Australian Government
Department of Health
Therapeutic Goods Administration

Clinical Evaluation Report
Prescription Medicines Authorisation Branch

Active substance: BNT162b2 (COVID-19 mRNA Vaccine)

Product name: COMIRNATY

Sponsor: Pfizer Australia

Submission number: PM-2020-05461-1-2

eSubmission number: e005671

First round evaluator:

Date of first round report: 08/01/2021

TRIM reference:

Second round evaluator:

Date of second round report:

TRIM reference:

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TGA Health Safety Regulation

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- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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List of abbreviations

Abbreviation	Definition
ACE-2	angiotensin-converting enzyme 2
ADR	adverse reaction
AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
CBER	(US Food and Drug Administration) Center for Biologics Evaluation and Research
CDC	(US) Centers for Disease Control and Prevention
CFR	case fatality rate
CHMP	Committee for Human Products for Medicinal Use
CMC	chemistry, manufacturing, and controls
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CTA	Clinical Trial Agreement
DART	developmental and reproductive toxicity
DMC	(US Study C4591001) Data Monitoring Committee
ELISPOT	enzyme-linked immuno-spot
EMA	European Medicines Agency
ERD	(vaccine-induced) enhanced respiratory disease
EU	European Union
FACS	fluorescence-activated cell sorting
FDA	(US) Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GMFR	geometric mean-fold rise
GMT/GMC	geometric mean titer/concentration
HIV	human immunodeficiency virus
ICH	International Council on Harmonisation
ICU	intensive care unit
ID	intradermal(ly)
IFNγ	interferon-gamma
IL-2	interleukin-2
IL-4	interleukin-4
IM	intramuscular(ly)
IND	Investigational New Drug application
iPSP	initial Pediatric Study Plan
IRC	(US Study C4591001) Internal Review Committee
IRR	illness rate ratio
LLN	lower limit of normal
LNP	lipid nanoparticle
LPX	lipoplex
MERS	Middle East respiratory syndrome
MHRA	(UK) Medicines & Healthcare Products Regulatory Agency

Abbreviation	Definition
modRNA	nucleoside-modified messenger RNA
mRNA	messenger RNA
NAAT	nucleic acid amplification testing
NHP	non-human primate
P2 S	SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein
PDCO	Paediatric Committee
PCR	polymerase chain reaction
PEI	(German) Paul Ehrlich Institute
PIP	Paediatric Investigational Plan
RBD	receptor binding domain
RNA-LNP	RNA lipid nanoparticle
saRNA	self-amplifying messenger RNA
SRC	(German Study BNT162-01) Safety Review Committee
ssRNA	single-stranded RNA
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
S glycoprotein, S	spike glycoprotein
Th1/Th2	helper T cell type 1/type 2
UK	United Kingdom
uRNA	non-modified uridine containing mRNA
US	United States
USP	United States Pharmacopeia
VE	vaccine efficacy
WHO	World Health Organization

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1. Submission details

1.1. Identifying information

Submission number	PM-2020-05461-1-2
eSubmission number	e005671
eSubmission sequences covered in this report	0000, 0002 ,0003 and 0004
Sponsor	Pfizer Australia Pty Ltd
Trade name	COMIRNATY
Active substance	BNT 162b2 (COVID-19 mRNA VACCINE)

1.2. Submission type

The sponsor has submitted this Category 1, Type A (Provisional) application (PM-2020-05461-1-2) for the proposed registration of COVID-19 VACCINE (BNT 162b2 mRNA vaccine), for use in 16 years and above age .Terms COMIRNATY, BNT 162b2 and COVID-19 VACCINE have been used interchangeably in this report.

Provisional determination for COVID-19 VACCINE was granted under subsection 22D of the Act on 14 October 2020 (PM-2020-05357-1-2) (D20-3548425).

1.3. Drug class and therapeutic indication

COVID-19 mRNA Vaccine BNT162b2 is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced by cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

Proposed indication for COVID-19 mRNA Vaccine is –

Active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

1.4. Dosage forms and strengths

COVID-19 mRNA Vaccine is presented in a multidose vial and must be diluted before use. 1 vial (0.45 mL) contains 5 doses of 30 micrograms of BNT162b2 RNA (embedded in lipid nanoparticles).

1.5. Dosage and administration

Individuals 16 years of age and older

COVID-19 mRNA Vaccine BNT162b2 is administered intramuscularly after dilution as a series of two doses (0.3 mL each) 21 days apart.

Method of administration

Administer the COVID-19 mRNA Vaccine BNT162b2 vaccine intramuscularly in the deltoid muscle after dilution.

Do not inject the vaccine intra-vascularly, subcutaneously or intra-dermally.

Preparation: The multi-dose vial is stored frozen and must be thawed prior to dilution.

1.6. Proposed changes to the product documentation

Not applicable.

2. Background

2.1. Information on the condition being treated

Coronaviruses are a large family of viruses that cause respiratory infections. These can range from the common cold to diseases that are more serious.

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause.[1] The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus).[2] SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV).3 The SARS-CoV-2 spike glycoprotein (S), which is a main target for neutralizing antibody, binds to its receptor human angiotensin converting enzyme 2 (hACE2) to initiate infection.[3] SARS-CoV-2 is the cause of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

Symptoms of COVID-19 can range from mild illness to pneumonia. Most people will recover easily, and few may get very sick very quickly. People with coronavirus may experience symptoms including fever , coughing sore throat, shortness of breath etc. Other symptoms can include runny nose, headache, muscle or joint pains, nausea, diarrhoea, vomiting, loss of sense of smell, altered sense of taste, loss of appetite and fatigue.

The virus can spread from person to person through:

- close contact with an infectious person (including in the 48 hours before they had symptoms)
- contact with droplets from an infected person's cough or sneeze
- touching objects or surfaces (like doorknobs or tables) that have droplets from an infected person, and then touching your mouth or face.

COVID-19 is a new disease, so there is no existing immunity in our community. This means that COVID-19 could spread widely and quickly.[4]

COVID-19 is a disease caused by a new form of coronavirus. It was first reported in December 2019 in Wuhan City in China.

COVID-19 was first confirmed in Australia in late January 2020. Following table shows the total number of COVID-19 cases and deaths reported in each state and territory since 22 January 2020 till **8th December 2020**.

[1] Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *The New England journal of medicine.* 2020;382(8):727-733.
[2] Coronaviridae Study Group of the International Committee on Taxonomy of V. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2.
[3] Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020;181(2):271-280.e278.
[4] https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/what-you-need-to-know-about-coronavirus-covid-19#what-is-covid19

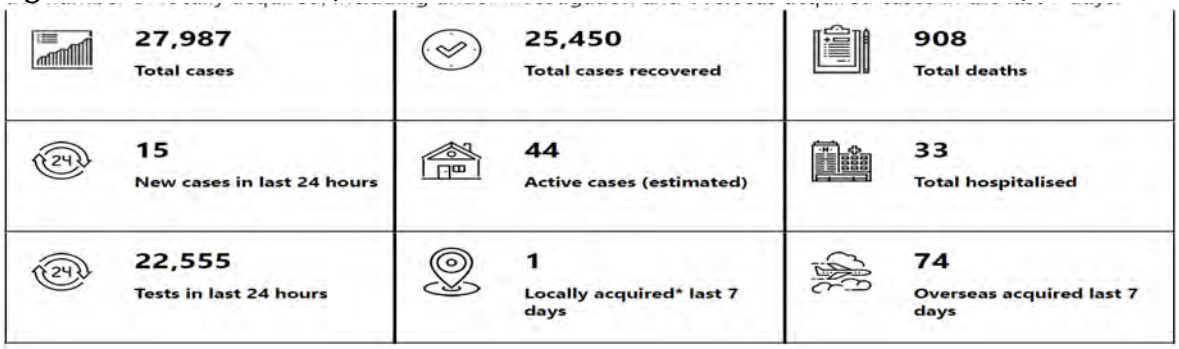
Table 1: state wise covid-19 cases (on 8 December 2020)

Source: Department of Health, States & Territories Report 8/12/2020

Jurisdiction	Total confirmed cases	New cases in last 24 hours	Deaths
Australia	27,987	15	908
ACT	117	0	3
NSW	4,620	6	53
NT	61	2	0
QLD	1,221	6	6
SA	562	0	4
TAS	230	0	13
VIC	20,345	0	820
WA	831	1	9

The following figure shows total number of COVID-19 cases, recovered cases and deaths recorded in Australia since 22 January 2020. The figure also includes the number of new cases and tests conducted in the last 24 hours and the current number of active and hospitalised cases.

Figure 1: COVID-19 cases, recovered cases and deaths recorded in Australia (on 8 December 2020)



2.2. Current treatment options

There are currently no approved vaccines in Australia to protect against SARS-CoV-2 infections or the COVID-19 disease. Mainstay of Covid-19 treatment is only supportive. Remdesivir is an antiviral drug , which is provisionally approved for used in a limited population (Patients who require supplemental oxygen). Thus, there is currently no adequate, approved, and available alternative for prevention of COVID-19.

2.3. Clinical rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019.

On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is still spreading globally.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries. There are currently no vaccines approved by the TGA to prevent or treat COVID-19, which is directly or indirectly affecting majority of Australian population. At

the time of the application for provisional approval for the Pfizer-BioNTech COVID-19 Vaccine (COMIRNATY) , new pockets of Covid-19 infection cluster are continuing to grow specially in the state of NSW and recently in Victoria. 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.

There is currently no well-tested vaccine approved in Australia to prevent SARS-CoV-2 viral infection or the disease it causes (COVID-19). There remains an urgent and unmet medical and public health need for a preventive vaccine. Vaccination is still 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 public health strategy to reduce COVID-19-related illnesses, hospitalizations, and deaths and to help restore societal functioning.

2.4. Formulation

2.4.1. Formulation development

COVID-19 Vaccine is based on an RNA-Lipid nanoparticles (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. The LNPs consists of four lipids, each has a functional or structural purpose. The formed RNA-containing LNPs are solid particles.. 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.

The BNT162b2 vaccine is provided in a multi-dose vial that contains a frozen concentrated solution that is preservative-free and must be thawed and diluted prior to administration. The BNT162b2 concentrate must be diluted in its original vial using 0.9% Sodium Chloride Injection, USP, resulting in an off-white suspension. The 0.9% Sodium Chloride Injection, USP is not packaged with the vaccine and must be sourced separately.

The concentrated multi-dose vaccine is stored frozen at -70 °C (±10 °C) to be thawed on the day of administration, diluted with sterile 0.9% Sodium Chloride Injection, USP and stored at 2-8 °C until administration.

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

2.4.2. Excipients

Two novel excipients are included in the finished product, the cationic lipid ALC-0315 and the PEGylated lipid ALC-0159. Limited information regarding the novel excipients are provided.

Following is the full list of the excipients:

- ALC-0315 = (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
- ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
- 1,2-Distearoyl-sn-glycero-3-phosphocholine
- Cholesterol
- Potassium chloride
- Monobasic potassium phosphate

- Sodium chloride
- Dibasic sodium phosphate dihydrate
- Sucrose
- Water for injections

2.5. Regulatory history

2.5.1. Australian regulatory history

New application.

2.5.2. Orphan drug designation

N/A

2.5.3. Related submissions

N/A

2.5.4. Overseas regulatory history

Emergency use approval has been granted (at the time of preparation of this report)by

- MHRA, EMA , US-FDA and Health Canada

2.6. Guidance

The evaluator referenced to the following guidance:

- Development and Licensure of Vaccines to Prevent COVID-19, Guidance for Industry https://www.fda.gov/media/139638/download
- Emergency Use Authorization for Vaccines to Prevent COVID-19, Guidance for Industry https://www.fda.gov/media/142749/download

TGA has not adopted a guidance specific for Covid-19 vaccine development at this stage. However, TGA has adopted following EMA guidelines for clinical evaluation of vaccines.

EMEA/CHMP/VWP/164653/2005 (Guideline on Clinical Evaluation of New Vaccines)

2.7. Evaluator's commentary on the background information

The background information provides sufficient rationale for this product including why the Sponsor is seeking provisional registration of the COMIRNATY for persons aged 16 years or older.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information (Majority of the evaluable data was submitted via sequence 0003) :

Module 1: Application letter, application form, draft Australian PI and CMI (submitted with sequence 0003); RMP.

Module 2: Clinical Overview; Summary of Clinical Efficacy; Summary of Clinical Safety; Literature References; details of drug product and drug substance.

Module 5:

1. Pivotal Study- **Study C4591001** , a Phase 1/2/3 Study
2. Supportive Study- **Study BNT162-01** , a Phase 1/2 study

3.2. Paediatric data

Submitted dossier contains paediatric data from 16 to 17 years age. Paediatric data for 12 years onward is planned to be submitted for a later date.

3.3. Good clinical practice

The sponsor provided assurance that the approvals to undertake the clinical studies were obtained from appropriately constituted institutional ethics committees/independent research boards, in accordance with the relevant national guidelines and regulations applicable. The studies presented in this Application were conducted in accordance with GCP.

3.4. Evaluator's commentary on the clinical dossier

The main objective of the clinical development programme for RNA-based SARS-CoV-2 vaccine candidate was to demonstrate clinical efficacy, immunogenicity and safety in persons aged 16 years or older. The submitted data with the application is appropriate and sufficient for clinical evaluation of the proposed provisional registration of BNT 162b2 mRNA vaccine (COMIRNATY).

4. Pharmacokinetics

Not applicable.

5. Pharmacodynamics (Immunogenicity)

5.1. Studies providing immunogenicity information

Immunogenicity data are derived from the following studies:

1. BNT162-01- Only Phase 1 data available.
2. C4591001-Phase 1 and phase 2 data

5.2. Summary of immunogenicity

Here phase 1 Immunogenicity data from study Study BNT162-01 and phase 1, 2 data from study C4591001 is discussed.

5.2.1. Phase 1 Immunogenicity Analysis

5.2.1.1. Study BNT162-01

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. The protocol was later amended to allow inclusion of older adult participants up to 85 years of age. However, only enterim data for 18 to 55 years of age are reported in this submission.

BNT162b1 group

A total of 84 participants in the 18 to 55 years of age group received Dose 1 of BNT162b1, 12 in each of the 7 dose level groups (1, 3, 10, 20, 30, 50, 60 μg). At the time of data cutoff, Dose 2 had been administered to a total of 63 participants: 12/12 participants in the 1 μg and 30 μg dose level groups, 11/12 participants in the 10, 20, and 50 μg groups, and 6/12 participants in the 3 μg group. No participants received the second dose of 60 μg BNT162b1 because the SRC recommended that a second dose of BNT162b1 at 60 μg not be administered due to reactogenicity observed after the second dose of 50 μg.

BNT162b2 group

A total of 60 participants 18 to 55 years of age received Dose 1 of BNT162b2, 12 in each of the 5 dose level groups for which data were available (1, 3, 10, 20, 30 μg). At the time of data cutoff, Dose 2 had been administered to a total of 43 participants: 8/12 participants in the 1 μg dose

level group, 11/12 participants in the 10 µg group, and 12/12 participants in the 20 and 30 µg groups.

T Cell Response Data

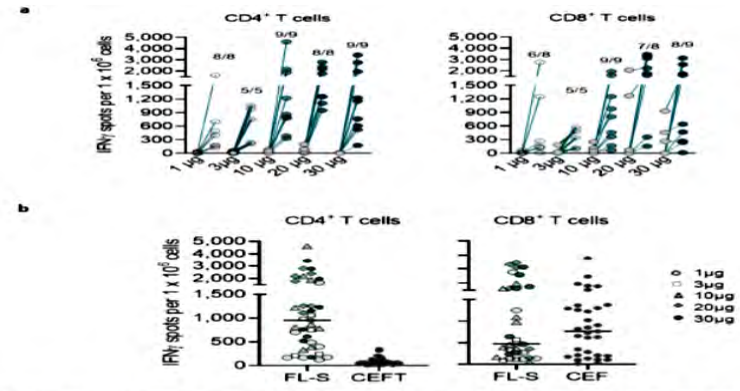
SARS-CoV-2 -specific CD4+ and CD8+ T-cell responses - ELISpot

Evaluable ELISpot data is provided for 62 participants, who received both doses of BNT162b1 (at 1, 3, 10, 20, 30, 50, 60 µg) and for 39 participants with both doses of BNT162b2 (at 1, 3, 10, 20, 30 µg).

BNT162b2 induced strong SARS-CoV-2 S protein-specific CD4+ and CD8+ T cell responses in 100% (39/39) and 89.7% (35/39) of participants, respectively.

BNT162b1 induced strong SARS-CoV-2 RBD-specific CD4+ and CD8+ T cell responses in 96.2% (51/53) and 77.4% (41/53) of participants, respectively.

Figure 2. Frequency and Magnitude of BNT162b2-induced CD4+ and CD8+ T-cell Responses across All Dose Levels (Study BNT162-01)



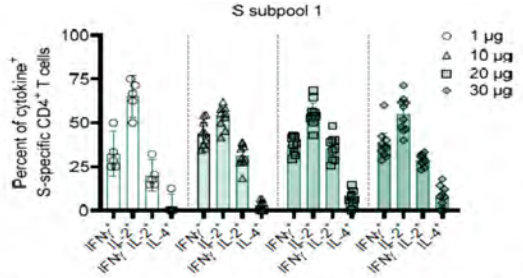
Peripheral blood mononuclear cell fractions obtained on Day 1 (pre-dose 1) and on Day 29 (7 d post-dose 2) were analyzed in ex vivo INFγ ELISpot. Common pathogen T-cell epitope pools CEF (CMV, EBV, influenza virus HLA class I epitopes) and CEFT (CMV, EBV, influenza virus, tetanus toxoid HLA class II epitopes) served to assess general T-cell reactivity; cell culture medium served as negative control. Each dot represents the sum of normalized mean spot count from duplicate wells stimulated with two peptide pools corresponding to the full length of the wild type S protein for one participant, after subtraction of the medium-only control. a. Ratios above post-dose data points are the number of subjects with detectable $CD4^+$ or $CD8^+$ T-cell response within the total number of tested participants per dose level. b. S protein-specific $CD4^+$ and $CD8^+$ T-cell responses in all participants with a positive response to S protein (n=22 for $CD4^+$ and n=19 for $CD8^+$ responses) and their baseline CEFT- and CEF-specific T-cell responses. Horizontal lines represent the median of each dose level.
CMV = Cytomegalovirus; CEF and CEFT = epitope pools; EBV = Epstein-Barr-Virus; ELISpot = enzyme-linked immuno-spot; FL-S = Full-length spike protein; HLA = human leukocyte antigen; INF = interferon.

Functional and Pro-inflammatory CD4+/CD8+ T-cell Responses

BNT162b2

PBMCs isolated from 36 participants 7 days after the second dose of BNT162b2 and stimulated with peptide pools representing the BNT162b2-encoded full length SARS-CoV-2 S protein demonstrated CD4+ T-cell responses with a Th1 cytokine profile, accumulating IFNγ or IL-2, or both, with only minor amounts of the Th2 cytokine IL-4 being produced **(Figure 3).**

Figure 3. S-specific CD4+ T-cells Producing the Indicated Cytokine as a Fraction of Total Cytokine-Producing S-specific CD4+ T-cells – BNT162b2 (Study BNT162-01)



Bar charts are arithmetic mean with 95% confidence interval. Cytokine production was calculated by summing up the fractions of all $CD4^+$ T-cells positive for either IFNγ, IL-2 or IL-4, setting this sum to 100% and calculating the fraction of each specific cytokine-producing subset thereof. Two participants from the 1 µg dose group and 1 subject from the 10 µg dose group were excluded from this analysis (frequency of total cytokine-producing $CD4^+$ T-cells < 0.03%).

S-specific CD8+ T-cells secreted IFNγ in 32/36 participants, and IL-2 secreting CD8+ T cells were also detectable. Overall, the mean fraction of S-specific CD4+ and CD8+ T cells was substantially higher than that observed in 18 patients who recovered from COVID-19 (eg, the S protein sub-pool 1 IFNγ CD8+ response of 30 µg recipients was 12.5-fold above).

BNT162b1

When PBMCs isolated from 63 participants who had received 2 doses of BNT162b1 were stimulated with peptides representing the vaccine-encoded SARS-CoV-2 RBD, CD4+ T-cell responses had a Th1 cytokine profile, predominantly accumulating IFNγ or IL-2, or both, while there was no production of Th2 cytokine IL-4 in samples from 60/63 participants.

Similarly, RBD-specific CD8+ T-cells secreted IFNγ in 46/63 participants, although lower levels of IL-2 secreting CD8+ cells were detected, as compared to CD4+ T-cells. The mean fraction of both RBD-specific CD4+ and CD8+ cytokine-producing T cells (ie, as a fraction of total circulating CD4+ or CD8+ T cells) in participants who received both doses of BNT162b1 was substantially higher than that observed in 15 patients who recovered from COVID-19 (eg, 11-fold above for 30 µg recipients). At the 60-µg dose level, which was only dosed once, mean fractions of cytokine-producing T-cells were lower compared to the other dose groups, indicating the importance of the second dose.

Serological Response Data

At the data cut-off, following results for serum neutralizing titres and binding antibody concentrations were available:

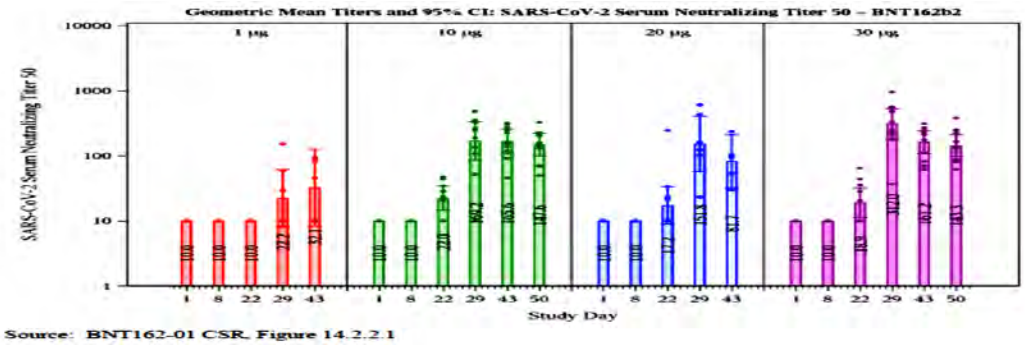
- BNT162b1: 60 participants in 5 dose level groups: 12 participants each in the 1 µg, 10 µg, 30 µg, 50 µg, and 60 µg groups.
- BNT162b2: 45 participants in 4 dose level groups: 9 in the 1 µg group, and 12 participants each in the 10 µg, 20 µg, and 30 µg groups.

SARS-CoV-2 Serum 50% Neutralizing Titers

BNT162b2 – 50% Neutralizing Titers

After Dose 1 of BNT162b2 at the 10, 20, and 30 µg dose levels, SARS CoV-2 50% neutralizing GMTs increased modestly from Day 1 to Day 22 (Figure 4), with substantial further increases observed 7 days after Dose 2 (Day 29). The highest GMTs were observed in the 30 µg group. GMTs decreased slightly from Day 29 to Day 43 and/or Day 50 in the 10, 20, and 30 µg dose level groups.

Figure 4. Geometric Mean Titers and 95% CI: SARS-CoV-2 Serum Neutralizing Titer 50 for Subjects Age 18-55 Years - BNT162b2 Immunogenicity Set (Study BNT162-01)



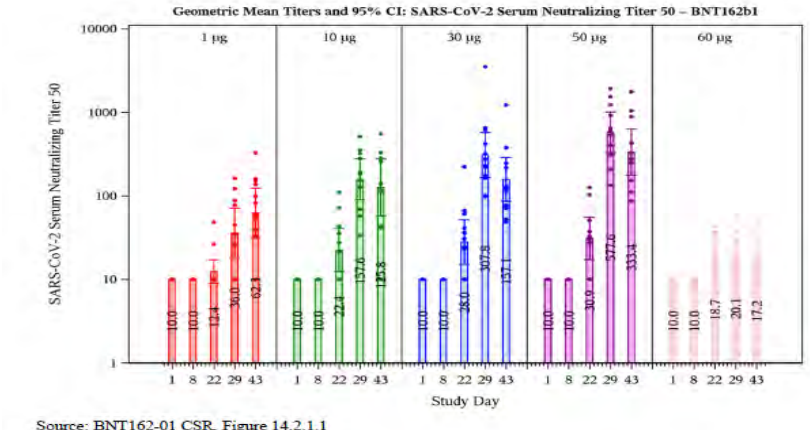
Source: BNT162-01 CSR, Figure 14.2.2.1

BNT162b1 – 50% Neutralizing Titers

After Dose 1 of BNT162b1, across all dose level groups, SARS-CoV-2 50% neutralizing GMTs increased modestly from Day 1 to Day 22 (Figure 5), with substantial further dose level

dependent increases observed 7 days after Dose 2 (Day 29) (except in the 60 µg dose group, which did not receive Dose 2). In the 60 µg dose group, neutralizing GMTs remained at a lower level, indicating that a booster dose is required to elicit a robust functional antibody response. GMTs decreased slightly from Day 29 to Day 43 in the 10, 30, and 50 µg dose level groups.

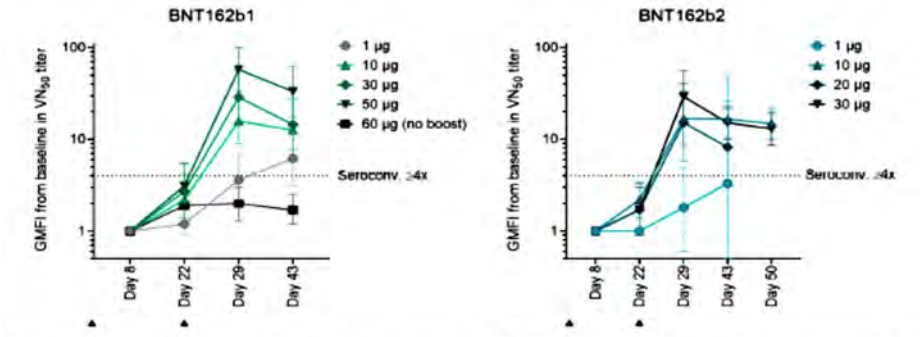
Figure 5. Geometric Mean Titers and 95% CI: SARS-CoV-2 Serum Neutralizing Titer 50 for Subjects Age 18-55 Years - BNT162b1 Immunogenicity Set (Study BNT162-01)



Geometric Mean Fold-Rise (GMFR) in 50% Neutralizing Titers

Results for GMFRs in SARS-CoV-2 50% neutralizing titers are consistent with the data described above for GMTs. For both vaccines, GMFRs from before vaccination to 7 days after Dose 2 (Day 29) were substantially higher compared to the respective GMFRs 21 days after Dose 1, and GMFRs declined slightly by Day 43.

Figure 6. Fold Increase From Baseline in Functional 50% SARS-CoV-2 Neutralizing Antibody Titers – BNT162b1 and BNT162b2 – Immunogenicity Set (Study BNT162-01)



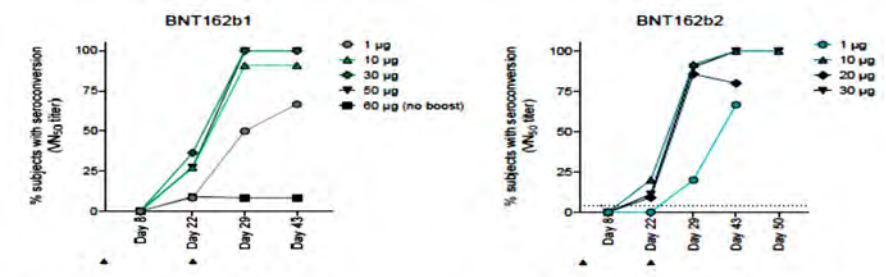
Geometric means fold increase (GMFI) from baseline in SARS-CoV-2 serum 50% neutralizing titer with 95% confidence intervals are shown for both BNT162b1 and BNT162b2 dose levels. Arrowheads indicate baseline (dose 1, Day 1) and dose 2 (Day 22). Dose 2 was not performed in the 60 µg dose group. The dotted horizontal line represents the threshold for seroconversion (fold increase ≥4).

Proportion of Participants Achieving ≥4-Fold Rise in 50% Neutralizing Titers

BNT162b2

By 7 days after Dose 2 of BNT162b2 (Day 29), the proportions of participants achieving a ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from baseline were 91.7% (11/12) in the 10 µg group, 85.7% (6/7) in the 20 µg group, and 90.0% (9/10) in the 30 µg dose level group (Figure 7). On both Day 43 and Day 50, the proportions were 100% in the 10 µg and 30 µg groups (data were incomplete for the 20 µg group).

Figure 7. Frequency of Subjects with SARS-CoV-2 GMT Seroconversion - BNT162b1 and BNT162b2 – Immunogenicity Set (Study BNT162-01)



Seroconversion is defined as a minimum of 4-fold increase of functional antibody response as compared to baseline. Note: At the cut-off date for this report, only limited data for the 20 µg dose level was available (7 sera evaluable for Day 29, 4 sera evaluable for Day 43).

BNT162b1

By 7 days after Dose 2 of BNT162b1 (Day 29), the proportions of participants achieving a ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from baseline were 90.9% (10/11 participants) in the 10 µg dose level group and 100% (11/11 participants) in both the 30 µg and the 50 µg groups.

SARS-CoV-2 Antigen-Specific Binding Antibody Concentrations

As measured by S1- and RBD-binding IgG GMCs, both BNT162b1 and BNT162b2 elicited strong, dose-dependent antibody responses.

Immunogenicity Conclusion

T Cell Responses

Based on the ELISpot and ICS assay results, BNT162b1 and BNT162b2 induced poly-functional and pro-inflammatory CD4+/CD8+ T cell responses in most participants. Re-stimulation of PBMCs with peptide pools representing the encoded antigens (RBD or full-length S protein) demonstrated a helper response characterized by a robust IFNγ/IL-2 response and only minor IL-4 production. This cytokine profile indicates a favourable Th1 response and only a minimal Th2 immune response.

Serological Responses

- For both BNT162b1 and BNT162b2, only modest immune responses were apparent by 21 days after Dose 1, while Dose 2 elicited rapid increases in neutralizing titers, with maximal response levels achieved by 7 days after Dose 2 (Day 29). These results demonstrate the importance of receiving 2 doses of investigational vaccine.
- Results for SARS-CoV-2 Serum 50% neutralizing titer GMTs and GMFRs for the 10 µg and 30 µg dose level groups were similar between BNT162b1 and BNT162b2.

5.2.1.2. Study C4591001 (Phase 1)

Study C4591001 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 trial.

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

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

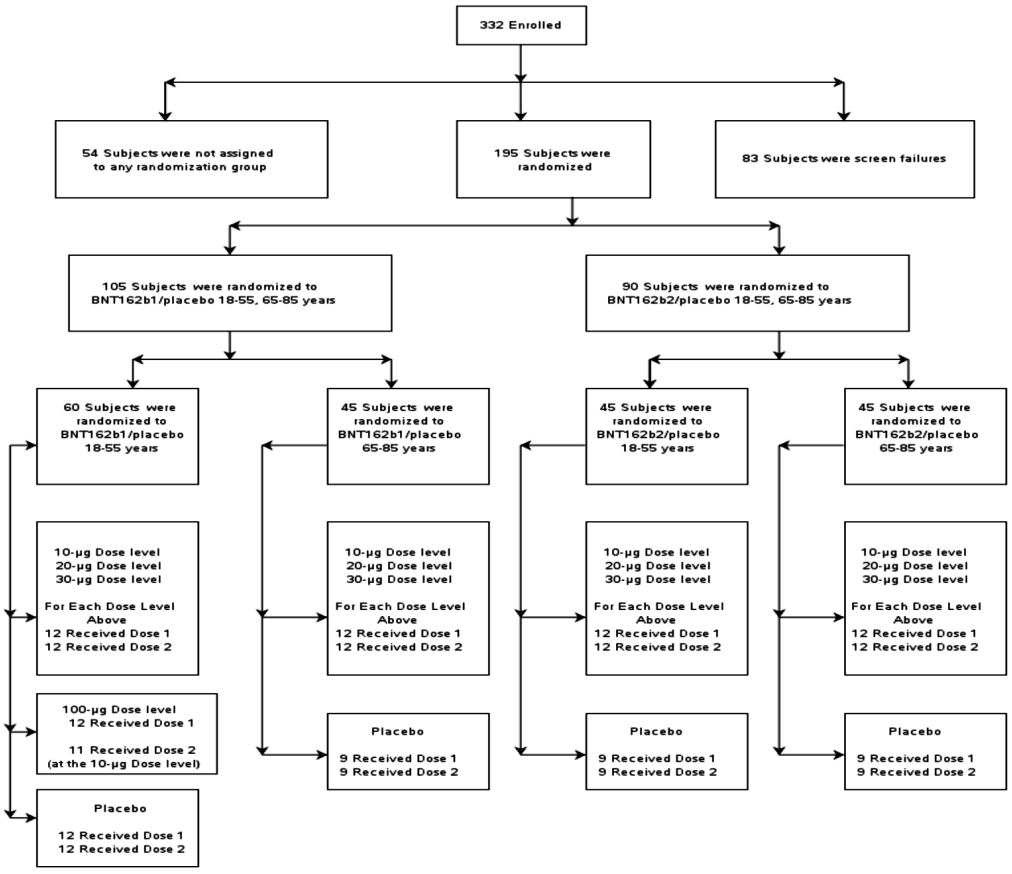
A total of 195 participants were randomized in 2 age groups (18-55 or 65-85 years of age) to receive 2 doses of BNT162b1 or placebo (N=105) or BNT162b2 or placebo (N=90).

In each age group, 15 participants were randomized at each successive dose level (eg, 10 µg, 20 µg, 30 µg) to receive either active vaccine (N=12) or placebo (N=3). In both the younger and older age groups, all participants randomized to BNT162b1 10-µg, 20-µg, and 30-µg dose groups and the corresponding placebo groups received both doses of BNT162b1 or placebo, and all participants randomized to BNT162b2 10-µg, 20-µg, and 30-µg dose groups and the corresponding placebo groups received both doses of BNT162b2 or the placebo.

In the BNT162b1 100-µg dose group, all 12 participants in the younger age group who were randomized received Dose 1. However, based on observed reactogenicity after Dose 1, a second dose not be administered. As of the data cutoff date, 11 of12 participants in this group had received 10 µg BNT162b1 for their second dose; and after the data cutoff date, the remaining participant received Dose 2 of BNT162b1 at 10 µg.

The 3 participants in the corresponding control group each received both Dose 1 and Dose 2 of placebo. In the older age group, 100-µg BNT162b1 was not administered.

Figure 8. Disposition of All Phase 1 Participants



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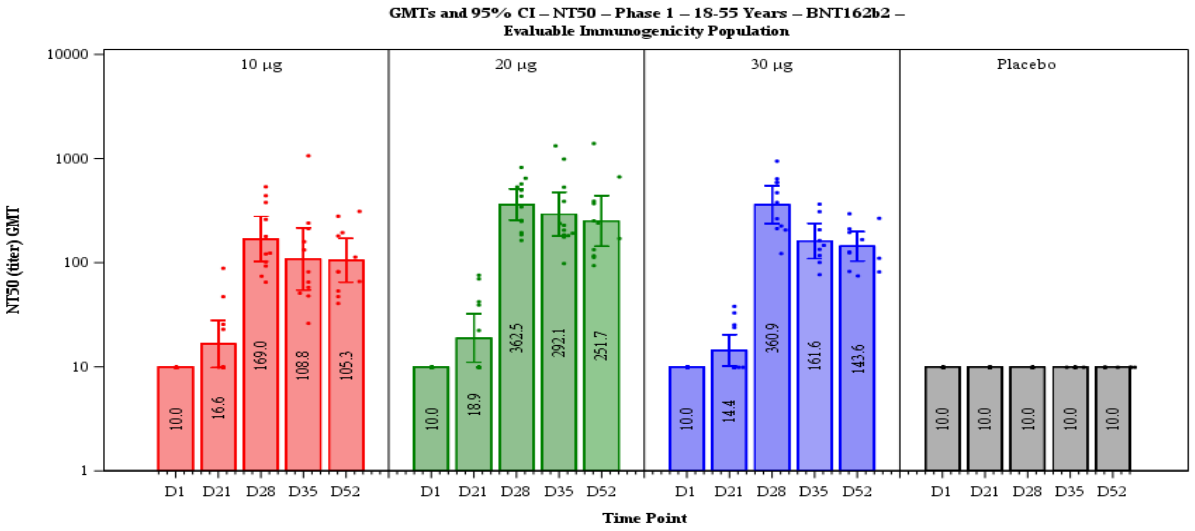
(Cutoff Date: 24AUG2020, Snapshot Date: 28AUG2020) Output File: (CDISC)/C4591001_IA_P1/consort_p1

SARS-CoV-2 Neutralizing Titers

Geometric Mean Titers

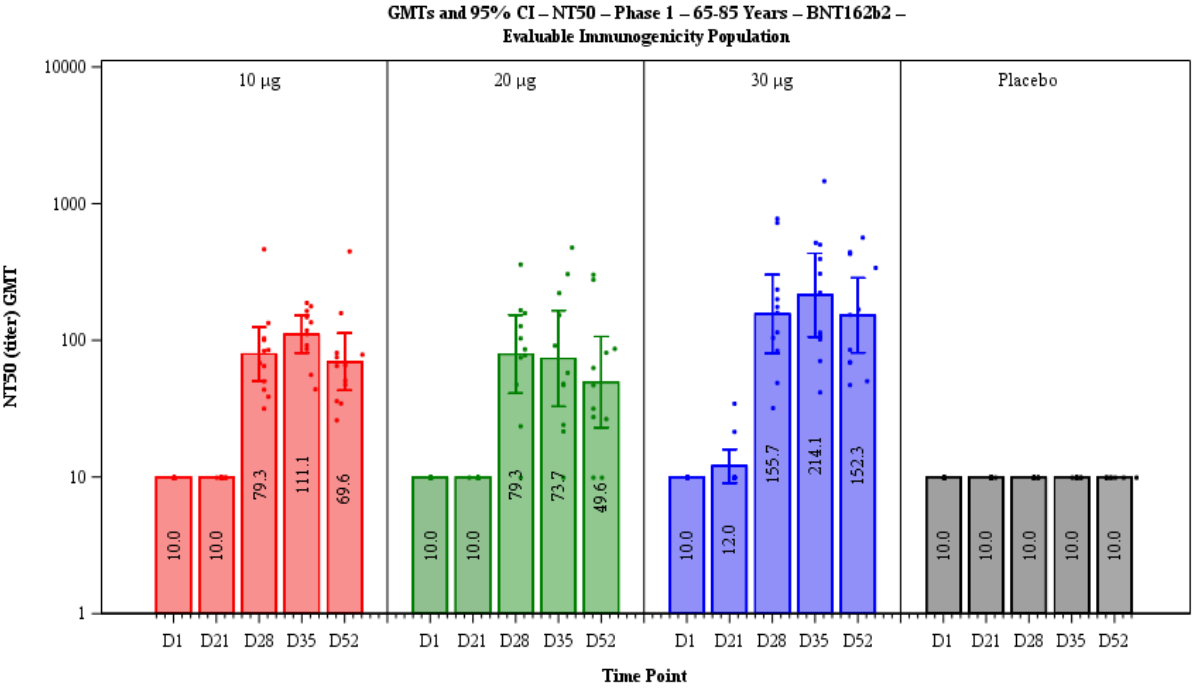
For both BNT162b1 and BNT162b2 recipients in both age groups, SARS-CoV-2 50% neutralizing GMTs modestly increased by Day 21 after Dose 1 and were substantially increased 7 days after Dose 2. At most time points, for both BNT162b1 and BNT162b2 recipients, GMTs in the older age group tended to be lower than GMTs in the younger age group at the same dose level.

Figure 9. 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 10. 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

Geometric Mean Fold-Rise (GMFR)

For the BNT162b1 and the BNT162b2 recipients, and in both age groups, GMFRs of SARS-CoV-2 50% neutralizing titers from before vaccination to 7 days after Dose 2 (Day 28) were

substantially higher compared to GMFRs 21 days after Dose 1. Among both BNT162b1 and BNT162b2 recipients, GMFRs in the older age group were generally lower than those in the younger age group at the same dose level.

Proportion of Participants Achieving ≥4-Fold Rise

Overall, for both BNT162b1 and BNT162b2 recipients, and in both age groups, most participants achieved a ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination to 7 days after Dose 2, except for participants receiving the 10-µg BNT162b1 dose in the older age group.

SARS-CoV-2 Antigen-Specific Binding IgG Levels

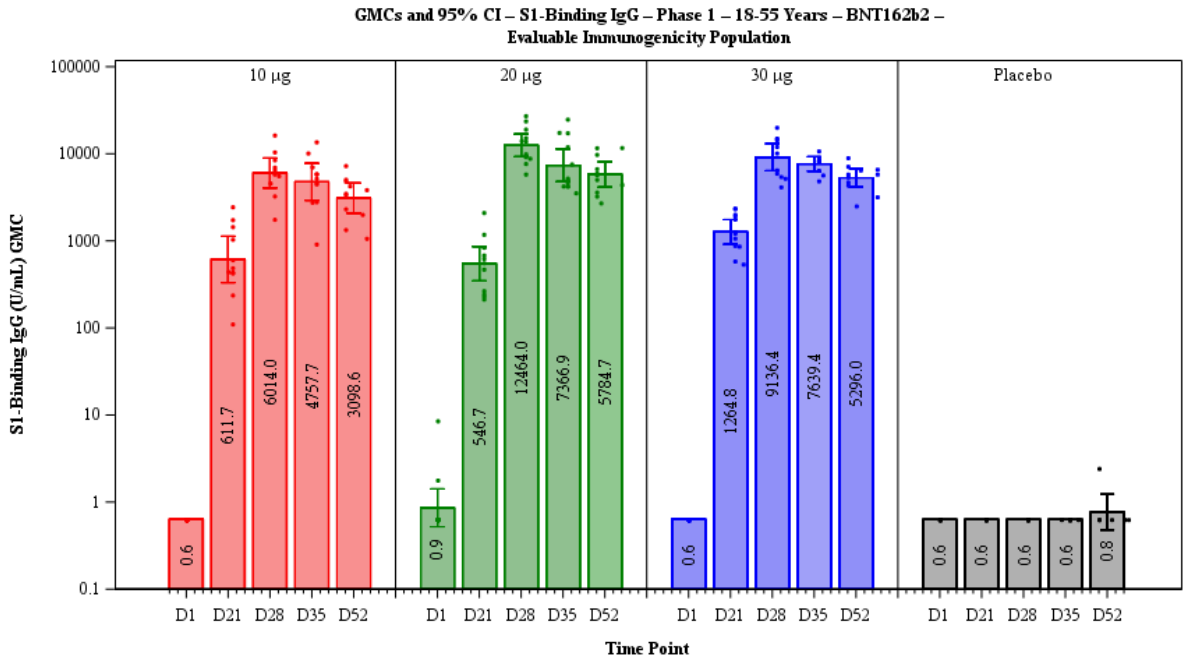
Vaccine candidate BNT162b2 encodes the P2 S, and BNT162b1 encodes the RBD of SARS-CoV-2. In this section, RBD-binding IgG responses are described for BNT162b1, and S1-binding IgG responses are described for BNT162b2.

Both BNT162b1 and BNT162b2 elicited substantial rises in antigen binding IgG levels 7 days after Dose 2, based on GMCs, GMFRs, and proportions of participants achieving a ≥4-fold rise in IgG-antigen specific binding. Responses were maintained through Day 52.

Geometric Mean Concentrations

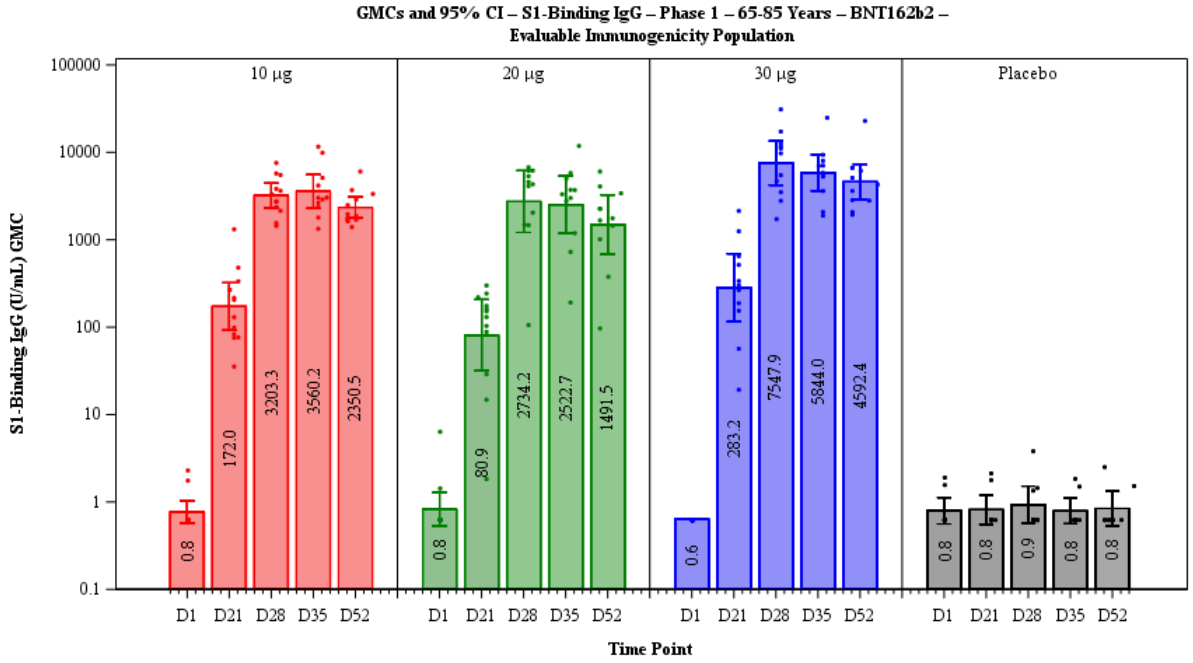
Overall, for both BNT162b1 and BNT162b2 recipients, and in both age groups, RBD- and S1-binding GMCs increased substantially by Day 21 after Dose 1 and were further increased 7 days after Dose 2. GMCs in the older age group were generally lower than the GMCs in the younger age group at the same dose level.

Figure 11. 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 12. 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

Geometric Mean Fold-Rise (GMFR)

For BNT162b1 and BNT162b2 recipients, and in both age groups, GMFRs of SARS-CoV-2 antigen-specific binding IgG were substantially higher 7 days after Dose 2 (Day 28) than 21 days after Dose 1. GMFRs peaked by 7 days or 14 days after Dose 2, and although decreased by 1 month after Dose 2, GMFRs at this time point were still substantially higher than at Day 21 after Dose 1.

Proportion of Participants Achieving ≥4-Fold Rise

BNT162b1-In both age groups, 100% of participants in each dose level group achieved a ≥4-fold rise in RBD-binding IgG levels at all time points after Dose 2 of BNT162b1, except for the 20-µg dose group at Day 7 after Dose 2 (91.7% in the younger age group). Similar trends were observed for participants achieving a ≥4-fold rise in S1-binding IgG levels after BNT162b1

BNT162b2- In both age groups, 100% of participants in each dose level group achieved a ≥4-fold rise in S1-binding IgG levels at all time points after Dose 2 of BNT162b2.Similar trends were observed for participants achieving a ≥4-fold rise in RBD-binding IgG levels after BNT162b2.

Geometric Mean Ratio (GMR – Neutralizing Titers/IgG Antigen Binding Levels)

The geometric mean ratio (GMR) of SARS-CoV-2 neutralizing titers to SARS-CoV-2 antigen-specific binding IgG levels provides a relative measure of the functional neutralizing antibody titer elicited per antigen-specific IgG concentrations across vaccine candidates and dose levels within each age group.

Overall, for BNT162b1 and BNT162b2 recipients, GMRs of SARS-CoV-2 50% neutralizing titers to RBD- or S1-binding IgG levels show a more robust RBD- or S1-binding levels relative to neutralizing titers, which were similar within each age group.

Study C4591001 Phase 1 Conclusions

Overall, the immunogenicity responses were similar between the 2 candidates. When selecting the dose level for Phase 2/3, the major driver was maximizing SARS-CoV-2 neutralizing antibody responses in the older age group, who are at highest risk of severe disease. A 2-dose vaccination series of BNT162b2 at 30 μg demonstrated a robust immune response in both younger and older adults.

Overall Phase 1 Conclusions

The Phase 1 immunogenicity data from both Studies C4591001 and BNT162-01 collectively showed robust immunogenicity elicited by BNT162b2 in both younger and older adults at the 30 μg dose level, which was ultimately selected to proceed to Phase 2/3 development.

In the Phase 1 part of Study C4591001, both BNT162b1 and BNT162b2 elicited robust SARS-CoV-2 neutralization and antigen-specific IgG binding in younger and older adults as shown by GMTs/GMCs, GMFRs, and proportions of participants achieving a ≥4-fold rise in neutralizing titers and antigen-binding IgG levels.

- Both BNT162b1 and BNT162b2 vaccine candidates demonstrated robust SARSCoV-2 neutralization and substantial rises in IgG-antigen binding levels following the second dose across dose levels and age groups.
- In older adults, who are at higher risk of severe COVID-19 disease, the neutralizing response to BNT162b2 was highest at the 30 μg dose level compared to the 20 μg dose level, favoring the 30 μg dose level for Phase 2/3 development.
- Study BNT162-01 provides evidence for robust T cell-mediated immunity, with antigen-induced IFN_γ expression demonstrating a Th1 CD4+ and CD8+ phenotype following the second dose of either BNT162b1 or BNT162b2.
- Immunogenicity data from Study BNT162-01 were generally concordant with results in pivotal Study C4591001, showing robust SARS CoV-2 neutralization and substantial rises in IgG-antigen binding levels following the second dose and complimentary T cell immune response data.

5.2.2. Phase 2 Immunogenicity Analysis

5.2.2.1. Study C4591001

The 360 participants enrolled as part of Phase 2 were randomized equally to the BNT162b2 and placebo groups (180 participants each). Among participants randomized to the BNT162b2 group, 88 participants were in the younger age group (18 to 55 years of age) and 92 participants were in the older age group (56 to 85 years of age) .

All 360 participants received both doses of study vaccine, except for 1 participant in the younger age group who was withdrawn from the study after Dose 1 of BNT162b2 but before Dose 2 because of an SAE of gastric adenocarcinoma 23 days after receiving Dose 1.

Immunogenicity results are only provided for the pre-vaccination and 1-month post Dose 2 time point.

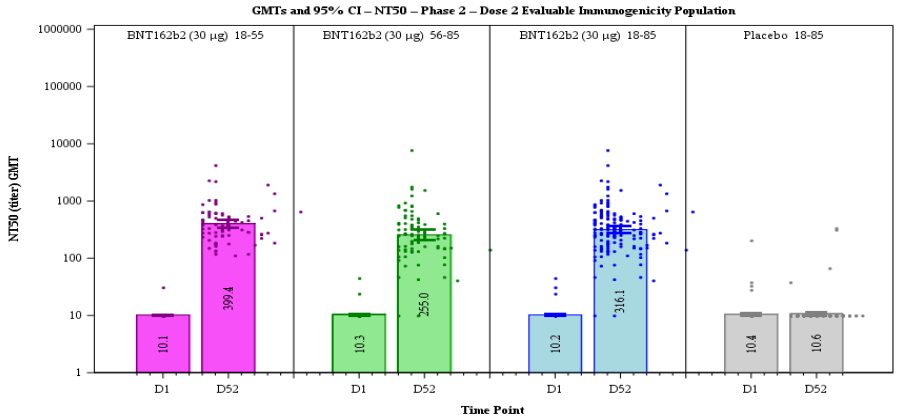
SARS-CoV-2 Neutralizing Titers and S1-Binding IgG Concentrations

Geometric Mean Titers/Concentrations (GMTs/GMCs)

BNT162b2 elicited robust SARS-CoV-2 immune responses at 1 month after Dose 2 as measured by both SARS-CoV-2 50% neutralizing titers (GMTs) and S1-binding IgG concentrations (GMCs). GMTs/GMCs were higher in younger participants (18-55 years of age) than in older participants (56-85 years of age).

The GMTs of a comparative panel of human convalescent serum(HCS) (GMT = 319) were similar to 50% neutralizing GMTs at 1-month post Dose 2 for both younger (GMT = 399.4) and older participants (GMT = 255.0).

Figure 13. Geometric Mean Titers: SARS-CoV-2 Neutralization Assay - NT50 – Evaluable Immunogenicity Population (Study C4591001, 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.
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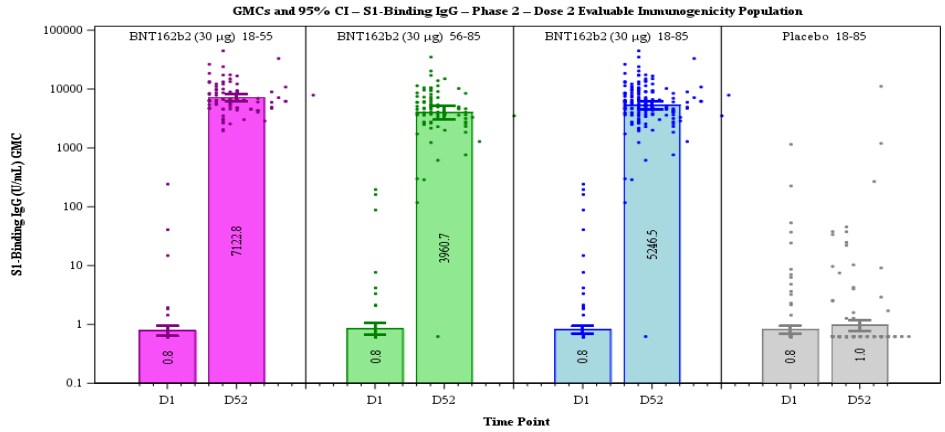
Figure 14. Geometric Mean Concentrations: SARS-CoV-2 S1-binding IgG Level Assay – Evaluable Immunogenicity Population (Study C4591001, Phase 2)



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.
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(Cutoff Date: 12OCT2020, Snapshot Date: 02NOV2020) Output File: /nda2_unblinded/C4591001_IA_P2_Serology/adva_f002_s1_p2

Geometric Mean Fold-Rise (GMFR) in Titers/Concentrations

Results for GMFRs in SARS-CoV-2 50% neutralizing titers and S1-binding IgG concentrations were robust at 1 month after Dose 2 of BNT162b2, with higher GMFRs observed in younger participants than in older participants.

SARS-CoV-2 Neutralizing Titers and S1-Binding IgG Concentrations by Baseline SARS-CoV-2 Status

Immunogenicity results were summarized by baseline SARS-CoV-2 status (positive or negative; ie, participants with or without serological or virological evidence of SARS-CoV-2 infection before vaccination).

Geometric Mean Titers/Concentrations (GMTs/GMCs)

A total of 9 participants with immunogenicity data at the prevaccination time point (5 who received BNT162b2 and 4 who received placebo) and 7 participants (3 who received BNT162b2 and 4 who received placebo) with immunogenicity data at the 1 month post Dose 2 time point, had a positive baseline SARS-CoV-2 status. These SARS-CoV-2 status positive participants were analysed separately from the baseline negative participants **Table 2**. In general, at 1 month post Dose 2 among BNT162b2 recipients, SARS-CoV-2 50% neutralizing GMTs in participants with a positive baseline SARS-CoV-2 status (n=3) and S1-binding IgG GMCs in participants with a positive baseline SARS-CoV-2 status were numerically higher than those observed in participants with a negative baseline SARS-CoV-2 status (n=163). Participants with baseline negative SARS-CoV-2 status had SARS-CoV-2 50% neutralizing GMTs and S1-binding IgG GMCs similar to those in the combined baseline positive and negative participant group.

Table 2. Summary of Geometric Mean Titers/Concentrations by Baseline SARS-CoV-2 Status – Phase 2 – Dose 2 Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2 (30 µg)						Placebo	
			18-55 Years		56-85 Years		18-85 Years		18-85 Years	
Assay	Dose/ Sampling Time Point[a]	Baseline SARS-CoV-2 Status[b]	n[c]	GMT/GMC[d] (95% CI[d])	n[c]	GMT/GMC[d] (95% CI[d])	n[c]	GMT/GMC[d] (95% CI[d])	n[c]	GMT/GMC[d] (95% CI[d])
SARS-CoV-2 neutralization assay - NT50 (titer)	1/Prevax	POS	1	31.0 (NE, NE)	4	18.1 (5.6, 58.2)	5	20.2 (8.7, 46.9)	4	38.4 (5.2, 282.5)
		NEG	79	10.0 (10.0, 10.0)	83	10.0 (10.0, 10.0)	162	10.0 (10.0, 10.0)	162	10.1 (9.9, 10.2)
	2/1 Month	POS	1	4233.0 (NE, NE)	2	3469.9 (0.1, 9.247E7)	3	3707.6 (495.5, 27743.3)	4	53.2 (5.5, 515.3)
		NEG	79	387.6 (335.4, 448.0)	84	237.7 (194.4, 290.7)	163	301.3 (264.7, 342.9)	162	10.2 (9.8, 10.7)
S1-binding IgG level assay (U/mL)	1/Prevax	POS	1	246.1 (NE, NE)	4	36.9 (0.5, 2848.7)	5	53.9 (2.4, 1222.0)	4	153.0 (12.7, 1844.4)
		NEG	79	0.7 (0.6, 0.8)	83	0.7 (0.6, 0.8)	162	0.7 (0.7, 0.8)	162	0.7 (0.7, 0.8)
	2/1 Month	POS	1	45474.1 (NE, NE)	2	23255.3 (106.2, 5.092E6)	3	29080.6 (6983.3, 121100.2)	4	144.4 (9.5, 2189.7)
		NEG	79	6957.6 (6113.5, 7918.3)	84	3759.2 (2847.3, 4963.2)	163	5066.1 (4308.9, 5956.5)	162	0.8 (0.7, 1.0)

Abbreviations: GMC = geometric mean concentration; GMT = geometric mean titer; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NE = not estimable; NEG = negative; NT50 = 50% neutralizing titer; POS = positive; S1 = spike protein S1 subunit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Note: Subjects whose baseline SARS-CoV-2 status cannot be determined due to missing N-binding antibody or NAAT at Visit 1 were not included in the analysis.

a. Protocol-specified timing for blood sample collection.

b. Positive = Positive N-binding antibody at Visit 1, or positive NAAT at Visit 1, or had medical history of COVID-19. Negative = Negative N-binding antibody at Visit 1 and negative NAAT at Visit 1.

c. n = Number of subjects with valid and determinate assay results for the specified assay at the given dose/sampling time point.

d. GMTs, GMCs, and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers or concentration and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

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Geometric Mean Fold-Rise (GMFR) in Titers/Concentrations

When analysing GMFRs stratified by SARS-CoV-2 status at 1 month post Dose 2, among BNT162b2 recipients, the GMFRs for SARS-CoV-2 50% neutralizing titers and S1-binding IgG were similar to those in the combined baseline positive and negative participant group.

Evaluator's Comments on Phase 2 immunogenicity analysis

Immunogenicity data from 360 participants demonstrated that BNT162b2 at 30 µg elicited robust SARS-CoV-2 neutralization and S1-binding IgG antibody responses at 1 month after Dose 2. This was similar to the previously observed Phase 1 data. SARS-CoV-2 neutralizing titers

were noted to be higher in the younger adult as compared to the older cohort. GMTs for younger and older participants at 1 month after Dose 2 were comparable to the GMTs of a comparative panel of HCS (Human convalescent serum). 18,19 S1-binding GMCs were generally higher in the younger age cohort compared to the older age cohort, similar to the phase study.

5.3. Evaluator's overall conclusions on immunogenicity

Phase 1 and phase 2 immunogenicity data from both the pivotal study C4591001 and supportive study BNT162-01 have shown robust humoral and T cell mediated responses after vaccination with 2 doses of BNT162b2 at 30 μg in both younger (18-55 years) and older adults (age groups 56-85 years and 65-85 years). This was in terms of both neutralising antibodies and IgG-antigen binding antibodies. The second dose given 21 days post-dose 1 induced a significant boosting effect in both younger and older adults. Overall responses were generally faster and higher in younger adults than in older adults. The levels of neutralizing antibodies titres were moderate 21 days after dose 1. The peak of neutralizing antibodies titres was reached 14 days post-dose 2 in older adults versus 7 days post-dose 2 in younger adults. Immune responses were maintained up to 1-month post-dose 2 in both age groups based on available data. The immune response data overall support the choice of vaccine candidate, BNT162b2, and the choice of a 2-dose schedule of 30 μg.

Immunogenicity data for Phase 3 (C4591001) has not been provided with the interim final report of this study.

6. Dosage selection for the pivotal studies

6.1. Rationale for Candidate and Dose Selection

The sponsor (BioNTech) has conducted a first in human (FIH) dose level–finding, Phase 1/2 study (BNT16201) in Germany to gather safety and immunogenicity data to evaluate multiple vaccine candidates.

This study was conducted under an approved German Clinical Trial agreement. The sponsor 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) was 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 and a robust immune response, likely to afford protection against COVID-19 in younger and older age groups.

6.2. Evaluator's conclusions on dose finding for the pivotal study

Based on the immunogenicity and safety data from the phase 1 part of Studies BNT162-01 and C4591001, the 30-μg dose level for candidate BNT162b2 was appropriate.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

Pivotal Phase 2/3 study C4591001 provided the efficacy data to support the provisional registration for COMIRNATY.

7.2. Pivotal or main efficacy studies

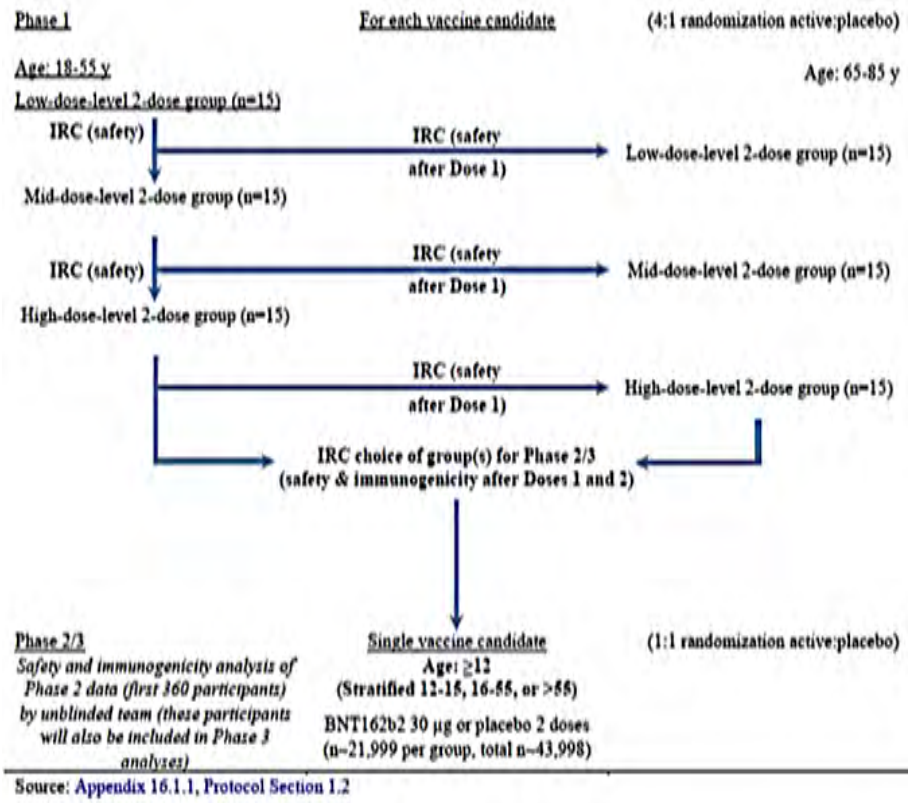
7.2.1. Study C4591001

7.2.1.1. Study design, objectives, locations and dates

Study C4591001 is an ongoing, randomized, observer-blind, placebo-controlled, phase 1/2/3 study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates against COVID-19 in Healthy Individuals. The study is being conducted in the US, Argentina, Brazil, Germany, South Africa and Turkey. In this section, only phase2/3 efficacy data is being discussed.

Initially the study was designed as a phase 1/2 study in healthy adults in the US for vaccine candidate and dosage selection, immunogenicity and preliminary efficacy. However, the protocol was amended to expand the study design for inclusion of a phase 2/3 portion, to evaluate clinical disease endpoint efficacy in individuals 12 years of age and older in the US and additional sites outside of the US.

Figure 15: Study Schema



Source: Appendix 16.1.1, Protocol Section 1.2

7.2.1.2. Inclusion and exclusion criteria

7.2.1.2.1. Main Inclusion criteria:

• Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3) at randomization.

• Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, could be included. Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfil the criteria specified in the protocol.
• Phase 2/3 only: Participants who, in the judgment of the investigator, were at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

• Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent.

7.2.1.2.2. Exclusion criteria:

• Other medical or psychiatric condition including recent or active suicidal ideation/behaviour or laboratory abnormality that increased the risk of study participation or, in the investigator's judgment, made the participant inappropriate for the study.

• History of severe adverse reaction associated with a vaccine and/or severe allergic reaction to any component of the study intervention.

• Receipt of medications intended to prevent COVID-19.

• Previous clinical or microbiological diagnosis of COVID-19.

• Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

• Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

• Women who are pregnant or breastfeeding.

• Previous vaccination with any coronavirus vaccine.

• Individuals who received treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, e.g., for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids were administered short term (<14 days) for treatment of an acute illness, participants should not have been enrolled into the study until corticosteroid therapy had been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids were permitted.

• Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

• Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation

• Previous participation in other studies involving study intervention containing lipid nanoparticles.

Evaluator's Comments:

Overall inclusion and exclusion criteria are acceptable and the study population is considered representative of the target population for vaccination, including subjects at higher risk of severe disease, i.e. age above 65 years (>20% with no upper age limit) and relevant underlying diseases (e.g. obesity, chronic pulmonary diseases, diabetes, hypertension, and cardiovascular disease). Individuals who had previous clinical or microbiological diagnosis of COVID-19 were excluded, since the natural infection would affect the vaccine immunogenicity .

7.2.1.3. Study treatments

The vaccine candidate selected for Phase 2/3 evaluation was BNT162b2 at a dose of 30 μg. In phase 2/3 the participants were randomized 1:1 to receive vaccine or placebo, normal saline (0.9% sodium chloride solution for injection). The injection was intramuscular for both vaccine and the placebo.

Evaluator's Comment:

The sponsor should confirm if the trial vaccine is exactly same as the mass-produced vaccine, which is to be used for general population immunization.

7.2.1.4. Efficacy variables and outcomes

7.2.1.4.1. Primary efficacy objectives

• To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19, occurring from 7 days after the second dose in participants without evidence of infection before vaccination.

• To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination.

7.2.1.4.2. Secondary efficacy objectives

• To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19, occurring from 14 days after the second dose in participants without evidence of infection before vaccination.

• To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination

• To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination

• To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination

• To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination.

To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination.

7.2.1.4.3. Exploratory objectives

• To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination

• To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study

• To describe the serological responses to the BNT vaccine candidate in cases of:

- Confirmed COVID-19

- Confirmed severe COVID-19

- SARS-CoV-2 infection without confirmed COVID-19

• To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease

• To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by two different manufacturing processes (see under Treatment).

7.2.1.4.4. 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.

7.2.1.4.5. Secondary Efficacy Endpoints

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.

7.2.1.5. Randomisation and blinding methods

Allocation of participants to vaccine groups were performed, using an IRT system (IWR). Participants were randomised 1:1 to active vaccine or placebo.

The trial included participants of ≥12 years of age, stratified as follows: 12 to 15, 16 to 55 years or >56 years. It was intended that a minimum of 40% of participants were to be enrolled in the >56-year stratum.

The Phase 2/3 portion of the study remained blinded to the 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 un-blinded submissions team is responsible for regulatory submissions.

The study staff receiving, storing, dispensing, preparing, and administering the study interventions were unblinded.

Exceptions to blinding were described, and found acceptable.

7.2.1.6. Analysis populations

For the purposes of analysis, the following populations are defined:

Table 3: Population Description

Population	Description
Enrolled	All participants who had a signed ICD.
Randomized	All participants who were assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who received the vaccine to which they were randomly assigned at the first dose, had at least 1 valid and determinate immunogenicity result from the blood collection within an appropriate window after Dose 1 (same as visit window, ie, within 19-23 days after Dose 1) and had no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who received 2 doses of the vaccine to which they were randomly assigned, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), had at least 1 valid and determinate immunogenicity result from the blood collection within an appropriate window after Dose 2 (within 6-8 days after Dose 2 for Phase 1 and within 28-42 days after Dose 2 for Phase 2/3), and had no other important protocol deviations as determined by the clinician.
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who received at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who received at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy (7 days)	All eligible randomized participants who received all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1) and had no other important protocol deviations as determined by the clinician.
Evaluable efficacy (14 days)	All eligible randomized participants who received all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1) and had no other important protocol deviations as determined by the clinician on or before 14 days after Dose 2.
Dose 1 all-available efficacy	All randomized participants who received at least 1 vaccination.
Dose 2 all-available efficacy	All randomized participants who completed 2 vaccination doses.
Safety	All randomized participants who received at least 1 dose of the study intervention.

7.2.1.7. Sample size (For Phase 2/3)

Assuming a true VE of 60% after the second dose of study intervention, a total of approximately 164 first confirmed COVID-19 illness cases would provide approximately 90% power. This should be achieved with 17,600 evaluable participants per group (or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo) for a total sample size of 43,998. This assumes a 1.3% illness rate per year in the placebo group, accrual of 164 primary endpoint cases within 6 months, and 20% of the participants being non-evaluable or having serological evidence of prior infection with SARS-CoV-2 (potentially making them immune to further infection).

7.2.1.8. Statistical methods

Assessment of VE of BNT162b2 for the first primary efficacy endpoint was performed for confirmed COVID-19 cases observed at least 7 days after the receipt of Dose 2 onwards among participants without serological or virological evidence of past SARS-CoV-2 infection (up to 7 days after receipt of the second dose). VE was estimated by 100% × (1 – IRR), where IRR was the ratio of COVID-19 illness rate in the BNT162b2 group to the corresponding illness rate in the placebo group. The Bayesian 95% credible interval and the posterior probability for the true vaccine efficacy greater than 30% conditioning on the available data, i.e. P[VE >30%|data], were calculated using a beta-binomial model and a pre- specified minimally informative beta distribution as prior. The calculation of posterior probability and 95% credible interval were adjusted for surveillance time.

The vaccine efficacy of BNT162b2 would be declared, if posterior probability of VE>30% is greater than 99.5% at any pre-planned interim analysis, or greater than 98.6% at the final analysis.

Less than 5.0% predicted posterior probability of demonstrating vaccine efficacy at the final analysis at any of the first 2 planned interim analyses, would stop the study for lack of benefit.

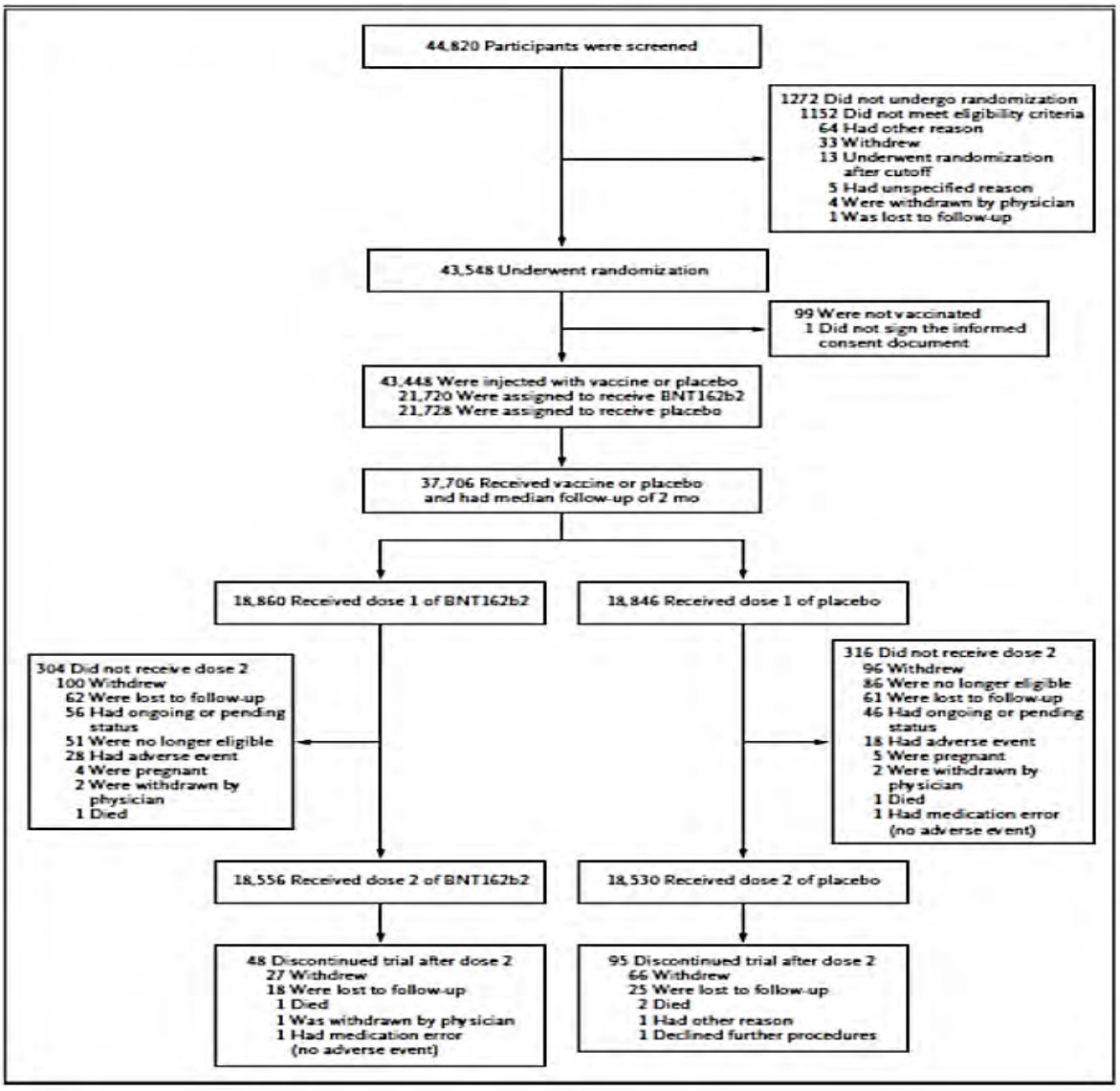
For the subgroup analysis of the primary efficacy endpoint, VE and the 2-sided 95% CI for VE derived based on the Clopper and Pearson method adjusted for surveillance time were provided.

Evaluator's Comment on **statistical analysis:**

A clinical expert advice was sought regarding statistical analysis performed in pivotal study C4591001.It concluded that the determination of efficacy based on 1000 person-years is appropriate, and irrespective of the statistical method used to compare the two groups, the result is highly statistically significant. This difference would translate to the VE and the corresponding Pr{VE ≥ 30%} .

7.2.1.9. Participant flow

Figure 16: Participants Flow



Source : https://www.nejm.org/doi/full/10.1056/NEJMoa2034577

7.2.1.10. Major protocol violations/deviations

There were 311 participants (1.4%) in the BNT162b2 group and 60 participants (0.3%) in the placebo group excluded for having important protocol deviations on or prior to 7 days after Dose 2. A post hoc evaluation was performed to assess the imbalance of these important protocol deviations in the BNT162b2 and placebo groups for the final analysis of efficacy**.**

The majority of exclusions from the evaluable efficacy (7 days) population in the BNT162b2 group were due to dosing/administration errors or administration of study intervention that was deemed not suitable for use.

7.2.1.11. Baseline data

Overall, the phase 2/3 evaluable efficacy population included 49.4% females, 81.9% White, 9.8% African American, 4.4% Asian participants, and <3% from other racial groups; 26.2% of participants were Hispanic/Latino; 21.4% of participants were >65 years of age. The median age was 51 years. The most frequently reported comorbidities were obesity (35.1%), diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%). Geographically, 76.7% of participants were from the US, 15.3% from Argentina, 6.1% from Brazil, and 2% from South Africa.

The demographic characteristics among vaccine and placebo participants in the all-available efficacy population were similar to the evaluable efficacy population. Please refer to the table 4 below.

Table 4. Demographic Characteristics – 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]=18242) n[b] (%)	Placebo (N[a]=18379) n[b] (%)	Total (N[a]=36621) n[b] (%)
Sex			
Male	9318 (51.1)	9225 (50.2)	18543 (50.6)
Female	8924 (48.9)	9154 (49.8)	18078 (49.4)
Race			
White	15110 (82.8)	15301 (83.3)	30411 (83.0)
Black or African American	1617 (8.9)	1617 (8.8)	3234 (8.8)
American Indian or Alaska native	118 (0.6)	106 (0.6)	224 (0.6)
Asian	815 (4.5)	810 (4.4)	1625 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)	77 (0.2)
Multiracial	448 (2.5)	402 (2.2)	850 (2.3)
Not reported	86 (0.5)	114 (0.6)	200 (0.5)
Ethnicity			
Hispanic/Latino	4886 (26.8)	4857 (26.4)	9743 (26.6)
Non-Hispanic/non-Latino	13253 (72.7)	13412 (73.0)	26665 (72.8)
Not reported	103 (0.6)	110 (0.6)	213 (0.6)
Country			
Argentina	2561 (14.0)	2539 (13.8)	5100 (13.9)
Brazil	1232 (6.8)	1223 (6.7)	2455 (6.7)
Germany	121 (0.7)	126 (0.7)	247 (0.7)
South Africa	287 (1.6)	279 (1.5)	566 (1.5)
USA	14041 (77.0)	14212 (77.3)	28253 (77.1)
Age group			
12-15 Years	46 (0.3)	42 (0.2)	88 (0.2)
16-55 Years	10428 (57.2)	10507 (57.2)	20935 (57.2)
>55 Years	7768 (42.6)	7830 (42.6)	15598 (42.6)
≥65 Years	3980 (21.8)	4038 (22.0)	8018 (21.9)
Age at vaccination (years)			
Mean (SD)	50.6 (15.70)	50.4 (15.81)	50.5 (15.76)
Median	52.0	52.0	52.0
Min, max	(12, 89)	(12, 91)	(12, 91)

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 (18:29)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adsl_demo_7d_eval_eff

Evaluator's Comment:

The demographic characteristics among vaccine and placebo participants in the all-enrolled population were similar. There were no significant imbalances in demographic and other baseline characteristics between the all-enrolled population and phase 2/3 safety population with median 2-month follow-up.

7.2.1.12. Results for the primary efficacy outcome

For the first primary efficacy endpoint, vaccine efficacy (VE) for BNT162b2 against confirmed COVID-19 was evaluated in participants without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with or without evidence of prior SARS-CoV-2 infection before and during vaccination regimen. Cases were counted from 7 days after Dose 2 for both endpoints. The success criterion was met if the posterior probability of VE>30% is greater than 99.5% at any pre-planned interim analysis, or greater than 98.6% at the final analysis (Using Bayesian statistics).

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

Among the subjects 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 as compared to 162 COVID-19 cases in the placebo group **(Table 5)**. The 95% credible interval for the vaccine efficacy was 90.3% to 97.6%.

The VE for the same primary efficacy endpoint based on the Dose 2 all-available efficacy population, was 95.2%, with 8 and 165 cases in the BNT162b2 and placebo group, respectively.

Table 5. 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)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_7pd2_wo_eval

2. **Vaccine Efficacy With or Without Prior Evidence of SARS-CoV-2 Infection – 7 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 7 days after Dose 2 was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively. The posterior probability was >99.99% for the true VE being greater than 30%. The 95% credible interval for the vaccine efficacy 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 6)**.

The vaccine efficacy of BNT162b2 for the same primary efficacy endpoint based on the Dose 2 all-available efficacy population was 94.8%, with 9 and 172 cases in the BNT162b2 and placebo group, respectively.

This analysis is mainly influenced by the subjects without evidence of prior infection, and therefore does not provide any additional information.

Table 6. 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

Only small number of participants had evidence of prior infection at the baseline (approximately 550 in each vaccine and placebo group). Additional analyses showed that very few COVID-19 cases occurred in these participants over the course of the entire study (9 in the placebo group and 10 in the BNT162b2 group and only 1 in each group occurred 7 days or more after completion of the vaccination regimen).

7.2.1.13. Results for the other efficacy outcomes

1. Vaccine Efficacy for All Confirmed Cases of COVID-19 after Dose 1 – Dose 1 All-Available Population

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. 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.

Based on the cumulative incidence curve for the all-available efficacy population after Dose 1 **(Figure 17)**, COVID-19 disease onset appears to occur similarly for both BNT162b2 and placebo groups until approximately 14 days after Dose 1. The curves diverge after 14 days timepoint, with more cases accumulating in the placebo group than in the BNT162b2 group, and there

does not appear to be evidence of waning protection during the follow-up time of approximately 2 months following the second dose .

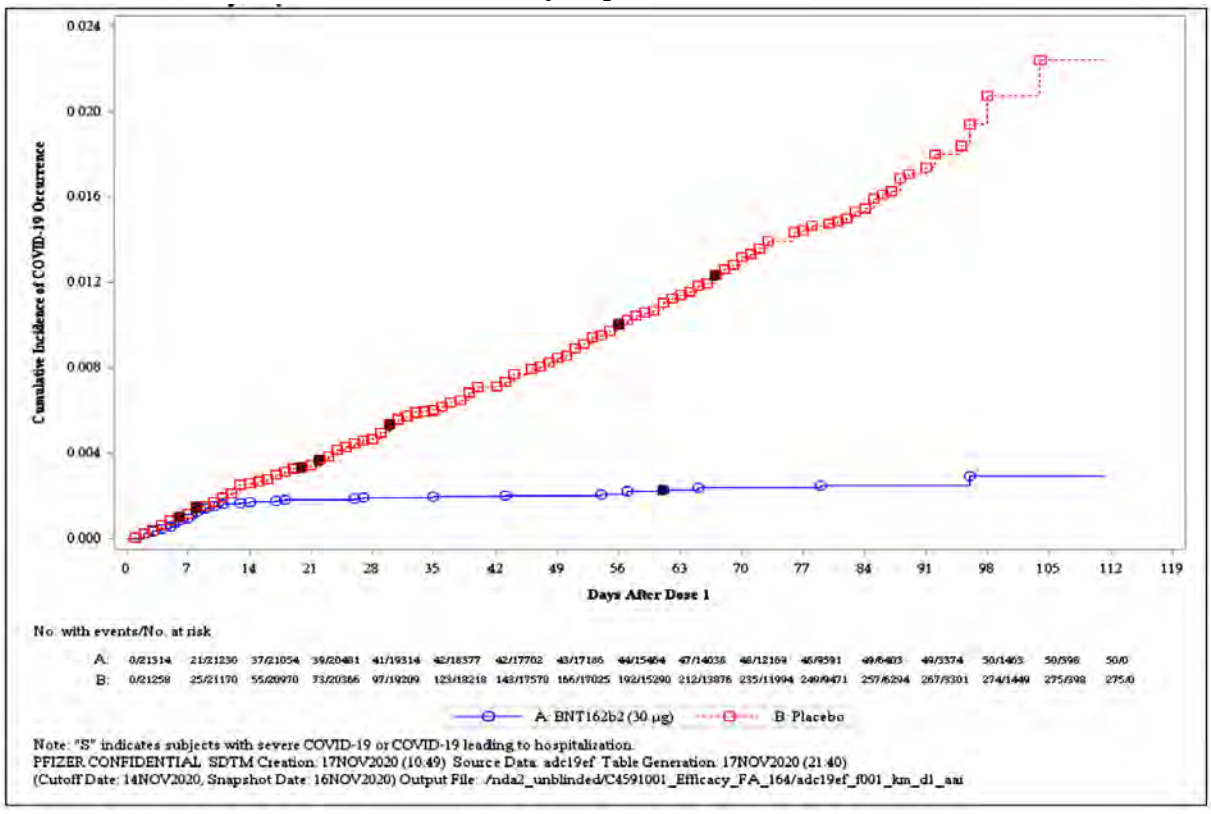
Table 7. Vaccine Efficacy – First COVID-19 Occurrence after Dose 1 – Dose 1 All-Available Efficacy Population

	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).
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 18NOV2020 (17:06)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_pd1_aai

Based on the cumulative incidence curve for the all-available efficacy population after Dose 1 **(Figure 17)**, COVID-19 disease onset appears to occur similarly for both BNT162b2 and placebo groups until approximately 14 days after Dose 1. The curves diverge after 14 days timepoint, with more cases accumulating in the placebo group than in the BNT162b2 group, and there does not appear to be evidence of waning protection during the follow-up time of approximately 2 months following the second dose .

Figure 17. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Dose 1 All-Available Efficacy Population



2. Vaccine Efficacy by Subgroup

VE was also evaluated both primary end points in the subgroups of subjects by age, sex race/ethnicity, and country, for without evidence of prior infection and with or without evidence of prior infection.

Among participants without prior evidence of SARS-CoV-2 infection before and during vaccination regimen, VE was >93% in all subgroups, with the exception of "all others" race group (89.3% VE) and Brazil (87.7% VE).

In subjects ≥65 years of age, VE was 94.7% (1 case in BNT162b2 group vs 19 cases in placebo group; 2-sided 95% CI: 66.7%, 99.9%) . VE in subjects ≥75 years of age was 100% (0 cases in BNT162b2 group vs 5 cases in placebo group+; 2-sided 95% CI: -13.1%, 100.0%) **(Table 8)**.

Among participants with or without prior evidence of SARS-CoV-2 infection before and during vaccination regimen, VE was >93% in all subgroups, with the exception of "all others" race group (78.2% VE), Brazil (75.4% VE), and positive prior SARS-CoV-2 infection at baseline (-7.1% VE, 1 case in each vaccine group).

Results for the all-available population were similar; no clinically meaningful differences were observed in VE on the basis of subgroup.

Table 8. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Requested 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)						
12 to 15	0	0.000 (14)	0	0.000 (13)	NE	(NE, NE)
16 to 17	0	0.002 (52)	0	0.003 (55)	NE	(NE, NE)
18 to 64	7	1.703 (13497)	143	1.708 (13563)	95.1	(89.6, 98.1)
65 to 74	1	0.406 (3074)	14	0.406 (3095)	92.9	(53.1, 99.8)
≥75	0	0.102 (774)	5	0.106 (785)	100.0	(-13.1, 100.0)
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)
American Indian or Alaska native	0	0.011 (100)	1	0.010 (96)	100.0	(-3429.0, 100.0)
Asian	1	0.092 (764)	4	0.093 (769)	74.6	(-156.6, 99.5)
Native Hawaiian or other Pacific Islander	0	0.006 (46)	1	0.003 (29)	100.0	(-2266.9, 100.0)
Multiracial	0	0.042 (414)	1	0.036 (359)	100.0	(-3231.3, 100.0)
Not reported	0	0.010 (81)	2	0.012 (102)	100.0	(-563.3, 100.0)

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 (09:54) Source Data: adc19ef Table Generation: 23NOV2020 (16:38)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_EUA_FAEF_RR/adc19ef_ve_cov_7pd2_worq_sg_eval

3. Post Hoc Subgroup Analyses by Risk Status

Additional analyses of the first primary efficacy endpoint were conducted to evaluate the vaccine efficacy, by comorbidity status. At-risk subjects were defined as those who had at least one Charlson Comorbidity Index condition **(Table 9**) or who were obese (defined as body mass index ≥30 kg/m2).

In subjects without prior evidence of SARS-CoV-2 infection prior or during vaccination, VE for participants at risk was 95.3%, as compared with 94.7% for those not at risk **(Table 10).** VE for participants ≥65 years of age and at risk was 91.7%, as compared with 100% for those ≥65 years of age and not at risk. VE was similar in obese (95.4%) and non-obese (94.8%) participants. However, small numbers of subjects and/or cases limits these VE point estimates results.

Table 9. Baseline Charlson Comorbidities – Phase 2/3 (All Subjects) – Safety Population

	Vaccine Group (as Administered)		
Charlson Comorbidity Index Category	BNT162b2 (30 µg) (N^a=21720) n^b (%)	Placebo (N^a=21728) n^b (%)	Total (N^a=43448) n^b (%)
Subjects with any Charlson comorbidity	4559 (21.0)	4419 (20.3)	8978 (20.7)
AIDS/HIV	99 (0.5)	98 (0.5)	197 (0.5)
Any Malignancy	808 (3.7)	753 (3.5)	1561 (3.6)
Cerebrovascular Disease	227 (1.0)	194 (0.9)	421 (1.0)
Chronic Pulmonary Disease	1730 (8.0)	1713 (7.9)	3443 (7.9)
Congestive Heart Failure	108 (0.5)	97 (0.4)	205 (0.5)
Dementia	7 (0.0)	11 (0.1)	18 (0.0)
Diabetes With Chronic Complication	112 (0.5)	125 (0.6)	237 (0.5)
Diabetes Without Chronic Complication	1692 (7.8)	1676 (7.7)	3368 (7.8)
Hemiplegia or Paraplegia	15 (0.1)	22 (0.1)	37 (0.1)
Leukemia	14 (0.1)	10 (0.0)	24 (0.1)
Lymphoma	25 (0.1)	36 (0.2)	61 (0.1)
Metastatic Solid Tumor	4 (0.0)	3 (0.0)	7 (0.0)
Mild Liver Disease	145 (0.7)	112 (0.5)	257 (0.6)
Moderate or Severe Liver Disease	1 (0.0)	2 (0.0)	3 (0.0)
Myocardial Infarction	220 (1.0)	216 (1.0)	436 (1.0)
Peptic Ulcer Disease	62 (0.3)	81 (0.4)	143 (0.3)
Peripheral Vascular Disease	144 (0.7)	132 (0.6)	276 (0.6)
Renal Disease	139 (0.6)	145 (0.7)	284 (0.7)
Rheumatic Disease	75 (0.3)	65 (0.3)	140 (0.3)

Note: MedDRA (v23.1) coding dictionary applied.
Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
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 with the specified characteristic. Subjects with multiple occurrences within each category are counted only once. For 'Subjects with any Charlson comorbidity', n = number of subjects reporting at least 1 occurrence of any Charlson comorbidity.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:04) Source Data: admh Table Generation: 17NOV2020 (16:25)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/admh_s002_risk_all_p3_saf

Table 10. 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)

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
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:54) Source Data: adc19ef Table Generation: 24NOV2020 (17:41)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: /nda2_unblinded/C4591001_EUA_FAEF_RR/adc19ef_ve_cov_7pd2_wo_rg_eval

Table 11. Vaccine Efficacy: First COVID-19 Occurrence From 7 Days After Dose 2, by Comorbidity Status, Among Participants Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population[5]

Efficacy Endpoint Subgroup	BNT162b2 (30 µg) N[a]=18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Overall	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.0, 97.9)
Comorbidity			
No comorbidity	4 1.189 (9381)	76 1.197 (9482)	94.7 (85.9, 98.6)
Any comorbidity[f]	4 1.025 (8030)	86 1.025 (8029)	95.3 (87.7, 98.8)
Any malignancy	1 0.092 (704)	4 0.090 (681)	75.7 (-145.8, 99.5)
Cardiovascular	0 0.067 (534)	5 0.062 (492)	100.0 (-0.8, 100.0)
Chronic pulmonary disease	1 0.175 (1374)	14 0.171 (1358)	93.0 (54.1, 99.8)
Diabetes	1 0.176 (1372)	19 0.176 (1374)	94.7 (66.8, 99.9)
Obese (BMI≥30.0 kg/m^2)	3 0.763 (6000)	67 0.782 (6103)	95.4 (86.0, 99.1)
Hypertension	2 0.567 (4413)	44 0.567 (4437)	95.4 (82.6, 99.5)
Diabetes (including gestational diabetes)	1 0.177 (1381)	20 0.178 (1384)	95.0 (68.7, 99.9)

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: Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., 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 participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants 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 participants 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] Subject who had 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the Charlson comorbidity index (Appendix B, page 52) category or BMI ≥30 kg/m2.

[5] https://www.fda.gov/media/144245/download

4. Secondary Efficacy Results

Secondary efficacy endpoints evaluated confirmed COVID-19 cases in participants either without or with or without evidence of prior SARS-CoV-2 infection before and during vaccination regimen. Cases were counted from 7 days after Dose 2 or from 14 days after Dose 2.

a. Vaccine Efficacy for COVID-19 (≥14 Days After Dose 2)

Participants Without Evidence of Infection Before and During Vaccination Regimen

Subjects with positive or unknown Nucleic Acid Amplification Test (NAAT) results at any illness visit prior to 14 days after Dose 2, were not included in efficacy endpoint analysis. 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 12**). The posterior probability of >99.99% for the true VE greater than 30% met the pre-specified success criterion of >98.6% for this endpoint. The 95% credible interval for the vaccine efficacy 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 12. 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

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

In this group, 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. The posterior probability of >99.99% for the true VE greater than 30% met the pre-specified success criterion of >98.6% for this endpoint. The 95% credible interval for the vaccine efficacy 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.

b. Vaccine Efficacy for Severe COVID-19 Cases

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

Participants Without Evidence of Infection Before and During Vaccination Regimen

Subjects with positive or unknown NAAT results at any illness visit prior to 7 days after Dose 2 were not included in this endpoint analysis. A total of 4 sever Covid-19 cases , with 1 and 3 cases in the BNT162b2 and placebo groups respectively **(Table 13)** were reported. The estimated VE against severe COVID-19 occurring at least 7 days after Dose 2 was 66.4%.. The posterior probability for the true vaccine efficacy 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.

The vaccine recipient who had severe COVID-19 disease met the severe case definition because oxygen saturation at the COVID-19 illness visit was 93% on room air. The subject was not hospitalized, did not seek further medical care, and did not have risk factors for severe disease.

Due to total number of severe cases being small, no conclusions regarding protection against severe Covid-19 can be drawn.

The results for efficacy against severe case in subjects **With or Without** Evidence of Infection Before and During Vaccination Regimen, were similar.

Table 13. 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

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

In the all-available efficacy population, ten participants had severe COVID-19 disease after Dose 1 (one subject in BNT162b2 and nine in placebo group). 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) against severe COVID-19 occurring at least 7 days after Dose 2.

Table 14. 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

C . Vaccine Efficacy for COVID-19 Cases per CDC Definition- 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

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 SARS-CoV-2 infection before and during vaccination regimen, VE against CDC-defined COVID-19 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.

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.

7.2.1.14. Evaluator comments on overall efficacy

Candidate BNT162b2 was selected for phase 2/3 (Study C4591001 and BNT162-01), based on the phase 1 safety and immunogenicity data.

Study C4591001 is a phase 1/2/3, multicentre, multinational, randomized, placebo-controlled, observer blind, dose finding, vaccine candidate efficacy and safety study in subjects that are healthy or have clinically stable comorbidities. The efficacy of the BNT162b2 vaccine against Covid-19 was investigated in this event-driven study.

In the Phase 2/3, approximately 44,000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo separated by 21 days. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. A 24 months follow up for these participants is planned.

The distribution of demographics and other baseline characteristics was similar between both arms among participants without evidence of infection up to 7 days after dose 2 in the final analysis evaluable efficacy population. There were 42.6% of participants in the older age group (>50 years), 26% of participants over 65 years of age and 0.7% (112 subjects) of participants adolescents (12-17 years). Across both treatment groups, 20.5% had any comorbidity (per the Charlson comorbidity index).

The date for data cut-off for the final efficacy analysis was November 14, 2020, when a total of 170 confirmed COVID-19 cases were accrued.

The protective efficacy in subjects without prior evidence of SARS-CoV-2 infection from 7 days after dose 2 was 95.0% (95% CI: 90.0; 97.9) in the primary efficacy population (8 cases and 162 cases in the BNT162b2 and placebo groups, respectively).

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%, 95%CI (88.7%, 97.2%) (8 and 139 cases in the BNT162b2 and placebo groups respectively).

Efficacy against severe COVID-19 occurring after the first dose was 88.9% (95% CI 20.1, 99.7), with an estimated VE of 75.0% (95% CI -152.6, 99.5) (1 case in BNT162b2 group and 4 cases in placebo group) against severe COVID-19 occurring at least 7 days after Dose 2.

In the all participants group (regardless of evidence of infection before or during the vaccination regimen), 50 cases of COVID-19 were reported after Dose 1 in the BNT162b2 group and 275 cases in the placebo group. The estimated VE was 82% (95% CI: 75.6%, 86.9%) against confirmed COVID-19 occurring after Dose 1 and 52.4% (95% CI: 29.5%, 68.4%) between Dose 1 and Dose 2. The efficacy after Dose 1 and before Dose 2, cannot support a conclusion on the efficacy of a single dose of the vaccine, as most of the participants received a second dose after three weeks and there was no single-dose arm to make an adequate comparison with 2 doses efficacy.

The results from this study demonstrated a high protective efficacy in subjects ≥65 years of age (95%, 95% CI: 66.8; 99.9).However due to small numbers vaccine efficacy in age group ≥75 years subjects remain uncertain.

A very low number of severe case were reported in this study .There was only 1 case in the vaccine group and 4 cases in the placebo group, 7 days post dose 2. None of the severe cases were baseline positive for SARS-CoV-2. This outcome did not meet the pre-specified success criterion for this endpoint, and no reliable conclusion towards protection against severe Covid-19 disease can be drawn based at the current data.

The cumulative incidence curves for the first COVID-19 occurrence after dose 1 (all-available efficacy population) showed that COVID-19 disease onset seems to be same for both BNT162b2 and placebo groups, then diverge after approximately 14 days post Dose 1 and more cases accumulate in the placebo group. Cumulative curve remained on same track during the follow-up time of approximately 2 months post-dose 2, which supports sustained protection. However longer follow-up is required to confirm the persistence of the vaccine efficacy.

Vaccine efficacy in subjects with prior COVID-19 could not be concluded due to very small number of SARS-CoV2 positive subjects at baseline. However, available data, while limited, do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection).

Paediatric subjects from 16 to 17yrs are included in the study but numbers are too small to evaluate efficacy in this group. Only one confirmed COVID-19 case was reported in the 16 to 17 yrs age group. No efficacy data are available for subjects aged 15 years and younger.

The phase 2/3 study data does not provide any information on the effect of the vaccine in preventing asymptomatic infection or effectiveness against transmission of SARS-CoV-2.

The short duration of efficacy follow up limits the vaccine efficacy conclusion. Mutation at the spike protein of SARS-CoV2 is already emerging[6]. Viral mutations leading to increased attack rates are also being reported. These changes in pandemic characteristics can potentially change the vaccine efficacy over time. Continued evaluation of vaccine effectiveness following issuance of provisional registration will be critical to address these uncertainties.

7.3. Other efficacy studies

N/A

7.4. Analyses performed across trials: pooled and meta analyses

N/A

7.5. Evaluator's conclusions on clinical efficacy

Based on the final interim Phase 2/3 data from study C4591001, a high vaccine efficacy (preventing symptomatic COVID-19) was demonstrated in subjects without evidence of prior SARS-Cov2 infection (VE 95.0% (95% CI: 90.3%, 97.6%) 7 days after dose 2, which was consistent across the relevant subgroups. The 2-dose schedule is considered justified based on the immune responses and the actual efficacy results.

The interim final study report has a limited follow-up of a median of 2 months. At this stage, sustained protective efficacy for vaccine cannot be concluded.

8. Clinical safety

8.1. Studies providing evaluable safety data

Study BNT162-01a is the first-in-human (FIH) phase 1/2 trial, using candidate BNT162b2 (conducted in Germany). Study C4591001is a Phase 1/2/3 study being conducted in USA the United States (US). The safety database for COMIRNATY is derived from these two studies.

8.1.1. Pivotal studies that assessed safety as the sole primary outcome

Assessment of safety for Comirnaty was the primary objective for the Phase 1 of following studies:

- **Study BNT162-01a - Phase 1**
- **Study C4591001 - Phase 1**

8.1.2. Pivotal and/or main efficacy studies

Study C4591001 Phase 2/3

8.1.3. Other studies

N/A

[6] https://www.ecdc.europa.eu/sites/default/files/documents/SARS-CoV-2-variant-multiple-spike-protein-mutations-United-Kingdom.pdf

8.2. Studies that assessed safety as the sole primary outcome

8.2.1. Study BNT162-01a

8.2.1.1. Study design, objectives, locations and dates

Study BNT162-01 commenced on 23 APR 2020 in Germany (Berlin and Mannheim). Study BNT162-01 is an ongoing, FIH, Phase 1/2 dose level-finding study, in which healthy adults aged 18 to 55 or 56 to 85 all receive active vaccine (open-label and non-randomized). Four vaccine candidates from 3 different RNA platforms are being tested.

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. The available Phase 1 safety and immunogenicity data for adults 18 to 55 years of age are reported in this application.

The trial has two parts: a dose-finding part (Part A) and a part dedicated to recruiting expansion cohorts with dose levels which were selected from data generated in Part A (Part B).

BNT162b1 and BNT162b2 were administered in a prime/boost two-dose regimen separated by approximately 21 days:

- BNT162b1 (dose levels: 1, 3, 10, 20, 30, 50, 60 µg)
- BNT162b2 (dose levels: 1, 3, 10, 20, 30, 50, 60 µg).

The safety review committee (SRC) recommended that a second dose of BNT162b1 at the 60 µg dose level not be administered due to the reactogenicity after the first dose.

Subject safety was to be monitored from Visit 0 (screening) until approximately 6 months after the last immunization.

Figure 18: Dose group schema for BNT162b1 and BNT162b2 (dose 1 and dose 2, ~21 d apart)

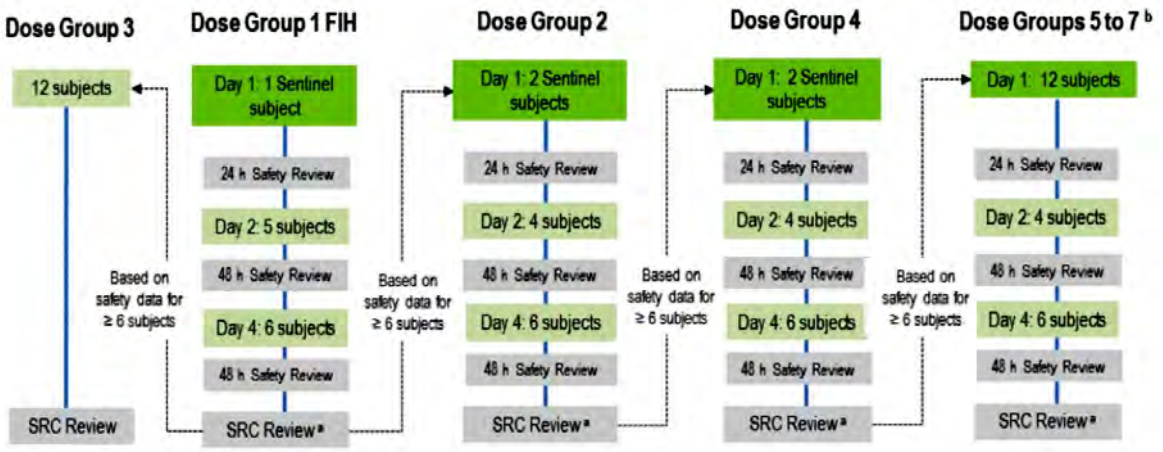


Figure 1: Dose group schema for BNT162b1 and BNT162b2 (dose 1 and dose 2, ~21 d apart) c

a) The data assessed by the SRC for progressing comprises 48 h data for 6 participants.
b) If these dose groups use doses lower than already tested, 12 participants may be dosed on one day in these dose groups and the dose groups may be conducted in parallel to each other / to any dose-escalation dose groups. If they use doses higher than already tested, participants were dosed using a sentinel dosing/participant (2-4-6) staggering process.
c) For the dose regimens, see the synopsis section "Study treatments".

Cohort = dose group; d = day(s); FIH = first in humans; SRC = Safety Review Committee; subject = participant.
Note: This report only presents data and background information relevant for reported younger adult dose groups 1 to 5.

Study Objectives:

Primary safety objectives and secondary immunogenicity objectives are as following:

Figure 19: Study Objectives for Study BNT 162-01

Objectives	Endpoints
Primary objective	
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after dose 1 only or after both dose 1 and dose 2.	• Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7±1 d (Day 8) after each IMP dosing. • Solicited systemic reactions (nausea, vomiting, diarrhoea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever) recorded up to 7±1 d (Day 8) after each IMP dosing. • The proportion of participants with at least 1 unsolicited treatment-emergent adverse event (TEAE) occurring up to 21±2 d after dose 1 (Day 22) and 28±4 d after dose 2 (Day 50).
Secondary objectives	
To describe the immune response in healthy adults after dose 1 only or after both dose 1 and dose 2 measured by a functional antibody titer, e.g., virus neutralization test or an equivalent assay available by the time of study conduct.	• At baseline and 7±1 d and 21±2 d after dose 1 (Days 8 and 22) and at 21±2 d, 28±4 d, 63±5 d, and 162±7 d after dose 2 (Days 43, 50, 85, and 184): - Functional antibody responses. - Fold increase in functional antibody geometric mean titers (GMTs). - Number of participants with seroconversion defined as a minimum of 4-fold increase of functional antibody GMTs as compared to baseline.

8.2.1.2. Study treatments

Drug: BNT162 vaccines - Antiviral RNA vaccines for active immunization against COVID-19.

Dose levels:

BNT162b1: 1 µg, 3 µg, 10 µg, 20 µg, 30 µg, 50 µg, and 60 µg.

BNT162b2: 1 µg, 3 µg, 10 µg, 20 µg, 30 µg (data for the dose levels of 50 µg and 60 µg are not available at this stage).

Dosage frequency: Two injections ~21 d apart. Injection volumes were up to 1.5 mL.

Dosing route: Intramuscular (IM)

8.2.1.3. Analysis populations

Healthy adults aged 18 to 55 yrs (dose groups 1 to 7; younger adults). There were no protocol waivers or exemptions to the inclusion/exclusion criteria.

8.2.1.4. Sample size

No formal sample size calculations were performed.

8.2.1.5. Statistical methods

There was no formal statistical hypothesis under test.

The inclusion of 12 participants per dose group was considered to be adequate for a safety assessment of each IMP per dose level. The probability to observe a particular TEAE with incidence of 15% at least once in 12 participants per dose group is 85.8%.

In general, data were summarized by dose groups and groups may be combined as appropriate. Continuous variables were summarized by dose group using descriptive statistics. Categorical variables were summarized by dose group presenting absolute and relative frequencies (n and %) of participants in each category.

In general, TEAEs were analyzed by dose group (i.e., by IMP and dose level), for each dose, and each observation interval, e.g., Day 1 to 21 (pre-dose 2). Additionally, TEAEs were summarized for all dose levels combined for each type.

For each analysis, the number and percentage of subjects reporting at least one AE , was summarized by PT included within SOC for each AE type. The number and percentage of subjects with any AE was summarized by worst grade by PT nested within SOC.