PFIZER-BIONTECH COVID-19 VACCINE (BNT162, PF-07302048)

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

BRIEFING DOCUMENT

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ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse events of special interest
BLA	Biologics License Application
BMI	body mass index
CDC	US Centers for Disease Control
CMC	Chemistry, Manufacturing, and Control
CoV	Coronavirus
2019-nCoV	2019 novel Coronavirus
COVID-19	Coronavirus Disease 2019
DART	developmental and reproductive toxicity
ELISpot	enzyme-linked immunospot
EUA	Emergency Use Authorization
FDA	(US) Food and Drug Administration
FIH	first-in-human
GMC	geometric mean concentration
GMFR	geometric mean fold-rise
GMT	geometric mean titer
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IFNγ	interferon gamma
IgG	immunoglobulin G
IL-2	interleukin 2
IL-4	interleukin 4
IM	intramuscular(ly)
IRR	illness rate ratio
LLN	lower limit of normal
LNP	lipid nanoparticle
MedDRA	Medical Dictional for Regulatory Activities
MERS	Middle East respiratory syndrome
modRNA	nucleoside-modified RNA
NAAT	nucleic acid amplification test
NHP	nonhuman primate
P2 S	P2 mutant
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PK	Pharmacokinetic
PT	preferred term
RBD	receptor binding domain
RNA	ribonucleic acid
RNA-LNP	RNA lipid nanoparticle
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing COVID-19
S	spike glycoprotein
SMQ	standardized MedDRA query
SOC	System Organ Class
Th1	T helper cell type 1
Th2	T helper cell type 2
US	United States
USP	United States Pharmacopeia

Abbreviation	Definition
TME	targeted medical event
V8	variant 8
V9	variant 9
VAED	vaccine-induced enhanced disease
VAERD	vaccine-associated enhanced respiratory disease
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
WHO	World Health Organization

EXECUTIVE SUMMARY

Pfizer and BioNTech submitted an Emergency Use Authorization (EUA) application for an investigational vaccine intended to prevent Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2; this EUA request (EUA 27034) was submitted on 20 November 2020. The vaccine is based on a SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA formulated in lipid nanoparticles (LNPs). In response to the current global health crisis, the Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) development has ensured the highest compliance and quality standards while progressing expeditiously to address this urgent and unmet medical need.

Safety and efficacy data from two clinical studies support the EUA request:

- Study BNT162-01 is the first-in-human, Phase 1/2 dose level-finding study conducted in Germany (N=60) to obtain safety and immunogenicity data for multiple vaccine candidates to inform the overall clinical development of a COVID-19 vaccine.

- Study C4591001 is an ongoing, randomized and placebo-controlled Phase 1/2/3 pivotal registration study. It was started as a Phase 1/2 study in the US, was then amended to expand to a global Phase 2/3 study enrolling ~44,000 participants for a well-powered, timely assessment of safety, immunogenicity, and efficacy endpoints, and includes adolescents 12 to 17 years of age. This study is being conducted at selected sites across the globe to ensure the diversity of the enrolled population.

Safety Summary

Data from approximately 38,000 participants randomized 1:1 to receive either vaccine or placebo with a median of 2 months of follow-up after Dose 2 of the 2-dose vaccine regimen in Study C4591001 show that BNT162b2 at 30 μg was safe and well-tolerated in participants ≥16 years of age. Reactogenicity and AEs were generally milder and less frequent in participants in the older group (≥56 years of age) compared with the younger group (≤55 years of age). Reactogenicity was mostly mild to moderate and short-lived after dosing for both adult age groups and for younger adolescents 12 to 15 years of age (whose preliminary data provide support of the intended indication including individuals 16 and 17 years of age), and the AE profile did not suggest any serious safety concerns. The incidence of serious adverse events (SAEs) and deaths were low in the context of the number of participants enrolled and comparable for BNT162b2 and placebo. The incidence of discontinuations due to AEs was also generally low and similar between BNT162b2 and placebo groups. Safety data from approximately 44,000 participants enrolled as of the data cutoff date (14 November 2020), with variable durations of follow-up after vaccine administration, overall showed a similar AE profile to those who had at least 2 months of follow-up after Dose 2. In this total population of all enrolled participants, incidences of SAEs and deaths were low and comparable for BNT162b2 and placebo, and incidence of discontinuations due to AEs was generally low and similar between BNT162b2 and placebo groups.

Immunogenicity Summary

The two-dose regimen of BNT162b2 elicited robust SARS-CoV-2 neutralization titers and S1-binding IgG levels in both younger and older adults. After the second dose of vaccine and up to

approximately Day 50 (1 month post dose 2), SARS-CoV-2 neutralization geometric mean titers (GMTs) were comparable to or higher than the GMT of a human convalescent serum (HCS) panel from individuals recovered from COVID-19. Further evaluation of antibody persistence is ongoing. Data from study BNT162-01 demonstrate that BNT162b2 also elicited strong Th1-biased CD4+ responses and strong CD8+ T cell responses.

Efficacy Summary

In the final efficacy analysis, among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, vaccine efficacy (VE) for the first primary endpoint against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%, with 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group. The 95% credible interval for the VE was 90.3% to 97.6%, indicating that the true VE is at least 90.3% with a 97.5% probability given the available data. For the second primary endpoint, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 in participants with and without evidence of SARS-CoV-2 infection before and during vaccination regimen was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively. The 95% credible interval for the VE was 89.9% to 97.3%, indicating that the true VE is at least 89.9% with a 97.5% probability given the available data.

Observed VE was >93% for the first primary efficacy endpoint across subgroups of age, sex, race/ethnicity, and country, with the exception of "all others" race group (89.3% VE) and Brazil (87.7% VE). In participants with comorbidities, VE was >91% for the first primary efficacy endpoint in all risk subgroups analyzed.

A total of 10 cases of severe COVID-19 occurred after Dose 1, 1 in the BNT162b2 group, compared with 9 cases in the placebo group.

Among all participants (regardless of evidence of infection before or during the vaccination regimen), 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared with 275 cases in the placebo group, indicating an estimated VE of 82% (95% CI: 75.6%, 86.9%) against confirmed COVID-19 occurring after Dose 1 of the 2-dose regimen, with VE of 52.4% (95% CI: 29.5%, 68.4%) between Dose 1 and Dose 2.

The early onset of protection is readily apparent from cumulative incidence curves, which show that disease onset tracks conjointly for BNT162b2 and placebo until approximately 14 days after Dose 1, at which point the curves diverge, with cases steadily accumulating in the placebo group, while remaining virtually flat in the BNT162b2 group.

Risk/Benefit Assessment

The ongoing COVID-19 pandemic has a significant impact on public health, and currently there is no broadly effective treatment or prevention available. An effective vaccine can impact the trajectory of the pandemic at this critical time.

The efficacy, safety, and immunogenicity data in this EUA application support a positive assessment of risk and benefit for the Pfizer-BioNTech COVID-19 Vaccine and fulfil the data requirements outlined in the Food and Drug Administration (FDA) EUA guidance.[1] The

registrational Phase 1/2/3 Study, C4591001, will continue as long as possible per protocol to monitor participants and obtain additional data supportive of a Biologics License Application (BLA) filing in the near future. An extensive post-authorization plan has been prepared for active long-term safety surveillance of Pfizer-BioNTech COVID-19 Vaccine recipients under an EUA.

1. BACKGROUND INFORMATION AND UNMET MEDICAL NEED

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel Coronavirus (2019-nCoV) was the underlying cause. In early January 2020, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the Betacoronavirus subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to other coronaviruses that infect humans, including the Middle East respiratory syndrome (MERS) coronavirus.[2,3]

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries. On 11 March 2020 the WHO characterized the COVID-19 outbreak as a pandemic. As of 19 November 2020, there have been >56 million globally confirmed COVID-19 cases and >1.3 million deaths, with 191 countries/regions affected. At this same time, in the US, there have been >11.5 million confirmed cases and >250,000 deaths.[4]

There are no vaccines approved by the FDA to prevent or treat COVID-19, which is affecting millions of individuals in the nation. At the time of the EUA request for the Pfizer-BioNTech COVID-19 Vaccine, confirmed cases and mortality continue to rise globally. Currently, there are few therapeutics available (eg, antivirals, steroids, monoclonal cocktails, and hyperimmune plasma) that may benefit certain populations. However, highly effective and safe vaccines and medications to prevent and treat COVID-19 remain a high unmet medical need.

Vaccination is the most effective medical countermeasure to decrease risk and mitigate spread of SARS-CoV-2. Immunization with a safe and effective COVID-19 vaccine is a critical component of the nation's strategy to reduce COVID-19-related illnesses, hospitalizations, and deaths and to help restore societal functioning.

1.1. Regulatory Considerations

The Pfizer-BioNTech COVID-19 Vaccine was developed in close consultation with the FDA and other global regulators. Vaccine development followed all applicable guidance documents from the FDA,[1,5,6,7] US Centers for Disease Control (CDC),[8] and the WHO[9] and contains all required information for an EUA for a vaccine to prevent COVID-19.

2. GENERAL PRODUCT INFORMATION

Sponsor Compound Number: BNT162, PF-07302048

The Pfizer-BioNTech COVID-19 Vaccine is a prophylactic vaccine developed by BioNTech and Pfizer to prevent COVID-19 caused by SARS-CoV-2 infection.

The Pfizer-BioNTech COVID-19 Vaccine, BNT162b2 (30 µg), is administered intramuscularly (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 dose followed by a second dose 21 days later.

BNT162b2 is supplied as a multiple-dose (5-dose) vial containing a frozen (between -80ºC to -60ºC (-112ºF to -76ºF) suspension that is preservative-free. BNT162b2 must be thawed and diluted in its original vial with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to administration. After dilution, the vial contains 5 doses of 0.3 mL per dose. After dilution, the multiple-dose vials must be stored between 2°C to 25°C (35°F to 77°F) and used within 6 hours from the time of dilution.

2.1. Coronavirus Spike Glycoprotein as Vaccine Target

Coronaviruses are a family of (+) ssRNA enveloped viruses that encode four structural proteins. Among these structural proteins, S is a key target of neutralizing antibodies and therefore an important antigen for vaccine development. The spike protein is an important vaccine target or antigen, as it mediates first the specific binding of the virus to the angiotensin-converting enzyme 2 (ACE2) host cell receptor and then the fusion of the viral envelope with a host cell membrane. By these actions, the virus can enter human cells where it replicates, often causing illness, and potentially spreading to other people. Data available from other coronaviruses such as SARS and MERS had established that antibodies to the S protein can block the binding of the virus to cells and prevent viral infection.[10,11] The Pfizer-BioNTech COVID-19 Vaccine encodes a membrane-anchored, full-length S protein with two point mutations to proline within the central helix domain to lock S protein in an antigenically preferred prefusion conformation.[12,13]

2.2. RNA-Lipid Nanoparticle Formulation

The Pfizer-BioNTech COVID-19 Vaccine is based on an RNA-LNP platform of nucleoside-modified RNA, which has blunted innate immune sensor activating capacity and thus augmented antigen expression. Pfizer-BioNTech COVID-19 Vaccine, BNT162b2 (30 µg), encodes a P2 mutant S (P2 S) and is formulated in LNPs. Encapsulation into LNPs enables transfection of the RNA into host cells after intramuscular (IM) injection. These LNPs are composed of four different lipids in a defined ratio. During mixing of the RNA and the dissolved lipids, the lipids form the nanoparticles encapsulating the RNA. After injection, the LNPs are taken up by the cells, and the RNA is released into the cytosol. In the cytosol, the RNA is translated to the encoded viral protein. The P2 S antigen incorporates into cellular membranes and induces an adaptive immune response. As S is the antigen that recognizes ACE2 and enables infection of the host cells, it is a key target of virus neutralizing antibodies. Furthermore, as RNA-expressed S is fragmented intracellularly, the resulting peptides can be presented at the cell surface, triggering a specific T cell-mediated immune response with activity against the virus.[14,15]

3. PROPOSED EUA INDICATION

Pfizer BioNTech COVID-19 Vaccine is authorized for use under an EUA for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

4. SUMMARY OF KEY NONCLINICAL DATA

Nonclinical evaluation of BNT162b2 included pharmacology (mouse immunogenicity and nonhuman primate [NHP] immunogenicity and SARS-Cov-2 challenge studies), pharmacokinetic (series of biodistribution, metabolism and pharmacokinetic studies), and toxicity (2 Good Laboratory Practice [GLP] rat repeat-dose toxicity) studies in vitro and in vivo. A developmental and reproductive toxicity (DART) study is ongoing in rats.

Administration of BNT162b2 by IM injection to male and female Wistar Han rats once every week, for a total of 3 weekly cycles of dosing (30 µg and 100 µg), was tolerated without evidence of systemic toxicity in GLP-compliant toxicity studies in the presence of a robust immune response.

Nonclinical studies in mice and NHP demonstrate that BNT162b2 elicits a rapid antibody response with measurable SARS-CoV-2 neutralizing titers after a single dose and substantial increases in titers after a second dose that exceed titers in sera from SARS-CoV- 2/COVID-19-recovered individuals. A Th1-dominant T cell response was evident in both mice and NHPs. S-specific CD8+ T cell responses were also detectable in BNT162b2-immunized animals. The strongly Th1-biased CD4+ T cell response and interferon-γ (IFNγ)+ CD8+ T cell response after immunization with BNT162b2 is a pattern favored for vaccine safety and efficacy and provided added reassurance for clinical safety.[16] In A SARS-CoV-2 rhesus challenge model, BNT162b2 provided complete protection from the presence of detectable viral RNA in the lungs compared to the saline control with no clinical, radiological or histopathological evidence of vaccine-elicited disease enhancement.[17]

The key nonclinical studies supporting the EUA of BNT162b2 administered twice by IM injection at a dose of 30 µg RNA are outlined in Table 1.

Table 1. Summary of Key Nonclinical Studies

Study Number	Study Type	Species / Test System	Test Item	Dose [RNA]	Study Outcome/Findings
Toxicology					
38166	Repeat-dose toxicity	Wistar Han Rats	BNT162b2 (V8)[a]	100 µg	BNT162b2 (V8) was tolerated without signs of systemic toxicity. All animals developed a robust immune response to the vaccine antigen.
20GR142	Repeat-dose toxicity	Wistar Han Rats	BNT162b2 (V9)	30 µg	BNT162b2 (V9) was tolerated without signs of systemic toxicity. All animals developed a robust immune response to the vaccine antigen.
20256434	Developmental and Reproductive Toxicity	Wistar Han Rats	BNT162b2 (V9)	30 µg	Ongoing

Table 1. Summary of Key Nonclinical Studies

Study Number	Study Type	Species / Test System	Test Item	Dose [RNA]	Study Outcome/Findings
Pharmacology					
VR-VTR-10671	In vivo immunogenicity and SARS-CoV-2 challenge	Rhesus macaques	BNT162b2 (V9)	30, 100 µg	BNT162b2 (V9) elicited a rapid antibody response with measurable SARS-CoV-2 neutralizing titers after a single dose and substantial increases in titers after a second dose that exceed titers in sera from SARS-CoV-2/COVID-19-recovered patients. A Th1-dominant T cell response was elicited. Complete protection in the lungs was observed in immunized animals compared to controls and there was no evidence of vaccine-elicited disease enhancement.

a. Two BNT162b2 variants (V8 and V9) were evaluated in the GLP repeat-dose toxicity studies. Although BNT162b2 (V9), the clinical candidate, has a different codon optimization to BNT162b2 (V8), both variants encode a protein with the same amino acid sequence.

5. OVERVIEW OF CLINICAL STUDIES

Studies contributing clinical data to the EUA application are summarized in Table 2 and described in the sections that follow.

Table 2. Summary of Clinical Studies

Sponsor	Study Number (Status)	Phase Study Design	Test Product (Dose)	Number of Subjects	Type of Subjects (Age)
BioNTech	BNT162-01 (ongoing)	Phase 1/2 randomized, open-label, dose-escalation, first-in-human	BNT162b2 (1, 3, 10, 20, 30 µg)	Phase 1: 60	Adults (18-55 years of age)
BioNTech (Pfizer)	C4591001 (ongoing)	Phase 1/2/3 randomized, observer-blind, placebo-control	Phase 1: BNT162b2 (10, 20, 30 µg) Placebo	Phase 1: 90 randomized 4:1 (within each dose/age group)	Phase 1: Adults (18-55 years of age, 65-85 years of age)
			Phase 2: BNT162b2 (30 µg) Placebo	Phase 2: 360 randomized 1:1	Phase 2: Adults (18-55 years of age, 65-85 years of age)
			Phase 3: BNT162b2 (30 µg) Placebo	Phase 3: ~44,000 randomized 1:1 (includes 360 in Phase 2)	Phase 3: Adolescents, Adults (12-15 years of age, 16-55 years of age, >55 years of age)

5.1. First-in-Human Phase 1/2 Study BNT162-01

Study BNT162-01 is the ongoing, first-in-human (FIH), Phase 1 dose level-finding study, in which healthy adults 18 to 55 years of age all receive active vaccine. This study is evaluating the safety and immunogenicity of several different candidate vaccines at various dose levels. The protocol was later amended to allow inclusion of older adult participants up to 85 years of age. Data for older adult participants were not available to be included in the EUA application. The available Phase 1 safety and immunogenicity data for adults 18 to 55 years of age are reported.

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

The BNT162-01 study population includes male and female adult participants deemed healthy and without COVID-19 symptoms or evidence of SARS-CoV-2 infection within 30 days prior to entering the study. Inclusion criteria allowed for preexisting stable disease defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment. Individuals with medical conditions considered to possibly confound evaluation of vaccine safety or immunogenicity were excluded.

In addition to serology immunogenicity data, T cells isolated from peripheral blood mononuclear cells (PBMCs) obtained from whole blood samples of vaccinated Phase 1 participants were evaluated by enzyme-linked immuno-spot (ELISpot) and intracellular cytokine staining visualized by flow cytometry. Blood samples were collected from study participants prior to the first vaccine dose and on Day 29 (7 days) after the second vaccine dose. Assessments included cytokines associated with Th1 responses such as IFNγ and IL-2 and those associated with Th2 responses such as IL-4, to analyze the induction of balanced versus Th1 dominant or Th2-dominant immune responses.

All participants in Phase 1 recorded reactogenicity (local reactions, systemic events, and antipyretic/pain medication usage) for 7 days after each dose and available adverse events (AEs) as of the study report cutoff date. Safety data are analyzed and reported using descriptive summary statistics.

5.2. Registration 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 ~44,000 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.

The Phase 1 portion of the study informed the decision on the vaccine candidate and dose level (Section 5.2.1). The Phase 2/3 portion of the study evaluated the safety, immunogenicity, and efficacy of the selected vaccine candidate, BNT162b2, and is intended to support licensure in the US and globally.

Phase 1

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).

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. 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.

Phase 2/3

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, and younger adolescents (12 to 15 years of age) were added 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, such as:

- Chronic condition (eg, hypertension; diabetes; asthma; pulmonary, liver, or kidney disease)
- Autoimmune disease requiring therapeutic intervention (or history of)
- Chronic HIV, HCV, or HBV infection that is stable and controlled
- Vaping or smoking (or history of smoking within the prior year)
- Resident in a long-term facility
- Occupation with high risk of SARS-CoV-2 exposure (eg, healthcare, emergency response)

Phase 2/3 of Study C4591001 commenced with the selected vaccine candidate and dose level administered to participants who were randomized 1:1 to receive vaccine or placebo.

Phase 2 was conducted in the US. The Phase 2 portion of the study evaluated reactogenicity and immunogenicity for 360 adult participants enrolled into the study when the Phase 2/3 part commenced, balancing younger and older adult 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. The final efficacy analysis was to be 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.

The Phase 2/3 portion of the study remains blinded to Sponsor and site personnel who are responsible for the ongoing conduct of the study, with regard to individual participants' randomization. Safety evaluation by the study team remains blinded until a decision is made to unblind the entire study. A separate (from study conduct) small unblinded submissions team is responsible for regulatory submissions including the EUA application data analysis and submission.

5.2.1. Rationale for Vaccine Candidate and Dose Selection for Phase 2/3 Development

BioNTech has evaluated multiple RNA-LNP platforms, including nucleoside-modified RNA (modRNA) which has blunted innate immune sensor activating capacity and thus augmented antigen expression. Two modRNA candidates were evaluated in the Phase 1 portions of Studies BNT162-01 and C4591001. The final candidate and dose level (BNT162b2 at 30 µg) were selected following review of immunogenicity and safety data from the Phase 1 part of Study C4591001 and available nonclinical data.

The final vaccine candidate selection for clinical development in Phase 2/3 was based on:

- Favorable reactogenicity for BNT162b2 in both younger and older participants in Phase 1
- NHP challenge studies showing BNT162b2 led to earlier virus clearance and no evidence of virus in the lung
- Robust immunogenicity in both younger and older participants at the 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 (Section 6.2.3.1) and a robust immune response (Section 6.2.2), likely to afford protection against COVID-19 in younger and older adults.

5.2.2. Continuation of Blinded Phase 3 Registration Study

Pfizer and BioNTech intend to continue the pivotal Phase 3 study with participants in both the vaccine and placebo groups as originally allocated for as long as possible, to obtain long-term data and to ensure sufficient follow-up to support traditional licensure. Nevertheless, we have an ethical responsibility to inform all ongoing study participants of the availability and eligibility criteria of any COVID-19 vaccine made available under an EUA. We will appeal to participants to remain in the ongoing Phase 3 study as originally randomized for as long as possible, ideally until a COVID-19 vaccine has full regulatory approval following the accumulation of 6 months

of safety follow-up data after Dose 2. The study team responsible for study conduct would remain blinded to individual participant randomization until this time.

When a COVID-19 vaccine is available under an EUA, placebo recipients who choose not to remain in the ongoing study will need to be unblinded to determine whether they received BNT162b2 or placebo, and given the option to receive BNT162b2 when they are practically eligible for a COVID 19 vaccine (ie, eligible under applicable regulatory approval and national immunization recommendations, and when the national program supply is available in the area in which they reside). In this situation, it is Pfizer's preference that such individuals are vaccinated within the study in order that both safety and efficacy data can continue to be collected. We believe this approach will minimize the number of current participants who choose to withdraw from the study once a vaccine is available and will maximize the collection of data that can inform the long-term efficacy and safety of BNT162b2. When there is full regulatory approval of a vaccine in the participants' country, BNT162b2 will be offered to all placebo participants. We recognize that we may be obliged to do this earlier, in accordance with ethics committee, clinical, and regulatory guidance, as the planned interim and final analyses of efficacy have been completed with overwhelming success.

In all cases, we intend to follow participants in the ongoing Phase 3 study up to the original planned 24 months post-vaccination, regardless of any participants opting to crossover from placebo to active vaccination. The statistical considerations and details regarding the appropriate protocol language, informed consent, and logistics of this process would need to be carefully developed with regulatory agency input.

If an EUA initially prioritizes vaccination for particularly vulnerable individuals, placebo participants in lower risk categories will continue within the placebo group, allowing some assessment of efficacy for a longer timeframe. Safety follow up of actively vaccinated participants, including monitoring for COVID-19 cases, will provide ongoing information on continuing effectiveness, even in the absence of a placebo group, particularly by reference to local COVID-19 rates. Comparison of safety events with rates in standing cohorts will provide support for continuing vaccine safety evaluation.

Pfizer and BioNTech anticipate collaborating with FDA on scientifically and statistically sound methods to assess long-term effectiveness and safety of BNT162b2 in the Phase 3 study.

5.2.3. Evaluation of Safety, Immunogenicity, and Efficacy in Study C4591001

5.2.3.1. Safety Analyses

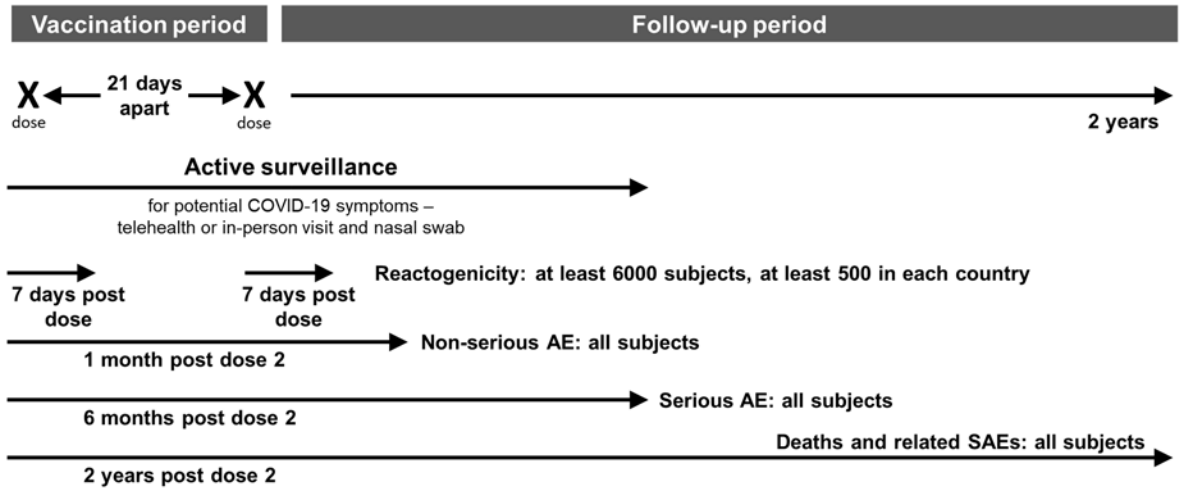
All participants in Phase 1 and a subset of at least 6000 participants in Phase 2/3 were planned to record local reactions, systemic events, and antipyretic/pain medication usage for 7 days, following administration of study intervention using an electronic diary (ediary) from Day 1 through Day 7 after each dose. At the data cutoff date for the EUA, reactogenicity events were not collected from older adolescents 16 to 17 years of age (enrolled prior to the implementation of Protocol Amendment 9, finalized 29 October 2020) using an e-diary but were detected and reported as AEs. For this reason, the available reactogenicity data for the 12 to 15 years of age group are included in support of the intended indication including individuals 16 and 17 years of

age. For any Phase 3 participants who were not in the reactogenicity subset, local reactions and systemic events consistent with reactogenicity were detected and reported as AEs.

AEs were recorded for up to 1 month after Dose 2 and categorized by frequency, severity, seriousness, and relationship to study intervention using System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictional for Regulatory Activities (MedDRA). Serious adverse events (SAEs) will be recorded for up to 6 months after Dose 2. For longer-term follow-up, AEs and SAEs continue to be reported until end of the study.

Safety evaluation periods for follow-up in Study C4591001 are depicted in Figure 1.

Figure 1. Safety Evaluation Follow-Up Periods in Study C4591001



AE data in the EUA application from Study C4591001 were summarized as of the safety data cutoff date of 14 November 2020 for the following participant populations:

- all Phase 1 participants who received BNT162b2 or placebo with up to approximately 4 months of follow-up after Dose 2
- all Phase 2 participants who received BNT162b2 or placebo with at least approximately 2 months of follow-up after Dose 2
- all Phase 2/3 participants (N~38,000) who received BNT162b2 or placebo who had a median follow-up time of 2 months after Dose 2. Safety data will be presented separately for the ~19,000 participants who have 2 months or more of safety follow-up after Dose 2
- all enrolled Phase 2/3 participants (N~44,000) regardless of duration of follow-up, which includes adolescents enrolled later in the study

Note that Phase 2 participants are a subset of the Phase 2/3 portion of the study and are therefore included in Phase 2/3 safety analyses.

While AEs of special interest (AESIs) were not prespecified in the protocol, Pfizer utilizes a safety review as part of the signal detection processes that highlights specified targeted medical

events (TMEs) of clinical interest. TMEs are specific AE terms reviewed on an ongoing basis by routine safety data review procedures throughout the clinical study. Although not pre-specified in the protocol, TMEs are maintained in a separate list as part of the Safety Surveillance Review Plan for the vaccine program. By definition, TMEs are considered to be AESIs specific for a product or program's protocol(s). They 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 is customized for each development program and is dynamic. For this study, the list of TMEs includes events of interest because of their association with COVID-19 and terms of interest for vaccines in general. Terms are chosen from the MedDRA dictionary and may include PTs, high level terms, high level group terms, or standardized MedDRA queries (SMQs; all evaluated as broad and narrow). At the time of this application, the safety review included the terms listed in Appendix 2.

Phase 2/3 AE data were analyzed for the safety population overall and by:

- Evidence of prior SARS-CoV-2 infection at baseline per nucleic acid amplification test (NAAT) or N-binding antibody assay
- Subgroup factors (ie, age, sex, race, ethnicity)

Abnormal hematology and chemistry laboratory values including grading shifts through Day 7 after Dose 2 were reported in Phase 1; abnormal clinical laboratory data were graded as mild, moderate, severe, or potentially life-threatening.

Safety data were analyzed and reported using descriptive summary statistics.

5.2.3.2. Immunogenicity Analyses

Immunogenicity was evaluated in Phase 1 using a SARS-CoV-2 serum neutralization assay to determine titers and a SARS-CoV-2 S1 binding IgG direct Luminex immunoassay to determine antibody binding levels. Fold rises were also assessed. Only qualified assays were used.

To facilitate interpretation of immunogenicity data generated in Study C4591001, a HCS panel was obtained from Sanguine Biosciences (Sherman Oaks, CA), MT Group (Van Nuys, CA), and Pfizer Occupational Health and Wellness (Pearl River, NY).[18,19] The 38 sera in the panel were collected from SARS-CoV-2 infected or COVID-19 diagnosed individuals 18 to 83 years of age ≥14 days after PCR-confirmed diagnosis at a time when they were asymptomatic. The serum donors predominantly had symptomatic infections (35 of 38) including 1 who had been hospitalized.

Immunogenicity data were analyzed and reported using descriptive summary statistics of GMTs/geometric mean concentrations (GMCs) and geometric mean fold-rises (GMFRs) for the evaluable immunogenicity population.

5.2.3.3. Vaccine Efficacy Analyses

Study C4591001 is the pivotal (and only) efficacy study. Efficacy was assessed based on confirmed cases of COVID-19, for which the case onset date was the date that symptoms were first experienced by the participant and the cases met evaluable criteria. For participants with multiple confirmed cases, only the first case contributed to the VE calculations. Evaluable cases consisted of a positive virological test plus at least one COVID-19 symptom as defined in Appendix 1.

Only the first primary endpoint was analyzed in the planned interim analysis. All primary and secondary efficacy endpoints were planned to be analyzed in the final analysis of at least 164 cases.

Primary Efficacy Endpoints

Study C4591001 has two primary endpoints:

- **First primary endpoint**: COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2
- **Second primary endpoint**: COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2.

Secondary Efficacy Endpoints

Study C4591001 has secondary endpoints based on different approaches to COVID-19 case evaluation criteria as follows:

- **COVID-19 confirmed at least 14 days after Dose 2**: COVID-19 incidence per 1000 person-years of follow up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2
- **Severe COVID-19**: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2
- **CDC-defined COVID-19**: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2.

VE is defined as 100% × (1 – IRR), where illness rate ratio (IRR) is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. VE is demonstrated if there is convincing evidence (ie, posterior probability greater than 99.5% at an interim analysis or greater than 98.6% at the final analysis) that the true

VE of BNT162b2 is >30% using a beta-binomial model, where VE represents efficacy for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of prior SARS-CoV-2 infection before and during the vaccination regimen. Participants with positive or unknown NAAT results at any illness visit prior to 7 days (or 14 days for some secondary efficacy endpoints) after Dose 2 were not included in the evaluation for VE. Cases were counted from 7 days after Dose 2 (or 14 days after Dose 2 for some secondary efficacy endpoints).

5.2.3.3.1. Interim and Final Analyses of Efficacy

During Phase 2/3, interim analyses were pre-specified in the protocol to be conducted after accrual of at least 62, 92, and 120 evaluable COVID-19 cases, where overwhelming efficacy could be declared if the primary endpoint was met with a posterior probability that the true VE is >30% (ie, Pr[VE >30%|data] >99.5% at an interim analysis or >98.6% at the final analysis). The success threshold for each interim analysis was calibrated to protect overall type I error at 2.5%. Futility was also assessed, and the study could be stopped for lack of benefit if the predicted probability of demonstrating VE at the final analysis was <5% at any of the first 2 planned interim analyses. Efficacy and futility boundaries were applied in a nonbinding way. The calculation of posterior probability and the credible interval were adjusted for surveillance time. For subgroup analyses of the primary efficacy endpoint, a 2-sided 95% confidence interval (CI) was calculated.

The interim analysis was performed for the first primary efficacy endpoint only. After the successful interim analysis, subsequent formal interim analyses were not conducted.

The final analysis of all protocol specified primary and secondary efficacy endpoints was prespecified in the protocol to be conducted after accrual of at least 164 cases.

6. SUMMARY OF CLINICAL DATA

6.1. Study BNT162-01 Phase 1

Study BNT162-01 is the ongoing, FIH, Phase 1 dose level-finding study, in which healthy adults 18 to 55 years of age all receive active vaccine. This study is evaluating the safety and immunogenicity of several different candidate vaccines at various dose levels. Only the data for BNT162b2 30 µg are presented herein.

6.1.1. Demographics and Disposition in Study BNT162-01 Phase 1

In the Phase 1 part of Study BNT162-01, BNT162b2 was administered to 60 participants among whom 43% were male and 57% were female, 100% were White, none were Hispanic/Latino, with a median 42 years of age.

All participants in the 20 µg and 30 µg dose groups received both doses, 11/12 participants received both doses of 10 µg, and 8/12 participants received both doses of 1 µg. As of the CSR data cutoff date (24 August 2020), no participants in the 3 µg received the second dose. Safety follow-up for the 10 µg and 30 µg dose levels were available to up to 7 days after Dose 2.

A total of 58 participants completed BNT162b2 dosing in the Phase 1 part of the study. The reasons for study discontinuation by each of 2 participants were AE (10 µg group) and participant withdrawal (1 µg group).

6.1.2. Immunogenicity in Study BNT162-01 Phase 1

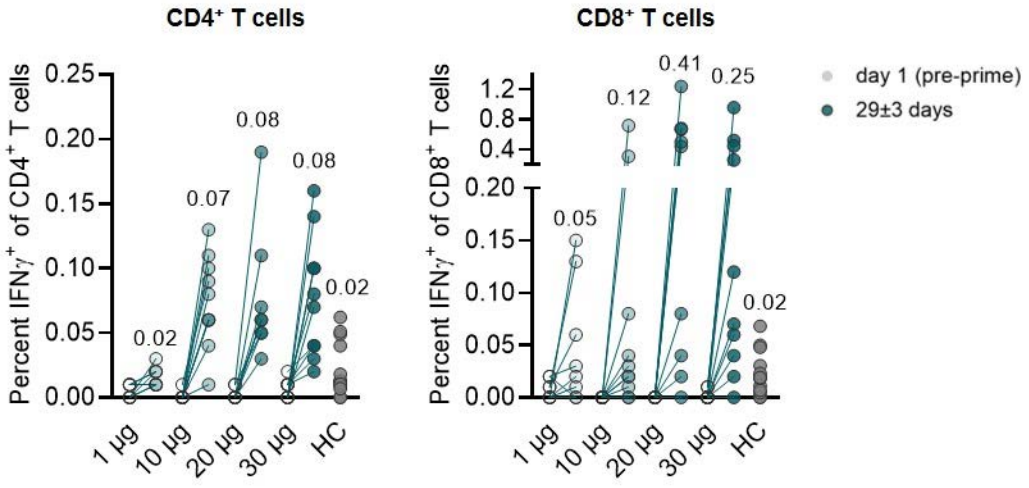
In Study BNT162-01, evaluable enzyme-linked immunospot (ELISpot) data were available from 39 participants across dose levels of BNT162b2. The data cutoff date for ELISpot data was 17 September 2020. Evaluable intracellular cytokine staining data were available 36 participants across dose levels of BNT162b2. The data cutoff dates for intracellular cytokine staining data was 04 September 2020. Data for serology results for serum neutralizing titers were available for 45 participants across dose levels of BNT162b2 with a data cutoff date of 18 September 2020.

6.1.2.1. T Cell Responses

Most participants who received both doses of BNT162b2 had strong SARS-CoV-2 S protein-specific $CD4^+$ (39/39, 100%) and $CD8^+$ (35/39, 89.7%) T cell responses. These T cell responses were directed against different parts of the antigen including epitopes in the receptor binding domain (RBD), indicating the induction of multi-epitope responses by BNT162b2.

Dosing twice with BNT162b2 led to a substantial increase in the incidence and magnitude of T cell responses (Figure 2). Overall, the mean fraction of S-specific CD4+ and CD8+ T cells was substantially higher (eg, S protein sub-pool 1 IFNγ CD8+ response of 30 µg dosed participants was 12.5-fold above) than that observed in 18 individuals who recovered from COVID-19.

Figure 2. Frequency and Magnitude of BNT162b2-induced $CD4^+$ and $CD8^+$ T Cell Responses



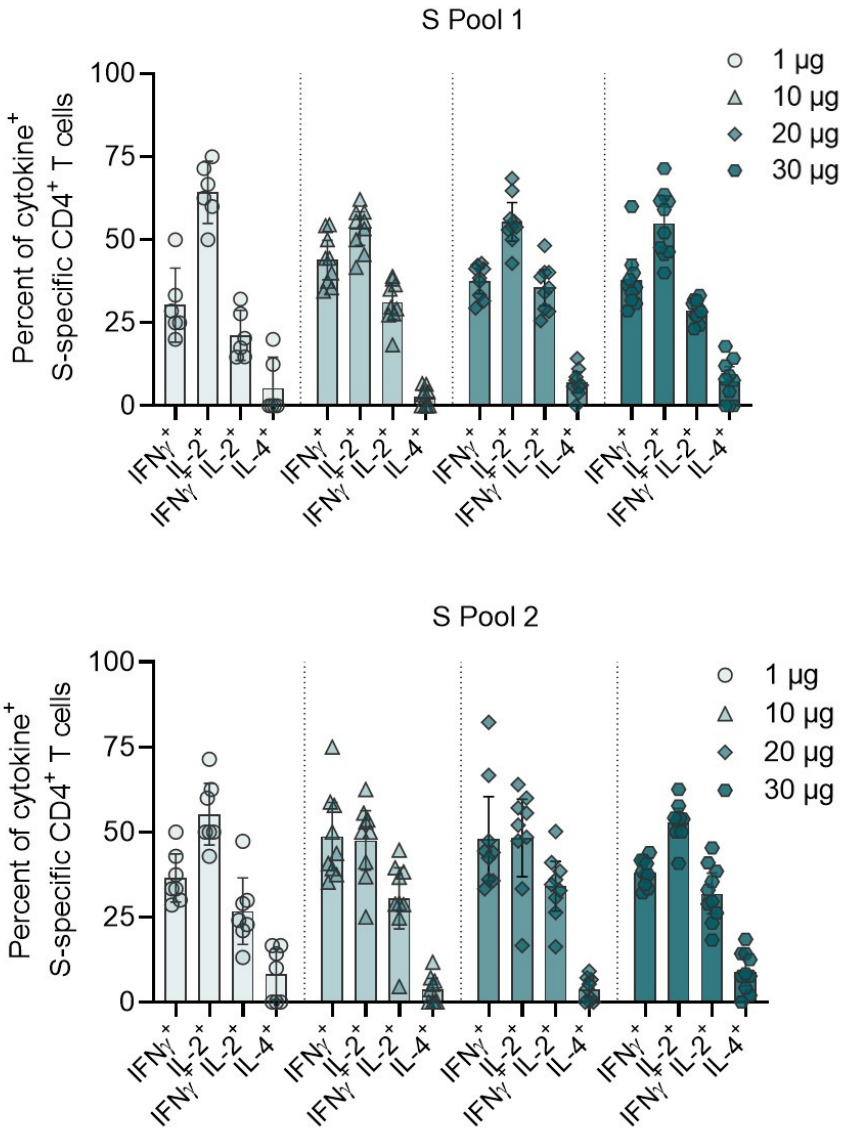
PBMCs of BNT162b2-immunized participants were obtained on Day 1 (pre-prime) and on Day 29 (7 days post dose 2) (cohorts 1 µg, n=8; 10 and 30 µg, n=10; 20 µg, n=9) and COVID-19-recovered human convalescent donors (HC, n=18) were stimulated overnight with an overlapping peptide pool representing the N-terminal portion of the wild-type sequence of SARS-CoV-2 S protein (S pool 1 [aa 1-643]) and were analyzed by intracellular cytokine staining flow cytometry analysis. Frequency of S-specific CD4+ and CD8+ T cells producing IFNγ in response to S pool 1 as a fraction of total circulating CD4 and CD8 T cells are shown. Numbers indicated in the graphs are the arithmetic mean fractions.

Functionality and polarization of S-specific BNT162b2-induced SARS-CoV-2 T cells were assessed by intracellular accumulation of cytokines IFNγ, IL-2, and IL-4 measured after stimulation with overlapping peptide pools representing the full-length sequence of the whole SARS-CoV-2 S protein: sub-pool 1 comprising overlapping peptides from the N-terminal region

(which is not equivalent to structural domains) and sub-pool 2 comprising C-terminal regions of the S protein. .

BNT162b2-induced T-cell responses, especially for CD8+ T cells, were not limited to the RBD, as pronounced and strong T cell recognition of non-RBD regions of the S protein were observed. BNT162b2 induced polyfunctional CD4+ and CD8+ T cell responses in most participants. The Th1 polarization of the T helper response was characterized by robust IFNγ and IL-2, and only minor IL-4, production upon antigen-specific (SARS-CoV-2 S protein peptide pools) re-stimulation (Figure 3).

Figure 3. S-Specific CD4+ T Cells Producing Each Cytokine as a Fraction of Total Cytokine-Producing S-specific CD4+ T Cells



PBMCs of vaccinated participants on day 29 (7 days post-boost) (cohorts 1 µg, n=8; 10 and 30 µg, n=10; 20 µg, n=9) and COVID-19 recovered donors (HCS, n=18) were evaluated for S-specific CD4+ T cells producing the indicated cytokine as a fraction of total cytokine-producing S-specific CD4+ T cells in response to S pool 1 and S

pool 2. CD4 non-responders (<0.03% total cytokine producing T cells: 1 µg, n=2 [S pool 1] and n=1 [S pool 2]; 10 µg, n=1) were excluded. Bars represent arithmetic mean with 95% CI. c, S-specific CD4+ (S pool 1, S pool 2 and RBD). Values above data points indicate mean fractions per dose cohort. Data for the 3 µg dose group were not available at the cutoff date.

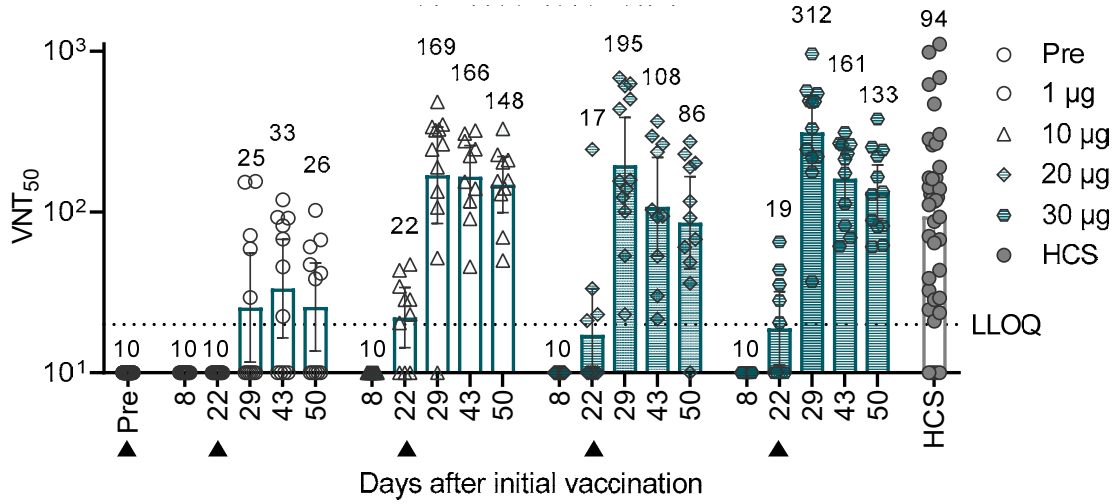
S-specific CD8+ T cells secreted IFNγ in 32/36 participants, with IL-2 secreting CD8+ T-cells also detectable. Strong pre-existing CD8+ T cell responses against the C-terminal region of the S protein were detected in 6/36 participants and were not further amplified upon dosing with BNT162b2.

6.1.2.2. SARS-CoV-2 Neutralizing Titers

In Study BNT162-01, after administration of Dose 1 and prior to administration of Dose 2, BNT162b2 showed modest increases in SARS-CoV-2 neutralizing geometric mean titers (GMTs) over baseline, followed by a boost effect after Dose 2 that was most pronounced at the 30 µg dose level.

At Day 50 post first vaccination, the neutralizing GMT in the 10 µg and 30 µg BNT162b2 participants remained above the GMT in the HCS (Figure 4). Further evaluation of antibody persistence is ongoing.

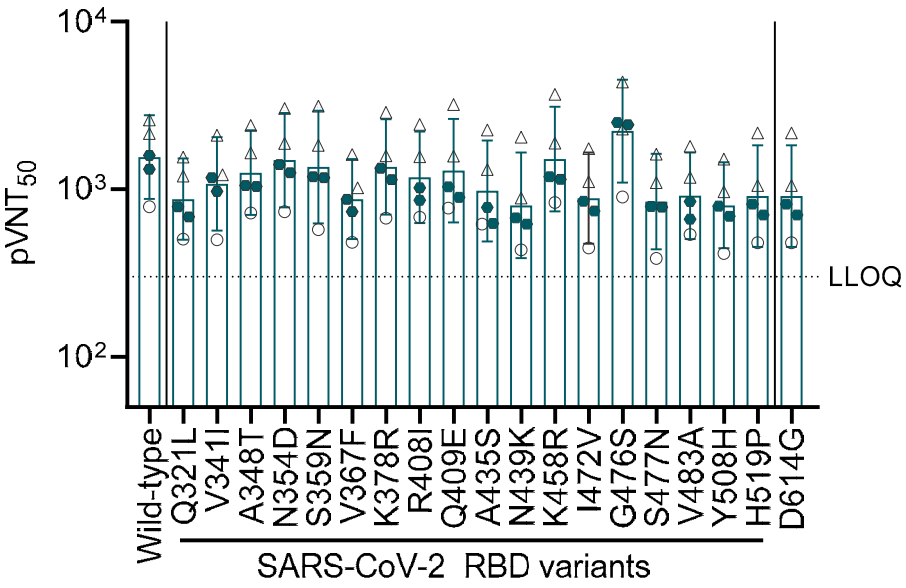
Figure 4. BNT162b2-Induced Virus Neutralization Titers



Arrowheads indicate days of vaccination. a, SARS-CoV-2 50% neutralization titers (VNT50) in immunized participants and HCS. Each serum was tested in duplicate and geometric mean titer plotted. For values below the lower limit of quantification (LLOQ) = 20, LLOQ/2 values were plotted. Group geometric mean titers (values above bars) with 95% confidence interval.

A panel of 18 SARS-CoV-2 RBD variants identified through publicly available information[20] and the dominant non-RBD spike variant D614G[21] were evaluated in pseudovirion neutralization assays. Sera collected 7 days after the second dose of BNT162b2 showed high neutralizing titers to each of the SARS-CoV-2 spike variants (Figure 5), demonstrating the breadth of the neutralizing response.

Figure 5. Breadth of BNT162b2-Induced Neutralization Against a Panel of Pseudovirus Spike Sequence Variants



Pseudovirus 50% neutralization titers (pVNT50) across a pseudovirus panel displaying 19 SARS-CoV-2 spike protein variants including 18 RBD mutants and the dominant spike protein variant D614G (dose levels 10, 30 and 50 µg, n=1-2 representative sera each; day 29). Each serum was tested in duplicate and geometric mean titer plotted. Lower limit of quantification (LLOQ) = 300. Group geometric mean titers with 95% confidence interval.

6.1.2.3. Immunogenicity Conclusions in BNT162-01 Phase 1

Based on immunogenicity results from Phase 1 participants in FIH Study BNT162-01, BNT162b2 elicited robust antibody-mediated SARS-CoV-2 neutralization and T cell-mediated cellular immune responses in healthy adults 18 to 55 years of age.

6.2. Study C4591001 Phase 1

Immunogenicity and safety data from the Phase 1 portion of Study C4591001 (based on an earlier data safety cutoff date than the EUA application) were published in October 2020.[18]

6.2.1. Demographics and Disposition in Study C4591001 Phase 1

BNT162b2 was administered to 45 younger participants among whom 42% were male and 58% were female, 87% were White, 4% were Hispanic/Latino, with a median 37 years of age.

BNT162b2 was administered to 45 older participants among whom 38% were male and 62% were female, 100% were White, none were Hispanic/Latino, with a median 68 years of age.

All participants received both vaccine doses and none discontinued the study as of the data cutoff date of 14 November 2020, after approximately 4 months of follow-up.

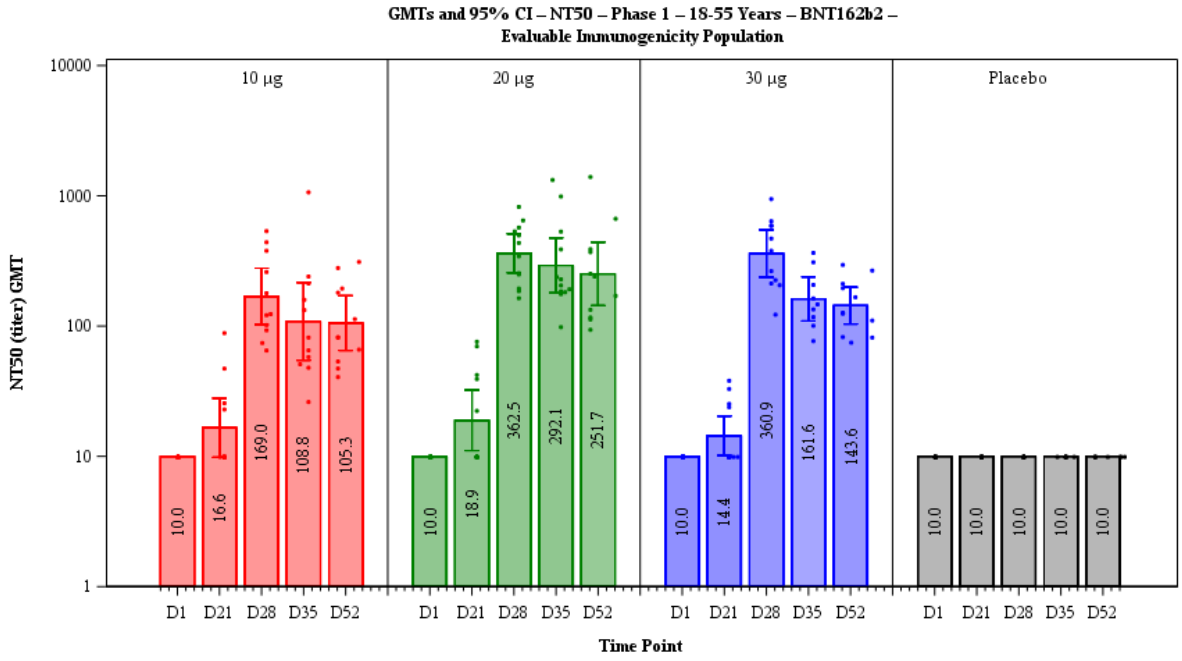
6.2.2. Immunogenicity in Study C4591001 Phase 1

6.2.2.1. SARS-CoV-2 50% Neutralizing Titers

In the Phase 1 portion of Study C4591001, after administration of Dose 1 and prior to administration of Dose 2, BNT162b2 showed modest increases in SARS-CoV-2 neutralizing GMTs over baseline across dose levels and younger and older groups.[18] Overall, BNT162b2 elicited higher antigen-binding and neutralizing responses in younger participants (Figure 6) than in older participants (Figure 7). The boost effect after receiving Dose 2 was most pronounced at the 30 µg dose level for older participants.

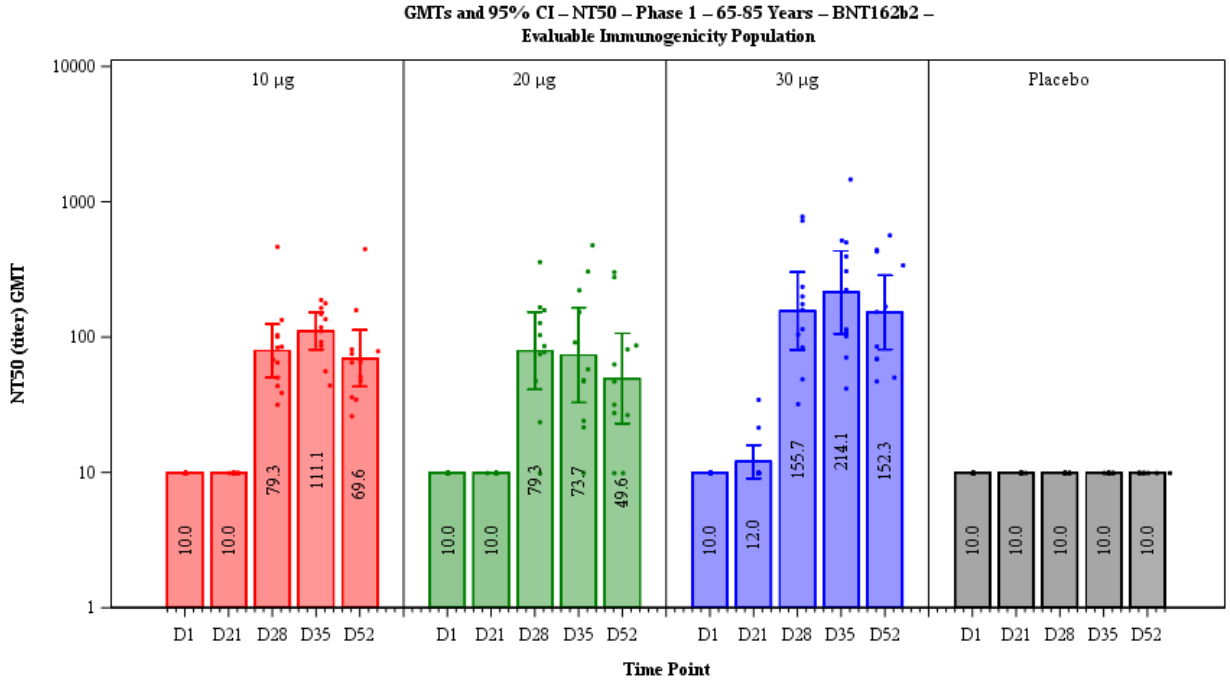
GMTs measured at 7 days after Dose 2 for BNT162b2 at the 30 µg dose were 360.9 in the younger group and 155.7 in the older group. When compared to an HCS panel GMT of 94, the GMT for the younger group was approximately 3.8-times that of HCS and for the older group was approximately 1.7-times that of HCS.[18] By 1 month after Dose 2, GMTs were generally stable and remained approximately 1.6- to 1.9-times that of HCS.

Figure 6. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b2 – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: /nda3/C4591001_IA_P1_Serology/adva_f002_sars_50_18_b2_p1

Figure 7. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 65-85 Years of Age – BNT162b2 – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: /nda3/C4591001_IA_P1_Serology/adva_f002_sars_50_65_b2_p1

6.2.2.2. S1-Binding IgG Levels

In the Phase 1 portion of Study C4591001, there was generally a dose-level response between 10 µg and 20 µg of BNT162b2, but a dose-level response between 20 µg and 30 µg was not consistent across age groups (Appendix 3).

6.2.2.3. Immunogenicity Conclusions in Study C4591001 Phase 1

Based on immunogenicity results from Phase 1 participants in Study C4591001, BNT162b2 elicited robust SARS-CoV-2 neutralization and S1-binding IgG antibody levels in younger healthy adults 18 to 55 years of age, and in older healthy adults 65 to 85 years of age. Immune responses were generally stronger in the younger group than in the older group. SARS-CoV-2 neutralizing titer GMTs were higher than those observed in an HCS[18] panel from people recovered from COVID-19. Responses were evident after the first dose and substantially boosted after the second dose, supporting the need for a 2-dose vaccination series.

6.2.3. Safety in Study C4591001 Phase 1

6.2.3.1. Reactogenicity in Study Reactogenicity in Study C4591001 Phase 1

For BNT162b2 recipients, the frequency of local reactions was lower for the older group compared to the younger group (Appendix 3). Local reactions were generally infrequent in placebo recipients. The majority of local reactions in the BNT162b2 groups were mild or

moderate in severity and resolved within several days of onset. No grade 4 (potentially life-threatening) reactions were reported. Pain at the injection site was the most frequent prompted local reaction across number of doses and dose levels in both age groups (33% to 92%), and redness (0% to 8%) and swelling (0% to 17%) were infrequent.

The frequency of systemic events was lower for the older group compared to the younger group (Appendix 3). Notably, in the older group, frequencies of systemic events after the first dose were similar between BNT162b2 and placebo recipients. Systemic events were generally infrequent in placebo recipients. Prompted systemic events generally increased in frequency and/or severity with increasing dose level and number of doses of BNT162b2. Use of antipyretic/pain medication also increased in frequency with increasing dose level and number of doses. Most systemic events were mild or moderate, arose within the first 1-4 days after dosing, and resolved within 1-3 days of onset. No grade 4 (potentially life-threatening) events were reported. The most frequent prompted systemic events across number of doses and dose levels in both age groups were fatigue (8% to 75%), headache (0% to 67%), chills (0% to 58%), and muscle pain (0% to 58%). Fever was infrequent (0% to 17%).

6.2.3.2. Overview of AEs in Study C4591001 Phase 1

In Study C4591001, AE reporting for Phase 1 participants was conducted for up to 1 month after Dose 2 for all BNT162b2 dose level groups, with additional available follow-up for participants who received 30 µg BNT162b2 up to the data cutoff date of 14 November 2020; this included up to approximately 4 months of follow-up for this group.

Fewer than half of participants in Phase 1 who received BNT162b2 across age groups and dose levels reported one or more AEs after vaccine dosing (from Dose 1 onwards). Overall, the majority of AEs reported for BNT162b2 recipients were considered by the investigator as not related to study intervention. Most AEs were mild to moderate in severity. Up to 1 month after Dose 2, incidences of AEs were higher across dose levels of BNT162b2 for younger participants (33.3% to 41.7%) compared to placebo (22.2%), whereas incidences across dose levels in the older BNT162b2 group (8.3% to 25.0%) were similar to or less than placebo (22.2%). Additional follow-up for the 30 µg dose level up to 4 months after Dose 2 showed a generally unchanged AE profile for both age groups.

No discontinuations due to AEs were reported in the Phase 1 part of the study. No deaths have been reported. During the entirety of Phase 1, for all BNT162b2 dose level groups and including the additional follow-up for those receiving 30 µg (to 4 months after Dose 2 to the data cutoff date of 14 November 2020), only 1 SAE (neuritis; considered by the investigator as not related to vaccination) has been reported, in the younger age group.

6.2.3.3. Analysis of Adverse Events in Study C4591001 Phase 1

In the Phase 1 portion of Study C4591001, for BNT162b2 recipients, the most common AEs overall by SOC and PT across dose levels in the younger group were general disorders and administration site conditions, which included injection site pain and injection site erythema. The most common AEs overall by SOC and PT across dose levels in the older group were nervous system disorders, which included sciatica and radiculopathy. No AEs were reported for >1 participant in either age group for BNT162b2 or placebo recipients.

In the younger group, 1 severe AE was reported: 1 participant in the 30 µg dose group reported severe migraine headache considered by the investigator as not related to study intervention (note: this participant had a history of migraine headache). In the older group, 2 severe AEs were reported: 1 participant in the 30 µg dose group reported severe muscle spasms, and 1 participant in the placebo group reported severe radiculopathy; both of these AEs were considered as not related to study intervention.

In the Phase 1 portion of Study C4591001, for BNT162b2 recipients in the younger group, general disorders and administration site conditions was the most commonly reported SOC for related AEs, which included injection site pain and injection site erythema. In the older group, only 1 participant in the 20 µg dose group reported a related AE of nausea.

Additional follow-up from 1 months to 4 months after Dose 2 to the data cutoff date (14 November 2020) included 1 severe SAE (neuritis) reported by 1 participant in the younger BNT162b2 30 µg group; per the participant's medical examination and history, this event was linked to a blood draw, and the investigator considered there was a reasonable possibility that the event neuritis was related to clinical trial procedure (blood draw) but unrelated to vaccination. The AE profile for remaining non-serious events was unchanged. No additional participants had related AEs.

6.2.3.4. Clinical Laboratory Assessments in Study C4591001 Phase 1

Clinical laboratory tests were routinely done only in the Phase 1 portion of Study C4591001.

Clinical chemistry abnormalities were observed infrequently. Only one abnormality was observed for a BNT162b2 recipient: one younger participant in the 10 µg group had a grade 2 bilirubin abnormality at screening that was noted as grade 3 at 1-3 days after Dose 1 and then recovered to grade 1 by 6-8 days.

The most commonly observed hematology laboratory changes were transient decreases in lymphocytes (<0.8 × lower limit of normal [LLN]) noted 1-3 days after Dose 1. These decreases returned to normal by the next measurement, within 6-8 days of the first dose. Most decreases in lymphocyte counts were grade 1 or 2. RNA vaccines are known to induce type I interferon,[22] and type I interferons regulate lymphocyte recirculation and are associated with transient migration and/or redistribution of lymphocytes.[23] This rapid rebound of lymphocytes supports that the lymphocytes were not depleted, but temporarily migrated out of the peripheral blood, and subsequently re-entered the bloodstream by the time of the next assessment.

6.2.3.5. Safety Conclusions in Study C4591001 Phase 1

Based on Phase 1 data from Study C4591001, BNT162b2 was safe and well-tolerated in younger healthy adults 18 to 55 years of age, and in older healthy adults 65 to 85 years of age, with no unanticipated safety findings. Reactogenicity and AEs were generally milder and less frequent in participants in the older group compared with the younger group and overall tended to increase with increasing BNT162b2 dose. Reactogenicity was mostly mild to moderate and short-lived after dosing, and the AE profile did not suggest any safety concerns. Clinical laboratory evaluations showed a transient decrease in lymphocytes that was observed in all age and dose groups after Dose 1, which resolved within approximately 1 week, was not associated with any

other clinical sequelae, and was not considered clinically relevant. No new safety signals were observed with additional safety follow-up data (up to 4 months after Dose 2).

6.3. Study C4591001 Phase 2/3

Safety (Section 6.3.3) and efficacy (Section 6.3.4) data from the combined Phase 2/3 portion of the study, and immunogenicity from the Phase 2 portion of the study (Section 6.3.2), are presented below.

6.3.1. Study Population in Study C4591001 Phase 2/3

6.3.1.1. Duration of Follow-Up in Study C4591001 Phase 2/3

In N=37,706 participants, the duration of follow-up was ≥2 months post Dose 2 for 50.6% of participants. Duration of follow up was ≥1 month post Dose 2 for 91.6% of participants (Table 3).

Table 3. Follow-Up Time After Dose 2 – ~38000 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=18860) n[b] (%)	Placebo (N[a]=18846) n[b] (%)	Total (N[a]=37706) n[b] (%)
Subjects (%) with length of follow-up of:			
<2 Months	9329 (49.5)	9310 (49.4)	18639 (49.4)
<2 Weeks	363 (1.9)	388 (2.1)	751 (2.0)
≥2 to <4 Weeks	1223 (6.5)	1200 (6.4)	2423 (6.4)
≥4 to <6 Weeks	3239 (17.2)	3235 (17.2)	6474 (17.2)
≥6 to <8 Weeks	4504 (23.9)	4487 (23.8)	8991 (23.8)
≥2 Months	9531 (50.5)	9536 (50.6)	19067 (50.6)
≥8 to <10 Weeks	6296 (33.4)	6329 (33.6)	12625 (33.5)
≥10 to <12 Weeks	2853 (15.1)	2809 (14.9)	5662 (15.0)
≥12 to <14 Weeks	382 (2.0)	398 (2.1)	780 (2.1)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 18NOV2020 (05:34) (Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adsl_s005_fup_time_d2_saf

6.3.1.2. Demographics and Disposition in Study C4591001 Phase 2/3

Demographics of participants with a median of 2 months of follow-up after Dose 2 were similar between BNT162b2 and placebo groups (Table 4). Overall, most participants were White

(82.9%), with 9.3% Black participants and 4.3% Asian participants, and other racial groups were <3%. There were 28% Hispanic/Latino participants. Median age was 52 years and 50.6% of participants were male. The younger and older age groups were 57.8% and 42.2% of participants, respectively. Obese participants made up 35.1% of this safety population.

Within each age group, most demographic characteristics were similar in the BNT162b2 and placebo groups. The safety population included 283 participants who were 16 or 17 years of age. Demographics for this age group were similar for the BNT162b2 and placebo groups and to the safety population in general.

There were no clinically meaningful differences in demographic characteristics by subgroups (age, sex, race/ethnicity, and baseline SARS-CoV-2 status).

Table 4. Demographic Characteristics – ~38000 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=18860) n[b] (%)	Placebo (N[a]=18846) n[b] (%)	Total (N[a]=37706) n[b] (%)
Sex			
Male	9639 (51.1)	9436 (50.1)	19075 (50.6)
Female	9221 (48.9)	9410 (49.9)	18631 (49.4)
Race			
White	15636 (82.9)	15630 (82.9)	31266 (82.9)
Black or African American	1729 (9.2)	1763 (9.4)	3492 (9.3)
American Indian or Alaska native	102 (0.5)	99 (0.5)	201 (0.5)
Asian	801 (4.2)	807 (4.3)	1608 (4.3)
Native Hawaiian or other Pacific Islander	50 (0.3)	26 (0.1)	76 (0.2)
Multiracial	449 (2.4)	406 (2.2)	855 (2.3)
Not reported	93 (0.5)	115 (0.6)	208 (0.6)
Ethnicity			
Hispanic/Latino	5266 (27.9)	5277 (28.0)	10543 (28.0)
Non-Hispanic/non-Latino	13482 (71.5)	13459 (71.4)	26941 (71.5)
Not reported	112 (0.6)	110 (0.6)	222 (0.6)
Country			
Argentina	2883 (15.3)	2881 (15.3)	5764 (15.3)
Brazil	1145 (6.1)	1139 (6.0)	2284 (6.1)
South Africa	372 (2.0)	372 (2.0)	744 (2.0)
USA	14460 (76.7)	14454 (76.7)	28914 (76.7)
Age group			
16-55 Years	10889 (57.7)	10896 (57.8)	21785 (57.8)
>55 Years	7971 (42.3)	7950 (42.2)	15921 (42.2)
Age at vaccination (years)			

Table 4. Demographic Characteristics – ~38000 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=18860) n[b] (%)	Placebo (N[a]=18846) n[b] (%)	Total (N[a]=37706) n[b] (%)
Mean (SD)	50.5 (15.65)	50.3 (15.72)	50.4 (15.68)
Median	52.0	52.0	52.0
Min, max	(16, 89)	(16, 91)	(16, 91)
Body mass index (BMI)			
Underweight (<18.5 kg/m^2)	201 (1.1)	235 (1.2)	436 (1.2)
Normal weight (≥18.5 kg/m^2 - 24.9 kg/m^2)	5517 (29.3)	5460 (29.0)	10977 (29.1)
Overweight (≥25.0 kg/m^2 - 29.9 kg/m^2)	6578 (34.9)	6481 (34.4)	13059 (34.6)
Obese (≥30.0 kg/m^2)	6556 (34.8)	6662 (35.3)	13218 (35.1)
Missing	8 (0.0)	8 (0.0)	16 (0.0)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 17NOV2020 (16:20) (Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adsl_s005_demo_p3_saf

Across both treatment groups, 20.5% had any comorbidity (per the Charlson Comorbidity Index). The most frequently reported comorbidities were diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%) and were reported at similar frequencies in each group. More participants had comorbidities in the older population (31.1%) than the younger population (12.8%), including diabetes (14.6% and 3.8%), malignancy (7.4% and 1.0%), and pulmonary disease (8.8% and 7%).

Overall, 0.3% of participants were HIV-positive and were evenly distributed between treatment groups. Note that HIV-positive participants were included in the safety population and are shown as part of the study demographics and disposition but did not have safety data available to contribute to the safety analyses at the time of the data cutoff.

Dispositions of 37,796 randomized participants were similar in the BNT162b2 and placebo groups (Table 5). Overall, 0.2% of randomized participants did not receive study vaccine. A small percentage of participants discontinued study vaccine after Dose 1 and before Dose 2 (0.6%) overall. The most frequently reported reasons for discontinuation included: no longer meets eligibility criteria (0.3% BNT162b2; 0.4% placebo; the most common reasons were previous clinical or microbiological diagnosis of COVID-19), withdrawal by participant, and AE. Withdrawals due to AE were reported for 0.1% of participants in both treatment groups.

Table 5. Disposition of All Randomized Subjects – ~38000 Subjects for Phase 2/3 Analysis

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=18904) n[b] (%)	**Placebo (N[a]=18892) n[b] (%)**	**Total (N[a]=37796) n[b] (%)**
Randomized	18904 (100.0)	18892 (100.0)	37796 (100.0)
Not vaccinated	46 (0.2)	43 (0.2)	89 (0.2)
Vaccinated			
Dose 1	18858 (99.8)	18849 (99.8)	37707 (99.8)
Dose 2	18555 (98.2)	18533 (98.1)	37088 (98.1)
Completed 1-month post–Dose 2 visit (vaccination period)	16902 (89.4)	16804 (88.9)	33706 (89.2)
Discontinued from vaccination period but continue in the study	121 (0.6)	111 (0.6)	232 (0.6)
Discontinued after Dose 1 and before Dose 2	121 (0.6)	107 (0.6)	228 (0.6)
Discontinued after Dose 2 and before 1-month post–Dose 2 visit	0	4 (0.0)	4 (0.0)
Reason for discontinuation from vaccination period			
No longer meets eligibility criteria	48 (0.3)	81 (0.4)	129 (0.3)
Withdrawal by subject	45 (0.2)	9 (0.0)	54 (0.1)
Adverse event	20 (0.1)	12 (0.1)	32 (0.1)
Pregnancy	4 (0.0)	4 (0.0)	8 (0.0)
Physician decision	2 (0.0)	1 (0.0)	3 (0.0)
Lost to follow-up	0	2 (0.0)	2 (0.0)
Medication error without associated adverse event	0	1 (0.0)	1 (0.0)
Other	2 (0.0)	1 (0.0)	3 (0.0)
Withdrawn from the study	180 (1.0)	259 (1.4)	439 (1.2)
Withdrawn after Dose 1 and before Dose 2	132 (0.7)	164 (0.9)	296 (0.8)
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	44 (0.2)	84 (0.4)	128 (0.3)
Withdrawn after 1-month post–Dose 2 visit	4 (0.0)	11 (0.1)	15 (0.0)
Reason for withdrawal from the study			
Withdrawal by subject	84 (0.4)	157 (0.8)	241 (0.6)
Lost to follow-up	80 (0.4)	86 (0.5)	166 (0.4)
Adverse event	8 (0.0)	5 (0.0)	13 (0.0)
Death	2 (0.0)	3 (0.0)	5 (0.0)
Physician decision	1 (0.0)	2 (0.0)	3 (0.0)
No longer meets eligibility criteria	1 (0.0)	2 (0.0)	3 (0.0)
Medication error without associated adverse event	1 (0.0)	0	1 (0.0)
Refused further study procedures	0	1 (0.0)	1 (0.0)
Other	3 (0.0)	3 (0.0)	6 (0.0)

Table 5. Disposition of All Randomized Subjects – ~38000 Subjects for Phase 2/3 Analysis

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=18904) n[b] (%)	Placebo (N[a]=18892) n[b] (%)	Total (N[a]=37796) n[b] (%)

Note: 1 subject was randomized but did not sign informed consent and is not included in any analysis population.
Note: Because of a dosing error, 2 subjects received an additional dose of BNT162b2 (30 µg) at an unscheduled visit after receiving one dose of BNT162b2 (30 µg) and one dose of placebo.
Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of randomized subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
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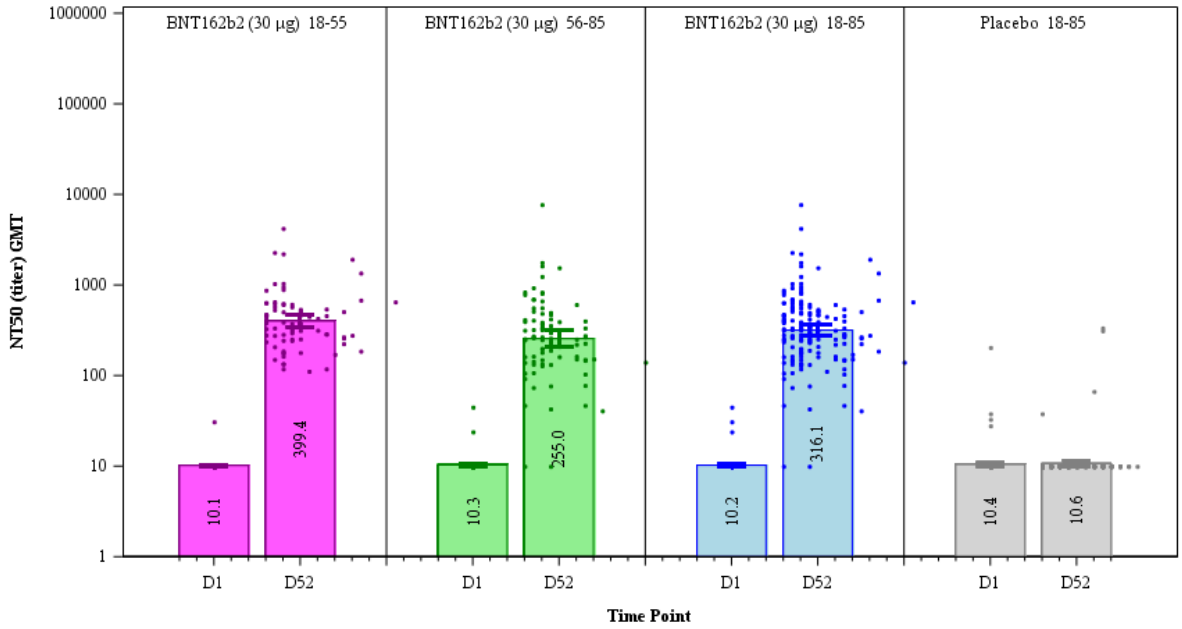
6.3.2. Immunogenicity in Study C4591001 Phase 2

In the Phase 2 portion of the study, 360 participants were enrolled and randomized 1:1 to BNTb16b2 and placebo. Immunogenicity results are currently available for the pre-vaccination and 1-month post Dose 2 time point for the immunogenicity-evaluable population.

BNT162b2 elicited robust SARS-CoV-2 immune responses at 1 month after Dose 2 defined by both SARS-CoV-2 50% neutralizing titers (GMTs) (Figure 8). GMTs were higher in younger participants (18 to 55 years of age) than in older participants (56 to 85 years of age). Of note, 50% neutralizing GMTs at 1-month post Dose 2 for both younger (GMT = 399.4) and older participants (GMT = 255.0) in the evaluable immunogenicity population were similar to the GMTs of a comparative panel of HCS (GMT = 319).[18,24] The HCS is the same panel described in Section 5.2.3.2 except that 5 sera from the N=38 serum panel had been depleted.

Figure 8. Geometric Mean Titers: SARS-CoV-2 Neutralization Assay – NT50 – Evaluable Immunogenicity Population – Phase 2



Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 02NOV2020 (19:23) Source Data: adva Table Generation: 12NOV2020 (00:12)
(Cutoff Date: 12OCT2020, Snapshot Date: 02NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P2_Serology/adva_f002_sars_50_p2

6.3.3. Safety in Study C4591001 Phase 2/3

6.3.3.1. Reactogenicity in Study C4591001 Phase 2/3

In this application, as of the time of the safety cutoff date (14 November 2020), the Phase 2/3 reactogenicity subset was comprised of 8183 participants (≥12 years of age), which included the 360 participants in Phase 2. The reactogenicity data were collected by participants' e-diary for reporting prompted local reactions and systemic events for 7 days after each dose. Reactogenicity events were not collected for adolescents 16 to 17 years of age as described in Section 5.2.3.1. Adolescents 12 to 15 years of age were analyzed in a separate group; these are preliminary data provided in support of the EUA indication which includes participants 16 and 17 years of age.

Local Reactions

In the BNT162b2 group, pain at the injection site was reported more frequently in the younger group (includes participants 16-55 years of age; Figure 9) than in the older group (>55 years of age; Figure 10), and frequency was similar after Dose 1 compared with Dose 2 of BNT162b2 in the younger group (83.1% vs 77.8%) and in the older group (71.1% vs 66.1%).

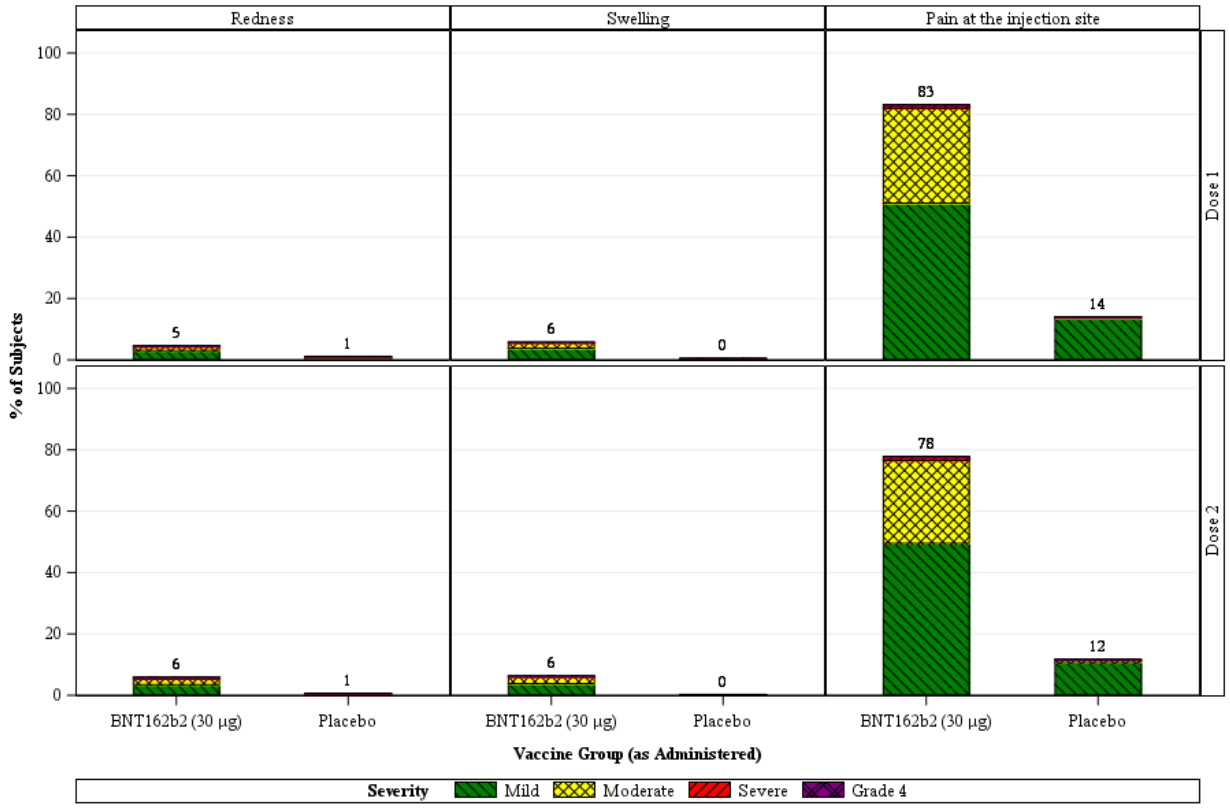
In the BNT162b2 group, frequencies of redness and swelling were similar in the younger and older age group after Doses 1 and 2. Frequencies of redness were similar after Dose 1 compared with Dose 2 of BNT162b2 in the younger age group (4.5% vs 5.9%) and in the older age group (4.7% vs 7.2%). Frequencies of swelling were similar after Dose 1 compared with Dose 2 of

BNT162b2 in the younger age group (5.8% vs 6.3%, respectively) and in the older age group (6.5% vs 7.5%). In the placebo group, redness and swelling were reported infrequently in the younger (≤1.1%) and older (≤1.1%) groups after Doses 1 and 2.

Overall, across age groups, pain at the injection site did not increase after Dose 2, and redness and swelling were generally similar in frequency after Dose 1 and Dose 2. Most local reactions were mild or moderate in severity. Few severe local reactions were reported after either dose. The frequency of any severe local reactions after Dose 1 and after Dose 2 was ≤0.6%. No grade 4 (potentially life threatening) reactions were reported.

Across age groups, local reactions for the BNT162b2 group after either dose had a median onset day between Day 1 and Day 3 (Day 1 was the day of vaccination) and ranges were similar in the younger and older age groups. Across age groups, local reactions for this group after either dose resolved with median durations between 1 to 2 days, which were similar in the younger and older age groups.

Figure 9. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose, by Age Group – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population Age Group: 16-55 Years



Note: Number above each bar denotes percentage of subjects reporting the reaction with any severity.
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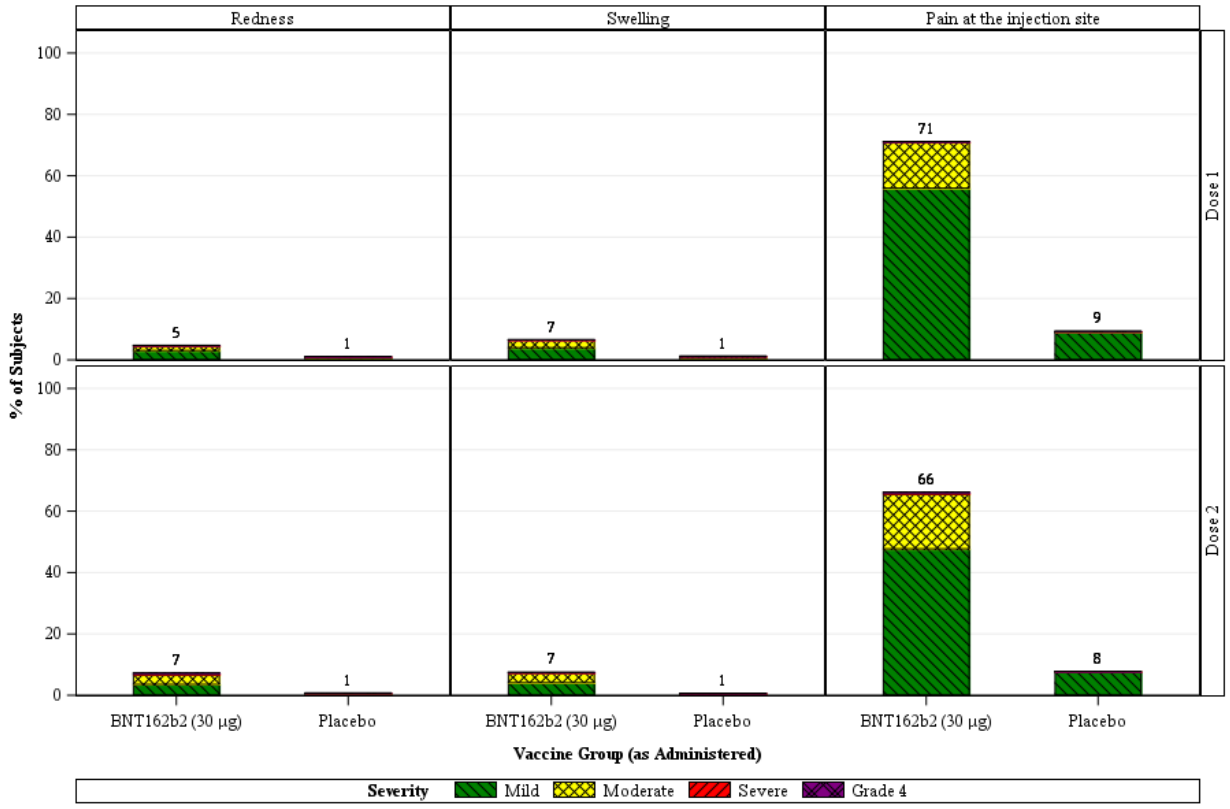
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adce_f001_lr_max_age_p3

Figure 10 Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose, by Age Group – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population Age Group: >55 Years



Note: Number above each bar denotes percentage of subjects reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:54) Source Data: adfacevd Table Generation: 17NOV2020 (16:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adce_f001_lr_max_age_p3

Local Reactions in Younger Adolescents

Younger adolescents 12 to 15 years of age (N=100; 49 in the BNT162b2 group and 51 in the placebo group) contributed preliminary data to the reactogenicity subset and were analyzed separately. In this age group, pain at the injection site was the most frequently prompted local reaction in the BNT162b2 group, reported in 71.4% of participants compared to 17.6% in the placebo group after Dose 1. The incidence of pain was reduced in the BNT162b2 group and placebo group after Dose 2 (down to 58.7% vs 8.7%,). Redness was reported in 1 participant in the BNT162b2 group after Dose 1 and in 2 participants after Dose 2, and in none in the placebo group after either dose. Swelling was reported in 2 participants in the BNT162b2 group after Dose 1 and in 3 participants after Dose 2, and in 1 in the placebo group after Dose 1 and none after Dose 2. Most local reactions were mild to moderate in severity. Two severe reactions were reported, both in the BNT162b2 group: severe redness and severe pain at the injection site.

Systemic Events

Systemic events were generally increased in frequency and severity in the younger age group (Figure 11) compared with the older age group (Figure 12), with frequencies and severity

increasing with number of doses (Dose 1 vs Dose 2). Vomiting and diarrhea were exceptions, with vomiting reported similarly infrequently in both age groups and diarrhea reported at similar incidences after each dose.

Systemic events in the younger group compared with the older group, with frequencies increasing with number of doses (Dose 1 vs Dose 2), were:

- fatigue: younger group (47.4% vs 59.4%) compared to older group (34.1% vs 50.5%)
- headache: younger group (41.9% vs 51.7%) compared to older group (25.2% vs 39.0%)
- muscle pain: younger group (21.3% vs 37.3%) compared to older group (13.9% vs 28.7%)
- chills: younger group (14.0% vs 35.1%) compared to older group (6.3% vs 22.7%)
- joint pain: younger group (11.0% vs 21.9%) compared to older group (8.6% vs 18.9%)
- fever: younger group (3.7% vs 15.8%) compared to older group (1.4% vs 10.9%)
- vomiting: reported less frequently in the older group and was similar after either dose
- diarrhea: reported less frequently in the older group and was similar after each dose.

Systemic events were generally reported less frequently in the placebo group than in the BNT162b2 group, for both age groups and doses, with some exceptions. In the younger age group, vomiting and diarrhea (after Dose 1 and Dose 2) were reported at similar frequencies in the placebo group and the BNT162b2 group (Figure 11). In the older age group, fever and joint pain (after Dose 1) and vomiting and diarrhea (after Dose 1 and Dose 2) were reported at similar frequencies in the placebo group and the BNT162b2 group (Figure 12).

Following both Dose 1 and Dose 2, use of antipyretic/pain medication was slightly less frequent in the older age group (19.9% vs 37.7%) than in the younger age group (27.8% vs 45.0%) after both doses, and medication use increased in both age groups after Dose 2 as compared with after Dose 1. Use of antipyretic/pain medication was less frequent in the placebo group than in the BNT162b2 group and was similar after Dose 1 and Dose 2 in the younger and older placebo groups (9.8% to 22.0%).

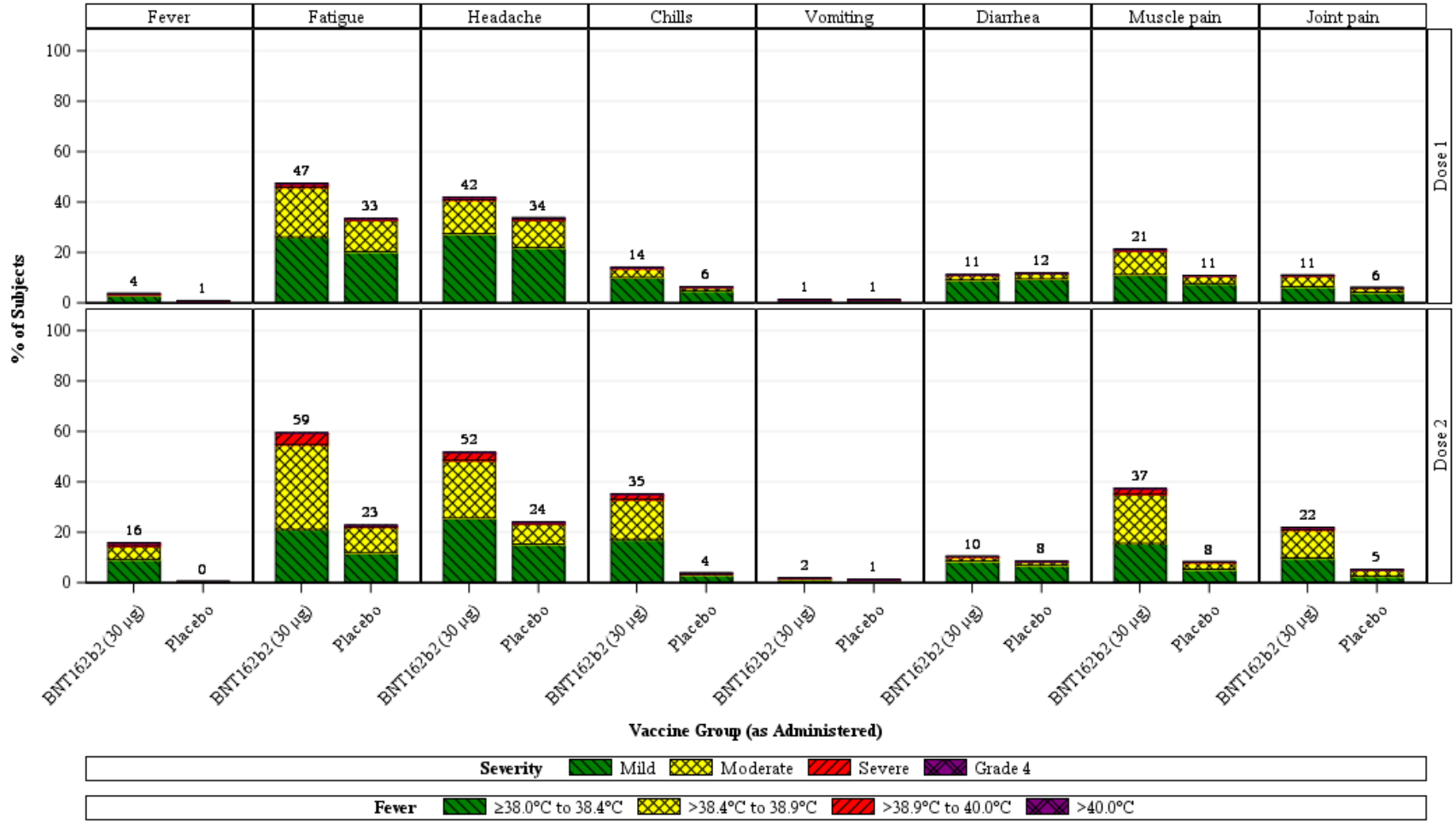
After the first and second dose and in both age groups, the majority of systemic events were mild or moderate in severity. Systemic events across age groups after Dose 1 of BNT162b2 were generally lower in frequency than after Dose 2: fever (2.7% vs 13.6%), fatigue (41.5% vs 55.5%), headache (34.5% vs 46.1%), chills (10.6% vs 29.6%), muscle pain (18.0% vs 33.5%), and joint pain (9.9% vs 20.5%). Diarrhea and vomiting frequencies were generally similar. Overall, the frequency of any severe systemic event after Dose 1 was ≤0.9%. After Dose 2, severe systemic events had frequencies of <2% with the exception after Dose 2 of fatigue (3.8%) and headache (2.0%).

Severe fever (>38.9°C to 40.0°C) was reported in the BNT162b2 group after Dose 1 for 0.2% and after Dose 2 for 0.8%, and in the placebo group after Dose 1 for 0.1% and after Dose 2 for 0.1%. Grade 4 fever (>40.0°C) was reported for 2 participants in each of the BNT162b2 and placebo groups.

Across age groups, median onset day for most systemic events after either dose of BNT162b2 was Day 2 to Day 3 (Day 1 was the day of vaccination), and ranges were similar in the younger and older age groups. Across age groups, all systemic events resolved with median duration of 1 day, which was similar in the younger and older age groups.

Other than fatigue and headache, most systemic events were infrequent in placebo recipients.

Figure 11. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, by Age Group – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population Age Group: 16-55 Years



Note: Number above each bar denotes percentage of subjects reporting the event with any severity.
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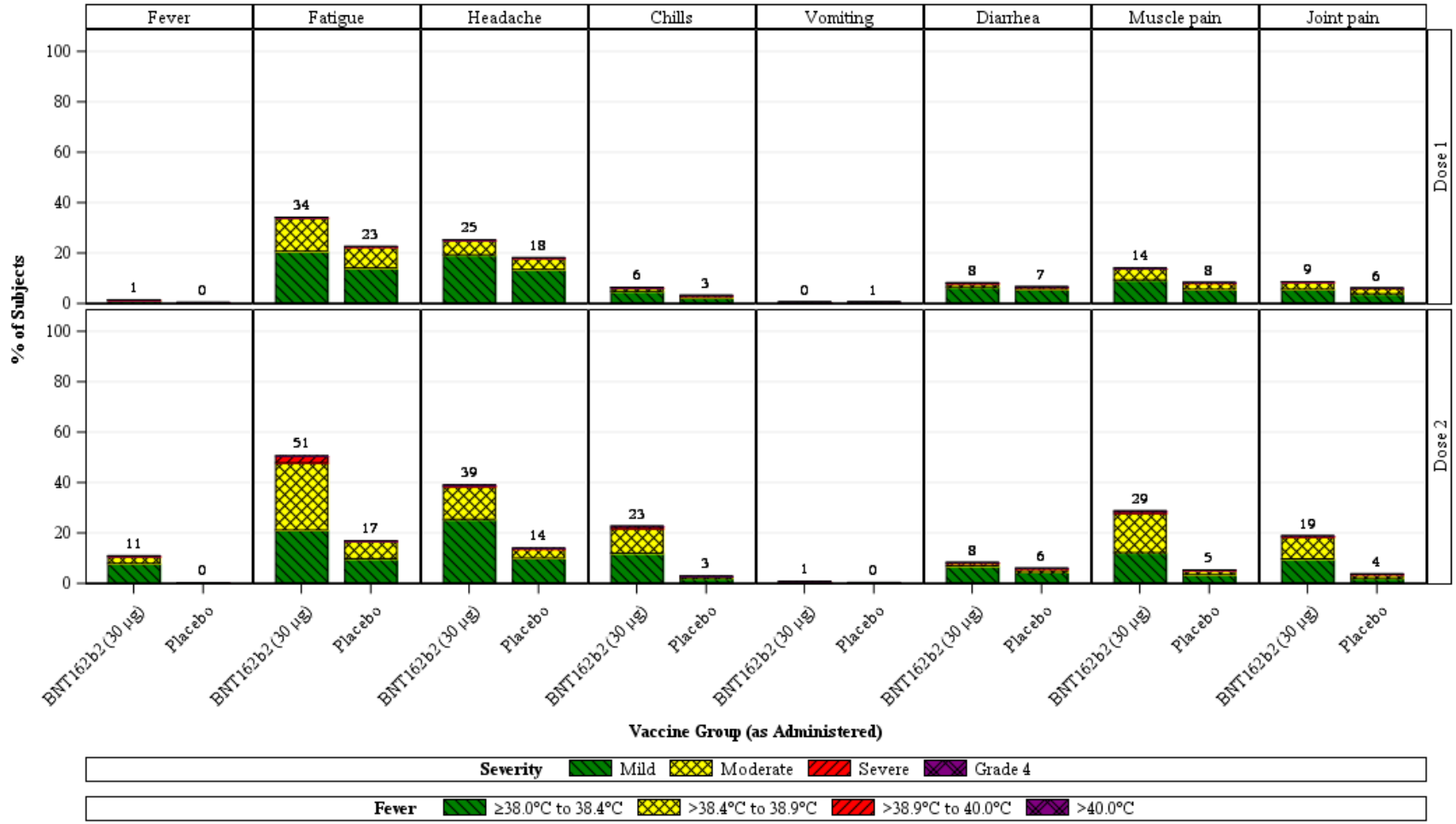
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adce_f001_se_max_age_p3

Figure 12 Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, by Age Group – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population Age Group: >55 Years



Note: Number above each bar denotes percentage of subjects reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:54) Source Data: adfacevd Table Generation: 17NOV2020 (16:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adce_f001_se_max_age_p3

Systemic Reactions in Younger Adolescents

Younger adolescents 12 to 15 years of age (N=100; 49 in the BNT162b2 group and 51 in the placebo group) contributed preliminary data to the reactogenicity subset and were analyzed separately. Most systemic events (other than vomiting and diarrhea, which had low incidences across groups) were reported at higher incidence in the BNT162b2 group than in the placebo group. However, there was no clear trend for increasing incidence or severity after Dose 1 compared to after Dose 2. In this age group, the most frequent prompted systemic events after Dose 1 compared to Dose 2 were (Dose 1 vs Dose 2):

- fatigue: BNT162b2 (49.0% vs 50.0%) compared to placebo (25.5% vs 6.5%)
- headache: BNT162b2 (42.9% vs 45.7%) compared to placebo (35.3% vs 21.7%)
- muscle pain: BNT162b2 (22.4% vs 30.4%) compared to placebo (13.7% vs 4.3%)
- chills: BNT162b2 (30.6% vs 28.3%) compared to placebo (7.8% vs 8.7%)
- joint pain: BNT162b2 (12.2% vs 17.4%) compared to placebo (9.8% vs 6.5%)
- fever: BNT162b2 (14.3% vs 19.6%) compared to placebo (0% vs 0%)
- vomiting: reported at similar frequencies in both groups and similar after each dose
- diarrhea: reported at similar frequencies in both groups and similar after each dose.

Most systemic events in younger adolescents were mild to moderate in severity. Severe events were relatively infrequent in both groups, occurring in no more than 1 or 2 participants after either dose.

Antipyretic/pain medication use in the younger adolescent group was modestly increased after Dose 2 compared to Dose 1 (30.6% vs 41.3%) and was greater than use in the placebo group (9.8% vs 13%).

6.3.3.2. Adverse Events

6.3.3.2.1. Overview of AEs in Study C4591001 Phase 2/3

As described in Section 6.3.1.1, 37,706 participants had a median follow-up time of 2 months after Dose 2. Of these, 19,067 (50.6%) had at least 2 months of follow-up after Dose 2. HIV-positive participants (120 participants) were included for counting purposes in demographic and disposition summaries; however, these participants were not included in the summary of safety or efficacy endpoint results. Therefore, 37,586 participants were included in the AE analyses presented in the sections below.

Results for all enrolled participants (N=43,252 participants) who had variable follow up from Dose 1 to the data cutoff date of 14 November 2020 are also presented below.

6.3.3.2.1.1. Participants with Median 2 Months of Follow-Up After Dose 2

An overview of AEs from Dose 1 to 1 month after Dose 2 for the 37,586 participants who had a median of at least 2 months of follow-up after Dose 2 (including those analyzed in Phase 2) is presented in Table 6. The numbers of overall participants who reported at least 1 AE and at least 1 related AE were higher in the BNT162b2 group as compared with the placebo group. This trend continued to be seen through the data cutoff date for all enrolled participants (43,252 participants) and is further described below for that population. Few participants in either group had severe AEs, SAEs, or AEs leading to study withdrawal. The incidences of deaths reported were low and similar in the BNT162b2 (1; 0.0%) and placebo (2; 0.0%) groups; (refer to Section 6.3.3.2.3).

In the younger age group, the number of participants who reported at least 1 AE from Dose 1 to 1 month after Dose 2 was 3177 (29.3%) and 1427 (13.2%) in the BNT162b2 and placebo groups, respectively. In the older age group, the number of participants who reported at least 1 AE from Dose 1 to 1 month after Dose 2 was 1894 (23.8%) and 929 (11.7%) in the BNT162b2 and placebo groups, respectively.

Among the 37,586 participants, no clinically meaningful differences in AEs by category were observed by age, sex, race/ethnicity, or baseline SARS-CoV-2 status subgroups.

Table 6. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – ~38000 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)	
Adverse Event	**BNT162b2 (30 µg) (N[a]=18801) n[b] (%)**	**Placebo (N[a]=18785) n[b] (%)**
Any event	5071 (27.0)	2356 (12.5)
Related[c]	3915 (20.8)	953 (5.1)
Severe	220 (1.2)	109 (0.6)
Life-threatening	18 (0.1)	20 (0.1)
Any serious adverse event	103 (0.5)	81 (0.4)
Related[c]	3 (0.0)	0
Severe	57 (0.3)	48 (0.3)
Life-threatening	18 (0.1)	19 (0.1)
Any adverse event leading to withdrawal	34 (0.2)	25 (0.1)
Related[c]	14 (0.1)	7 (0.0)
Severe	13 (0.1)	7 (0.0)
Life-threatening	2 (0.0)	4 (0.0)
Death	1 (0.0)	2 (0.0)

Table 6. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – ~38000 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N^a=18801)	Placebo (N^a=18785)
Adverse Event	n^b (%)	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 event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:21) (Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adae_s091_all_pd2_p3_saf

Participants with At Least 2 Months of Follow-Up After Dose 2

Table 7 presents an AE summary of the subset of 19,067 participants, within the 37,586 group, who had at least 2 months of follow-up after Dose 2. The results regarding the number of overall participants who reported at least 1 AE, related AEs, severe AEs, SAEs, AEs leading to discontinuation, and deaths were consistent with what was seen in the 37,586 participants with 1 month of follow-up after Dose 2. Overall, in the 19,067 participants, from Dose 1 to the data cutoff date, 21.4% and 13.6% of participants in the BNT162b2 group experienced at least 1 AE and 1 related AE, respectively, and 12.6% and 3.6% of participants in the placebo group experienced at least 1 AE and 1 related AE, respectively. Incidences of severe AEs, SAEs, AEs leading to discontinuation, and deaths were ≤1.1%, 0.6%, 0.0%, and 0.0%, respectively, in both the BNT162b2 and placebo groups.

Table 7. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to Data Cutoff Date (14NOV2020) – Subjects With 2 Months Follow-Up Time After Dose 2 for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N^a=9531)	Placebo (N^a=9536)	Total (N^a=19067)
Adverse Event	n^b (%)	n^b (%)	n^b (%)
Any event	2044 (21.4)	1197 (12.6)	3241 (17.0)
Related[c]	1297 (13.6)	343 (3.6)	1640 (8.6)
Severe	105 (1.1)	69 (0.7)	174 (0.9)
Life-threatening	10 (0.1)	11 (0.1)	21 (0.1)

Table 7. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to Data Cutoff Date (14NOV2020) – Subjects With 2 Months Follow-Up Time After Dose 2 for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=9531)	Placebo (N[a]=9536)	Total (N[a]=19067)
Adverse Event	n[b] (%)	n[b] (%)	n[b] (%)
Any serious adverse event	57 (0.6)	53 (0.6)	110 (0.6)
Related[c]	2 (0.0)	0	2 (0.0)
Severe	32 (0.3)	33 (0.3)	65 (0.3)
Life-threatening	10 (0.1)	11 (0.1)	21 (0.1)
Any adverse event leading to withdrawal	1 (0.0)	0	1 (0.0)
Related[c]	0	0	0
Severe	0	0	0
Life-threatening	1 (0.0)	0	1 (0.0)
Death	1 (0.0)	0	1 (0.0)

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 event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
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6.3.3.2.1.2. All Enrolled Participants

An overview of AEs reported for all enrolled participants (N=43,252 participants) who had variable follow-up from Dose 1 to the data cutoff date, is presented in Table 8. From Dose 1 to the data cutoff date, the numbers of overall participants who reported at least 1 AE and at least 1 related AE remained higher in the BNT162b2 group as compared with the placebo group. This imbalance in the BNT162b2 and placebo groups is further described in Section 6.3.3.2.2. Few participants in either group had severe AEs, SAEs, or AEs leading to study withdrawal. The incidences of deaths reported were low and similar in the BNT162b2 (2; 0.0%) and placebo groups (4; 0.0%) (refer to Section 6.3.3.2.3).

In the younger age group, the number of participants who reported at least 1 AE was 3660 (28.8%) and 1605 (12.6%) in the BNT162b2 and placebo groups, respectively. In the older age group, the number of participants who reported at least 1 AE was 2110 (23.7%) and 1033 (11.6%) in the BNT162b2 and placebo groups, respectively.

In the 16 to 17 years of age group, 16 participants (11.6%) in the BNT162b2 group and 7 participants (4.8%) in the placebo group experienced at least 1 AE from Dose 1 to the data cutoff date.

Table 8. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to Data Cutoff Date (14NOV2020) – Phase 2/3 (All Subjects) – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=21621)	Placebo (N[a]=21631)
Adverse Event	n[b] (%)	n[b] (%)
Any event	5770 (26.7)	2638 (12.2)
Related[c]	4484 (20.7)	1095 (5.1)
Severe	240 (1.1)	139 (0.6)
Life-threatening	21 (0.1)	24 (0.1)
Any serious adverse event	126 (0.6)	111 (0.5)
Related[c]	4 (0.0)	0
Severe	71 (0.3)	68 (0.3)
Life-threatening	21 (0.1)	23 (0.1)
Any adverse event leading to withdrawal	37 (0.2)	30 (0.1)
Related[c]	16 (0.1)	9 (0.0)
Severe	13 (0.1)	9 (0.0)
Life-threatening	3 (0.0)	6 (0.0)
Death	2 (0.0)	4 (0.0)

Note: Data for subjects randomized on or after 10OCT2020 are included to comprehensively show all data reported but are subject to change with additional follow-up.
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 event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
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6.3.3.2.2. Analysis of Adverse Events

6.3.3.2.2.1. Participants with Median 2 Months of Follow-Up After Dose 2

Among the 37,586 participants with a median of 2 months of safety follow-up after Dose 2, most AEs reported up to 1 month after Dose 2 were reactogenicity, in SOCs of:

- general disorders and administration site conditions (18.6% BNT162b2 vs 3.9% placebo)
- musculoskeletal and connective tissue disorders (7.3% BNT162b2 vs 2.0% placebo)
- nervous system disorders (6.1% BNT162b2 vs 2.4% placebo)
- infections and infestations (1.5% BNT162b2 vs 1.5% placebo)

- gastrointestinal disorders (2.9% BNT162b2 vs 1.9% placebo)

In the younger versus older BNT162b2 age groups, AE incidences in these SOCs were:

- general disorders and administration site conditions (21.1% vs 15.2%)
- musculoskeletal and connective tissue disorders (8.3% vs 5.9%)
- nervous system disorders (6.9% vs 4.9%)
- infections and infestations (1.5% vs 1.6%)
- gastrointestinal disorders (3.0% vs 2.8%)

Any imbalances in the SOCs were primarily accounted for with an increased frequency of AEs that were reactogenicity events: general disorders and administration site conditions (includes injection site pain, fatigue, pyrexia, chills), musculoskeletal and connective tissue disorders (includes myalgia and arthralgia), and nervous system disorders (includes headaches).

The most frequently reported AEs in the BNT162b2 group by PT overall were injection site pain (2108 [11.2%]), pyrexia (1144 [6.1%]), chills (998 [5.3%]), fatigue (1026 [5.5%]), headache (966 [5.1%]), and myalgia (904 [4.8%]). During this time period from Dose 1 to 1 month after Dose 2, most of these AEs were reported during the e-diary 7-day reporting period. The majority of these PTs were reported in the younger age group: injection site pain (1358 [12.5%]), pyrexia (819 [7.6%]), chills (693 [6.4%]), fatigue (690 [6.4%]), headache (649 [6.0%]), and myalgia (628 [5.8%]).

AEs of lymphadenopathy were reported in 64 participants (0.3%) in the BNT162b2 group and 6 participants (0.0%) in the placebo group. Among the AEs of lymphadenopathy in the BNT162b2 group, the majority (47 of 64) were judged by the investigator as related to study intervention, occurred in the arm and neck region, and were reported within 2 to 4 days after vaccination. Events of lymphadenopathy are described in Section 6.3.3.2.6.

Adverse Events Reported in >1% of Participants in Either Treatment Group

The following AEs were reported in >1% of participants in either treatment group in the 37,586 participants with a median of 2 months of safety follow-up after Dose 2, events reported from Dose 1 to 1 month after Dose 2 (BNT162b2 group vs placebo group):

- Gastrointestinal disorders
  - Nausea (1.1% vs 0.3%)
- General disorders and administration site conditions
  - Injection site pain (11.2% vs 1.5%)
  - Pyrexia (6.1% vs 0.3%)
  - Fatigue (5.5% vs 1.4%)

  - Chills (5.3% vs 0.5%)
  - Pain (2.4% vs 0.2%)
- Musculoskeletal and connective tissue disorders
  - Myalgia (4.8% vs 0.7%)
  - Arthralgia (1.1% vs 0.4%)
- Nervous system disorders
  - Headache (5.1% vs 1.6%)

Participants with At Least 2 Months of Follow-Up After Dose 2

There were 19,067 participants with at least 2 months of follow-up time after Dose 2, and similar to the 37,586 participants with a median of 2 months of safety follow up after Dose 2, most AEs reported after Dose 1 up to the safety data cutoff date were reactogenicity, in SOCs of:

- general disorders and administration site conditions (11.9% BNT162b2 vs 2.9% placebo)
- musculoskeletal and connective tissue disorders (5.5% BNT162b2 vs 2.1% placebo)
- nervous system disorders (4.2% BNT162b2 vs 2.1% placebo)
- infections and infestations (1.9% BNT162b2 vs 1.6% placebo)
- gastrointestinal disorders (2.6% BNT162b2 vs 1.8% placebo)

In the younger versus older BNT162b2 age groups, AE incidences in these SOCs were:

- general disorders and administration site conditions (13.1% vs 10.4%)
- musculoskeletal and connective tissue disorders (6.0% vs 4.9%)
- nervous system disorders (4.8% vs 3.5%)
- infections and infestations (1.9% vs 1.9%)
- gastrointestinal disorders (2.7% vs 2.5%)

In the BNT162b2 group, the most frequently reported AEs by PT overall were injection site pain (621 [6.5%]), pyrexia (362 [3.8%]), chills (314 [3.3%]), fatigue (331 [3.5%]), headache (320 [3.4%]), and myalgia (304 [3.2%]). During this time period from Dose 1 to the safety data cutoff date, most of these AEs were reported during the e-diary 7-day reporting period. The majority of these PTs were reported in the younger age group: injection site pain (373 [7.0%]), pyrexia (256 [4.8%]), chills (211 [3.9%]), fatigue (209 [3.9%]), headache (206 [3.9%]), and myalgia (192 [3.6%]).

Severe or Life-Threatening Adverse Events – Participants with Median 2 Months of Follow-Up After Dose 2

From Dose 1 to 1 month after Dose 2, severe AEs reported by the 37,586 participants who had at least 1 month of follow-up were low in frequency, reported in 1.2% of BNT162b2 recipients and 0.6% of placebo recipients. Most of the severe AEs in the BNT162b2 group were reactogenicity events in the SOCs general disorders and administration site conditions (eg, pyrexia, fatigue, injection site pain, chills), musculoskeletal and connective tissue disorders (eg, myalgia and arthralgia), and nervous system disorders (eg, headache).

There were 18 participants (0.1%) in the BNT162b2 group and 20 participants (0.1%) in the placebo group who had at least 1 life-threatening AE from Dose 1 to 1 month after Dose 2.

Severe and life-threatening events of appendicitis were observed. These SAEs of appendicitis, observed in both treatment groups and not considered related to study intervention, are discussed in Section 6.3.3.2.4 (SAEs).

For the subset of 19,067 participants within the 37,586 group who had at least 2 months of follow-up after Dose 2, the numbers of severe or life-threatening AEs were consistent with what was seen in the 37,586 participants with 1 month of follow-up after Dose 2. Overall, in the 19,067 participants, from Dose 1 to the data cutoff date, 1.1% and 0.1% of participants in the BNT162b2 group experienced at least 1 severe AE and 1 life-threatening AE, respectively, and 0.7% and 0.1% of participants in the placebo group experienced at least 1 severe AE and 1 life-threatening AE, respectively. The results by age group were also similar.

Related Adverse Events - Participants with Median 2 Months of Follow-Up After Dose 2

From Dose 1 to 1 month after Dose 2, among the 37,586 participants with a median of 2 months of follow-up after Dose 2, AEs assessed as related by the investigator were reported by 20.8% of participants in the BNT162b2 group and 5.1% participants in the placebo group. Most related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions, reported by 3426 (18.2%) BNT162b2 recipients and 628 (3.3%) placebo recipients. Among the participants who had AEs of lymphadenopathy in the BNT162b2 group, 47 of 64 participants had events assessed by the investigator as related to study intervention; the majority of lymphadenopathy events occurred in the arm and neck region and were reported within 2 to 4 days after vaccination. Events of lymphadenopathy are described in Section 6.3.3.2.6.

Immediate Adverse Events - Participants with Median 2 Months of Follow-Up After Dose 2

After Dose 1, among the 37,586 participants with a median of 2 months of follow-up after Dose 2 immediate AEs were low in frequency (0.4%). Most immediate AEs after Dose 1 were in the SOC of general disorders and administration site conditions, primarily injection site reactions, in the BNT162b2 versus placebo groups with injection site pain (0.3% vs 0.2%) most frequently reported.

After Dose 2, participants with immediate AEs were low in frequency (≤0.3%). Most immediate AEs after Dose 2 were in the SOC of general disorders and administration site conditions,

primarily injection site reactions, in the BNT162b2 versus placebo groups with injection site pain (0.2% vs 0.1%) most frequently reported.

After either BNT162b2 dose, no participant reported an immediate allergic reaction to vaccine.

6.3.3.2.2.2. All Enrolled Participants

Similar to the 37,586 participants with a median of 2 months of safety follow-up, most AEs reported after Dose 1 up to the safety data cutoff date for all 43,252 enrolled participants were reactogenicity events.

The incidence of AEs in the BNT162b2 versus placebo groups in the following SOCs consistent with reactogenicity events were reported:

- general disorders and administration site conditions (18.5% vs 3.8%)
- musculoskeletal and connective tissue disorders (7.0% vs 2.0%)
- nervous system disorders (5.9% vs 2.3%)

In the 16 to 17 years of age group, from Dose 1 to the data cutoff date, most AEs were in the general disorders and administration site conditions (15 [10.9%] in the BNT162b2 group and 5 [3.4%] in the placebo group), including the following PTs: pyrexia, injection site pain, chills, pain, fatigue, injection site erythema, and injection site swelling.

6.3.3.2.3. Deaths in Study C4591001 Phase 2/3

There were 6 participants, all in Phase 3, who died through the data cutoff date of 14 November 2020. This included 2 participants in the BNT162b2 group and 4 participants in the placebo group. None of these deaths were assessed by the investigator as related to study intervention.

Details of the 6 reported deaths among all enrolled participants include:

- One participant in the older BNT162b2 group experienced an SAE of arteriosclerosis and died 3 days after Dose 1.
- One participant in the older BNT162b2 group experienced an SAE of cardiac arrest 60 days after Dose 2 and died 3 days later.
- One participant in the younger placebo group experienced an SAE of unevaluable event (unknown of unknown origin; no additional information currently available at the time of this report) 8 days after Dose 1 and died the same day.
- One participant in the older placebo group experienced an SAE of hemorrhagic stroke 15 days after Dose 2 and died the next day.
- One participant in the younger placebo group experienced an SAE of death (cause unknown; no additional information currently available at the time of this report) 34 days after Dose 2.
- One participant in the older placebo group experienced an SAE of myocardial infarction 16 days after Dose 1 and died the same day.

6.3.3.2.4. Serious Adverse Events in Study C4591001 Phase 2/3

6.3.3.2.4.1. Participants with Median 2 Months of Follow-Up After Dose 2

Among the 37,586 participants with a median of 2 months of follow-up after Dose 2, from Dose 1 to 1 month after Dose 2 the proportions of participants who reported at least 1 SAE was similar in the BNT162b2 group (0.5%) and in the placebo group (0.4%) (Appendix 4).

The most frequently reported SAEs were in the Cardiac Disorders SOC (0.1% in each treatment group), Nervous System Disorders SOC (0.1% in each treatment group), and Infections and Infestations SOC (0.1% in each treatment group).

Three of the SAEs in the BNT162b2 group and none in the placebo group were assessed by the investigator as related to study intervention: 1 SAE each of shoulder injury related to vaccine administration, ventricular arrhythmia, and lymphadenopathy.

There were a total of 12 participants with SAEs of appendicitis; 8 in the BNT162b2 group (SAEs of appendicitis [7], appendicitis perforated [1]) and 4 in the placebo group (appendicitis [2], appendicitis perforated [1], complicated appendicitis [1]) . Of the 8 total appendicitis cases in the BNT162b2 group, 6 occurred in the younger age group and 2 occurred in the older age group (one of the cases in the older age group was perforated). One of the 6 participants with appendicitis in the younger age group also had a peritoneal abscess. None of the cases were assessed as related to study intervention by the investigators.

With 8496.05 years of participant follow up as of 16 November 2020, an observation of 12 appendicitis cases across both treatment groups is not greater than expected based on background rates estimated in a US Electronic Health Records database. The ratio of the observed number of cases compared with the expected number of cases was 1.19 (95% CI 0.62 - 2.09) overall, 0.98 (95% CI, 0.39 - 2.02) within the 18-54 age category and 1.73 (95% CI, 0.56 - 4.03) in the 55 and older age category.

Among the 37,586 participants with a median of 2 months of safety follow-up after Dose 2, no clinically meaningful differences in SAEs were observed by age, sex, race/ethnicity, or baseline SARS CoV 2 status subgroups.

With additional follow-up to the data cutoff date of 14 November 2020 for the 37,586 participants with a median of 2 months of follow-up after Dose 2, the number of participants who reported SAEs was similar in the BNT162b2 group (0.7%) and the placebo group (0.5%). With the additional follow-up time, another SAE assessed by the investigator as related to study intervention in the BNT162b2 younger age group was reported: 1 event of lower back pain and bilateral lower extremity pain with radicular paresthesia (onset Day 47 after Dose 2).

6.3.3.2.4.2. All Enrolled Participants

Among all 43,448 enrolled participants, from Dose 1 to the data cutoff date, the proportions of participants who reported at least 1 SAE were similar in the BNT162b2 group (0.6%) and in the placebo group (0.5%). An additional 23 participants in the BNT162b2 group and 30 participants in the placebo group had at least 1 SAE compared with the N~38,000 population.

The most frequently reported SAEs were the same as those reported in the N~38,000 population. No additional SAEs related to study intervention were reported in the BNT162b2 placebo group.

In participants 16 to 17 years of age, 1 participant in the BNT162b2 group experienced an SAE of facial bones fracture, not considered related to study intervention by the investigator.

6.3.3.2.5. Adverse Events Leading to Study Withdrawal

6.3.3.2.5.1. Participants with Median 2 Months of Follow-Up After Dose 2

Among the 37,706 participants with a median of 2 months of follow-up after Dose 2, from Dose 1 to 1 month after Dose 2 few participants in the BNT162b2 group (0.2%) and in the placebo group (0.1%) were withdrawn because of AEs. Thirty-four (34) participants in the BNT162b2 group and 25 participants in the placebo group had an AE leading to withdrawal. The most frequently reported AEs leading to study withdrawal were in the SOCs of gastrointestinal disorders (5 participants in BNT162b2 group vs 4 in placebo group); general disorders and administration site conditions (7 vs 1); injury, poisoning and procedural complications (6 vs 4); musculoskeletal and connective tissue disorders (5 vs 0; events of muscular weakness, muscle spasms, myalgia, and pain in extremity); and nervous system disorders (5 vs 6).

6.3.3.2.5.2. All Enrolled Participants

Among all 43,448 enrolled participants included in the safety database up to the data cutoff date, few participants in the BNT162b2 group (0.2%) and in the placebo group (0.1%) were withdrawn because of AEs. The results were similar to the AEs leading to withdrawal in the 37,706 population: AEs leading to withdrawal were reported for 3 additional participants in the BNT162b2 group (37 total) and 5 additional participants in the placebo group (30 total).

No participants in the 16 to 17 years of age group experienced an AE leading to withdrawal.

6.3.3.2.6. Adverse Events of Clinical Interest in Study C4591001 Phase 2/3

No AESIs were prespecified in the Study C4591001 protocol. Pfizer routinely reviews the data from the ongoing study for the terms of potential clinical interest as listed in Section 5.2.3.

Adverse events of clinical interest, such as the CDC's list of AESIs for COVID-19, which both includes terms potentially indicative of severe COVID-19 or serious autoimmune and neuroinflammatory disorders, were considered in the review of reported events.

In the BNT162b2 group, there were 64 participants (0.3%) who reported an AE of lymphadenopathy: 54 (0.5%) in the younger age group and 10 (0.1%) in the older age group, and 6 in the placebo group. This included 26 male participants (0.3%) and 38 female participants (0.4%). In cases where location was specified, AEs of lymphadenopathy occurred in the arm and neck region (in axillary, left axillary, left para clavicular, left supra clavicular, bilateral cervical, or unspecified lymph nodes). Most lymphadenopathy events were reported within 2 to 4 days after vaccination (15 events were reported ≥8 days after vaccination, including 1 event reported 98 days after). The average duration of these events was approximately 10 days, with 11 events ongoing at the time of the data cutoff.

In the younger age group, an AE of angioedema 13 days after Dose 1 (both eyes) and hypersensitivity (allergy attack; no additional information available at the time of this report, unrelated to study intervention) were reported in 1 participant each (BNT162b2 group), and an AE of drug hypersensitivity (oral penicillin reaction) was reported in 1 participant who received placebo; all were assessed by the investigator as unrelated to study intervention.

6.3.3.2.7. Severe COVID-19 Cases in Study C4591001 Phase 2/3

The protocol had prespecified stopping rules that included monitoring of severe COVID-19 cases, and these stopping criteria were not met. The confinement of the majority of severe cases to the placebo groups suggests no evidence for vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD).

A description of severe COVID-19 cases evaluated for efficacy in Phase 2/3 is presented in Section 6.3.4.2.3.3 (final analysis).

6.3.3.2.8. Pregnancies

At the time of the data cutoff in Study C4591001 (14 November 2020), a total of 23 participants had reported pregnancies in the safety database, including 9 participants who withdrew from the study due to pregnancies. These participants continue to be followed for pregnancy outcomes.

6.3.3.3. Safety Conclusions in Study C4591001 Phase 2/3

Based on Phase 3 data from approximately 38,000 participants with a median of 2 months of follow-up after Dose 2 in Study C4591001, BNT162b2 at 30 µg was safe and well-tolerated in participants ≥16 years of age. Reactogenicity and AEs were generally milder and less frequent in participants in the older group (≥56 years of age) compared with the younger group (≤55 years of age). Reactogenicity was mostly mild to moderate and short-lived after dosing for both adult age groups and for younger adolescents 12 to 15 years of age (whose preliminary data provide support to ≥16 years of age indication), and the AE profile did not suggest any serious safety concerns. The incidence of SAEs and deaths were low in the context of the number of participants enrolled and comparable for BNT162b2 and placebo. The incidence of discontinuations due to AEs was also generally low and similar between BNT162b2 and placebo groups. This profile was consistent for the subset of approximately 19,000 participants who had at least 2 months of follow-up after Dose 2.

Safety data from approximately 44,000 participants enrolled as of the data cutoff date (14 November 2020), with variable durations of follow-up after vaccine administration, overall showed a similar AE profile to those who had at least 2 months of follow-up after Dose 2. In this total population of all enrolled participants, incidence of SAEs and deaths were low and comparable for BNT162b2 and placebo, and incidence of discontinuations due to AEs was generally low.

6.3.4. Efficacy in Study C4591001 Phase 2/3

The first primary efficacy endpoint from the interim analysis of efficacy is presented in Section 6.3.4.1. Primary and secondary efficacy endpoints from the final analysis of efficacy are presented in Section 6.3.4.2.

6.3.4.1. Interim Analysis of Efficacy in Study C4591001

A prespecified interim analysis of the first primary efficacy endpoint was conducted after accrual of 94 COVID-19 cases. Among participants included in the evaluable efficacy population at the time of the interim analysis, 32,279 participants overall (16,061 in the BNT162b2 group and 16,218 in the placebo groups) did not have evidence of prior infection with SARS-CoV-2 before and during vaccination regimen.

As of the time of the interim analysis, there were 4 confirmed COVID-19 cases in the BNT162b2 group and 90 confirmed COVID-19 cases in the placebo group. All evaluable cases were confirmed by tests conducted at the central laboratory.

VE of BNT162b2 was 95.5% with a 99.99% posterior probability for the true VE being >30% conditioning on available data, to overwhelmingly meet the prespecified interim analysis success criterion (>99.5%). The 95% credible interval for the VE was 88.8% to 98.4%, indicating that given these observed data there was a 95% probability that the true VE lies in this interval. Also, note that the posterior probability that true VE >86.0% is 99.5% and VE >88.8% is 97.5%.

6.3.4.2. Final Analysis of Efficacy in Study C4591001

Efficacy data for the Phase 3 portion of Study C4591001 were analyzed for all enrolled participants who met the protocol-specified criteria for efficacy evaluation, with a final analysis cutoff date of 14 November 2020.

COVID-19 case evaluation for primary and secondary efficacy endpoints is provided in Appendix 1.

6.3.4.2.1. Final Analysis of Primary Efficacy Endpoints

6.3.4.2.1.1. Vaccine Efficacy Without Prior Evidence of SARS-CoV-2 Infection – 7 Days After Dose 2 – Final Analysis

Among participants included in the evaluable efficacy population at the time of the final analysis, 36,621 participants overall (18242 in the BNT162b2 group and 18,379 in the placebo groups) did not have evidence of prior infection with SARS-CoV-2 through 7 days after Dose 2.

As noted above, overwhelming efficacy was declared at the first (and only) interim analysis for the first primary efficacy endpoint. An update based on 170 evaluable cases accrued at the time of the final analysis (of the other efficacy endpoints) is summarized below.

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%, with 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group (Table 9). The 95% credible interval for the VE was 90.3% to 97.6%, indicating that the true VE is at least 90.3% with a 97.5% probability given the observed data.

Table 9. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	**n1[b]**	**Surveillance Time[c] (n2[d])**	**n1[b]**	**Surveillance Time[c] (n2[d])**	**VE (%)**	**(95% CI[e])**	**Pr (VE >30% | data)[f]**
First COVID-19 occurrence from 7 days after Dose 2	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.3, 97.6)	>0.9999

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 17NOV2020 (16:46)
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6.3.4.2.1.2. Vaccine Efficacy With and Without Prior Evidence of SARS-CoV-2 Infection – 7 Days After Dose 2 – Final Analysis

For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID 19 was evaluated in participants with and without evidence of prior SARS-CoV-2 infection through 7 days after Dose 2. Cases were counted from 7 days after Dose 2.

Among participants with and without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively. The posterior probability of >99.99% for the true VE greater than 30% met the prespecified success criterion of >98.6% for this endpoint. The 95% credible interval for the VE was 89.9% to 97.3%, indicating that the true VE is at least 89.9% with a 97.5% probability given the available data (Table 10). Note that with a posterior probability of 98.6%, the true VE is at least 89.2% with the available data.

Table 10. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=19965)		Placebo (N[a]=20172)				
Efficacy Endpoint	**n1[b]**	**Surveillance Time[c] (n2[d])**	**n1[b]**	**Surveillance Time[c] (n2[d])**	**VE (%)**	**(95% CI[e])**	**Pr (VE >30% | data)[f]**
First COVID-19 occurrence from 7 days after Dose 2	9	2.332 (18559)	169	2.345 (18708)	94.6	(89.9, 97.3)	>0.9999

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 17NOV2020 (16:46)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_7pd2_eval

All Confirmed Cases of COVID-19 After Dose 1

A number of confirmed cases of COVID-19 are not captured in the analyses of the first primary endpoint for the evaluable efficacy population because they occurred less than 7 days after Dose 2, or because they occurred in participants who were excluded from the evaluable efficacy population or who had evidence of infection before or during the vaccination regimen.

All reports of COVID-19 with onset at any time after Dose 1 are accounted for in Table 11, which provides a summary of cases for all participants in the Dose 1 all-available efficacy (modified intention-to-treat) population, regardless of evidence of infection before or during the vaccination regimen. Among these participants, 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared to 275 cases in the placebo group.

Notably, in the BNT162b2 group, most cases occurred before Dose 2. The estimated VE against confirmed COVID-19 occurring after Dose 1 was 82% (2-sided 95% CI: 75.6 %, 86.9%), with an estimated VE of 52.4% (2-sided 95% CI: 29.5%, 68.4%) against confirmed COVID-19 occurring after Dose 1 but before Dose 2.

Table 11. Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=21669)		Placebo (N[a]=21686)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	50	4.015 (21314)	275	3.982 (21258)	82.0	(75.6, 86.9)
After Dose 1 to before Dose 2	39		82		52.4	(29.5, 68.4)
Dose 2 to 7 days after Dose 2	2		21		90.5	(61.0, 98.9)
≥7 Days after Dose 2	9		172		94.8	(89.8, 97.6)

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method (adjusted for surveillance time for overall row).
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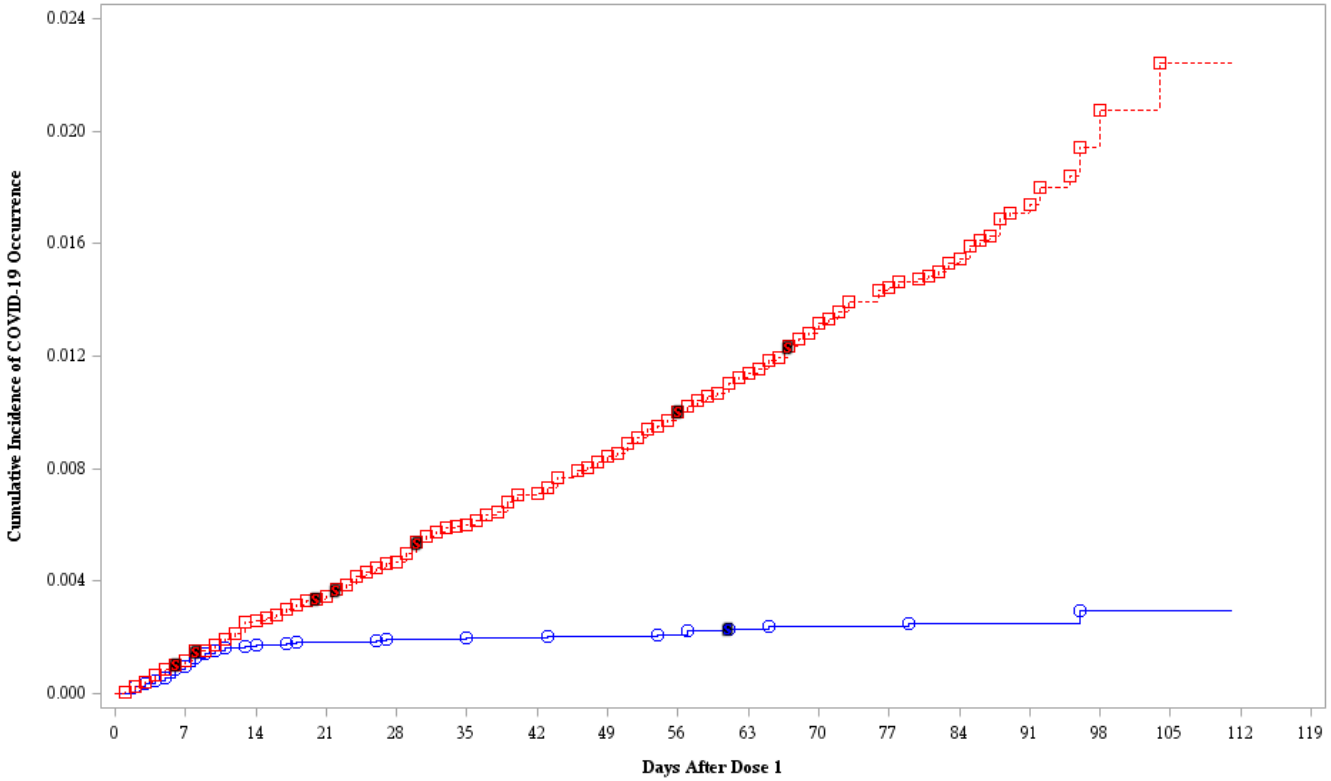
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_pd1_aai

The early onset of protection is readily apparent in Figure 13, which displays cumulative incidence for the first COVID-19 occurrence after Dose 1 among all vaccinated participants based on Dose 1 all-available efficacy (modified intention-to-treat) population. Disease onset appears to track together for BNT162b2 and placebo until approximately 14 days after Dose 1, at which point the curves diverge, with cases steadily accumulating in the placebo group, while remaining virtually flat in the BNT162b2 group.

Figure 13 Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population



No. with events/No. at risk

A:	0/21314	21/21230	37/21054	39/20481	41/19314	42/18377	42/17702	43/17186	44/15464	47/14038	48/12169	48/9591	49/6403	49/3374	50/1463	50/398	50/0	
B:	0/21258	25/21170	55/20970	73/20366	97/19209	123/18218	143/17578	166/17025	192/15290	212/13876	235/11994	249/9471	257/6294	267/3301	274/1449	275/398	275/0	

A: BNT162b2 (30 µg) B: Placebo

Note: "S" indicates subjects with severe COVID-19 or COVID-19 leading to hospitalization.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adc19ef Table Generation: 17NOV2020 (21:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_f001_km_d1_aai

6.3.4.2.2. Vaccine Efficacy by Subgroup – Final Analysis

6.3.4.2.2.1. Subgroups of Age, Sex, Race/Ethnicity, Geographic Location

Among participants without prior evidence of SARS-CoV-2 infection, the observed VE was >93% in all subgroups, with the exception of "all others" race group (89.3% VE) and Brazil (87.7% VE) (Table 12). Notably, VE was 94.7% in participants ≥65 years of age. In participants ≥75 years of age, the observed VE was 100% (0 vs 5 cases; 2-sided 95% CI: -13.1%, 100.0%) (data not shown).

Among participants with or without prior evidence of SARS-CoV-2 infection, VE was >93% in all subgroups, with the exception of "all others" race group (78.2% VE) and Brazil (75.4% VE) (data not shown).

Table 12. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2						
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Age group (years)						
16 to 55	5	1.234 (9897)	114	1.239 (9955)	95.6	(89.4, 98.6)
>55	3	0.980 (7500)	48	0.983 (7543)	93.7	(80.6, 98.8)
≥65	1	0.508 (3848)	19	0.511 (3880)	94.7	(66.7, 99.9)
Sex						
Male	3	1.124 (8875)	81	1.108 (8762)	96.4	(88.9, 99.3)
Female	5	1.090 (8536)	81	1.114 (8749)	93.7	(84.7, 98.0)
Race						
White	7	1.889 (14504)	146	1.903 (14670)	95.2	(89.8, 98.1)
Black or African American	0	0.165 (1502)	7	0.164 (1486)	100.0	(31.2, 100.0)
All others[f]	1	0.160 (1405)	9	0.155 (1355)	89.3	(22.6, 99.8)
Ethnicity						
Hispanic/Latino	3	0.605 (4764)	53	0.600 (4746)	94.4	(82.7, 98.9)
Non-Hispanic/non-Latino	5	1.596 (12548)	109	1.608 (12661)	95.4	(88.9, 98.5)
Country						
Argentina	1	0.351 (2545)	35	0.346 (2521)	97.2	(83.3, 99.9)
Brazil	1	0.119 (1129)	8	0.117 (1121)	87.7	(8.1, 99.7)
USA	6	1.732 (13359)	119	1.747 (13506)	94.9	(88.6, 98.2)

Table 12. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. All others = American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.
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6.3.4.2.2.2. Subgroups of Risk Status

Among participants without prior evidence of SARS-CoV-2 infection, the observed VE was >91% in subgroups by risk status in Table 13. At-risk participants are defined as those meeting at least one Charlson Comorbidity Index condition or obesity (defined as body mass index [BMI] ≥30 kg/m^2).

Table 13. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	**n1[b]**	**Surveillance Time[c] (n2[d])**	**n1[b]**	**Surveillance Time[c] (n2[d])**	**VE (%)**	**(95% CI[e])**
First COVID-19 occurrence from 7 days after Dose 2						
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
At risk[f]						
Yes	4	1.025 (8030)	86	1.025 (8029)	95.3	(87.7, 98.8)
No	4	1.189 (9381)	76	1.197 (9482)	94.7	(85.9, 98.6)
Age group (years) and at risk						
16-64 and not at risk	4	0.962 (7671)	69	0.964 (7701)	94.2	(84.4, 98.5)
16-64 and at risk	3	0.744 (5878)	74	0.746 (5917)	95.9	(87.6, 99.2)
≥65 and not at risk	0	0.227 (1701)	7	0.233 (1771)	100.0	(29.0, 100.0)
≥65 and at risk	1	0.281 (2147)	12	0.279 (2109)	91.7	(44.2, 99.8)
Obese[g]						
Yes	3	0.763 (6000)	67	0.782 (6103)	95.4	(86.0, 99.1)
No	5	1.451 (11406)	95	1.439 (11404)	94.8	(87.4, 98.3)
Age group (years) and obese						
16-64 and not obese	4	1.107 (8811)	83	1.101 (8825)	95.2	(87.3, 98.7)
16-64 and obese	3	0.598 (4734)	60	0.609 (4789)	94.9	(84.4, 99.0)
≥65 and not obese	1	0.343 (2582)	12	0.338 (2567)	91.8	(44.5, 99.8)
≥65 and obese	0	0.165 (1265)	7	0.173 (1313)	100.0	(27.1, 100.0)

Table 13. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least one of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2).
g. Obese is defined as BMI ≥30 kg/m^2.
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(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_EUA_FAEF_RR/adc19ef_ve_cov_7pd2_wo_rg_eval

6.3.4.2.3. Final Analysis of Secondary Efficacy Endpoints

6.3.4.2.3.1. Vaccine Efficacy Without Prior Evidence of SARS-CoV-2 Infection – 14 Days After Dose 2 – Final Analysis

For this efficacy endpoint, participants with positive or unknown NAAT results at any illness visit prior to 14 days after Dose 2 were not included in the evaluation for efficacy.

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 14 days after Dose 2 was 94.2%, with 8 and 139 cases in the BNT162b2 and placebo groups respectively (Table 14). The posterior probability of >99.99% for the true VE greater than 30% met the prespecified success criterion of >98.6% for this endpoint. The 95% credible interval for the VE was 88.7% to 97.2%, indicating that the true VE is at least 88.7% with a 97.5% probability given the available data.

Table 14. Vaccine Efficacy – First COVID-19 Occurrence From 14 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 14 Days After Dose 2 – Evaluable Efficacy (14 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18175)		Placebo (N[a]=18261)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First COVID-19 occurrence from 14 days after Dose 2	8	1.887 (16612)	139	1.893 (16663)	94.2	(88.7, 97.2)	>0.9999

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 14 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 14 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 14 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 17NOV2020 (16:46)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_14pd2_wo_eval

6.3.4.2.3.2. Vaccine Efficacy With and Without Prior Evidence of SARS-CoV-2 Infection – 14 Days After Dose 2 – Final Analysis

Among participants with or without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 14 days after Dose 2 was 94.4%, with 8 and 144 cases in the BNT162b2 and placebo groups respectively (Table 15). The posterior probability of >99.99% for the true VE greater than 30% met the prespecified success criterion of >98.6% for this endpoint. The 95% credible interval for the VE was 89.1% to 97.3%, indicating that the true VE is at least 89.1% with a 97.5% probability given the available data.

Table 15. Vaccine Efficacy – First COVID-19 Occurrence From 14 Days After Dose 2 – Subjects With or Without Evidence of Infection Prior to 14 Days After Dose 2 – Evaluable Efficacy (14 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=19965)		Placebo (N[a]=20171)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First COVID-19 occurrence from 14 days after Dose 2	8	1.984 (17645)	144	1.995 (17746)	94.4	(89.1, 97.3)	>0.9999

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 14 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 17NOV2020 (16:46)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_14pd2_eval

6.3.4.2.3.3. Vaccine Efficacy for Severe COVID-19 Cases – Final Analysis

Efficacy Against Severe COVID-19 (≥7 Days After Dose 2)

Participants Without Evidence of Infection Before and During Vaccination Regimen

For this efficacy endpoint, participants with positive or unknown NAAT results at any illness visit prior to 7 days after Dose 2 were not included in the evaluation for efficacy.

Among participants without evidence of severe SARS-CoV-2 infection before and during vaccination regimen, the estimated VE against severe COVID-19 occurring at least 7 days after Dose 2 was 66.4%, with 1 and 3 cases in the BNT162b2 and placebo groups respectively (Table 16). The posterior probability for the true VE greater than 30% is 74.29%, which did not meet the prespecified success criterion of >98.6% for this endpoint due to the small number of severe cases observed after Dose 2 in the study.

Table 16. Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	**n1[b]**	**Surveillance Time[c] (n2[d])**	**n1[b]**	**Surveillance Time[c] (n2[d])**	**VE (%)**	**(95% CI[e])**	**Pr (VE >30% | data)[f]**
First severe COVID-19 occurrence from 7 days after Dose 2	1	2.215 (17411)	3	2.232 (17511)	66.4	(-124.8, 96.3)	0.7429

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 17NOV2020 (16:47)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_sev_cov_7pd2_wo_eval

Participants With and Without Evidence of Infection Before and During Vaccination Regimen

Among participants with and without evidence of severe SARS-CoV-2 infection before and during vaccination regimen, VE against severe COVID-19 occurring at least 7 days after Dose 2 was 66.3%, with 1 and 3 cases in the BNT162b2 and placebo groups respectively Table 17. The posterior probability for the true VE greater than 30% is 74.19%.

Table 17. Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=19965)		Placebo (N[a]=20172)				
Efficacy Endpoint	**n1[b]**	**Surveillance Time[c] (n2[d])**	**n1[b]**	**Surveillance Time[c] (n2[d])**	**VE (%)**	**(95% CI[e])**	**Pr (VE >30% | data)[f]**
First severe COVID-19 occurrence from 7 days after Dose 2	1	2.333 (18566)	3	2.358 (18733)	66.3	(-125.5, 96.3)	0.7419

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 17NOV2020 (16:46)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_sev_cov_7pd2_eval

All Confirmed Cases of Severe COVID-19 After Dose 1 – All-Available Population

Among participants in the Dose 1 all-available efficacy (modified intention-to-treat) population, 1 case of severe COVID-19 occurred after Dose 1 in the BNT162b2 group compared to 9 cases in the placebo group (Table 18). The estimated VE against severe COVID-19 occurring after Dose 1 was 88.9% (2-sided 95% CI: 20.1%, 99.7%), with an estimated VE of 75.0% (1 case in BNT162b2 and 4 cases in placebo groups) against severe COVID-19 occurring at least 7 days after Dose 2.

Table 18. Vaccine Efficacy – First Severe COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=21669)		Placebo (N[a]=21686)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First severe COVID-19 occurrence after Dose 1	1	4.021 (21314)	9	4.006 (21259)	88.9	(20.1, 99.7)
After Dose 1 to before Dose 2	0		4		100.0	(-51.5, 100.0)
Dose 2 to 7 days after Dose 2	0		1		100.0	(-3800.0, 100.0)
≥7 Days after Dose 2	1		4		75.0	(-152.6, 99.5)

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method (adjusted for surveillance time for overall row).
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 18NOV2020 (17:43)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_sev_cov_pd1_aai

Efficacy Against Severe COVID-19 (≥14 Days After Dose 2)

Participants Without Evidence of Infection Before and During Vaccination Regimen (14 Days) – Severe

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, the estimated VE against severe COVID-19 occurring at least 14 days after Dose 2 was 66.4%, with 1 and 3 cases in the BNT162b2 and placebo groups respectively (Table 19). The posterior probability for the true VE greater than 30% is 74.32%.

Table 19. Vaccine Efficacy – First Severe COVID-19 Occurrence From 14 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 14 Days After Dose 2 – Evaluable Efficacy (14 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18175)		Placebo (N[a]=18261)				
Efficacy Endpoint	**n1[b]**	**Surveillance Time[c] (n2[d])**	**n1[b]**	**Surveillance Time[c] (n2[d])**	**VE (%)**	**(95% CI[e])**	**Pr (VE >30% | data)[f]**
First severe COVID-19 occurrence from 14 days after Dose 2	1	1.888 (16612)	3	1.901 (16663)	66.4	(-124.7, 96.3)	0.7432

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 14 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 14 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 14 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 17NOV2020 (16:46)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_sev_cov_14pd2_wo_eval

Participants With or Without Evidence of Infection Before and During Vaccination Regimen (14 Days) – Severe

Among participants with or without evidence of SARS-CoV-2 infection before and during vaccination phase, VE against severe COVID-19 occurring at least 14 days after Dose 2 was 66.3%, with 1 and 3 cases in the BNT162b2 and placebo groups respectively (Table 20). The posterior probability for the true VE greater than 30% is 74.18%.

Table 20. Vaccine Efficacy – First Severe COVID-19 Occurrence From 14 Days After Dose 2 – Subjects With or Without Evidence of Infection Prior to 14 Days After Dose 2 – Evaluable Efficacy (14 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=19965)		Placebo (N[a]=20171)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First severe COVID-19 occurrence from 14 days after Dose 2	1	1.985 (17652)	3	2.007 (17792)	66.3	(-125.6, 96.3)	0.7418

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 14 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 17NOV2020 (16:47)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_sev_cov_14pd2_eval

6.3.4.2.3.4. Vaccine Efficacy for COVID-19 Cases Based on CDC Definition – Final Analysis

Efficacy Against COVID-19 Based on CDC-Defined Symptoms (≥7 Days After Dose 2)

Participants Without Evidence of Infection Before and During Vaccination Regimen – CDC Defined – 7 Days

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against CDC-defined COVID-19 (defined in Appendix 1) occurring at least 7 days after Dose 2 was 95.1% (2-sided 95% CI: 90.2%, 97.9%), with 8 and 165 cases in the BNT162b2 and placebo groups, respectively (Table 21).

Table 21. Vaccine Efficacy – First COVID-19 Occurrence Based on CDC-Defined Symptoms From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint	**n1[b]**	**Surveillance Time[c] (n2[d])**	**n1[b]**	**Surveillance Time[c] (n2[d])**	**VE (%)**	**(95% CI[e])**
First COVID-19 occurrence based on CDC-defined symptoms from 7 days after Dose 2	8	2.213 (17399)	165	2.220 (17495)	95.1	(90.2, 97.9)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 18NOV2020 (07:39)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_7pd2_wo_cdc_eval

Participants With and Without Evidence of Infection Before and During Vaccination Regimen – CDC Defined – 7 Days

Among participants with and without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against CDC-defined COVID-19 occurring at least 7 days after Dose 2 was 94.7% (2-sided 95% CI: 89.8%, 97.6%), with 9 and 172 cases in the BNT162b2 and placebo groups, respectively (Table 22).

Table 22. Vaccine Efficacy – First COVID-19 Occurrence Based on CDC-Defined Symptoms From 7 Days After Dose 2 – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=19965)		Placebo (N[a]=20172)			
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence based on CDC-defined symptoms from 7 days after Dose 2	9	2.330 (18544)	172	2.343 (18690)	94.7	(89.8, 97.6)

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 18NOV2020 (07:39)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_7pd2_cdc_eval

6.3.4.3. Efficacy Conclusions from Study C4591001

The first primary efficacy objective met success criteria at the first interim analysis performed on an accrued 94 cases of COVID-19. BNT162b2 achieved VE of 95.5% with a 95% credible interval of 88.8% to 98.4% among participants without evidence of infection before and during vaccination regimen, and a >99.99% posterior probability for the true VE being >30%, conditioning on available data.

In the final efficacy analysis, among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE for the first primary efficacy endpoint against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%, with 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group. The 95% credible interval for the VE was 90.3% to 97.6%, indicating that the true VE is at least 90.3% with a 97.5% probability given the available data. For the second primary endpoint, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 in participants with and without evidence of SARS-CoV-2 infection before and during vaccination regimen was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively. The posterior probability of >99.99% for the true VE greater than 30% met the prespecified success criterion of >98.6% for this endpoint. The 95% credible interval for the VE was 89.9% to 97.3%, indicating that the true VE is at least 89.9% with a 97.5% probability given the available data.

Observed VE was very high for the first primary efficacy endpoint across subgroups of age, sex, race/ethnicity, and country, as VE was >93% in all subgroups, with the exception of "all others" race group (89.3% VE) and Brazil (87.7% VE). In participants with comorbidities, VE was >91% for the first primary efficacy endpoint in all risk subgroups analyzed.

A total of 10 cases of severe COVID-19 occurred after Dose 1, 1 in the BNT162b2 group, compared with 9 cases in the placebo group. After Dose 2 (≥7 days after Dose 2), 1 case of severe COVID-19 was observed in the BNT162b2 group, and 4 in the all-available placebo groups respectively. These findings are consistent with the overall high VE against COVID-19.

Among all participants (regardless of evidence of infection before or during the vaccination regimen) 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared with 275 cases in the placebo group, indicating an estimated VE of 82% (95% CI: 75.6%, 86.9%) against confirmed COVID-19 occurring after Dose 1, with VE of 52.4% (95% CI: 29.5%, 68.4%) between Dose 1 and Dose 2.

The early onset of protection is readily apparent from cumulative incidence curves, which show that disease onset tracks conjointly for BNT162b2 and placebo until approximately 14 days after Dose 1, at which point the curves diverge, with cases steadily accumulating in the placebo group, while remaining virtually flat after BNT162b2.

In conclusion, the final efficacy results show that BNT162b2 at 30 μg provided protection against COVID-19 in participants who had no evidence of prior infection with SARS-CoV-2, including across demographic subgroups, with severe cases observed predominantly in the placebo group.

7. PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY PLAN

The collection of safety data in vaccine recipients is critical to progress our understanding of the vaccine safety profile and to enable efficient safety signal detection and further risk mitigation after an EUA of the Pfizer-BioNTech COVID-19 Vaccine. In addition to the collection and monitoring of AEs reported voluntarily by healthcare professionals providing the vaccine and individuals receiving the vaccine, three post-authorization active surveillance epidemiologic safety studies, employing primary and secondary data collection methods, are planned to characterize the real-world incidence of safety events of interest, including events indicative of severe or atypical COVID-19 disease, among individuals vaccinated with the Pfizer-BioNTech COVID-19 Vaccine under an EUA.

Active surveillance of large numbers of individuals vaccinated with the Pfizer-BioNTech COVID-19 Vaccine is necessary to confirm the safety profile demonstrated in the clinical study in the short-, medium-, and long-term in a broader population studied for a longer duration as well as at-risk subpopulations, as possible (ie, people >85 years of age or pregnant people). Individuals receiving vaccine under EUA provide the earliest opportunity to initiate these studies. Pfizer-BioNTech plan to conduct active surveillance studies of individuals vaccinated with Pfizer-BioNTech COVID-19 Vaccine in populations anticipated to be eligible for vaccine in the early stages of the EUA (eg, healthcare workers and active military). Additional populations will be sought for inclusion as vaccine roll-out staging expands. The studies will be conducted for 30 months and will capture hospitalization, death, and other adverse events of special interest

(including severe COVID-19) and compare observed rates to appropriate comparator populations to explore the theoretical risk of VAED. Additionally, the availability of medical record data permits the evaluation of unspecified but emergent safety events of interest.

Pfizer will conduct test-negative design studies to demonstrate effectiveness against severe endpoints including hospitalization and emergency department visits and in specific populations (eg, by race/ethnicity, elderly, nursing home residents, and healthcare workers). These studies will help to understand vaccine effectiveness in real-world conditions and in broader populations. These studies will complement other effectiveness studies planned by the CDC.

An EUA Safety Surveillance Study Plan and a Pharmacovigilance Plan were submitted as part of the EUA application. These plans are summarized below.

Pharmacovigilance

As per usual pharmacovigilance practice, Pfizer will collect and analyze all AEs reported to Pfizer by individuals, such as vaccinated persons and health care providers. To strengthen this data collection, Pfizer has implemented a new web-based tool for capture of AEs. All such reports are subsequently shared by Pfizer with CDC's Vaccine Adverse Event Reporting System (VAERS) as per regulations. The analyses conducted by Pfizer aim to identify patterns of adverse events in time or persons suggesting potential association with vaccine (ie, signal detection). For identified signals, next steps for further evaluation may include careful case review, characterization of the context in which individual events occur, review of clinical data, review of literature, or conduct a study designed to make formal statistical comparisons within a defined sampling frame.

Pharmacoepidemiology

Multiple long-term pharmacoepidemiology safety studies will be conducted. Three studies will identify cohorts of persons in the US receiving vaccine and estimate the incidence rate of adverse events of special interest over a 30-month period following vaccine availability under the EUA. These studies are designed to enable comparison with unvaccinated rates. Two secondary data analysis studies will include all patients documented as receiving vaccine within Department of Defense and Veteran's Healthcare Administration, which cover 10 million and 18 million lives, respectively. A third primary data collection study aims to enroll 20,000 health care workers vaccinated with Pfizer-BioNTech COVID-19 Vaccine. These large studies conducted over a long period of time will allow for the study of rare outcomes in diverse populations including subgroups not yet studied in the clinical trial such as pregnant, immunocompromised and very elderly (>85 years of age) persons.

Four additional pharmacoepidemiology safety studies (two in the US, two in the EU), are planned for implementation post-approval by respective regulatory agencies. Taken together these planned studies employ a variety of data sources and analytic methods that are intended to complement FDA/CDC active surveillance safety monitoring initiatives.

Proactive Risk Minimization

Pfizer is also taking multiple enhanced measures to proactively mitigate risks in addition to routine labeling activities including: EUA Fact Sheets for both vaccination providers and recipients, development of multiple educational materials for providers emphasizing key messages about appropriate handling, storage, and preparation of the vaccine to ensure the safe handling and administration of the vaccine and the assurance of complete vaccination regimen. Multiple methods will be utilized to instruct providers and vaccine recipients to report any adverse events. In addition, Pfizer will employ near real-time monitoring, and will communicate as necessary with vaccination sites during cold-chain distribution to ensure quality of the product.

Collaboration with Vaccine Safety Stakeholders

Finally, we have planned these enhanced activities with input from and coordination with external vaccine policy experts including CDC. To ensure transparency, our results will be exchanged with a planned vaccine safety subcommittee that will enable communication between government agencies and manufacturers and the public. Additionally, through this effort, we will learn of emerging safety signals that we will then follow up on in our studies.

8. RISK/BENEFIT ASSESSMENT

The ongoing COVID-19 pandemic has a significant impact on public health, and currently there is no broadly effective treatment or prevention available. An effective vaccine can impact the pandemic at this critical time. According to the Institute for Health Metrics and Evaluation, there will be >55,000 deaths per month in the US over the next few months.[25] A COVID-19 vaccination program implemented soon can likely prevent many deaths.[26] A vaccine must be introduced before the peak of reported cases to have a significant impact on the pandemic course.[26,27] A highly effective vaccine, with sufficient uptake as supplies become available, may be able to induce population herd immunity to bring the pandemic under control.[28]

The available clinical evidence for Pfizer-BioNTech COVID-19 Vaccine effectiveness includes induction of strong immune responses and overwhelmingly high VE, suggesting the vaccine confers protection against COVID-19 in individuals ≥16 years of age.

The potential risks are based on the observed safety profile to date, which shows mostly mild reactogenicity, low incidence of severe or serious events, and no clinically concerning safety observations. The vaccine appears to be safe and well-tolerated across the safety population and within demographic subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status. The preponderance of severe cases of COVID-19 in the placebo group relative to the BNT162b2 group (9 of 10) suggests no evidence of VAED.

Vaccine efficacy was remarkably high in participants without evidence of prior SARS-CoV-2 infection, at ≥95% for participants without prior evidence of SARS-CoV-2 infection and >94% for those with and without prior infection, in the planned interim and final analyses. Observed VE was >93% across subgroups identified by age, sex, race/ethnicity, and country with the exception of “all others” race group (89.3% VE) and Brazil (87.7% VE).

Severe cases evaluated for efficacy were confined predominantly to the placebo group; only 1 severe case was reported in the BNT162b2 group in the final analysis. The efficacy data suggest

highly effective protection against COVID-19 in a broad population of individuals across demographic characteristics. The efficacy, safety, and immunogenicity data in this EUA application support a positive assessment of risks and benefits for the Pfizer-BioNTech COVID-19 Vaccine and fulfil the data requirements outlined in the FDA EUA guidance. The registrational Phase 1/2/3 Study, C4591001, will continue as long as possible per protocol to monitor participants and obtain additional data to support a BLA filing in the near future. An extensive post-authorization plan has been prepared to monitor and evaluate the safety of Pfizer-BioNTech COVID-19 Vaccine in persons vaccinated under an EUA.

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Appendix 1. COVID-19 Case Definition

Participants who developed any potential COVID-19 symptoms listed in the protocol were to contact the site immediately and, if confirmed, to participate in an in-person or telehealth visit as soon as possible (optimally within 3 days of symptom onset). At the visit, investigators were to collect clinical information and results from local standard-of-care tests sufficient to confirm a COVID-19 diagnosis.

Investigators were to obtain a nasal swab (mid-turbinate) for testing at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA) to detect SARS-CoV-2. If the evaluation was conducted by telehealth, the participant was to self-collect a nasal swab and ship for assessment at the central laboratory. A local nucleic acid amplification test (NAAT) result was acceptable if it met protocol-specified criteria.

Identification of participants with or without evidence of prior infection was determined by virological testing via NAAT on mid-turbinate swab or serological testing for N-antigen antibodies.

COVID-19 cases were defined by SARS-CoV-2 positive test result per central laboratory or local testing facility (using an acceptable test) and presence of at least 1 of the following:

- 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

CDC criteria-defined COVID-19 cases could include the following additional symptoms:

- Fatigue
- Headache
- Nasal congestion or runny nose
- Nausea

Severe COVID-19 cases (defined per FDA guidance) included at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness:
  - Respiratory rate ≥30 breaths per minute
  - Heart rate ≥125 beats per minute
  - SpO_2 ≤93% on room air at sea level or PaO_2/FiO_2 <300 mm Hg

- Respiratory failure:
  - Needing high-flow oxygen

  - Noninvasive ventilation
  - Mechanical ventilation
  - ECMO

- Evidence of shock:
  - Systolic blood pressure <90 mm Hg
  - Diastolic blood pressure <60 mm Hg
  - Requiring vasopressors

- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to an intensive care unit
- Death.

Source: US Food and Drug Administration. Development and Licensure of Vaccines to Prevent COVID-19. Guidance for Industry. June 2020. Available at: https://www.fda.gov/media/139638/download.

Appendix 2. Targeted Medical Events of Potential Clinical Interest for Safety Review

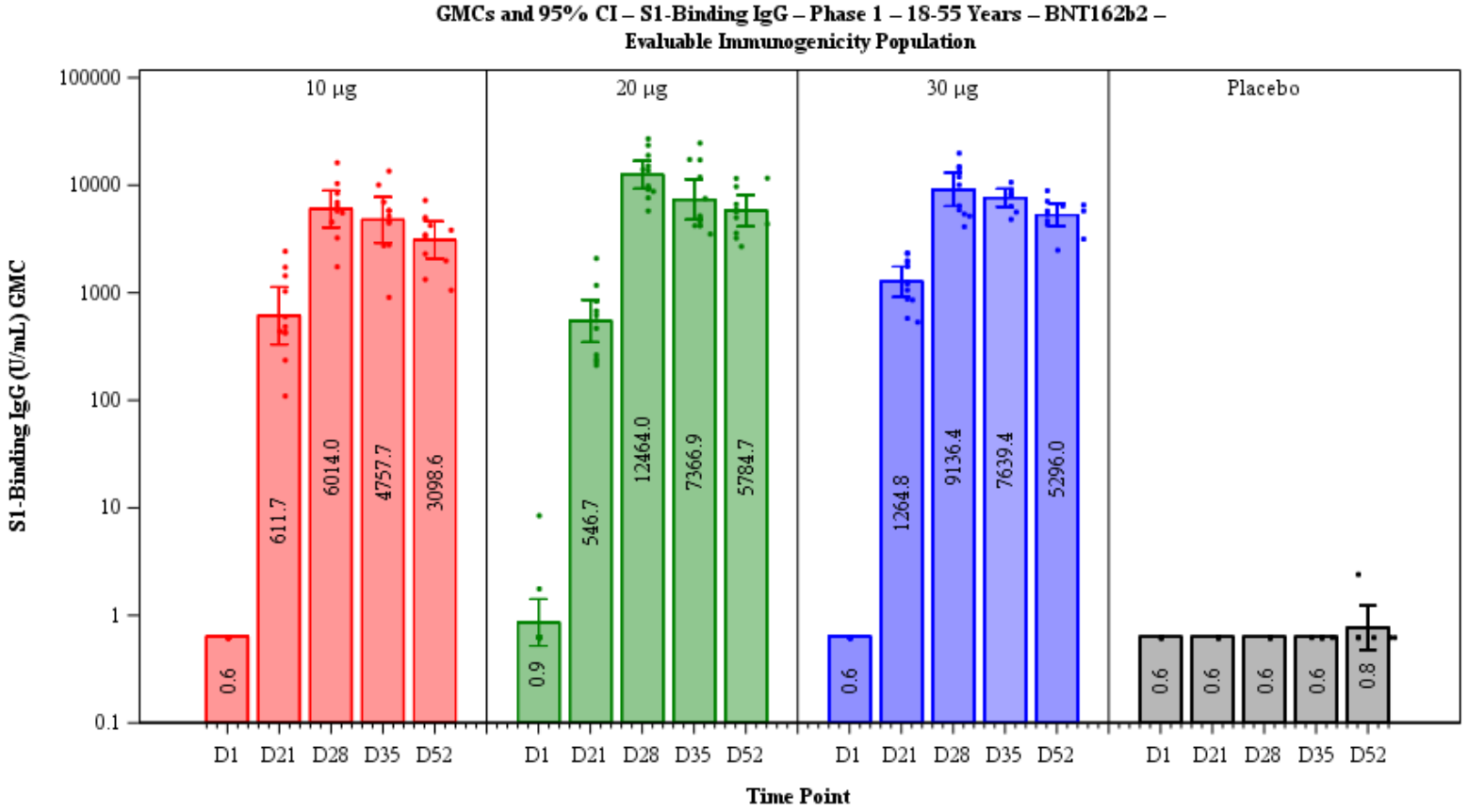
At the time of the EUA application, highlighted TMEs for special attention during review of safety data (based on terms which may be expected to be related to COVID-19 or are of general interest in vaccine surveillance) are:

Anaphylactic reaction (SMQ)	Fibromyalgia
Convulsions (SMQ)	Haemorrhage
COVID-19 (SMQ)	Haemorrhagic disorder
Demyelination (SMQ)	Hypersensitivity
Immune-mediated/autoimmune disorders (SMQ)	Inflammation
Liver related investigations, signs and symptoms (SMQ)	Kawasaki's disease
Autoimmune disorders	Liver injury
Herpes viral infections	Manufacturing laboratory analytical testing issue
Leukopenias NEC	Manufacturing materials issue
Lower respiratory tract infections NEC	Manufacturing production issue
Neutropenias	Meningitis
Respiratory failures (excl neonatal)	Meningitis aseptic
Vasculitides	MERS-CoV test
Viral lower respiratory tract infections	MERS-CoV test negative
Acute kidney injury	MERS-CoV test positive
Acute myocardial infarction	Microangiopathy
Acute respiratory distress syndrome	Middle East respiratory syndrome
Adverse event following immunisation	Multiple organ dysfunction syndrome
Ageusia	Myocardial infarction
Arrhythmia	Narcolepsy
Arthralgia	Occupational exposure to communicable disease
Arthritis	Patient isolation
Ataxia	Peripheral ischaemia
Cardiac failure	Polyneuropathy
Cardiogenic shock	Post viral fatigue syndrome
Cataplexy	Product availability issue
Cerebrovascular accident	Product distribution issue
Chillblains	Product supply issue
Chronic fatigue syndrome	Pulmonary embolism
Coronary artery disease	Pyrexia
Cytokine release syndrome	Quarantine
Cytokine storm	SARS-CoV-1 test
Deep vein thrombosis	SARS-CoV-1 test negative
Disseminated intravascular coagulation	SARS-CoV-1 test positive
Embolism	Severe acute respiratory syndrome
Embolism venous	Stress cardiomyopathy
Endotracheal intubation	Tachycardia
Facial paralysis	Thrombocytopenia

Note: list of targeted medical events current as of 12 November 2020.

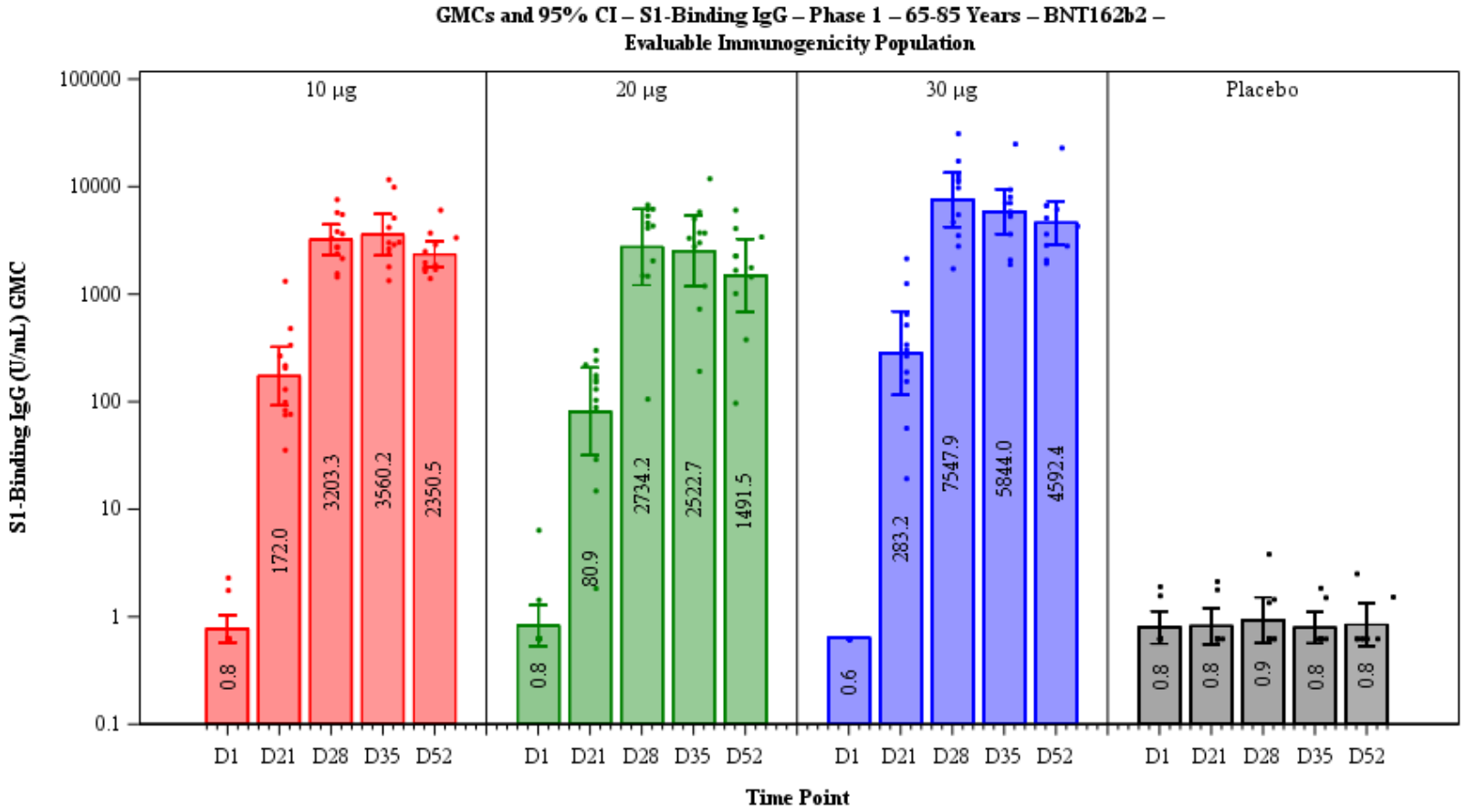
Appendix 3. Supplemental Figures – Study C4591001 Phase 1

Figure A3.1. Geometric Mean Concentrations and 95% CI: SARS-CoV-2 S1-binding IgG Level Assay – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b2 – Evaluable Immunogenicity Population



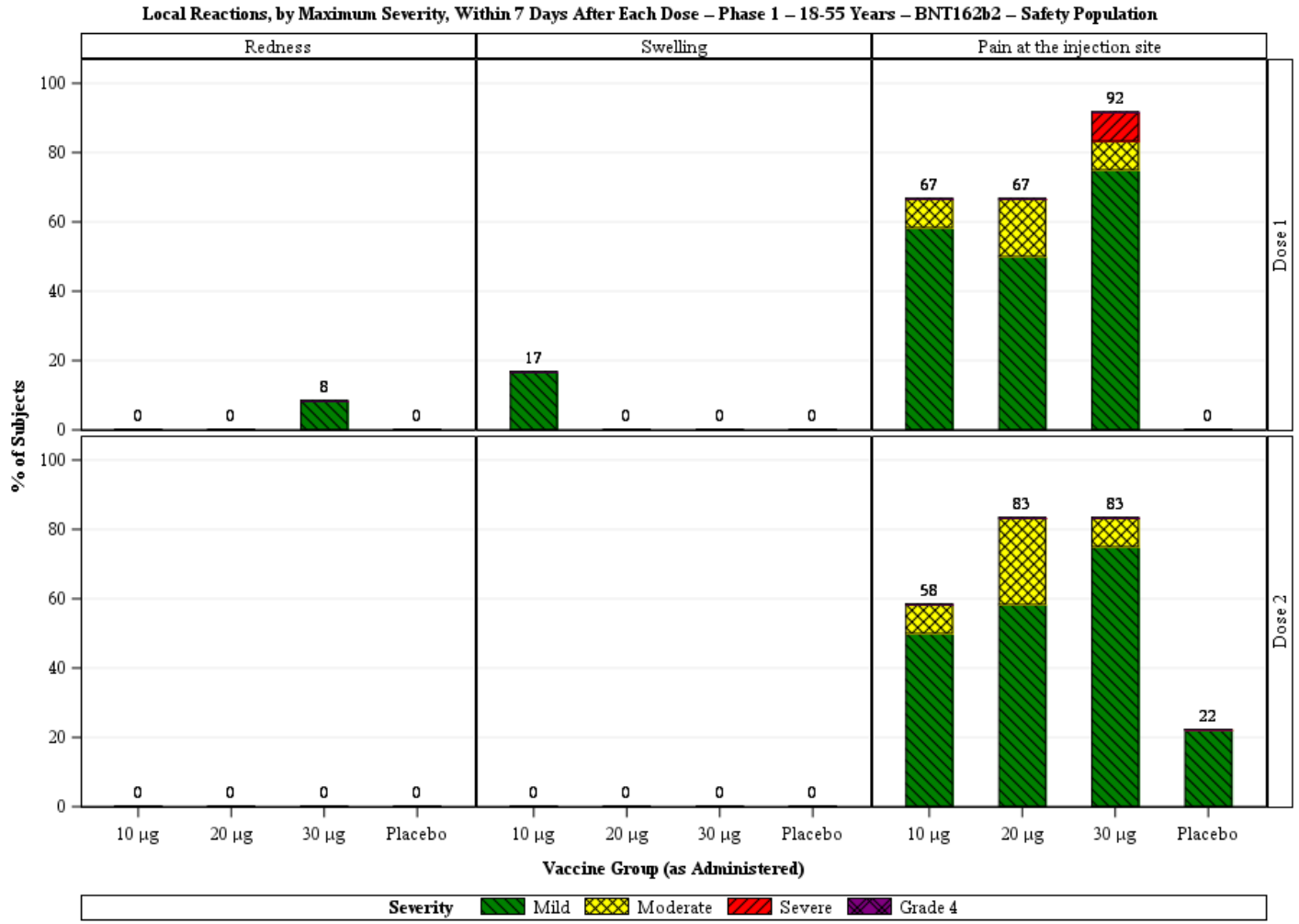
Abbreviations: GMC = geometric mean concentration; IgG = immunoglobulin G; S1 = spike protein S1 subunit.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: ./nda3/C4591001_IA_P1_Serology/adva_f002_s1_18_b2_p1

Figure A3.2. Geometric Mean Concentrations and 95% CI: SARS-CoV-2 S1-binding IgG Level Assay – Phase 1, 2 Doses, 21 Days Apart – 65-85 Years of Age – BNT162b2 – Evaluable Immunogenicity Population



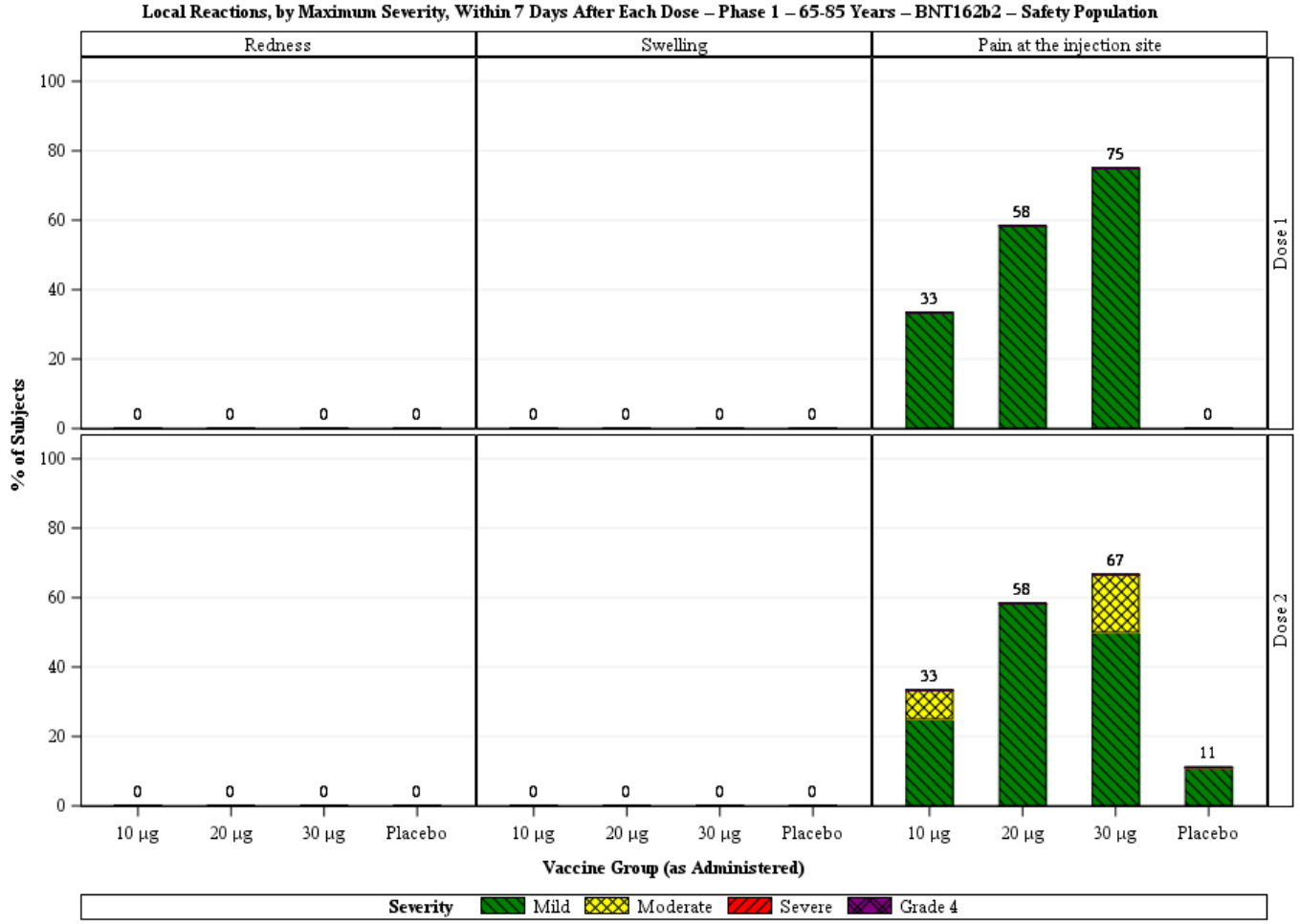
Abbreviations: GMC = geometric mean concentration; IgG = immunoglobulin G; S1 = spike protein S1 subunit.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: ./nda3/C4591001_IA_P1_Serology/adva_f002_s1_65_b2_p1

Figure A3.3. Subjects Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b2 – Safety Population



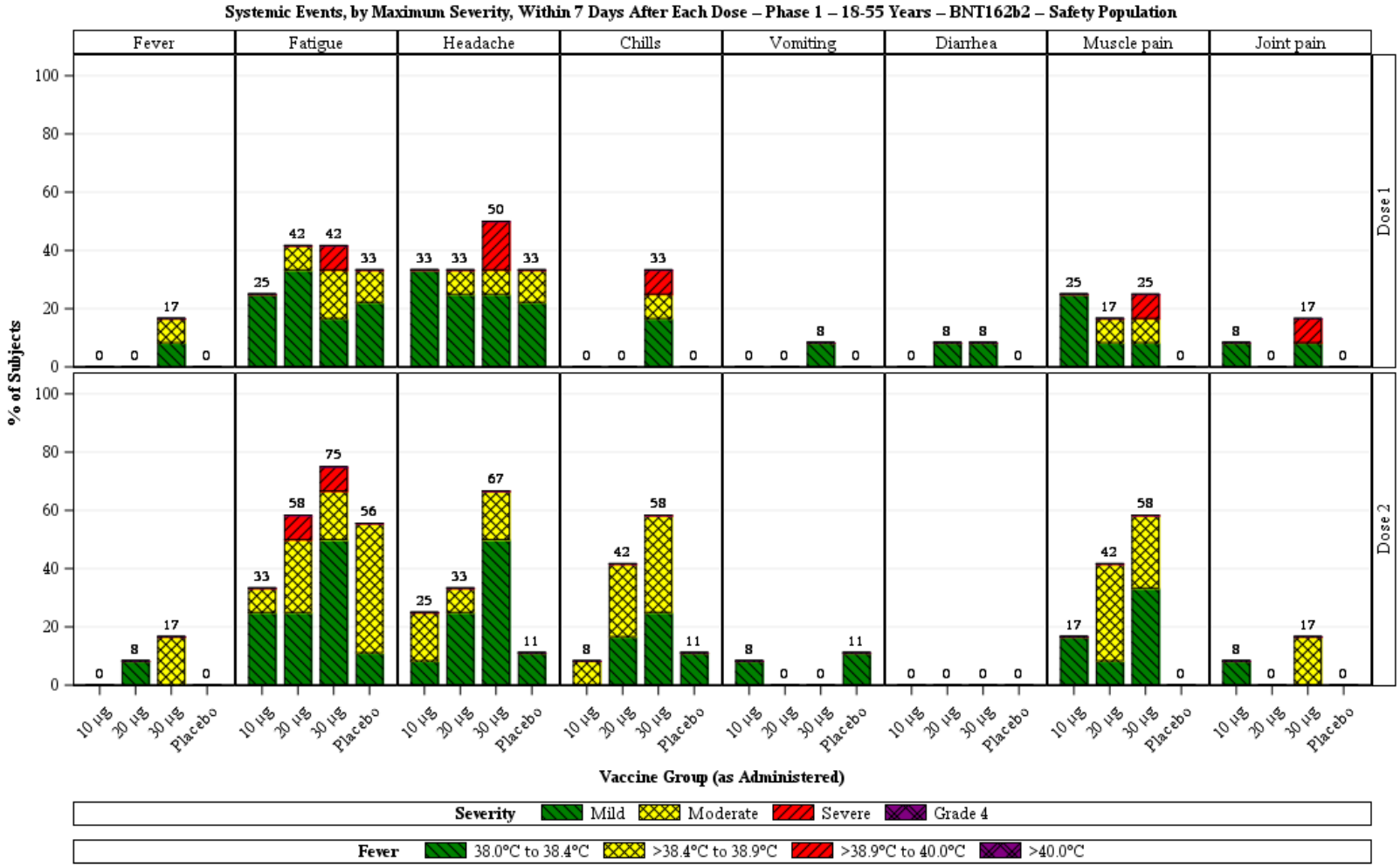
Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 28AUG2020 (16:29) Source Data: adfacevd Table Generation: 29AUG2020 (00:51)
(Cutoff Date: 24AUG2020, Snapshot Date: 28AUG2020) Output File: (CDISC)/C4591001_IA_P1/adce_f001_lr_maxsev_18_b2_p1

Figure A3.4. Subjects Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 1, 2 Doses, 21 Days Apart – 65-85 Years of Age – BNT162b2 – Safety Population



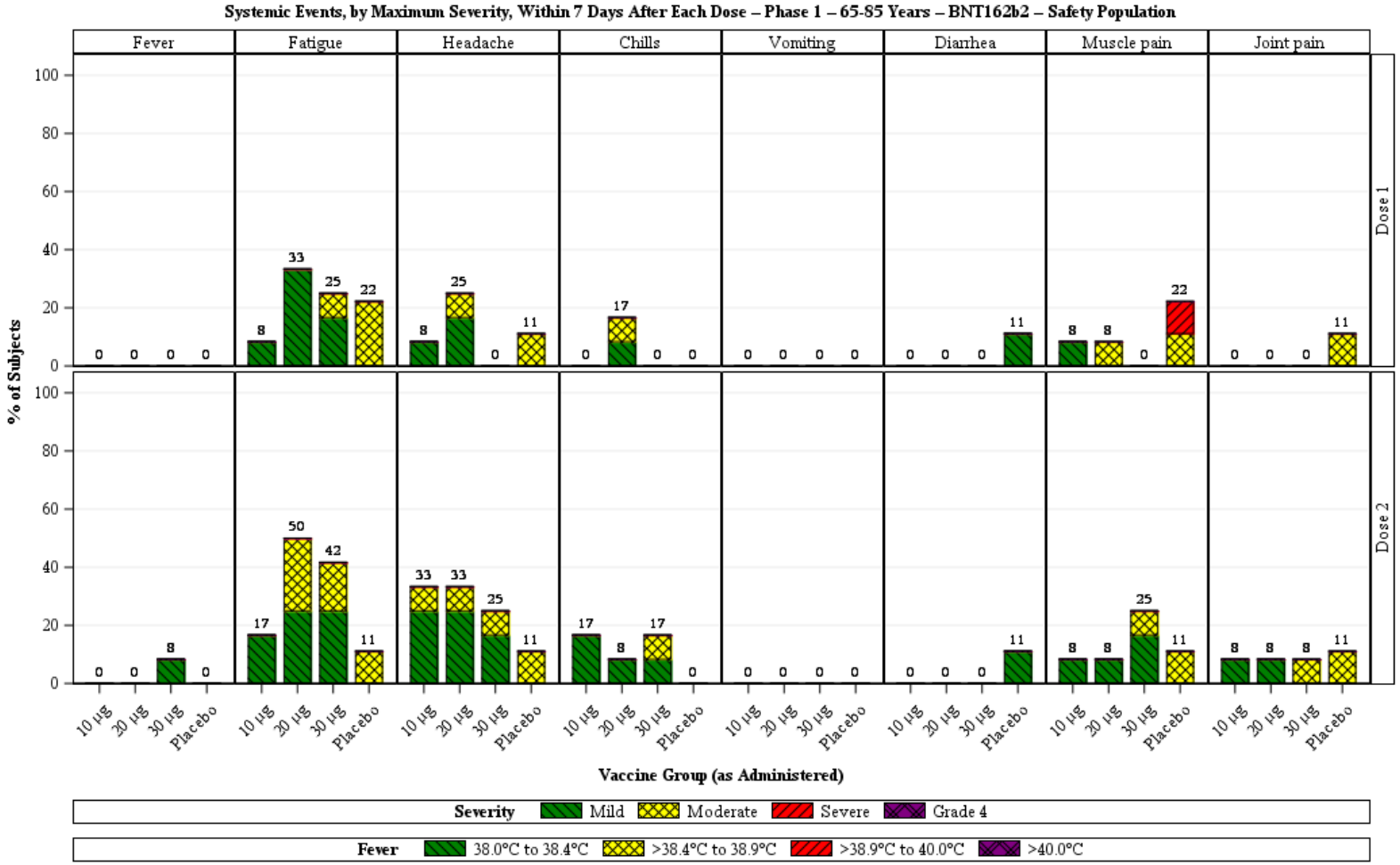
Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 28AUG2020 (16:29) Source Data: adfacevd Table Generation: 29AUG2020 (00:51)
(Cutoff Date: 24AUG2020, Snapshot Date: 28AUG2020) Output File: (CDISC)/C4591001_IA_P1/adce_f001_lr_maxsev_65_b2_p1

Figure A3.5. Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b2 – Safety Population



Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 28AUG2020 (16:29) Source Data: adfacevd Table Generation: 29AUG2020 (00:51)
(Cutoff Date: 24AUG2020, Snapshot Date: 28AUG2020) Output File: (CDISC)/C4591001_IA_P1/adce_f001_se_maxsev_18_b2_p1

Figure A3.6. Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1, 2 Doses, 21 Days Apart – 65-85 Years of Age – BNT162b2 – Safety Population



Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 28AUG2020 (16:29) Source Data: adfacevd Table Generation: 29AUG2020 (00:52)
(Cutoff Date: 24AUG2020, Snapshot Date: 28AUG2020) Output File: (CDISC)/C4591001_IA_P1/adce_f001_se_maxsev_65_b2_p1

Appendix 4. Supplemental Tables

Table 23. Number (%) of Subjects Reporting at Least 1 Serious Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – ~38000 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=18801)		Placebo (N[a]=18785)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	103 (0.5)	(0.4, 0.7)	81 (0.4)	(0.3, 0.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Lymphadenopathy	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Neutropenia	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Thrombocytopenia	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
CARDIAC DISORDERS	14 (0.1)	(0.0, 0.1)	12 (0.1)	(0.0, 0.1)
Atrial fibrillation	2 (0.0)	(0.0, 0.0)	3 (0.0)	(0.0, 0.0)
Acute myocardial infarction	3 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Acute coronary syndrome	1 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Cardiac failure congestive	1 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Myocardial infarction	0	(0.0, 0.0)	2 (0.0)	(0.0, 0.0)
Angina pectoris	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Angina unstable	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Aortic valve incompetence	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Arrhythmia supraventricular	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Arteriospasm coronary	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Bradycardia	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Coronary artery disease	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Coronary artery dissection	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Coronary artery occlusion	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Tachyarrhythmia	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Tachycardia	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Ventricular arrhythmia	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Heart disease congenital	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
EAR AND LABYRINTH DISORDERS	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Vertigo	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
EYE DISORDERS	2 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Choroidal neovascularisation	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Diplopia	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Retinal artery occlusion	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
GASTROINTESTINAL DISORDERS	8 (0.0)	(0.0, 0.1)	6 (0.0)	(0.0, 0.1)
Small intestinal obstruction	2 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Abdominal adhesions	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)

Table 23. Number (%) of Subjects Reporting at Least 1 Serious Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – ~38000 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=18801)		Placebo (N[a]=18785)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Abdominal pain upper	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Colitis	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Diarrhoea	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Diverticular perforation	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Gastrointestinal haemorrhage	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Intestinal obstruction	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Obstructive pancreatitis	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Oesophageal food impaction	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Pancreatic mass	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Pancreatitis	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Salivary gland calculus	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (0.0)	(0.0, 0.1)	3 (0.0)	(0.0, 0.0)
Chest pain	1 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Influenza like illness	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Non-cardiac chest pain	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Shoulder injury related to vaccine administration	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Unevaluable event	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Vascular stent occlusion	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
HEPATOBILIARY DISORDERS	4 (0.0)	(0.0, 0.1)	2 (0.0)	(0.0, 0.0)
Cholecystitis acute	0	(0.0, 0.0)	2 (0.0)	(0.0, 0.0)
Cholelithiasis	2 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Bile duct stone	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Cholecystitis	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
IMMUNE SYSTEM DISORDERS	2 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Anaphylactic reaction	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Anaphylactic shock	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Drug hypersensitivity	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
INFECTIONS AND INFESTATIONS	25 (0.1)	(0.1, 0.2)	14 (0.1)	(0.0, 0.1)
Appendicitis	7 (0.0)	(0.0, 0.1)	2 (0.0)	(0.0, 0.0)
Pneumonia	3 (0.0)	(0.0, 0.0)	5 (0.0)	(0.0, 0.1)
Cellulitis	2 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Urinary tract infection	2 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Appendicitis perforated	1 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Diverticulitis	2 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Pyelonephritis	2 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Suspected COVID-19	2 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Abscess	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Abscess intestinal	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)

Table 23. Number (%) of Subjects Reporting at Least 1 Serious Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – ~38000 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=18801)		Placebo (N[a]=18785)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Brain abscess	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Complicated appendicitis	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Empyema	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Osteomyelitis	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Peritoneal abscess	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Peritonitis	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Pharyngitis streptococcal	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Postoperative wound infection	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Pyelonephritis acute	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Staphylococcal infection	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Urosepsis	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	6 (0.0)	(0.0, 0.1)	11 (0.1)	(0.0, 0.1)
Facial bones fracture	2 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Road traffic accident	1 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Alcohol poisoning	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Cervical vertebral fracture	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Colon injury	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Flail chest	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Foot fracture	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Forearm fracture	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Hip fracture	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Lower limb fracture	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Multiple injuries	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Overdose	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Procedural haemorrhage	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Skin laceration	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Spinal cord injury cervical	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Toxicity to various agents	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Traumatic intracranial haemorrhage	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Ulna fracture	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
INVESTIGATIONS	1 (0.0)	(0.0, 0.0)	2 (0.0)	(0.0, 0.0)
Cardiac stress test abnormal	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Hepatic enzyme increased	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
SARS-CoV-2 test positive	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
METABOLISM AND NUTRITION DISORDERS	2 (0.0)	(0.0, 0.0)	3 (0.0)	(0.0, 0.0)
Fluid retention	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Hyperglycaemia	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Hypoglycaemia	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)

Table 23. Number (%) of Subjects Reporting at Least 1 Serious Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – ~38000 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=18801)		Placebo (N[a]=18785)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Hypokalaemia	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Type 2 diabetes mellitus	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Intervertebral disc protrusion	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Musculoskeletal chest pain	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Osteoarthritis	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Osteochondritis	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	7 (0.0)	(0.0, 0.1)	8 (0.0)	(0.0, 0.1)
Malignant melanoma	1 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Adenocarcinoma gastric	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Adrenal gland cancer	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Breast cancer	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Chronic myeloid leukaemia	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Hepatic cancer metastatic	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Intraductal proliferative breast lesion	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Invasive ductal breast carcinoma	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Leydig cell tumour of the testis	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Meningioma	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Metastases to central nervous system	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Penile neoplasm	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Prostate cancer	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Uterine leiomyoma	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
NERVOUS SYSTEM DISORDERS	15 (0.1)	(0.0, 0.1)	13 (0.1)	(0.0, 0.1)
Subarachnoid haemorrhage	4 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.0)
Syncope	1 (0.0)	(0.0, 0.0)	4 (0.0)	(0.0, 0.1)
Cerebrovascular accident	3 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Ischaemic stroke	1 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Transient ischaemic attack	2 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Cerebral infarction	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Diplegia	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Dizziness	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Haemorrhagic stroke	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Hemiplegic migraine	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Idiopathic intracranial hypertension	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Loss of consciousness	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Paraesthesia	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Transient global amnesia	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)

Table 23. Number (%) of Subjects Reporting at Least 1 Serious Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – ~38000 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=18801)		Placebo (N[a]=18785)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Uraemic encephalopathy	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Abortion spontaneous incomplete	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
PSYCHIATRIC DISORDERS	2 (0.0)	(0.0, 0.0)	4 (0.0)	(0.0, 0.1)
Suicidal ideation	0	(0.0, 0.0)	2 (0.0)	(0.0, 0.0)
Bipolar disorder	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Mental disorder	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Psychotic disorder	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Suicide attempt	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
RENAL AND URINARY DISORDERS	5 (0.0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.0)
Nephrolithiasis	2 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Acute kidney injury	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Renal colic	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Subcapsular renal haematoma	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Urinary bladder polyp	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Breast hyperplasia	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Ovarian cyst	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Ovarian mass	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Uterine prolapse	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5 (0.0)	(0.0, 0.1)	4 (0.0)	(0.0, 0.1)
Pneumonia aspiration	1 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Pulmonary embolism	1 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Acute respiratory failure	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Cough	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Dyspnoea	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Hypoxia	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Interstitial lung disease	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Pneumonitis	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Pulmonary mass	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
UNCODED TERM	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
JAMMED RIGHT INGUINAL HERNIA@@	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
VASCULAR DISORDERS	5 (0.0)	(0.0, 0.1)	3 (0.0)	(0.0, 0.0)
Deep vein thrombosis	1 (0.0)	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Hypertension	2 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)
Orthostatic hypotension	0	(0.0, 0.0)	2 (0.0)	(0.0, 0.0)
Arteriosclerosis	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)

Table 23. Number (%) of Subjects Reporting at Least 1 Serious Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – ~38000 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=18801)		Placebo (N[a]=18785)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Hypertensive urgency	1 (0.0)	(0.0, 0.0)	0	(0.0, 0.0)

Note: MedDRA (v23.1) coding dictionary applied.
Note: Preferred terms with @@ denote uncoded terms.
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.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (22:02) (Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adae_s130_1md2_ser_p3_saf