days after onset. All of these events were considered by the investigator as related to study intervention. This participant also had severe fatigue recorded as a systemic event in the e-diary on Day 3 after Dose 3.

Lymphadenopathy

A total of 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 located in axillary nodes. Only 1 participant who had lymphadenopathy after receiving Dose 3 had also previously experienced lymphadenopathy (with onset on the fourth day after Dose 2) during the blinded placebo-controlled period, as reported in the Module 5.3.5.1 C4591001 6-Month Update Interim CSR. No participants in the booster safety population reported a past medical history of lymphadenopathy. All lymphadenopathy cases occurring after Dose 3 were Grade 1, with one exception that is summarized below.

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 PPD participant 40 years of age 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.

Overall, the incidence of lymphadenopathy in this Phase 3 booster group was higher than previously observed in Phase 2/3 AE analyses. Lymphadenopathy has been identified as an adverse reaction causally associated with the vaccine (see Section 2.5.5.2.2.4) and is more common after a booster (Dose 3) is administered reflecting a potent immune response. Further details are provided in the CO conclusions (Section 2.5.6.2).

2.5.5.2.2.2. Severe COVID-19 Cases

No AEs were reported that suggested any potential cases of severe COVID-19 among participants in the Phase 3 BNT162b2 booster group, from Dose 3 to the data cutoff date (17 June 2021).

2.5.5.2.2.3. Pregnancies

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

2.5.5.2.2.4. 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 increase in frequency of lymphadenopathy after Dose 3 (5.2%) compared to lymphadenopathy associated with the first two doses (0.4%) in individuals ≥16 years of age and 0.8% in adolescents.

Lymphadenopathy has been observed proximal to vaccination 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.

2.5.5.3. Safety in Special Groups and Situations

2.5.5.3.1. Geriatric Use

Clinical studies of BNT162b2 (30 µg) include participants ≥65 years of age whose data contribute to overall assessment of safety and efficacy. The clinical data have demonstrated a predominantly mild reactogenicity profile in older adults, overall and compared with younger adults. This is coupled with evidence of robust immune response following the two-dose vaccination regimen, and overwhelming efficacy comparable to younger adults (>90%).

The safety and effectiveness of a booster dose of BNT162b2 in individuals 65 and older is based on safety and effectiveness data in adults at least 18 to 55 years of age.

2.5.5.3.2. Pediatric Use

Further study of pediatric use of the vaccine and/or immunobridging study will be undertaken to characterize the vaccine response in children.

The safety and effectiveness of a booster dose of BNT162b2 in individuals 16 and 17 years of age is based on safety and effectiveness data in adults at least 18 to 55 years of age.

2.5.5.3.3. Use During Pregnancy and Lactation

Women who were pregnant or breastfeeding were not eligible to participate in Study C4591001.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In a DART study, no vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for vaccination with BNT162b2 and any potential adverse effects on the breastfed child from BNT162b2 or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

2.5.5.3.4. Use in Immunocompromised Individuals

Individuals who are immunocompromised or taking immunosuppressive therapy at the time of vaccine administration may have diminished response to immunization. Study C4591001 included enrollment of individuals with medical history of immunocompromised condition or immunosuppressive therapy. There are limited data on the safety and effectiveness of the vaccine in this patient population at the time of this submission.

2.5.5.3.5. Other Safety Considerations

Overdose

In Study C4591001, any dose of study intervention exceeding 30 µg within a 24-hour time period was considered an overdose. An error in dilution during Study C4591001 resulted in 52 participants ≥16 years of age receiving a higher than intended dose of BNT162b2: instead of receiving 30 µg, an actual dose of 58 µg BNT162b2 was administered. These participants did not report an increase in reactogenicity or AEs.

Drug Abuse and Withdrawal and Rebound

Not applicable for BNT162b2.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

BNT162b2 has no or negligible influence on the ability to drive and use machines.

2.5.5.4. Post-Authorization Safety Summary

Post-authorization safety data are continually monitored by Pfizer and BioNTech for pharmacovigilance and risk management purposes, including weekly reviews of the Safety database. Pfizer's safety database contains AEs reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of SAEs reported from clinical studies regardless of causality assessment.

Post-authorization safety data are communicated in the following contexts:

- The first Periodic Safety Update Report covering the period of 19 December 2020 through 18 June 2021 that evaluated safety data and signal detection, and concluded:

  "Risks have been evaluated in the context of the benefits of the vaccine. Based on the available safety and efficacy/effectiveness data from the reporting interval for BNT162b2, the benefit-risk profile of BNT162b2 remains favourable."

- Post-authorization Summary Monthly Safety Reports (SMSRs) that include safety events reported from countries in which BNT162b2 is authorized or conditionally approved and are submitted monthly to regulatory authorities. These monthly reports provide information on safety signals and risks determined from signal detection activity.

Overall, review of the post-authorization safety data has continued to confirm the overall favorable risk-benefit assessment of the vaccine for individuals ≥12 years of age.

2.5.5.5. Safety Conclusions

Phase 3 data from 306 adult participants at least 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, any withdrawals due to AEs, or any deaths were reported following Dose 3 administration.

2.5.6. Benefits and Risks Conclusions

2.5.6.1. Benefits

COVID-19 is a serious and potentially fatal or life-threatening human infection. Based on the available clinical data, it is expected that BNT162b2 elicits an immune response that confers protection against COVID-19. The duration of such protection is currently unknown, and recent data from Israel and the US suggest that vaccine protection may wane approximately 6 to 8 months following the second dose (as detailed in Section 2.5.6.3); therefore, booster (Dose 3) administration is warranted to ensure durable protection. In preparation for the possibility of a booster (Dose 3) requirement in the setting of rapidly evolving viral variants that could affect the efficacy demonstrated in randomized-controlled clinical studies, Pfizer/BioNTech designed a booster (Dose 3) substudy of the C4591001 pivotal study that addresses the requirements outlined in the FDA Emergency Use Authorization for Vaccines to Prevent COVID-19 (Appendix 2).[11]

The Phase 3 booster study data reported in this CO showed administration of a third dose of BNT162b2 30 µg elicited substantially boosted neutralizing GMTs in adults up to 55 years of age who had completed the two-dose regimen approximately 6 months prior and who were without evidence of SARS-CoV-2 infection through 1 month after Dose 3. SARS-CoV-2 50% neutralizing titers following Dose 3 of BNT162b2 (30 µg) were noninferior to titers observed at 1 month 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 >0.67 and point estimate ≥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%). These data provide reassurance that a third dose of BNT162b2 (30 µg), administered approximately 6 months after completing the two-dose regimen, elicits a boosted immune response greatly increased over the immune response seen post-Dose 2.

Based on the strength of these booster immunogenicity data, and in accordance with FDA Guidance[11] as well as in line with the approved indication and age usage of BNT162b2 (30 µg) for individuals ≥16 years of age, Pfizer/BioNTech propose to revise the currently approved dosing regimen to include that a booster dose (third dose) may be administered from approximately 6 months after Dose 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. This extrapolation is in accordance with FDA's May 2021 Guidance for Industry[11] which states that booster studies "may be conducted in a single age group (e.g., adults 18-55 years of age), with extrapolation of results to other age groups for which the prototype vaccine has been authorized and to previously infected individuals in those age groups."

This proposal is therefore in line with established regulatory guidance, available epidemiology, real-world evidence, and supported by the totality of the pivotal study clinical data as summarized below.

Vaccine efficacy has been well established in pivotal Study C4591001 for all participants ≥12 years of age. Efficacy of BNT162b2 (30 µg) to prevent COVID-19 was overwhelmingly demonstrated in the final analyses of 170 cases reported in participants without evidence of past SARS-CoV-2 infection before or during the vaccination regimen, with VE of 95.0% (data cutoff date: 14 November 2020). Updated analyses of efficacy for cases confirmed from at least 7 days after Dose 2 and accrued up to the BLA submission cutoff date (13 March 2021), which represents up to approximately 6 months of blinded follow-up after Dose 2, included estimated VE of >91% for evaluable efficacy populations. With >4 months of follow-up time after Dose 2, vaccine efficacy was observed to be 83.7%. Descriptive efficacy analyses for adolescents 12 to 15 years of age were also conducted, based on confirmed COVID-19 cases reported from at least 7 days after Dose 2 through the data cutoff date (13 March 2021), and showed an observed VE of 100.0% with no severe cases reported in that age group; this represented approximately 2 months of follow-up for this group at the time of the data cutoff.

Immunogenicity data from C4591001 Phase 1 and Phase 2 participants have shown robust immune responses after vaccination with 2 doses of BNT162b2 at 30 µg in younger and older adults. However, as booster immunogenicity data in this submission reflect, immune responses wane with increasing time after Dose 2 but can be substantially improved by a third dose of BNT162b2.

Available booster data in Phase 1 younger (18 to 55 years of age) and older (65 to 85 years of age) participants who were given Dose 3 of BNT162b2 at 30 µg 7 to 9 months after completing the two-dose series of BNT162b2 30 µg had boosted serum neutralizing responses against the original SARS-CoV-2 wild-type (reference) strain, resulting in 1 month post-Dose 3 neutralizing titers >5-times those observed 1 month after Dose 2. Both age groups also had substantially boosted serum neutralizing titers against recombinant SARS-CoV-2 with the B.1.351 (Beta) variant spike mutations, which at 1 month post-Dose 3 were up to >15-times those observed at 1 month post-Dose 2. B.1.351 (Beta) variant neutralizing GMTs increased more after Dose 3 than did wild-type GMTs, indicating a broad breadth of the immune response to Dose 3. These data are available in Module 5.3.5.1 C4591001 Phase 1 Booster Beta Report. Similarly, data from the same Phase 1 younger and older adult participants showed increased neutralizing titers against recombinant SARS-COV-2 virus with the B.1.617.2 (Delta) spike variant, which at 1 month post-Dose 3 were 4.76- to 7.51-times the titers seen after Dose 2 of the initial vaccine regimen. These data are available in Module 5.3.5.1 C4591001 Phase 1 Booster Delta Report. In summary, the difference in neutralizing titers against the wild-type and the B.1.351 (Beta), and B.1.617.2 (Delta) variant viruses narrowed after the third dose compared with 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.

The totality of these efficacy and immunogenicity data strongly support administration of a booster (third dose) to address waning immunity and to increase the breath of response to variants using the licensed vaccine, BNT162b2 at 30 µg.

Strong BNT162b2-elicited immune responses have been demonstrated down to 12 years of age and have shown increased responsiveness with younger age. This was evident based on additional data from C4591001 adolescent participants 12 to 15 years of age including

immunobridging analyses following the two-dose regimen, based on noninferiority of SARS-CoV-2 neutralizing GMTs compared to young adults 16 to 25 years of age. Declaration of noninferiority was based on a 1.5-fold margin for the GMR of adolescent versus young adult groups, with adolescent immune responses meeting success criterion for immunobridging (ie, lower bound of the 2-sided 95% CI for GMR >0.67) and statistically exceeding that of young adults. Given the two-dose immunogenicity data in adolescents and young adults 16 to 25 years of age, it is rational and biologically plausible to correspondingly expect a booster immunogenicity effect observed in individuals 16 to 17 years of age who were not included in the Phase 3 evaluation of the booster (Dose 3) in this study. Likewise, BNT162b2 administered at 30 µg has been shown to elicit strong immune responses in older individuals including >55 years of age who would therefore also be expected to benefit from booster dosing.

Taken together, the available efficacy and immunogenicity data in pivotal Study C4591001 with the present booster (Dose 3) immunogenicity data strongly support a positive benefit for BNT162b2 as a two-dose regimen followed by a third dose to extend the duration of immune responsiveness. Overall, the present Phase 3 booster data show that a third dose of BNT162b2 administered approximately 6 months after completing the two-dose regimen induces a strong immune response that is expected to confer extended protection against COVID-19.

2.5.6.2. Risks

The reactogenicity and AE profile observed after the booster (Dose 3) was generally similar to that observed following Dose 2 of the initial two-dose regimen in previous analyses reported in the EUA and BLA, which suggests no potentiation of reactogenicity or any new safety concern arising from administration of a third dose. Available safety data from all participants in C4591001, which includes at least 2 months of follow-up after Dose 2 for adolescents 12 to 15 years of age and at least 6 months of follow-up after Dose 2 for participants ≥16 years of age, have been consistent across age groups and over time. The current booster (Dose 3) data in young adults 18 to 55 years of age remain consistent with the known safety and tolerability profile for BNT162b2 at 30 µg.

This submission includes evaluation of safety data from Study C4591001 for 306 Phase 3 participants re-randomized from the younger adult age group (18 to 55 years of age) who received a booster (Dose 3) of BNT162b2 30 µg, approximately 6 months after completing the two-dose regimen. These participants 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 since receiving Dose 3 of BNT162b2 30 µg.

The reactogenicity profile during the 7-day period after booster (Dose 3) was typically mild to moderate, arose within the first 1 to 2 days after dosing, and was short-lived. The most common prompted local reaction after Dose 3 was injection site pain. The most common prompted systemic events included fatigue, headache, muscle and joint pain, and chills, and the frequency of any severe systemic event after Dose 3 was low.

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 (Dose 2, Dose 3): pain at injection site (78.3%, 83.0%), fever (16.4%, 8.7%), fatigue

(61.5%, 63.7%), headache (54.0%, 48.4%), chills (37.8%, 29.1%), muscle pain (39.3%, 39.1%), joint pain (23.8%, 25.3%), diarrhea (10.0%, 8.7%), and vomiting (2.2%, 1.7%).

The AE profile up to at least 2 months (as of the data cutoff date of 17 June 2021) 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. Similarly, the AE and adverse reaction profile among approximately 22,000 participants ≥16 years of age and 1100 adolescents 12 to 15 years of age enrolled and vaccinated with BNT162b2 in double-blinded placebo follow-up, as of the most recent safety cutoff date (13 March 2021), was mostly reflective of reactogenicity events with low incidences of severe and/or related events. The incidence of SAEs was low and few participants withdrew from the study due to AEs. Few deaths occurred overall in participants ≥16 years of age, and no deaths were reported in adolescents. Review of AEs of clinical interest have suggested no clear patterns or safety concerns.

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. As Dose 3 is a booster, it is not surprising that lymph nodes would be stimulated by vaccination 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.

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.

2.5.6.3. Benefit-Risk Conclusions

2.5.6.3.1. Clinical Data from C4591001 – Phase 3 Booster (Dose 3) Benefits and Risks

The available clinical trial evidence for BNT162b2 includes induction of strong immune responses and high vaccine efficacy, with highly effective protection against COVID-19 in a broad population of individuals across demographic characteristics. Clinical study immunogenicity data have shown strong immune responses across age groups, which begins to wane by 6 months post-Dose 2. Phase 3 participants who received a booster (Dose 3) of BNT162b2 µg approximately 6 months after Dose 2 had robust immune responses elevated beyond those observed after Dose 2.

Potential risks are based in part on the observed clinical study safety profile to date, which shows mostly mild to moderate reactogenicity, low incidence of related or severe events, no

serious events reported within 1 month after Dose 3, and no new clinically concerning safety observations or safety concerns. The vaccine has been shown to be safe and well-tolerated in pivotal Study C4591001, across age groups and demographics. Post-Dose 3 reactogenicity and AE profiles did not show new safety concerns.

2.5.6.3.2. Post-Authorization Safety Evaluation of BNT162b2

Additionally, post-authorization SMSRs include safety data reported from countries in which BNT162b2 is authorized or conditionally approved and are submitted monthly to regulatory authorities. SMSRs provide information on safety signals and risks determined from signal detection activity. Myocarditis and pericarditis are important potential risks that have been identified for mRNA COVID-19 vaccines, including BNT162b2, during post-authorization use. Pfizer/BioNTech have made commitments to conduct studies to elucidate the risk and long-term sequelae of these conditions (even if subclinical) after vaccination. Indeed, one such commitment includes obtaining blood samples within the first 4 days after a booster (Dose 3) for potential troponin testing. No risks identified in the post-authorization period have changed the overall favorable risk-benefit assessment of the vaccine for individuals ≥12 years of age.

The totality of the safety and tolerability profile, combined with the efficacy and immunogenicity data to date, show that the benefit: risk profile for BNT162b2 30 µg remains favorable, including after administration of a third dose.

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

A recent real-world, retrospective cohort study conducted in Israel correlated time-from-vaccine to the incidence of breakthrough infections between individuals ≥16 years of age who were PCR-negative for SARS-CoV-2 at the study start and who received both doses of BNT162b2 30 µg within the prescribed interval, during a study period between January and April 2021.[17] The analysis utilized healthcare records data which cover 25% of the Israeli population and provides a representative sample.

The correlation between time-from-vaccine and breakthrough infection was evaluated using two logistic regression models. After adjusting for comorbidities, the first model found the risk of breakthrough infection was statistically significant increased, by 53% (95% CI: 40%, 68%), 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 early versus late for each month-group; 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.

This vaccination period corresponded to a time when the B.1.617.2 (Delta) was the predominant SARS-CoV-2 strain in circulation in Israel, with the data suggesting a significant correlation between time-from-vaccine and the corresponding protection against SARS-CoV-2 infection. The risk for breakthrough infection was significantly higher for individuals who were vaccinated early compared to those vaccinated later, which suggests a possible relative decrease in long-term protection of BNT162b2 against the B.1.617.2 variant.

Decreased neutralizing antibody titers have been associated with vaccinees' breakthrough infections along with increased viral load,[18] underscoring that an additional vaccine dose which has been shown to boost neutralizing antibody titers is likely to strengthen protection against contracting or spreading COVID-19.

2.5.6.3.4. Real-World Data on Public Health Impact of Booster Doses of mRNA Vaccines

Emerging evidence has suggested that the need for booster doses of COVID-19 mRNA vaccines is potentially an urgent emerging public health issue.

The Israel Ministry of Health (MoH) recently conducted an observational study to assess the effectiveness of the BNT162b2 against various SARS-CoV-2 outcomes between 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,[19] vaccine effectiveness (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. Hospitalizations are classified as *severe* if a patient has a resting respiratory rate of >30 breaths per minute, oxygen saturation on room air of <94%, or a ratio of PaO_2 to FiO_2 <300, or as *critical* in the event of mechanical ventilation, shock, or cardiac, hepatic, or renal failure. Individuals were defined as unvaccinated if they had never received a COVID-19 vaccine, and 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, for individuals ≥16 years of age, BNT162b2 effectiveness against SARS-CoV-2 infection was only 39% (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.[19] 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, which was not statistically significantly different from zero. 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.[20] 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 55 to <60% for persons vaccinated early on in the Israeli MoH vaccine campaign (ie, January or February).[21]

As a result, Israel MoH initiated a booster program for older adults and immunocompromised individuals who were previously fully immunized, a program that is expected to be expanded to the entire vaccine-eligible population.[22] 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.[23] These initial booster data show 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. As Israel embarked on an early mass vaccination program with BNT162b2, such real-world effectiveness data serve as a predictor of effectiveness over time (ie, time-from-vaccine) and in the presence of emerging variant viruses.

On 18 August 2021, the CDC published two studies[24,25] showing similar reductions in effectiveness against SARS-CoV-2 infections. The first study[24] estimated 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 US. 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 in 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 US. A nearly identical trend was observed for the Moderna COVID-19 mRNA-1273 vaccine. The authors suggested 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,[25] 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 suggested the effects of waning and the introduction of the B.1.617.2 (Delta) variant could not be fully teased apart.

While 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,[25,26] this should be carefully monitored as preliminary data from Israel (as described above) suggest reduced effectiveness against severe disease could eventually follow observed reductions in effectiveness against SARS-CoV-2 infections.[26] 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 vaccine effectiveness 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.

2.5.6.3.5. Conclusions

Overall, the potential risks and benefits as assessed by the safety profile and by the efficacy and immunogenicity of BNT162b2, and the emerging real-world data and public health need, are balanced in favor of the potential benefits to prevent COVID-19 that includes administration of a third dose of BNT162b2 approximately 6 months after completion of the initial two-dose series.

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