Saudi Medicinal Assessment Report

Pfizer-BioNTech COVID-19 Vaccine

BNT162b2

Published by Saudi Food and Drug Authority

Product Summary:

Active Pharmaceutical Ingredient(s): RNA-lipid nanoparticle (LNP) of nucleoside-modified mRNA (modRNA)

Pharmaceutical/Dosage Form: Solution for injection

Route of Administration: Intramuscular

Dosage Strength: 30 microgram

Pack Size: 195 Multiple Dose Vials (each vial contains five doses of 0.3 mL)

Marketing Authorization Holder: Pfizer Saudi Limited

Manufacturer: Pfizer Manufacturing Belgium NV

Shelf life: 6 months

Storage conditions: Store at - 80°C to - 60°C (-112°F to -76°F). Store in original carton to protect from light. After dilution, store the vaccine at 2°C to 25°C (35°F to 77°F). Discard after 6 hours.

Decision: Conditional approval.

Date of Decision: 10 December 2020

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1. Terms, Definitions, Abbreviations

Abbreviations

AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical Code
BNT162b2	Pfizer-BioNTech COVID-19 Vaccine
CCS	Container Closure System
COVID-19	Coronavirus Disease 2019
FPPs	Finished Pharmaceutical Products
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
HCP	Healthcare Professional
HCS	Human Convalescent Sera
IM	Intramuscular
INN	International Nonproprietary Name
ISMP	Institute for Safe Medication Practices
LA/SA	Look –Alike/Sound-Alike
LNPs	Lipid Nanoparticle
MOH	Ministry of Health
NAAT	Nucleic Acid Amplification Test
PASS	Post Authorization Safety Study
PIL	Patient Information Leaflet
PK	Pharmacokinetics
PSURs	Periodic Safety Update Reports
RMP	Risk Management Plan
RNA	Ribonucleic Acid
SMAR	Saudi Medicinal Assessment Report
SPC	Summary Product Characteristics
TEAE	Treatment Emergent Adverse Event

USAN	United States Adopted Names
VAED	Vaccine Associated Enhanced Disease
VAERD	Vaccine Associated Enhanced Respiratory Disease
WHO	World Health Organization

2. Executive Summary

Pfizer and BioNTech submitted a priority review application for an investigational vaccine intended to prevent Coronavirus disease (COVID-19) caused by SARS-CoV-2; the priority review request was submitted via rolling submission on 4 October 2020. The vaccine is based on a SARS-CoV-2 spike glycoprotein (S) antigen encoded by mRNA formulated in lipid nanoparticles (LNPs). The Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) was developed in response to the current global pandemic to address the current urgent and unmet medical need.

The provided quality data of BNT162b2 vaccine has demonstrated a well-described manufacturing process and controlled through appropriate process parameters and in-process controls. The manufacturing process has been validated/qualified through sufficient number of active substance batches/finished product lots. In addition, all the provided active substance batches and finished product lots met the predetermined specifications at release, which support the consistency of the manufacturing process. The provided stability studies—until the last available time points—support the initial shelf life at the proposed storage condition.

The safety and efficacy of the applicant vaccine was assessed in two clinical studies to support the conditional approval request: Study BNT162-01, which is an ongoing first-in-human, phase I/II dose level-finding study conducted in Germany (N=60) to obtain safety and immunogenicity data for multiple vaccine candidates. Study C4591001 is an ongoing, randomized, placebo-controlled phase I/II/III pivotal registration study, which started as a phase I/II study in the US then expanded to include global sites upon the start of the phase II/III part of the study enrolling almost 44,000 participants at various age groups to assess the safety, immunogenicity, and efficacy endpoints, at a global level to ensure generalizability through including a diverse population.

After a comprehensive review of the quality, safety, and efficacy data, SFDA has granted conditional approval for the BNT162b2 vaccine

In addition, SFDA will conduct both passive and active surveillance activities for continued BNT162b2 vaccine safety monitoring, via a collaboration with the relevant stakeholders and international regulatory counterparts, as well as through rapid detection of the potential safety signals, which will enable SFDA to take the appropriate regulatory actions regarding any emerging safety concerns.

3. Introduction

A new strain of novel Coronavirus appeared in Wuhan, China, late last year (December 2019), as a locally spreading epidemic disease that was rapidly carried over the world by global travelers. As of today, the virus has caused almost 94 million confirmed infections while killing almost 2 million patients worldwide. In the Kingdom of Saudi Arabia, COVID-19 reached 365 thousand laboratory confirmed cases and more than 6,300 deaths.

The novel coronavirus happens to spread with great speed from person to person causing an alarming global pandemic that is difficult to contain. The World Health Organization (WHO) has officially named the new Coronavirus disease COVID-19, which is caused by the SARS-CoV-2 virus. The SARS-CoV-2 is a beta-coronavirus member of the Coronavirus family, which includes Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) that affects the lower respiratory system and appears as pneumonia.

The Pfizer-BioNTech COVID-19 Vaccine (also known as BNT162b) is a prophylactic vaccine developed by BioNTech and Pfizer to prevent Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA that encodes a perfusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. Pfizer-BioNTech COVID-19 Vaccine will be referred to as BNT162b2 throughout this report.

Type of submission: New Biological Product Application (Vaccine).

Review type: The application qualified for priority review in accordance to SFDA guidance for priority review.

Active pharmaceutical ingredient: RNA-lipid nanoparticle (LNP) of nucleoside-modified messenger ribonucleic acid [mRNA] (modRNA).

Therapeutic indication: The intended use of BNT162b2 vaccine is to vaccinate individual's ≥16 years of age against COVID-19.

Dosing and administration: BNT162b2 vaccine is administered intramuscularly (IM) as a series of two 30-µg doses of the diluted vaccine solution (0.3 mL each) according to the following schedule: a single dose followed by a second dose 21 days later.

4. Scientific discussion

4.1 Quality Aspects

4.1.1 Active Substance

- **General Information**

BNT162b2 active substance is a single-stranded mRNA that encodes the full-length of a mutant spike glycoprotein (S1S2) of the SARS-CoV-2. In addition, the mRNA contains structural elements to enhance its stability and translational efficiency—including (5'-Cap, 5'-UTR, 3'-UTR and Poly (A)-tail. In addition, the uridine in mRNA is replaced by modified N1-methylpseudouridine during mRNA synthesis, which increases mRNA persistence *in vivo* through weakening of innate immune response to modified mRNA.

- **Manufacturer and manufacturing process development**

The manufacturing process of active substance consists of several steps performed at multiple sites. During product development, changes were implemented to the manufacturing process for commercial purposes. A comparability assessment—including release testing results and side-by-side comparison—was performed to support the manufacturing changes that demonstrated consistency between the active substance batches.

- **Control of the materials**

Information regarding the used materials in the manufacturing process was provided—including a list of raw materials and their use in the process that were classified to compendial and non-compendial materials. Specifications for non-compendial raw materials were provided. In addition, a list of solutions and buffers used in the manufacturing processes were provided.

The provided information demonstrated that the raw materials are well defined and controlled.

- **Control of critical steps and intermediate**

Controls of critical process steps employed during manufacture of BNT162b2 active substance to ensure that product quality is maintained. Process parameters and in-process controls that are employed to control the process and quality of active substance were provided.

The applied control strategy is considered sufficient to ensure the robustness and consistency of the manufacturing process.

- **Process validation**

The validation of BNT162b2 manufacturing process has been demonstrated through a number of consecutive batches. The process parameters and in-process controls met the predefined limits/ranges.

The results of process validation demonstrated the robustness and consistency of the manufacturing process.

- **Characterization**

Different elucidation and characterization studies have been conducted on BNT162b2 active substance, using appropriate analytical methods. Several quality attributes were characterized such as primary structure, 5'-Cap and 3' Poly (A)-tail.

The elucidation and characterization results showed that the BNT162b2 has the expected structural properties.

- **Impurities**

Process and product related impurities and potential contaminants have been identified and controlled through the release specification of active substance.

- **Specification, analytical methods, and batch analysis**

The specification includes a battery of testing parameters—such as identity, purity, impurities, composition and strength —that are employed to monitor the quality of active substance at release and throughout the shelf life.

Description of all analytical procedures has been provided along with qualification/validation of in-house analytical methods.

Batch analysis data for several active substance batches of BNT162b2 was provided and all results complied with the predetermined acceptance criteria, which demonstrated a consistency in the manufacturing process of active substance.

- **Container closure system (CCS)**

The CCS of active substance has been well described and complies with the required quality standards for the intended storage condition.

- **Stability**

Different stability studies—at accelerated, long term, and stressed conditions—were conducted using batches manufactured using the commercial process. In addition, supportive stability studies have been performed using clinical batches. The current stability data supports the initial shelf life and storage condition, which will be revised based on the availability of additional stability data for future testing points.

4.1.2 Finished Product

- **Description of the product and Pharmaceutical Development**

BNT162b2 is supplied as a preservative-free, multi-dose concentrate of 0.45 mL to be diluted to 30 µg of mRNA in 0.3 mL for intramuscular injection, intended for five doses. The finished product is a sterile dispersion of mRNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer. LNPs protect the mRNA from degradation and deliver the mRNA into host cells after IM injection.

The excipients in the finished product are sucrose, sodium chloride, potassium chloride, dibasic sodium phosphate dihydrate, monobasic potassium phosphate and water for injection, in which their quality grades comply with European Pharmacopoeia.

In addition to those excipients, the vaccine contains four lipids. ALC-0315 is a novel aminolipid that regulates the endosomal escape of mRNA into the cytosol. ALC-0159 is a novel polyethylene glycol lipid conjugate that enhances the LNP stability and reduces the non-specific protein binding. DSPC is a phospholipid that provides a stable bilayer-forming structure. The cholesterol is used to support bilayer structures and enhance mobility of the lipid components within the LNP structure.

The provided specifications and characterization for these lipids in addition to the applied acceptance criteria in the finished product specification were considered sufficient to control these lipids.

- **Manufacture and process controls**

The manufacturing process of finished product consists of several stages—formulation, filtration, filling and packaging—performed at multiple sites. All process parameters and in-process controls have been provided, which is considered sufficient to ensure the robustness and consistency of the manufacturing process.

Number of process performance qualification lots have been provided to demonstrate the consistency of the manufacturing process, which was considered satisfactory.

- **Specification, analytical methods, and batch analysis**

The specification includes a list of testing parameters—such as composition and strength, identity, purity, potency, and adventitious agents —that are employed to monitor the quality of BNT162b2 vaccine at release and throughout the shelf life.

Description of all analytical procedures has been provided along with qualification/validation of in-house analytical methods.

Batch analysis data for several finished product lots was provided, and all results complied with the predetermined acceptance criteria, which demonstrated a consistency in the manufacturing process of finished product.

- **Characterization of impurities**

The impurity profile of the finished product is based primarily on the impurity profile of the materials used during the manufacturing process.

The impurities from the used lipids are controlled through pre-determined acceptance criteria and the impurities from other excipients are controlled through their specifications.

All process-related impurities are present only in low amounts and are further reduced during the finished product manufacturing process.

- **Container closure system (CCS)**

The CCS of the vaccine has been well described and complies with the required quality standards for the intended storage condition.

- **Stability of the product**

Different stability studies—at accelerated, long term, and stressed conditions—were conducted using several emergency supply finished product lots. In addition, supportive stability studies have been provided. The current stability data supports the initial shelf life of 6 months when stored at -70 °C (-60 °C to -80 °C), which will be revised based on the availability of additional stability data for future testing points.

4.1.3 Conclusion on quality aspects

During the review process, some inquiries were raised to the applicant—related to the manufacturing, controls, characterization, stability, and comparability studies—which have been resolved adequately.

The manufacturing process and applied control strategy were appropriately described and defined, and the manufacturing process was qualified/validated through sufficient number of active substance batches and finished product lots, which demonstrates the consistency of the manufacturing process. The batch and lot release of active substance batches and finished product, respectively, were within predetermined release specifications. The stability data demonstrated that the quality attributes of active substance and finished product remained within the predetermined shelf life specifications at the proposed storage conditions until the last available time points in the stability studies, which support the initial shelf life.

Overall, the provided information related to the manufacturing, controls, characterization, and stability studies were considered sufficient to support the conditional approval of BNT162b2 vaccine.

4.2 Non-clinical Aspects

The applicant submitted the following preclinical studies to support the safety and efficacy BNR162 vaccine against COVID-19:

Pharmacology:

Type of study	Test system	Method of administration	Study number
Primary Pharmacodynamics			
COVID-19: Immunogenicity Study of the LNP-Formulated ModRNA Encoding the Viral S Protein-V9	BALB/c mice	IM Injection	R-20-0085
Characterizing the Immunophenotype in Spleen and Lymph Node of Mice Treated With SARS-CoV-2 Vaccine Candidates	BALB/c mice	IM Injection	R-20-0112
In Vitro Expression of BNT162b2 Drug Substance and Drug Product	In vitro cell culture	IM Injection	R-20-0211
BNT162b2 (V9) Immunogenicity and Evaluation of Protection against SARS-CoV-2 Challenge in Rhesus Macaques	Rhesus macaques	IM Injection	VR-VTR-10671

Pharmacokinetics:

Type of study	Test system	Method of administration	Study number
Absorption			

Single Dose Pharmacokinetics and Excretion in Urine and Feces of ALC-0159 and ALC-0315	Wistar Han Rat	IV bolus	PF-07302048_06Jul20_072424
Distribution			
Expression of Luciferase-encoding modRNA after I.M application of GMP- ready acuitas LNP Formulation	Mice BALB/c	IM Injection	R-20-0072
Metabolism			
In Vitro Metabolic Stability of ALC-0315 in CD-1/ICR Mouse, Sprague Dawley Rat, Wistar Han Rat, Cynomolgus Monkey, and Human Liver Microsomes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human liver microsomes	In vitro	01049-20008
In Vitro Metabolic Stability of ALC-0315 in CD-1/ICR Mouse, Sprague Dawley Rat, Cynomolgus Monkey, and Human Liver S9 Fractions	Mouse (CD-1/ICR), rat (Sprague Dawley), monkey (Cynomolgus), and human S9 liver fractions	In vitro	01049-20009
In Vitro Metabolic Stability of ALC-0315 in CD-1/ICR Mouse, Sprague Dawley Rat, Wistar Han Rat, Cynomolgus Monkey, and Human Hepatocytes.	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human hepatocytes	In vitro	01049-20010
In Vitro Metabolic Stability of ALC-0159 in CD-1/ICR Mouse, Sprague Dawley Rat, Wistar Han Rat, Cynomolgus Monkey, and Human Liver Microsomes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human liver microsomes	In vitro	01049-20020
In Vitro Metabolic Stability of ALC-0159 in CD-1/ICR Mouse, Sprague Dawley Rat, Cynomolgus Monkey, and Human Liver S9 Fractions	Mouse (CD-1/ICR), rat (Sprague Dawley), monkey (Cynomolgus), and human S9 fractions	In vitro	01049-20021
In Vitro Metabolic Stability of ALC-0159 in CD-1/ICR Mouse, Sprague Dawley Rat, Wistar Han Rat, Cynomolgus Monkey, and Human Hepatocytes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human hepatocytes	In vitro	01049-20022

Biotransformation of ALC-0159 and ALC-0315 In vitro and In vivo in Rats	In vitro: CD-1 mouse, Wistar Han rat, cynomolgus monkey, and human blood, liver S9 fractions and hepatocytes In vivo: male Wistar Han rats	In vitro or IV (in vivo in rats)	PF07302048_05Aug20_043725

Toxicology

Type of study	Test system	Method of administration	Study number
Repeat-Dose Toxicity			
Repeat-Dose Toxicity Study of Three LNP-Formulated RNA Platforms Encoding for Viral Proteins by Repeated Intramuscular Administration to Wistar Han Rats.	Wistar Han Rat	IM Injection	38166
17-Day Intramuscular Toxicity Study of BNT162b2 (V9) and BNT162B3c in Wistar Han Rats with a 3-week Recovery (Interim Data).	Wistar Han Rat	IM Injection	20GR142

4.2.1 Pharmacology

The primary pharmacodynamics studies in mice and nonhuman primates elucidate the mechanism of action for this vaccine. It works by intracellular translation of mRNA to the SARS-CoV-2 S protein to induce an immune response, a humoral neutralizing antibody response and Th1-type CD4+ and CD8+ cellular response, to inhibit virus infection and kill virus-infected cells, respectively.

The efficacy of the vaccine was examined in a mammalian cell population in vitro, two studies in mice, and one study in rhesus monkeys including challenge with SARS CoV-2 virus in rhesus monkeys.

Study R-20-0211 aimed to analyze the expression of drug substances (DS; BNT162b2-RNA), and as LNP-formulated drug product (DP; BNT162b2) in HEK293T cells. Both BNT162b2 DS and DP led to high frequencies of transfected cells when compared to non-transfected cells. In addition, Co-localization of the antigen expressed by DS encoding the full-length S protein with an endoplasmic reticulum ER marker was detected.

Study R-20-0085 aimed to evaluate the immunogenicity of this vaccine. Four groups of eight female BALB/c mice were immunized once via IM route on day 0 with 0.2 µg, 1 µg or 5 µg RNA/animal of COVID-19 mRNA Vaccine BNT162b2, or with the buffer alone (control group). Antibody response was evaluated at days 7, 14, 21 and 28.

Study R-20-0112 aimed to characterize T- and B-cell responses in the spleen, lymph nodes and blood of this vaccine. Eight BALB/c mice per group were immunized with five µg of COVID-19 mRNA vaccine BNT162b2 or buffer (control) on day 0 by intramuscular injection.

In Studies R-20-0112 and R-20-0085 conducted on mice, vaccination with BNT162b2 induced IgGs that bind S1 and RBD, whereas these antibodies were not observed in control animals. A dose-response effect was observed in the IgG responses specific for the SARS CoV-2 S1 protein fragment and its receptor-binding domain. In addition, the high and dose-dependent pseudovirus neutralizing antibody response was demonstrated. CD4+ and CD8+ T cell cellular responses with a Th1 pattern of response were detected in immunized mice compared to control animals. Booster responses were not assessed in these studies.

Study VR-VTR-10671 aimed to evaluate the immune response and protection effect against SARS-CoV-2 challenge in rhesus macaques (Macaca mulatta). This study was conducted on male rhesus macaques aged 2-4 years. Rhesus macaques were immunized with 30 µg or 100 µg of BNT162b2 (n=6 per group) or with saline control (n=6) on days 0 and 21, administered in a 0.5 mL dose volume by the intramuscular (IM) injection. The findings demonstrated that the COVID-19 mRNA vaccine BNT162b2 was immunogenic in

rhesus macaques, eliciting IgG responses after a single dose, which were boosted by a second dose. In addition, the dose-response was observed. The neutralizing geometric mean titer in a SARS-CoV-2 neutralization assay was compared to that seen in convalescent serum (HCS) from humans recovered COVID-19 and shown to be 8-fold higher at 30 µg BNT162. Seven days after Dose 2 of 100-µg dose level, the neutralizing GMT found to be 18-fold that of the HCS GMT and stayed 3.3-fold higher than this benchmark five weeks after the last vaccination. Strongly Th1-biased CD4+ T cell response with a concurrent interferon-γ (IFNγ) + CD8+ T cell response was shown in rhesus macaques.

For the challenge part of the study, Infection SARS-CoV-2 challenge was performed on the COVID-19 mRNA Vaccine BNT162b2-immunised animals (100 µg/animal dose level) and on animals dosed with a control. The challenged monkeys showed no signs of clinical illness. Total viral RNA was observed in bronchoalveolar lavage (BAL) fluid of control rhesus macaques but not detected in rhesus macaques vaccinated with BNT162b2; in the nasal swabs viral RNA was observed in rhesus macaques administered by BNT162 but clearance was faster than in controls. In lung tissues, the monkeys given COVID-19 mRNA Vaccine BNT162b2 had lower scores on computed tomography scans when compared to control. Immunization with this vaccine provided protection in the lungs from infectious SARS-CoV-2 challenge in rhesus macaques.

Secondary Pharmacodynamics and safety pharmacology studies were not conducted with BNT162b2, in line with relevant regulatory guidance (WHO Guidelines on nonclinical evaluation of vaccines, 2005).

4.2.2 Pharmacokinetics:

The ADME profile of BNT162b2 vaccine included evaluation of the PK and metabolism of the two novel lipid excipients (ALC-0315 and ALC-0159) in the LNP and potential in vivo bio-distribution using luciferase expression as a surrogate reporter.

- **Absorption:**

Study PF-07302048_06Jul20_072424 "Single dose pharmacokinetics study of ALC-0315 and ALC-0159 following intravenous bolus injection of a nanoparticle formulation in rats" aimed to evaluate the pharmacokinetics and elimination of the two novel excipients (ALC-0315 and ALC-0159). This study was conducted using LNPs containing surrogate luciferase RNA, with the lipid composition being identical to BNT162b2, to test the in vivo disposition of ALC-0159 and ALC-0315.

Concentrations of ALC-0159 dropped approximately 8000- and >250-fold in plasma and liver, respectively, during this 2-week study. For ALC-0315, the elimination of the molecule from plasma and liver was slower, but concentrations fell approximately 7000- and 4-fold in two weeks for plasma and liver, respectively. Overall, the apparent terminal t½ in plasma and liver were similar in both tissues and were 2-3 and 6-8 days for ALC-0159 and ALC-0315, respectively. The apparent terminal t½ in plasma likely represents the re-distribution of the respective lipids from the tissues into which they have distributed as the LNP, back to plasma where they are eliminated.

- **Distribution:**

Study R-20-0072 aimed to assess the bio-distribution of BNT162b2 in BALB/c mice using luciferase expression as a surrogate reporter. Protein expression was demonstrated at the site of injection and to a lesser extent, and more transiently, in the liver after BALB/c mice administered an IM injection of RNA encoding luciferase in an LNP formulation like BNT162b2. Luciferase expression was detected at the injection site at 6 hours after injection and decreased to near baseline levels by day 9. Expression in the liver was also present at 6 hours after injection and was not detected by 48 hours after injection.

- **Metabolism:**

The in vitro metabolism of ALC-0315 and ALC-0159 was assessed in blood, liver microsomes, S9 fractions, and hepatocytes from mice, rats, monkeys, and humans. The in vivo metabolism was examined in rat plasma, urine, feces, and liver samples from the PK study (PF-07302048_05Aug20_043725). Metabolism of ALC-0315 and ALC-0159 appears to occur slowly in vitro and in vivo. ALC-0315 and ALC-0159 are metabolized by hydrolytic metabolism of the ester and amide functionalities, respectively, and this hydrolytic metabolism is observed across the species evaluated.

- **Excretion:**

No excretion studies have been performed with BNT162b2 vaccine. In the PK study, it appears that 50% of ALC-0159 was eliminated unchanged in faeces. Metabolism played a role in the elimination of ALC-0315, as little to no unchanged material were detected in either urine or faeces. Investigations of urine, faeces and plasma from the rat PK study identified a series of ester cleavage products of ALC-0315. The applicant has proposed that this likely represents the primary clearance mechanism acting on this molecule, although no quantitative data is available to confirm this hypothesis. In vitro, ALC-0159 was metabolized slowly by hydrolytic metabolism of the amide functionality.

4.2.3 Toxicology

- Single dose toxicity:

No single dose toxicity studies have been conducted and is in line with relevant guidelines (WHO 2005; WHO 2014).

- **Repeat-dose toxicity:**

Study 38166 was a GLP-compliant repeat-dose study conducted in Wistar Han rats to assess the potential toxicity of the LNP and mRNA platform used in BNT162b2.

Study 20GR142 was a GLP-compliant repeat-dose study conducted in Wistar Han rats to assess the potential toxicity of COVID-19 mRNA Vaccine BNT162b2 (Ongoing).

In Study 38166, male and female Wistar Han rats were administered BNT162b2 via IM injection(s) into the hind limb on three occasions once a week for 3 weeks (dosing days 1, 8 and 15). Rats were administered 0 (buffer control) or 100 µg RNA/animal/dosing day BNT162b2 as two injections (one in each hind limb) of 100 µL each. The control was phosphate buffered saline/300 mM sucrose, corresponding to the storage buffer of the vaccine product. Each group had 18 male and 18 female Wistar Han rats, assigned as 10 to the main study, 5 for recovery groups and 3 as additional rats for cytokine analyses. The recovery period was 3 weeks after the last dose. Necropsy was conducted on study day 17, ~48 hours after the last dose, and after the 3-week recovery period.

No unscheduled deaths were noted. Dosing was considered well tolerated without evidence of systemic toxicity; there was transiently higher in body temperature in the hours after dosing and some loss in body weight over the same period but these were not of a magnitude to be considered adverse.

Local inflammatory reactions were noted at the intramuscular injection site. Injection site changes observed were of oedema, erythema, and induration, more severe and more frequent after the second and/or third doses compared to the first; however, these observations resolved prior to subsequent dosing and were fully recovered at the end of the 3-week recovery period.

The most common macroscopic observation in the vaccinated group was induration or thickening, occasionally accompanied by encrustation, which was observed for nearly all animals. This correlated microscopically with inflammation and variable fibrosis, edema, and myofiber degeneration. Inflammation at the injection site was accompanied by elevations in circulating white blood cells and acute phase proteins (fibrinogen, alpha-2 macroglobulin, and alpha-1 acid glycoprotein).

Enlargement of the draining (iliac) lymph nodes was evident at the end of dosing. This correlated with increased cellularity of germinal centers and increased plasma cells in the draining (iliac) lymph node and is an anticipated immune response to the injected vaccine.

Enlargement of spleen and increased spleen weights correlated microscopically to minimal to mild increased hematopoiesis, and increased haematopoiesis was also evident in the bone marrow. These results are likely secondary to the immune/inflammatory responses to the vaccine.

At the end of the 3-week recovery phase, injection sites were normal, clinical pathology findings, and macroscopic observations had resolved and there was evidence of recovery of the injection site inflammation microscopically.

Microscopic vacuolation of portal hepatocytes was observed. There were no elevations in alanine aminotransferase (ALT). Higher gamma-glutamyltransferase (GGT) was noted in all vaccinated animals, but there were no macroscopic or microscopic findings consistent with cholestasis or hepatobiliary injury to explain the increased GGT activity, which was completely resolved at the end of the 3-week recovery period. The vacuolation may be related to hepatic distribution of LNP lipid. No changes were shown in serum cytokine concentrations.

There were no effects observed on ophthalmological and auditory assessments, nor on external appearance or behavior and no vaccine-related changes were seen in serum cytokine concentrations.

Immunogenicity assessment showed that BNT162b2 vaccine elicited a specific IgG antibody response to SARS CoV-2 spike protein directed against the S1 fragment and the receptor-binding domain. A neutralizing antibody response was also detected with the vaccine in a pseudovirus neutralization assay.

In conclusion, administration of vaccine candidates BNT162b2 was well tolerated without any signs of systemic toxicity and produced inflammatory changes at the injection sites and the draining lymph nodes, increased haematopoiesis in the bone marrow and spleen, and clinical pathology changes consistent with an immune response or inflammation in the injection sites.

- **Reproductive and developmental toxicity**

Reproductive and developmental toxicity studies are ongoing with BNT162b2.

4.2.4 Conclusion on non-clinical aspects

Overall, the submitted preclinical documentation is considered sufficient to support the conditional approval of BNT162b2. The pharmacological properties as well as the PK and toxicity profiles of BNT162b2 were adequately characterized.

4.3 Clinical Aspects

4.3.1 Introduction

Two clinical studies were submitted to support the safety and efficacy of the Pfizer-BioNTech COVID-19 Vaccine [BNT162b2] in this application:

- **BNT162-01:** A multi-site, phase I/II, 2-part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID- 19 using different dosing regimens in healthy adults. (Ongoing)
- **C4951001:** A phase I/II/III, placebo-controlled, randomized, observer-blind, dose-finding Study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-COV-2 RNA vaccine candidates against COVID-19 in healthy individuals. (Ongoing)

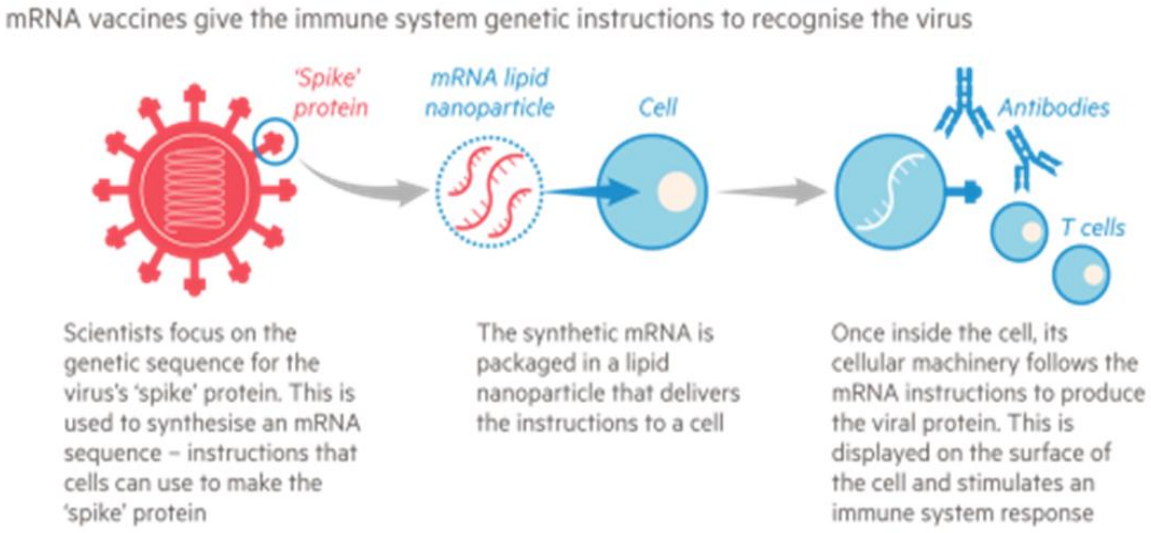
Table 4: Summary of submitted clinical studies:

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

4.3.2 Clinical Pharmacology

The Pfizer-BioNTech COVID-19 Vaccine encodes a P2 mutant S (P2 S) and is formulated as an RNA-lipid nanoparticle (LNP) of nucleoside-modified mRNA (modRNA) which has blunted innate immune sensor activating capacity and thus augmented antigen expression. Encapsulation into LNPs enables transfection of the mRNA into host cells after IM injection. The LNPs are composed of four different lipids in a defined ratio. During mixing of the RNA and the dissolved lipids, the lipids form the nanoparticles encapsulating the RNA. After injection, the LNPs are taken up by the cells, and the RNA is released into the cytosol. In the cytosol, the RNA is translated into the encoded viral protein. The P2 S antigen induces an adaptive immune response.

As S is the antigen that recognizes the host cell receptor and enables infection of the host cells, it is a key target of virus neutralizing antibodies. Furthermore, as RNA-expressed S is being degraded intracellularly, the resulting peptides can be presented at the cell surface, triggering a specific T cell-mediated immune response with activity against the virus.



Source: Pfizer

4.3.2.1 Pharmacokinetic/ Pharmacodynamic studies

No pharmacokinetic/ pharmacodynamic data have been submitted nor were they required for this application.

4.3.3 Clinical Immunogenicity

Clinical Immunogenicity was assessed in both submitted studies.

- **BNT162-01:**

Methods:

Qualified assays were used to assess both humoral and cellular immune responses of the vaccine candidate in 60 healthy adult male and female participants aged 18-55 years, who received two doses of BNT162b2, ~21 days apart with different dose groups (1 µg, 3 µg, 10 µg, 20 µg and 30 µg). Older adults (aged between 56-85 years) have also been enrolled.

Humoral immunity was evaluated at baseline, day 8, and 22 days after BNT162b2 dose 1 and days 29, 43 and 50 after dose 2, through SARS-CoV-2 serum neutralization and binding assays. In addition, cellular immunity was assessed through enzyme-linked immuno-spot (ELISPOT) and intracellular cytokine staining visualized with fluorescence activated cell sorting (FACS) at baseline and on day 29 (7 days) after the second vaccine dose. Assessments are planned up to 162 days after the second dose.

- **C4951001:**

Methods:

Phase I assessed the humoral immunogenicity of the vaccine candidate in 90 healthy adult male and female participants in two age groups (18-55 years and 65-85 years of age), who were randomized to receive either 10 µg, 20 µg or 30 µg of BNT162b2 or Placebo, two injections ~21 days apart. The immune response was assessed through SARS-CoV-2 serum neutralization and binding assays at baseline and days 8 and 22 after dose 1 and at days 43, 50, 85, and 184 after dose two.

In phase II, immunogenicity was assessed as an exploratory endpoint and a secondary (12 to 15-year olds compared with 16 to 25 year olds) and an exploratory endpoint for the Phase III part of the study. Assessments were planned to be performed at different time points up to 24 months.

BNT162-01 and C4951001 study results:

Humoral immune response:

The results of both phase I trials reflected the findings observed in the larger phase II population.

Phase II (C4951001) enrolled 360 healthy participants. Of which, 335 were included in the Dose 2 evaluable immunogenicity population (168 in BNT162b2 and 167 in the placebo arm), were BNT162b2 at 30 µg elicited robust SARS-CoV-2 neutralization and S1-binding

IgG antibody responses at 1 month after Dose 2. SARS-CoV-2 neutralizing titers were observed at a higher level in the younger adult group (18-55 years) compared to the older adult group (56-85 years). Notably, geometric mean titers (GMTs) for younger and older participants at 1 month after Dose 2 were comparable to the GMTs of a comparative panel of COVID-19 human convalescent sera (HCS), as was observed in Phase I of the study. S1-binding GMCs were generally higher in the younger age group compared to the older age group, which was also comparable to the phase I findings.

Immunogenicity data for the secondary phase II endpoint and phase III will be reported later and were not included in the submitted report.

Table 5: Summary of Geometric Mean Titers/Concentrations by Baseline SARS-CoV-2 Status – Phase II – 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)

Cellular immune response:

Cellular immunogenicity was assessed in the BNT162-01 trial. At cutoff date, responses were reported from 39 participants across dose levels in the younger adult group (18 to 55 years of age).

Of 39 subjects receiving prime-boost vaccination of BNT162b2, 39 (100%) mounted CD4+ T cell response and almost 90% of subjects rising a CD8+ T-cell response against the full-length Spike protein of SARS-CoV-2. T-cell responses were directed against different parts of the Spike protein indicating induction of multi-epitopic responses with this vaccine candidate. In addition, vaccine-induced, S-specific CD4+ T cells had a robust IFNy/lL-2 secretion with only a few Th2 cytokine IL-4 upon antigen-specific (SARSCoV-2 S protein peptide pools) re-stimulation indicating a favorable Th1 profile.

Figure 1: Frequency and Magnitude of BNT162b2-induced CD4+ and CD8+ T Cell Responses across Dose Levels

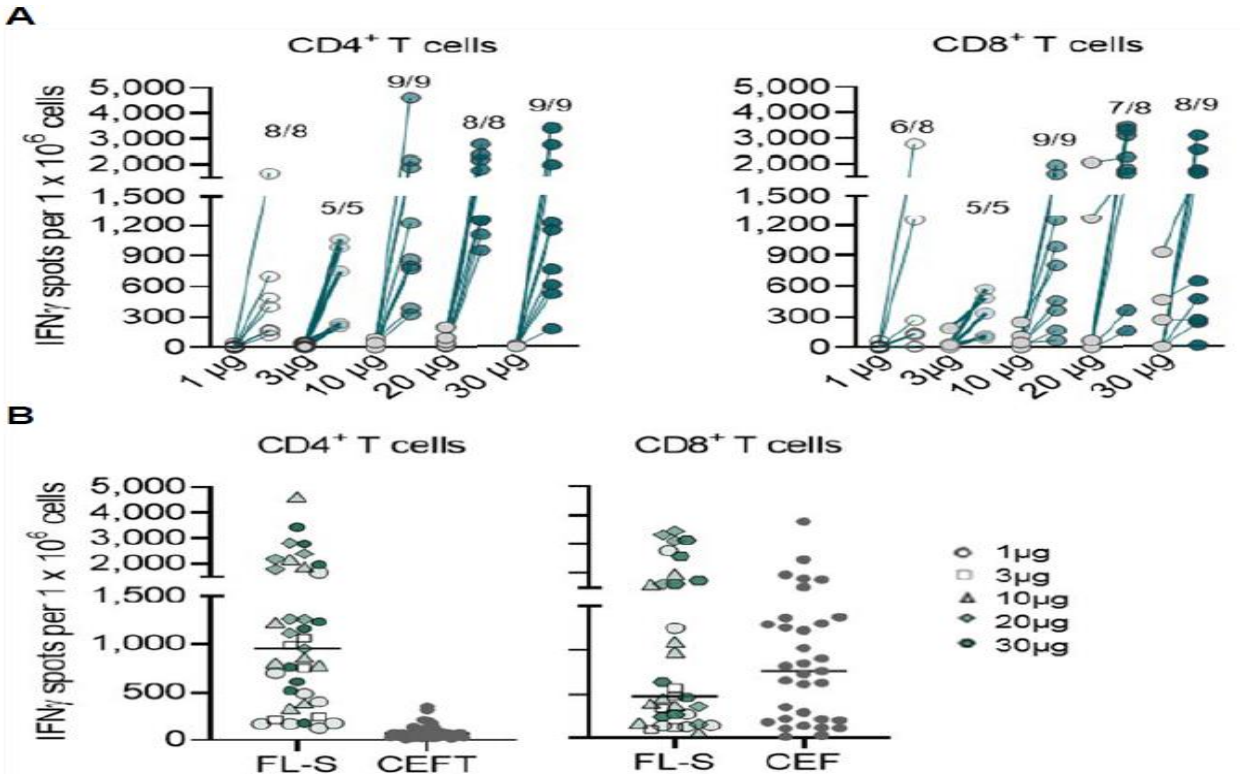
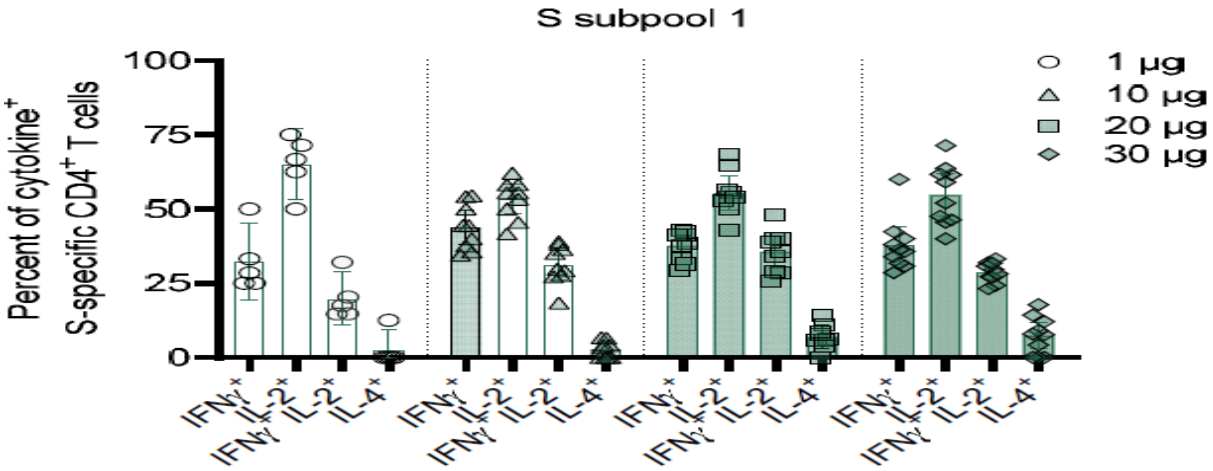


Figure 2: S-Specific CD4+ T Cells Producing Each Cytokine as a Fraction of Total Cytokine-Producing S-specific CD4+ T Cells – BNT162b2



Assessor comments

Overall, the data presented from the BNT162-01 trial was encouraging, as BNT162b2 displayed strong dose-dependent antibody response and substantial dose-dependent booster response in antigen binding IgG levels 7 days after Dose 2. All participants dosed with the first dose with ≥30 µg BNT162b2 seroconverted by either 7 days or 21 days after the second dose (Day 29 or Day 43). Although by Day 43, the observed responses decreased for the 20-µg and 30-µg dose level, participants dosed at ≥10 µg BNT162b2 Day 43 virus neutralizing GMTs were comparable or even superior to those of a COVID-19 HCS panel. BNT162b2 also induced strong cellular immunity with a favorable Th1 profile through the detection of a higher level of IFNγ and IL-2 compared to a low level of Th2 cytokine IL-4. Of note, the immunogenicity data of the older age group (65 - 85 years old) were not available at the time of this report.

For the phase I part of C4591001 trial, results seemed highly promising as BNT162b2 elicited robust SARS-CoV-2 neutralization and substantial increase in antigen binding IgG levels 7 days after Dose 2 in both age groups. Responses were maintained through Day 52 (data cut off). These findings reflected the results observed in the phase II part of the study.

4.3.4 Clinical Efficacy

Efficacy Analysis

Efficacy was evaluated in the phase II/III part of the global, randomized, observer-blind, placebo-controlled, superiority trial (C4591001). The assessment of BNT162b2 Vaccine Efficacy (VE) for the first primary efficacy endpoint was performed for confirmed COVID-19 cases observed at least 7 days after receiving the second dose onwards among participants without serological or virological evidence of past SARS-CoV-2 infection. 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.

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, the vaccine efficacy of BNT162b2 would be declared.

If the predicted posterior probability of demonstrating vaccine efficacy at the final analysis were less than 5.0% at any of the first two planned interim analyses, the study would stop due to lack of benefit (futility).

Analysis Timing

During Phase II/III, interim analyses were planned to be performed by an un-blinded statistical team after accrual of at least 62, 92, and 120 cases. For operational reasons, the first interim analysis was conducted after accrual of greater than 62 cases. Final analysis was planned after accumulation of 162 cases and futility after accrual of at least 62 and 92 cases.

Study Participants

The phase III part of the study enrolled healthy participants (stable disease in the previous 6 weeks) ≥12 years willing to participate and at higher risk of COVID—19. Patients were excluded if they complained from a psychiatric condition, history of severe adverse reactions, recipient of medications intended to prevent COVID-19 or blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study, previous clinical diagnosis of COVID-19, bleeding diathesis, women who are pregnant or breastfeeding, previous vaccination with any coronavirus vaccine, individuals who received treatment with immunosuppressive therapy, participation in clinical studies or other studies involving study intervention containing lipid nanoparticles and Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

Table 6: Disposition of all participant in Phase II

	Vaccine Group (as Randomized)				
	BNT162b2 (30 µg)			Placebo	
	18-55 Years (N^a=88) n^b (%)	56-85 Years (N^a=92) n^b (%)	18-85 Years (N^a=180) n^b (%)	18-85 Years (N^a=180) n^b (%)	Total (N^a=360) n^b (%)
Randomized	88 (100.0)	92 (100.0)	180 (100.0)	180 (100.0)	360 (100.0)
Not vaccinated	0	0	0	0	0
Vaccinated					
Dose 1	88 (100.0)	92 (100.0)	180 (100.0)	180 (100.0)	360 (100.0)
Dose 2	87 (98.9)	92 (100.0)	179 (99.4)	179 (99.4)	358 (99.4)
Withdrawn after Dose 1 and before Dose 2	1 (1.1)	0	1 (0.6)	0	1 (0.3)
Withdrawn after Dose 2	0	0	0	0	0
Reason for withdrawal					
Adverse event	1 (1.1)	0	1 (0.6)	0	1 (0.3)

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.

Table 7: Disposition of all participant in Phase II/III

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N^a=18448) n^b (%)	Placebo (N^a=18466) n^b (%)	Total (N^a=36914) n^b (%)
Randomized	18448 (100.0)	18466 (100.0)	36914 (100.0)
Not vaccinated	31 (0.2)	31 (0.2)	62 (0.2)
Vaccinated			
Dose 1	18407 (99.8)	18434 (99.8)	36841 (99.8)
Dose 2	14666 (79.5)	14667 (79.4)	29333 (79.5)
Completed 1-month post–Dose 2 visit (vaccination period)	3782 (20.5)	3761 (20.4)	7543 (20.4)
Discontinued from vaccination period but continue in the study	103 (0.6)	94 (0.5)	197 (0.5)
Discontinued after Dose 1 and before Dose 2	99 (0.5)	89 (0.5)	188 (0.5)
Discontinued after Dose 2 and before 1-month post–Dose 2 visit	2 (0.0)	2 (0.0)	4 (0.0)
Reason for discontinuation from vaccination period			
No longer meets eligibility criteria	35 (0.2)	52 (0.3)	87 (0.2)
Refused further study procedures	37 (0.2)	2 (0.0)	39 (0.1)
Withdrawal by subject	14 (0.1)	21 (0.1)	35 (0.1)
Adverse event	8 (0.0)	6 (0.0)	14 (0.0)
Physician decision	2 (0.0)	2 (0.0)	4 (0.0)
Pregnancy	1 (0.0)	3 (0.0)	4 (0.0)
Medication error without associated adverse event	1 (0.0)	1 (0.0)	2 (0.0)
Lost to follow-up	0	1 (0.0)	1 (0.0)
Other	5 (0.0)	6 (0.0)	11 (0.0)
Withdrawn from the study	79 (0.4)	92 (0.5)	171 (0.5)
Withdrawn after Dose 1 and before Dose 2	55 (0.3)	58 (0.3)	113 (0.3)
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	7 (0.0)	16 (0.1)	23 (0.1)
Withdrawn after 1-month post–Dose 2 visit	0	3 (0.0)	3 (0.0)
Reason for withdrawal from the study			
Withdrawal by subject	45 (0.2)	56 (0.3)	101 (0.3)
Lost to follow-up	15 (0.1)	18 (0.1)	33 (0.1)
Adverse event	6 (0.0)	3 (0.0)	9 (0.0)
Protocol deviation	3 (0.0)	5 (0.0)	8 (0.0)
No longer meets eligibility criteria	3 (0.0)	4 (0.0)	7 (0.0)
Death	1 (0.0)	2 (0.0)	3 (0.0)
Refused further study procedures	2 (0.0)	1 (0.0)	3 (0.0)
Physician decision	1 (0.0)	1 (0.0)	2 (0.0)
Pregnancy	0	1 (0.0)	1 (0.0)
Other	3 (0.0)	1 (0.0)	4 (0.0)

Table 8: Analysis population

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=16061) n[b] (%)	Placebo (N[a]=16218) n[b] (%)	Total (N[a]=32279) n[b] (%)
Sex			
Male	8197 (51.0)	8144 (50.2)	16341 (50.6)
Female	7864 (49.0)	8074 (49.8)	15938 (49.4)
Race			
White	13502 (84.1)	13692 (84.4)	27194 (84.2)
Black or African American	1298 (8.1)	1303 (8.0)	2601 (8.1)
American Indian or Alaska native	88 (0.5)	82 (0.5)	170 (0.5)
Asian	712 (4.4)	716 (4.4)	1428 (4.4)
Native Hawaiian or other Pacific Islander	40 (0.2)	26 (0.2)	66 (0.2)
Multiracial	341 (2.1)	297 (1.8)	638 (2.0)
Not reported	80 (0.5)	102 (0.6)	182 (0.6)
Ethnicity			
Hispanic/Latino	4415 (27.5)	4383 (27.0)	8798 (27.3)
Non-Hispanic/non-Latino	11553 (71.9)	11736 (72.4)	23289 (72.1)
Not reported	93 (0.6)	99 (0.6)	192 (0.6)
Country			
Argentina	2445 (15.2)	2415 (14.9)	4860 (15.1)
Brazil	889 (5.5)	889 (5.5)	1778 (5.5)
South Africa	215 (1.3)	218 (1.3)	433 (1.3)
USA	12512 (77.9)	12696 (78.3)	25208 (78.1)
Age group			
16-55 Years	9093 (56.6)	9172 (56.6)	18265 (56.6)
>55 Years	6968 (43.4)	7046 (43.4)	14014 (43.4)
Age at vaccination (years)			
Mean (SD)	50.9 (15.58)	50.7 (15.68)	50.8 (15.63)
Median	52.0	52.0	52.0
Min, max	(16, 89)	(16, 91)	(16, 91)

Note: Data from subjects who are not confirmed 7 days post dose 2 cases are included in the analysis to comprehensively show all data reported and/or contribute to the total surveillance time calculation but may be subject to change with additional follow-up.

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.

Table 9: Demographic Characteristics – Subjects without Evidence of Infection Prior to 7 Days after Dose 2 – Evaluable Efficacy Population (7 Days) – Interim Analysis 1

Efficacy Results

Interim analysis:

Vaccine efficacy of BNT162b2 against COVID-19 among participants without evidence of past SARS-CoV-2 infection was demonstrated in the first interim analysis that was conducted after the accrual of at least 62 cases following the protocol and SAP. The primary efficacy results presented in this section are from that interim analysis.

Only the vaccine efficacy of BNT162b2 for the first primary efficacy endpoint (COVID-19 incidence based on central laboratory or locally confirmed nucleic acid amplification test (NAAT) in participants without serological or virological evidence of past SARS-CoV-2 infection prior to 7 days after receiving the second dose) was analyzed and presented at this interim analysis. The vaccine efficacy from the second primary efficacy endpoint was reported in the final analysis.

First Primary Efficacy Endpoint:

Among participants included in the evaluable efficacy population, 32,279 participants (16,061 in BNT162b2 group and 16,218 in placebo group) did not have evidence of infection with SARS-CoV-2 7 days after the second dose. There were four COVID-19 cases in the BNT162b2 group compared to 90 COVID-19 cases reported in the placebo group. These data give an estimated vaccine efficacy of 95.5% for BNT162b2. The posterior probability of >99.99% met the pre-specified interim analysis success criterion of > 99.5%. The 95% credible interval for the vaccine efficacy was 88.8% to 98.4%, indicating that given the current observed data, there is a 95% probability that the true VE lies in this interval. Also, note that the posterior probability of true VE > 86.0% is 99.5% and VE > 88.8% is 97.5%.

Table 10: 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 Population (7 Days) – Interim Analysis 1.

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=16061)		Placebo (N[a]=16218)				
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	4	1.722 (15899)	90	1.732 (16010)	95.5	(88.8, 98.4)	>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 at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
Note: Data from subjects who are not confirmed 7 days post dose 2 cases are included in the analysis to comprehensively show all data reported and/or contribute to the total surveillance time calculation but may be subject to change with additional follow-up.
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. This probability must be at least 99.5% at the interim analysis in order to conclude that the vaccine is efficacious.

The vaccine efficacy of BNT162b2 for the same primary efficacy endpoint based on all available efficacy populations was 95.7%, with 4 and 93 cases in the BNT162b2 and placebo groups, respectively.

No clinically meaningful differences in VE by subgroup were observed by age group, country, ethnicity, sex, or race in the Dose 2 evaluable efficacy population, with VE estimates that ranged from 91.2% to 100.0%.

Final analysis:

First primary endpoint:

Among participants included in the evaluable efficacy population, 36,523 participants (17,411 in BNT162b2 group and 17,511 in placebo group) did not have evidence of infection with SARS-CoV-2 through 7 days after the second dose. There were eight COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases reported in the placebo group. These data give an estimated vaccine efficacy of 95% for BNT162b2. The posterior

probability of >99.99% met the pre-specified interim analysis success criterion of > 98.6%. The 95% credible interval for the vaccine efficacy was 90.3% to 97.6%, indicating that given the current observed data there is a 95% probability that the true VE lies in this interval.

Table 11: 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 Population (7 Days)

	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.

Second primary endpoint:

Among participants included in the evaluable efficacy population, with or without evidence of infection with SARS-CoV-2 through 7 days after the second dose. There were

nine COVID-19 cases in the BNT162b2 group compared to 169 COVID-19 cases reported in the placebo group (VE= 94.6% for BNT162b2 with a 95% credible interval of 89.9% to 97.3%).

Severe COVID-19 cases in subjects without evidence of infection with SARS-CoV-2 through 7 days after the second dose was very low, there was one severe COVID-19 case reported in the BNT162b2 group compared to three in the placebo group (VE= 66.4% with a broad 95% credible interval of -124.8% to 96.3%), similar results were also observed in subjects with or without evidence of infection with SARS-CoV-2.

Assessor comments

Overall, efficacy results for both the first and second primary endpoints were very promising and exceeded the proposed requirements in the WHO Target Product Profiles for COVID-19 Vaccines of VE around 50% point estimate. However, the efficacy of the vaccine in preventing severe COVID-19 disease is not well-understood yet since only 4 cases (1 in the vaccine arm and 3 in the placebo arm) occurred 7 days after the second dose and 10 cases after dose 1 (1 in the vaccine arm and 9 in the placebo arm) . Moreover, it is acknowledged that the study did not use severe COVID-19 cases as the primary endpoint; as such, data needs longer follow-up time beyond the current available times in order to accumulate cases in the study. However, the efficacy of the vaccine against severe COVID19 cases is more clinically relevant and should be monitored over time until mature data becomes available to ensure the efficacy and safety (vaccine-associated enhancement of respiratory disease) of the vaccine.

One of the efficacy uncertainties is the lack of data on the Arab population in the study. Results of individuals from 12 to 15 years of age and HIV positive subjects were not available at the time of this report, thus no recommendation can be drawn at this time.

4.3.5 Clinical Safety

Safety data was submitted for both BNT162-01 and C4591001 trials. Adverse events (AEs) were assessed up to 1 month after the second dose. Serious adverse events (SAEs) will be assessed up to 6 months after the second dose and participants' follow-up will continue up to 26 months. In the phase I (BNT162-01 and phase I of the C4591001 trial), 36 subjects received at least one dose of 30 µg of BNT162b2. As for phase II/III (C4591001 trial), 43,448 participants received at least one dose of vaccine or placebo. Demographic characteristics were similar between both groups as displayed in table 12.

Table 12: Demographic characteristics – Phase 2/3 (All Subjects) - Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=21720) n[b] (%)	Placebo (N[a]=21728) n[b] (%)	Total (N[a]=43448) n[b] (%)
Sex			
Male	11183 (51.5)	10942 (50.4)	22125 (50.9)
Female	10537 (48.5)	10786 (49.6)	21323 (49.1)
Race			
White	17839 (82.1)	17857 (82.2)	35696 (82.2)
Black or African American	2091 (9.6)	2107 (9.7)	4198 (9.7)
American Indian or Alaska native	160 (0.7)	159 (0.7)	319 (0.7)
Asian	934 (4.3)	930 (4.3)	1864 (4.3)
Native Hawaiian or other Pacific Islander	57 (0.3)	31 (0.1)	88 (0.2)
Multiracial	536 (2.5)	514 (2.4)	1050 (2.4)
	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=21720) n[b] (%)	Placebo (N[a]=21728) n[b] (%)	Total (N[a]=43448) n[b] (%)
Not reported	103 (0.5)	130 (0.6)	233 (0.5)
Ethnicity			
Hispanic/Latino	5672 (26.1)	5668 (26.1)	11340 (26.1)
Non-Hispanic/non-Latino	15928 (73.3)	15940 (73.4)	31868 (73.3)
Not reported	120 (0.6)	120 (0.6)	240 (0.6)
Country			
Argentina	2883 (13.3)	2881 (13.3)	5764 (13.3)
Brazil	1452 (6.7)	1448 (6.7)	2900 (6.7)
Germany	249 (1.1)	250 (1.2)	499 (1.1)
South Africa	401 (1.8)	399 (1.8)	800 (1.8)
Turkey	249 (1.1)	249 (1.1)	498 (1.1)
USA	16486 (75.9)	16501 (75.9)	32987 (75.9)
Age group			
16-55 Years	12780 (58.8)	12822 (59.0)	25602 (58.9)
>55 Years	8940 (41.2)	8906 (41.0)	17846 (41.1)
Age at vaccination (years)			
Mean (SD)	50.1 (15.68)	49.9 (15.78)	50.0 (15.73)
Median	51.0	51.0	51.0
Min, max	(16, 89)	(16, 91)	(16, 91)
Body mass index (BMI)			
Underweight (<18.5 kg/m^2)	247 (1.1)	275 (1.3)	522 (1.2)
Normal weight (≥18.5 kg/m^2 - 24.9 kg/m^2)	6363 (29.3)	6357 (29.3)	12720 (29.3)
Overweight (≥25.0 kg/m^2 - 29.9 kg/m^2)	7614 (35.1)	7513 (34.6)	15127 (34.8)
Obese (≥30.0 kg/m^2)	7488 (34.5)	7575 (34.9)	15063 (34.7)
Missing	8 (0.0)	8 (0.0)	16 (0.0)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
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, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.

BNT162-01:

Solicited local reactions within 7±1 d after BNT162b2 dose

Within 7 days after dose 1 and 7 days after dose 2, about 82% vs 81% of participants reported at least one local reaction of any grade on at least one occasion. The commonly reported solicited local reactions of any severity in the combined time intervals were tenderness (78%) and pain (73%). The remaining symptom terms were infrequently described. In the combined time interval, after both doses of BNT162b2, the majority of the participants experienced mild (85%) followed by moderate (35%) solicited local reactions. None experienced severe solicited local reactions.

Solicited systemic reactions within 7±1 d after each BNT162b2 dose

Within 7 days after dose 1 and 7 days after dose 2, nearly 80% vs 72% of participants reported any systemic reaction of any grade. Across the two intervals combined, only 6% of participants reported grade ≥3 with a possible dose dependency. Overall, in the combined time interval, after both doses, the majority of the participants experienced mild (88%) followed by moderate (37%) and severe (10%) solicited systemic reactions. The most frequently reported solicited systemic reactions of any severity, were fatigue (65%), headache (53%), and myalgia (38%), malaise (40%), and followed by chills (23%). The remaining symptom terms were infrequently described.

Unsolicited treatment emergent adverse events (TEAEs) after BNT162b2 dosing

Across the two intervals combined 36% vs 8% participants had vaccine related TEAEs. The most frequently reported TEAEs were general disorders and administration site conditions [i.e. injection site reaction and influenza like illness].

Death: No death cases were reported.

C4591001- Phase I:

Local reactions

The most frequently reported local reactions for BNT162b2 recipients in both age groups, were pain at the injection site (33.3% to 91.7%). Of note, the frequency of local reactions were lower

in the older age group compared to the younger age group, with a trend of a higher frequency of local reactions with increased dose.

Systemic reactions

Within 7 days after Dose 1 of BNT162b2, headache and fatigue were most frequently reported in the younger cohort and fatigue in the older population. The most frequently reported systemic event within 7 days after Dose 2, however, was fatigue in both BNT162b2 age groups.

Overall, across the two intervals combined in both age groups, most systemic events were mild or moderate in severity, with no Grade 4 systemic events reported. Prompt systemic events in the older age group after each dose were milder and less frequent than those observed in the younger age group.

Adverse events

Overall, general disorders and administration site conditions (injection site pain, pyrexia, chills, fatigue, and injection site swelling) were the most commonly reported SOC in the younger age group. In the older BNT162b2 group, nausea, reported in one participant, was the only related AE. Most reported AEs were mild or moderate in severity. There were no serious adverse events (SAEs) or discontinuations because of AEs.

Death: There were no death cases reported in either group.

C4591001- Phase II/III:

Phase II

Local reactions for up to 7 days following each dose (using e-diary)

In the BNT162b2 group, pain at the injection site was reported more frequently in the younger age group than in the older age group, and frequency was similar after Dose 1 compared with Dose 2 of BNT162b2 in the younger age group (85.2% vs. 80.2%, respectively) and in the older age group (70.7% vs. 72.5%, respectively). In the placebo group, pain at the injection site was reported

at similar frequencies (7.8% to 10.2%) in the younger and older age groups after Dose 1 and Dose 2.

In the BNT162b2 group, redness and swelling were similar in both age groups after Dose 1. After Dose 2, the frequency of redness and swelling were slightly higher in the older (7.7% and 12.1%, respectively) than in the younger age group (3.5% and 3.5%, respectively). In the placebo group, only one participant in the older age group reported redness after Dose 1, and no swelling was reported.

One participant in the BNT162b2 group (older age group) reported severe injection site pain after Dose 1 and one reported severe redness after Dose 2. In the younger age group, one participant reported severe injection site pain after Dose 2.

Overall, across age groups, pain at the injection site was the most frequent local reaction, which did not increase after Dose 2, and redness and swelling were generally similar in frequency after both doses.

Systemic events for up to 7 days following each dose (using e-diary)

In the BNT162b2 group, systemic events were generally reported more frequently and were of higher severity in the younger group than in the older group, increasing frequency and severity with number of doses (Dose 1 vs Dose 2). Vomiting and diarrhea were exceptions, with vomiting infrequent and similar in both age groups and vomiting and diarrhea similar after each dose. Frequencies of systemic events in the younger and older BNT162b2 groups (Dose 1 vs Dose 2) are listed below:

- Fatigue: younger group (50.0% vs 59.3%) compared to older group (35.9% vs 52.7%)
- Headache: younger group (31.8% vs 51.2%) compared to older group (27.2% vs 36.3%)
- Muscle pain: younger group (23.9% vs 45.3%) compared to older group (14.1% vs 28.6%)
- Chills: younger group (9.1% vs 40.7%) compared to older group (7.6% vs 20.9%)
- Joint pain: younger group (9.1% vs 17.4%) compared to older group (4.3% vs 16.5%)
- Fever: younger group (3.4% vs 17.4%) compared to older group (0.0% vs 11.0%).
- Vomiting: similar in both age groups and after either dose.
- Diarrhea: reported less frequently in the older group and was similar after each dose.

Systemic events were generally reported less frequently in the placebo group than in the BNT162b2 group, for both age groups and doses, with some exceptions. In the younger age group, fever, headache, chills, vomiting, and diarrhea after Dose 1, and vomiting after Dose 2 were reported at similar frequencies in both the placebo and BNT162b2 groups .

In the older age group, vomiting, diarrhea, muscle pain, and joint pain after Dose 1, and vomiting and diarrhea after Dose 2 were reported at similar frequencies in the placebo and BNT162b2 groups.

AEs from Dose 1 to 7 days after the second dose

The number of participants who reported at least one AE were similar in the BNT162b2 group compared to the placebo group from Dose 1 to 7 days after Dose 2.

In the younger age group, 8 (9.1%) and 10 (11.1%) participants reported at least one AE in the BNT162b2 and placebo group, respectively. In the older age group, 4 (4.3%) and 8 (8.9%) participants reported at least one AE in the BNT162b2 group and the placebo group, respectively.

Overall, most AEs reported up to 7 days after Dose 2 were in the SOCs of gastrointestinal disorders (3 [1.7%] in the BNT162b2 group and 2 [1.1%] in the placebo group), general disorders and administration site conditions (3 [1.7%] in the BNT162b2 group and 7 [3.9%] in the placebo group), and musculoskeletal and connective tissue disorders (3 [1.7%] in the BNT162b2 group and 1 [0.6%] in the placebo group).

The most frequently reported AE by preferred term (PT) was injection site pain (3 [3.4%]) in the younger BNT162b2 group, which all occurred on the day of vaccination with Dose 1 during the reporting period for local reactions. Two events resolved within 3 days, and one event resolved 11 days later. All other AEs by PT were reported in ≤2 participants in each vaccine group.

One participant in the older BNT162b2 group had an AE of contusion in the upper left arm deltoid region, which was assessed by the investigator as related to study intervention.

Related Adverse Events from Dose 1 to 7 days after the second dose

The number of participants with AEs assessed by the investigator as related to study intervention from Dose 1 to 7 days after Dose 2 were low in frequency and similar in the BNT162b2 and placebo

groups. Within the BNT162b2 group, a similar proportion of participants in both age groups reported related AEs. Most investigator-assessed related AEs were reactogenicity events in the SOC of general disorders and administration site conditions, which were reported by similar proportion of participants in the BNT162b2 group overall, compared to the placebo group, with injection site pain being the PT reported most frequently and exclusively in the BNT162b2 younger age group.

Immediate Adverse Events

There were no immediate AEs after any dose of BNT162b2 30 µg or placebo.

Severe adverse events

Two participants (both in the BNT162b2 younger age group) reported severe events of myalgia (AE) and gastric adenocarcinoma. The participant who reported myalgia had scapular muscle pain, which began 2 days after Dose 2 and was ongoing at the time of the data cutoff. Both events were assessed by the investigator as not related to study intervention.

Serious adverse events from Dose 1 to 7 days after the second dose

One participant had an SAE from Dose 1 to 7 days after Dose 2. One participant, who was in the BNT162b2 younger age group, had an SAE of gastric adenocarcinoma 23 days after Dose 1, which was assessed by the investigator as not related to study intervention. The SAE was ongoing at the time of the data cutoff, and the participant was withdrawn from the study because of the SAE.

From 7 days after Dose 2 to the data cutoff date (02 September 2020), no additional participants reported any SAE.

Deaths: There were no Phase II participants who died through the data cutoff date (02 September 2020) in the submitted report.

Phase II/III

Local reactions for up to 7 days following each dose in ~6000 subjects using e-diary

In the BNT162b2 group, pain at the injection site was reported more frequently in the younger age group than in the older age group, and frequency was similar after Dose 1 compared with Dose 2 of BNT162b2 in the younger age group (85.3% vs. 79.5%, respectively) and in the older age group (71.7% vs. 66.6%, respectively). In the placebo group, pain at the injection site after Doses 1 and 2 was reported at slightly higher frequencies in the younger age group (13.8% and 11.9%, respectively) than in the older age group (8.8% and 7.7%, respectively).

In the BNT162b2 group, frequencies of redness and swelling were similar in both age groups after Doses 1 and 2. Frequencies of redness were similar after Dose 1 compared with Dose 2 of BNT162b2 in the younger age group (4.3% vs 5.4%, respectively) and in the older age group (4.5% vs 6.6%, respectively).

Frequencies of swelling were similar after Dose 1 compared with Dose 2 of BNT162b2 in the younger age group (5.5% vs 5.9%, respectively) and in the older age group (6.5% vs 7.0%, respectively). In the placebo group, redness and swelling were reported infrequently in the younger (≤0.8%) and older (≤1.3%) age groups after Doses 1 and 2.

Overall, across age groups, pain at the injection site did not increase after Dose 2, and redness and swelling were generally similar in frequency after Dose 1 and Dose 2. Severe local reactions (≤0.8%) were reported infrequently in the BNT162b2 group after either dose overall but occurred more frequently in the younger group. After the first and second dose and in both age groups, the majority of local reactions were mild or moderate in severity, with no Grade 4 local reactions being reported.

Systemic events for up to 7 days following each dose in ~ 6000 subjects using e-diary

Systemic events were generally increased in frequency and severity with increased number of doses (Dose 1 vs Dose 2) in the younger group compared with the older group. Vomiting and diarrhea were exceptions as both were reported similarly infrequent in both age groups after each dose. Frequencies of systemic events in the younger and older BNT162b2 groups (Dose 1 vs Dose 2) are listed below:

- Fatigue: younger group (49.0% vs 61.6%) compared to older group (34.3% vs 51.2%)
- Headache: younger group (42.9% vs 53.1%) compared to older group (25.4% vs 39.5%)

- Muscle pain: younger group (22.0% vs. 38.6%) compared to older group (14.0% vs 28.5%)
- Chills: younger group (14.4% vs 36.5%) compared to older group (6.2% vs 22.8%)
- Joint pain: younger group (10.9% vs 22.4%) compared to older group (8.3% vs 18.9%)
- Fever: younger group (3.7% vs 16.6%) compared to older group (1.4% vs 11.5%).
- Vomiting: similar in both age groups and after either dose.
- Diarrhea: reported less frequently in the older group and was similar after each dose.

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

Use of antipyretic/pain medications was slightly less frequent in the older age group (20.1% to 37.4%) than in the younger age group (28.1% to 45.8%) after both doses. However, medication use increased in both age groups after Dose 2. The use of antipyretic/pain medications was less frequent in the placebo group than in the BNT162b2 group and was similar after Dose 1 and Dose 2 in the younger and older placebo groups (9.8% to 13.7%).

Severe systemic events across age groups after Dose 1 of BNT162b2 were generally lower in frequency than after Dose 2: fever (0.1% vs 0.8%), fatigue (0.8% vs 3.7%), headache (0.5% vs 1.9%), chills (0.2% vs 1.7%), muscle pain (0.3% vs. 1.6%), and joint pain (0.1% vs 0.6%). Diarrhea and vomiting frequencies were generally similar.

In the placebo group, severe fever was reported at a similar frequency (0.1%) after Dose 1 and Dose 2. One participant in the younger BNT162b2 group reported a fever of 41.2°C only on Day 2 after Dose 2 and was nonfebrile for all other days of the reporting period.

After the first and second dose and in both age groups, the majority of systemic events were mild or moderate in severity, with no Grade 4 (potentially life-threatening) systemic events reported other than a one day fever occurring in one participant (41.2°C) in the BNT162b2 group.

Adverse events (all participants)

From Dose 1 to data cutoff, the number of overall participants who reported at least one AE was higher in the BNT162b2 group as compared with the placebo group. Severe AEs, SAEs, and AEs leading to withdrawal were reported by ≤0.8%, 0.3%, and 0.1%, respectively, in both groups. Discontinuations due to related AEs were reported in six participants in the BNT162b2 group and four participants in the placebo group.

Three phase III participants died one participant in the BNT162b2 group and two participants in the placebo group. The participant in the BNT162b2 group who died experienced an SAE of arteriosclerosis, which was assessed by the investigator as not related to study intervention.

In the younger age group, the number of participants who reported at least one AE were 1920 (18.1%) and 880 (8.3%) in the BNT162b2 and placebo groups, respectively. In the older age group, the number of participants who reported at least one AE were 1166 (14.9%) and 582 (7.4%) in the BNT162b2 and placebo groups, respectively.

From Dose 1 to data cutoff, the number of overall participants who reported at least one AE was higher in the BNT162b2 group (3086 [16.8%]) as compared to the placebo group (1462 [7.9%]). Most AEs reported in all participants from Dose 1 to data cutoff were reactogenicity and in the SOCs of general disorders and administration site conditions (1941 [10.5%] in the BNT162b2 group and 438 [2.4%] in the placebo group), musculoskeletal and connective tissue disorders (742 [4.0%] in the BNT162b2 group and 227 [1.2%] in the placebo group), and nervous system disorders (567 [3.1%] in the BNT162b2 group and 251 [1.4%] in the placebo group).

In the BNT162b2 group, the most frequently reported AEs by PT were injection site pain (1222 [6.6%]), pyrexia (504 [2.7%]), fatigue (481 [2.6%]), headache (470 [2.6%]), chills (458 [2.5%]), and myalgia (454 [2.5%]). The majority of these PTs were reported in the younger age group: injection site pain (787 [7.4%]), pyrexia (351 [3.3%]), fatigue (309 [2.9%]), headache (303 [2.9%]), chills (316 [3.0%]), and myalgia (304 [2.9%]).

Beyond the first 6610 participants, events related to reactogenicity are no longer reported using an e-diary but are instead reported as AEs. Therefore, a post hoc analysis was conducted to evaluate if the imbalance in AEs observed in the overall participants from Dose 1 to data cutoff but not observed in the first 6610 participants from Dose 1 to 1 month after Dose 2 was attributed to reactogenicity events. The analysis examined the AEs reported within 7 days after each dose,

which represented the reactogenicity reporting period. The time period was chosen because many AEs were reported in the SOCs of general disorders and administration site conditions, musculoskeletal and connective tissue disorders, and nervous system disorders, which contains AEs consistent with reactogenicity events, and could only be attributed to reactogenicity if they occurred during this time period as opposed to occurring up to a month from each dose.

From Dose 1 to 7 days after Dose 1 (as of the data cutoff date), 1494 (8.1%) participants reported at least one AE in the BNT162b2 group, which represented approximately half of the total number of the 3086 [16.8%] participants who reported at least one AE up to data cutoff. In the placebo group, 555 (3.0%) participants reported at least one AE from Dose 1 to 7 days after Dose 1, compared with the total number of 1462 (7.9%) participants who reported at least one AE up to the data cutoff date.

From Dose 2 to 7 days after Dose 2 (data cutoff date), 1165 (6.3%) participants reported at least one AE in the BNT162b2 group (Supplemental Table 14.298), which represented approximately 38% of the total number of the 3086 [16.8%] participants who reported at least one AE up to the data cutoff date. From Dose 2 to 7 days after Dose 2, fewer participants reported AEs in the placebo group than the BNT162b2 group. In the placebo group, 268 (1.5%) participants reported at least one AE from Dose 2 to 7 days after Dose 2, compared with the total number of 1462 (7.9%) participants who reported at least one AE up to the data cutoff date.

AEs were reported from Dose 1 to 7 days after Dose 1 in the SOC of general disorders and administration site conditions (1127 [6.1%] in the BNT162b2 group and 251 [1.4%] in the placebo group), which represented more than half of the total number of participants reporting at least one AE in this SOC (1941 [10.5%] in the BNT162b2 group and 438 [2.4%] in the placebo group) up to the data cutoff date. Musculoskeletal and connective tissue disorders (252 [1.4%] in the BNT162b2 group and 76 [0.4%] in the placebo group) and nervous system disorders (220 [1.2%] in the BNT162b2 group and 115 [0.6%] in the placebo group) were also commonly reported, representing a smaller proportion of the total number of participants reporting AEs for these SOCs.

In the BNT162b2 group, the most frequently reported AEs from Dose 1 to 7 days after Dose 1 by PT were injection site pain (881 [4.8%]), fatigue (231 [1.3%]), headache (181 [1.0%]), myalgia (147

[0.8%]), pyrexia (110 [0.6%]), and chills (100 [0.5%]). The majority of these PTs were reported in the younger age group: injection site pain (566 [5.3%]), fatigue (153 [1.4%]), headache (118 [1.1%]), myalgia (99 [0.9%]), pyrexia (82 [0.8%]), and chills (75 [0.7%]). Injection site pain reported from Dose 1 to 7 days after Dose 1 (881 [4.8%]) represented a large proportion of the total participants who reported AEs for this PT (1222 [6.6%]).

AEs were reported from Dose 2 to 7 days after Dose 2 in the SOCs of general disorders and administration site conditions (828 [4.5%] in the BNT162b2 group and 93 [0.5%] in the placebo group), musculoskeletal and connective tissue disorders (377 [2.0%] in the BNT162b2 group and 38 [0.2%] in the placebo group), and nervous system disorders (294 [1.6%] in the BNT162b2 group and 40 [0.2%] in the placebo group). Musculoskeletal and connective tissue disorders and nervous system disorders reported from Dose 2 to 7 days after Dose 2 represented at least half of the total number of participants who reported at least one AE in these SOCs.

In the BNT162b2 group, the most frequently reported AEs from Dose 2 to 7 days after Dose 2 by PT were pyrexia (375 [2.0%]), chills (327 [1.8%]), injection site pain (313 [1.7%]), myalgia (282 [1.5%]), headache (258 [1.4%]), and fatigue (227 [1.2%]). The majority of these PTs were reported in the younger age group: pyrexia (251 [2.4%]), chills (216 [2.0%]), myalgia (185 [1.7%]), injection site pain (183 [1.7%]), headache (154 [1.5%]), and fatigue (134 [1.3%]). AEs for most of these PTs reported from Dose 2 to 7 days after Dose 2 represented at least half of the total number of participants who reported an AE for these PTs: pyrexia (504 [2.7%]), chills (458 [2.5%]), myalgia (454 [2.5%]), headache (470 [2.6%]), and fatigue (481 [2.6%]).

Overall, AEs reported from Dose 1 to 7 days after Dose 1 and from Dose 2 to 7 days after Dose 2 were largely attributable to reactogenicity events. This observation provides a reasonable explanation for the greater rates of AEs observed overall in the BNT162b2 group compared to the placebo group.

From Dose 1 to the data cutoff date, there were a total of 44 (0.2%) participants in the BNT162b2 group who reported an AE of lymphadenopathy, inclusive of those reported in the first 6610 participants (10 [0.3%]).

Up to data cutoff, 34 additional participants in the BNT162b2 group and 4 additional participants in the placebo group reported an AE of lymphadenopathy. In the BNT162b2 group,

lymphadenopathy was reported in 34 (0.3%) participants in the younger age group and 10 (0.1%) participants in the older age group compared to 4 (0.0%) in the placebo group (3 in the younger age group and 1 in the older age group). Lymphadenopathy occurred predominantly in the arm and neck region with most events reported in left axillary lymph node(s). Most lymphadenopathy events occurred after Dose 2, ≤3 days after Dose 1 or Dose 2, were Grade 1 or Grade 2 in severity, and 32 of 48 events were resolved by the data cutoff date. In one participant in the younger BNT162b2 age group, Grade 1 lymphadenopathy (swollen right axillary lymph nodes) was an immediate AE, which occurred after Dose 1 and was continuing at the data cutoff date.

In the younger age group, there was one participant each with an AE of suspected COVID-19 in the BNT162b2 (SAE) and placebo groups.

In the BNT162b2 group, six participants reported immunization reactions (vaccine reaction or systemic vaccine reaction [no additional information currently available at the time of this report]) assessed as related to study intervention. Three participants reported drug hypersensitivity in the BNT162b2 group, in addition to the drug hypersensitivity in a participant in the placebo group. Drug hypersensitivity (allergic reaction) was assessed as related in one participant in the BNT162b2 group and drug hypersensitivity (drug allergy or allergic reaction to dipyrone) was assessed as unrelated to study intervention in two participants in the BNT162b2 group.

Nineteen (0.1%) participants in the BNT162b2 group (14 in the younger age group and 5 in the older age group reported at least one vaccine complication (most were descriptive of reactogenicity events) compared to none in the placebo group. All were assessed as related to the study intervention, which included post vaccination myalgia, fever, body aches, headache, chills, nausea, adverse reaction, arthralgia, fatigue, aches, muscle aches, malaise, and sore left shoulder. Most events were Grade 1, started within 3 days of vaccination, and lasted from one to 3 days.

In addition to the 4 participants with appendicitis (including one appendicitis perforated in the placebo group) in the first 6610 participants, there were an additional 3 participants with appendicitis (including 1 participant with a perforated appendicitis) reported in the BNT162b2 group from Dose 1 through the data cutoff date for all participants. Therefore, six participants in the BNT162b2 group reported append. In addition, one participant in the placebo group (older

age group) reported appendicitis (perforated). All events were severe or life threatening and none were assessed as related to study intervention.

Related Adverse Events

From Dose 1 to the data cutoff date, 2303 (12.5%) participants in the BNT162b2 group and 593 (3.2%) participants in the placebo group reported at least one AE assessed as related by the investigator. Most related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions (1869 [10.1%] in the BNT162b2 group and 365 [2.0%] in the placebo group).

The AEs of lymphadenopathy reported in 30 of 44 participants in the BNT162b2 group and 2 of 4 participants in the placebo group were assessed by the investigator as related to study intervention.

In the BNT162b2 group, based on all the currently available information at the time of this report:

- Six participants reported immunization reaction (vaccine reaction or systemic vaccine reaction) assessed as related to the study intervention. In most participants, immunization reactions occurred 1 or 2 days after Dose 2, lasted 2 or 3 days (one participant was recovering at data cutoff date), and were Grade 1 or Grade 2 in severity. In one participant, immunization reactions (systemic vaccine reactions) occurred 2 days after Dose 1 (Grade 1) and lasted 2 days, and 1 day after Dose 2 (Grade 3) and lasted 4 days.
- One participant reported an AE each of drug hypersensitivity (allergic reaction), urticaria (allergic reaction), and headache, which were all Grade 2 and assessed by the investigator as related to study intervention. The AEs of drug hypersensitivity and urticaria both occurred within 1 day after Dose 1 and resolved that same day. The AE of headache occurred the following day after vaccination and lasted 4 days.

Immediate Adverse Events

After Dose 1, 0.3% of participants in each group reported immediate AEs. Most immediate AEs were in the SOC of general disorders and administration site conditions and most events were related to the injection site reactions with injection site pain most frequently reported (40 [0.2%] participants in the BNT162b2 group and 27 (0.1%) participants in the placebo group). One

participant had an immediate AE of lymphadenopathy after Dose 1. All other immediate AEs were reported by ≤3 participants each in the BNT162b2 group. After Dose 2, 0.1% of participants in each group reported immediate AEs. Most immediate AEs were in the SOC of general disorders and administration site conditions and most events were injection site reactions with injection site pain most frequently reported (10 [0.1%] participants in the BNT162b2 group and 7 [0.0%] participants in the placebo group). All other immediate AEs were reported by ≤2 participants each. After either dose of BNT162b2, no participant reported an immediate allergic reaction to the vaccine.

Severe adverse events

Severe AEs reported up to the data cutoff date were reported by 142 [0.8%] participants in the BNT162b2 group and 70 (0.4%) in the placebo group.

In the BNT162b2 group:

- One participant from Phase II had a severe event of gastric adenocarcinoma (SAE).
- Two participants had severe events of appendicitis: one event began 9 days after Dose 1 and the other event began 15 days after Dose 2, which were assessed by the investigator as not related to the study intervention.
- One participant had two life-threatening AEs of appendicitis and peritoneal abscess 7 days after Dose 1; both events were assessed by the investigator as not related to the study intervention.
- One participant had eight severe events: anemia, cardiac failure congestive, abdominal adhesions, sepsis, hypokalaemia, mental status changes, acute kidney injury, and acute respiratory failure. None of the events were assessed by the investigator as related to the study intervention.
- Two participants in the BNT162b2 group had a severe event each of appendicitis: 1 event began 17 days after Dose 1 and the other event began 11 days after Dose 1 which were assessed by the investigator as not related to the study intervention.
- One participant in the BNT162b2 group had a severe event of perforated appendicitis on the same day after Dose 1, which was assessed by the investigator as not related to the study intervention.

- Nine participants (0.0%) in the BNT162b2 group and 12 (0.1%) participants in the placebo group had at least one life-threatening AE from Dose 1 to the data cutoff date. None of these events were assessed by the investigator as related to the study intervention.

Serious adverse events (SAEs)

From Dose 1 to the data cutoff date, the number of participants who reported at least one SAE were similar in the BNT162b2 group (63 [0.3%]) and in the placebo group (49 [0.3%]).

In the BNT162b2 group, there were two participants in the younger age group with an SAE each assessed by the investigator as related to the study intervention:

- One participant had an SAE of lymphadenopathy (right axilla) 13 days after Dose 1, which was not resolved at the time of the data cutoff. The participant was a 48-year-old woman with a relevant medical history of eczema and topical crisaborole use who had the BNT162b2 vaccine administered in the left deltoid and had right axillary pain and lymphadenopathy. She had no injuries to the right arm, no fever, and no history of a similar incident. Her WBC was normal with a normal lymphocyte count. A right axilla ultrasound showed four enlarged lymph nodes (largest 2.5 × 1.1 × 2.4 cm). A biopsy was performed and was reported to be normal and without markers for lymphoma or other cancer types. A follow-up visit with oncology (and possible repeated ultrasound) was planned in 3 months' time.
- One participant had an SAE of shoulder injury related to vaccine administration (SIRVA, erroneously administered into or near the shoulder joint capsule) after Dose 2, which was recovering at the time of the data cutoff.

Additional serious adverse events occurred and assessed by the investigator as not related to the study intervention:

From Dose 1 to the data cutoff date, six participants in the BNT162b2 group reported an SAE of appendicitis.

- Four participants had an SAE each of appendicitis: 1 event began 9 days after Dose 1, 1 event began 15 days after Dose 2, 1 event began 17 days after Dose 1 which lasted for 3 days (younger age group), and the other event began 11 days after Dose 1 which lasted 5 days (older age group).

- One participant had an SAE each of appendicitis and peritoneal abscess 7 days after Dose 1, which was considered life threatening. Both events lasted for 17 days.
- One participant in the older age group had an SAE of perforated appendicitis on the same day after Dose 1, which was resolving at the time of the data cutoff.
- One participant had eight SAEs 17 days after Dose 1: anemia, cardiac failure congestive, abdominal adhesions, sepsis, hypokalaemia, mental status changes, acute kidney injury, and acute respiratory failure (all were severe). The SAEs of abdominal adhesions and acute respiratory failure lasted for 2 and 14 days, respectively. All other SAEs lasted for 19 days.
- One participant had an SAE of anaphylactic reaction 9 days after Dose 2 because of a bee sting, which was considered life threatening. The event resolved on the same day.
- One participant in the younger age group had an SAE of suspected COVID-19 on the same day after Dose 2, which lasted for 6 days. The nasal swab result was negative.
- In the placebo group, one participant had an SAE each of perforated appendicitis and peritonitis, 13 and 15 days after Dose 2, respectively (both severe). Both events lasted 4 and 5 days, respectively.

Deaths

There were three Phase III participants (1 in the BNT162b2 group and 2 in the placebo group), who died up to the data cutoff date of 06 October 2020.

- One participant in the older BNT162b2 group experienced a Grade 4 SAE of arteriosclerosis 4 days after Dose 1 and died 15 days after Dose 1.
- One participant in the younger placebo group experienced a Grade 4 SAE of unevaluable event (unknown of unknown origin [no additional information currently available at the time of this report) 8 days after Dose 1 and died the same day.
- One participant in the older placebo group experienced a Grade 4 SAE of hemorrhagic stroke 15 days after Dose 2 and died 35 days after Dose 2.

Assessor comments

Phase I

Safety was assessed in the BNT162-01 phase I trial as well as the phase I part of the C4591001 trial. The majority of local and systemic events were mild or moderate in severity with no Grade 4 systemic events reported. Phase I of the C4591001 trial showed prompt events in the older age group after each dose were milder and less frequent than the young age group. The reported AEs were mild or moderate in severity. There were no SAEs or discontinuations because of AEs nor death cases reported.

Overall, no major safety concerns were raised by the given data for both age groups in Phase I of the C4591001 trial and the young age group (18y - 55y) in the BNT162-01 trial, as the majority of events were anticipated for IM-administered vaccines. However, it should be noted that the safety profile for the older age group (65 - 85 years old) in study BNT162-01 was not available at the time of this report.

Phase II/III part of the C4591001 study

Local and systemic reactions

During phase II/III study, all participants in the phase II study (360 individuals who were included in phase III) and a subset of phase III participants (~6000 participants) were required to report all solicited local and systemic reactions for 7 days after each dose using an e-diary system.

Local and systemic reactions in the BNT162b2 group occurred in higher frequencies and severity than placebo. The most common local reaction after any dose was pain at the injection site (85.3%) followed by swelling (10%) and redness (9%). No grade 4 local reactions were reported, and severe local reactions were reported in 1.3% for pain at the injection site, 0.3 % for swelling and 0.5% for redness. For systemic events, the most commonly reported events after the first dose (vaccine vs placebo) were fatigue

(42% vs 28%), headache (35% vs 26%), muscle pain (18% vs 10%), chills (11% vs 5%), joint pain (10% vs 6%) and fever (3% vs 1%), whereas vomiting and diarrhea had similar frequencies to placebo. After the second dose, frequencies of fatigue (57% vs 20%), headache (47% vs 19%), muscle pain (34% vs 7%), chills (30% vs 3%), joint pain (21% vs 4%), and fever (14% vs 0%) diarrhea (10% vs 7%) increased while vomiting was reported in a similar frequency to placebo. Severe systemic events were reported more frequently after the second dose of the vaccine compared to the first dose.

Overall, no major safety concern was raised by the given data for local and systemic reactions in the mentioned subset of subjects.

Adverse events, related AEs, immediate AEs and serious AEs

Safety data available up to the cutoff date were from 36,855 participants with different follow-up times. Given the current data, after dose 1, overall participants who reported at least one adverse event were higher in the vaccine group (3086 [16.8%]) as compared with the placebo group (1462 [7.9%]).

The most commonly reported adverse events were part of the expected local and systemic events classified by system organ class and preferred term. It was followed by lymphadenopathy (44 events reported) and most of the events were grade 1 and 2 in severity. Lymphadenopathy is considered vaccine-related and an expected adverse event occurring due to the immune reaction, especially in the same side the vaccine was administered. In addition, six participants reported immunization reactions related to the vaccine and a number of appendicitis cases were also reported but were assessed as non-related to the vaccine. However, it could indicate the need for additional monitoring in a post marketing setting.

Related adverse events were higher in the vaccine arm in both frequency and severity, which mainly consisted of local and systemic reactions followed by 30 related events out of the 44 total events reported in the study. Furthermore, six cases of

immunization reactions and one case of drug hypersensitivity were assessed as related to the vaccine. Most immediate AEs occurred in the SOC of general disorders and administration site conditions, as well as a few other cases that were numerically low.

Severe adverse events occurred in (142[0.8%]) participants in the vaccine arm and (70[0.4%]) in the placebo arm. Of them, six participants reported severe adverse events of appendicitis and one had peritoneal abscess. Participants who reported at least one serious adverse event did not differ between vaccination arm (18 (0.5%]) and placebo arm (17 [0.5%]). Two participants reported serious adverse events, which were vaccine-related; the first case reported lymphadenopathy, which did not resolve by the data cutoff time and the other participant reported a shoulder injury due to the vaccine administration. Death occurred in three participants (one in the vaccine group and two in the placebo group), which were all deemed not related to the study intervention.

Overall, the vaccine was well tolerated with most of the adverse events occurring due to local and systemic reactogenicity, in addition to multiple cases of lymphadenopathy being reported and assessed as vaccine-related. Moreover, multiple cases of appendicitis occurred however, were not assessed as related, although it will need to be closely monitored via post-marketing surveillance.

Nevertheless, one of the uncertainties is the study's short-term follow-up with almost 50% of the subjects followed up for less than two months. Thus, additional safety data should be submitted when participants complete one-month follow up for AE and six months follow up for SAE. In addition, there is a lack of participants coming from the arab population, which might affect the generalizability of safety results.

4.4 Pharmacovigilance Activities

4.4.1 Artwork assessment (Artwork available in appendix)

BNT162b2 vaccine name and artwork have been evaluated

Proposed trade Name (On the Global Packaging)	Previous product name	Dosage Form
Pfizer-BioNtech COVID- 19 Vaccine	BNT162	Suspension for Intramuscular Injection after dilution

Look –alike/Sound-alike (LA/SA) Error Risk Potential:

BNT162b2 name LA/SA confusion risk potential has been assessed based on the evaluation of LA/SA similarities from our data sources (SFDA registered Drug List, Martindale, ISMP Confused Drug Name List, INN and USAN STEM) and the pharmaceutical characteristic of the product:

LA/SA for Product name	SFDA	Shared File/ Excel Sheet	Martindale	Stem Book 2018
Pfizer-BioNTech COVID- 19 Vaccine	NO	NO	NO	NO

Trade Name Recommendation:

Based on the submitted data, the proposed name Pfizer-BioNTech COVID- 19 Vaccine is accepted.

Outer and Inner Package:

Based on the submitted data, the proposed artwork is accepted.

4.4.2 Risk Management Plan

Every new medicinal product approved in Saudi Arabia has a RMP in place to ensure the medicine or vaccine is used as safety as possible. RMP is a comprehensive document that describes the current knowledge about the safety and efficacy of a medicinal product. In addition, RMP provides information about measures to be undertaken to prevent or minimize risks associated with the use of medicines or vaccines and information on plans for studies and other activities to have more knowledge about the safety and efficacy of the medicinal product. The SFDA has reviewed the version (1.16) of BNT162b2 vaccine RMP and concluded the following:

- There are no important identified risks during the clinical trials.
- Vaccine-associated enhanced disease (VAED) including vaccine associated enhanced respiratory disease (VAERD) has been considered Important Potential Risks. As there is currently no evidence from non-clinical or clinical data of an association of VAED/VAERD with BNT162b2 vaccine; this potential risk will be further investigated as part of the pharmacovigilance plan of this vaccine.

- Pregnancy, lactation, and vaccine effectiveness were considered as missing information, because these information have not been assessed in the clinical trials and are relevant to the use of the vaccine and require further information to be collected after approving the vaccine.
    - Provided educational materials targeting HCP and vaccine receivers as additional risk minimization measures. (in appendix)

4.4.3 Active Surveillance Safety Monitoring Initiative

Rare and unknown adverse events may not be detected at the time of SFDA conditional authorization and may only occur after the vaccine is used over a longer period and in much larger, diverse groups of people. Therefore, an additional source of pharmacovigilance activity is necessary for monitoring the COVID-19 vaccine safety in

real-world through the active surveillance program which will be conducted by the SFDA in order to track BNT162b2 vaccination subjects' data, and to have the ability to capture any adverse events following immunization (AEFIs) of the enrolled subjects.

4.4.4 Routine pharmacovigilance activities

Passive surveillance activities will be carried out for monitoring the safety profile of BNT162b2 vaccine, which include but not limited to:

- Evaluation the Periodic Safety Update Reports (PSURs) that will be submitted by MAHs at 6 months intervals in the first few years of authorization with decreasing frequency thereafter.
- Reviewing the spontaneous reports of adverse events that will be submitted by MAH which include serious adverse events that result in hospitalization or death irrespective of attribution to BNT162b2 vaccination.
- Detection, collection, analyzing and data management of individual case reports of suspected adverse reactions associated with the BNT162b2 vaccine.
- Evaluation BNT162b2 vaccine quality in case of reporting any defect or presence of transportation and storage issues through stability study data of the finished product evaluation.

4.4.5 Conclusion on pharmacovigilance activities

Overall, the provided information related to the pharmacovigilance activities were considered sufficient to support the conditional approval of BNT162b2 vaccine. However, due to the limited information we have about the BNT162b2 vaccine. The SFDA has requested all the required information about the important identified risks, which have been demonstrated to be associated with the BNT162b2 vaccine and require additional measures as part of the authorization to minimize any potential risk to users. Also, requested additional data about the important potential risks which are possibly associated with the BNT162b2 vaccine but has not been confirmed and further information needs to prove the association, and requested further assessment about the

missing information which have not been fully evaluated in the clinical trials and are relevant to the use of BNT162b2 vaccine and require further information to be gathered through PASS. Moreover, routine pharmacovigilance activity will be performed to ensure BNT162b2 vaccine safety.

5. Overall Conclusion

The provided manufacturing, controls and characterization data demonstrated a robust manufacturing process that is capable of producing consistent active substance batches and finished product lots within the pre-determined release specifications. The stability data has demonstrated that the BNT162b2 vaccine remained within the shelf life specification at the proposed storage condition until the last available time point, which supports the initial shelf life of 6 months when stored at -70 °C (-60 °C to -80 °C).

The submitted clinical efficacy data showed very promising results, which exceeded the proposed requirements in the WHO Target Product Profiles for COVID-19 Vaccines of VE around 50% point estimate. Through inducing strong immune responses and high vaccine efficacy (≥95% for participants without prior evidence of SARS-CoV-2 infection and >94% for those with and without prior infection), suggesting the vaccine protects against symptomatic COVID-19 infection in individuals ≥16 years of age.

BNT162b2 potential risks were based on the observed safety profile to data cut off, which mostly displayed events anticipated for intramuscularly-administered vaccines, such as mild reactogenicity, low incidence of severe or serious events, and no clinically concerning safety observations or concerns. The vaccine generally appears to be safe and well tolerated across the study safety population and across demographic subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status.

Further monitoring and reporting of severe COVID-19 cases is warranted. Results of individuals from 12 to 15 years of age and HIV positive subjects were not available at

the time of the current report, thus no recommendation can be drawn at this time. Nor is there data supporting the vaccination of pregnant and breastfeeding women. Moreover, additional safety data with a longer follow up period should be submitted (i.e. assessing for AE, SAEs, and VAED). Moreover, the lack of participants coming from the Arab population might affect the generalizability of safety results. Based on the clinical assessment for the submitted data, the following points should be reflected in the product information:

- Vaccine should be administered only to healthy subjects with preexisting stable disease (Not requiring significant change in therapy or hospitalization for worsening disease during the previous 6 weeks).
- Vaccinating pregnant and breastfeeding women is not permitted.
- Patients using immunosuppressive (including long-term use of corticosteroids) agents should be excluded.
- No data is available yet on subjects 12 to 15 years of age.
- No data is available yet on HIV or immunocompromised patients.
- No data is available regarding concomitant vaccinations. Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each vaccination with BNT162b2.

- Add the following adverse effects to the Saudi SPC and PIL:
    - **Blood Disorders**: lymphadenopathy
    - **Gastrointestinal Disorders**: diarrhea, nausea
    - **General Disorders:** Fever, Malaise, Asthenia, Influenza like illness
    - **Administration site reactions**: injection site pain, injection site swelling, Redness at injections site, fatigue, chills, pyrexia
    - **Musculoskeletal Reactions:** myalgia, pain in extremity, back pain, arthralgia

- **Nervous System Disorders:** Headache

The provided information related to the pharmacovigilance activities were considered sufficient to support the conditional approval of BNT162b2 vaccine. However, due to the limited information about the BNT162b2 vaccine, SFDA has requested all the required information about the important identified risks, which have been demonstrated to be associated with the BNT162b2 vaccine and require additional measures as part of the authorization to minimize any potential risk to users.

Finally, the submitted data on quality, non-clinical, clinical, and pharmacovigilance activities were considered sufficient by SFDA to grant a conditional approval for the marketing authorization application of BNT162b2. SFDA decision was made taking into consideration that the applicant will be committed to provide all necessary data to support a final approval.

6. Regulatory recommendation

Based on the comprehensive review of the available quality, safety, and efficacy data, the benefits outweigh the risks of the BNT162b2 vaccine, accordingly the SFDA has granted the applicant a conditional approval, with the following commitments to be submitted when the data becomes available:

- The applicant will provide additional stability data, when it becomes available, which is required to grant the full marketing authorization for BNT162b2 vaccine.
- SFDA acknowledges that the applicant submitted the interim data of study No: 20GR142 “the 17-Day Intramuscular Toxicity Study of BNT162b2 (V9) and BNT162b3c in wistar han rats with a 3-week recovery”. Kindly, provide the final report once it is completed to continue assessing the product.
- In the submitted studies related to the immunogenicity, SFDA has some concerns related to antibody dependent enhancement (ADE) phenomena. Kindly, provide a

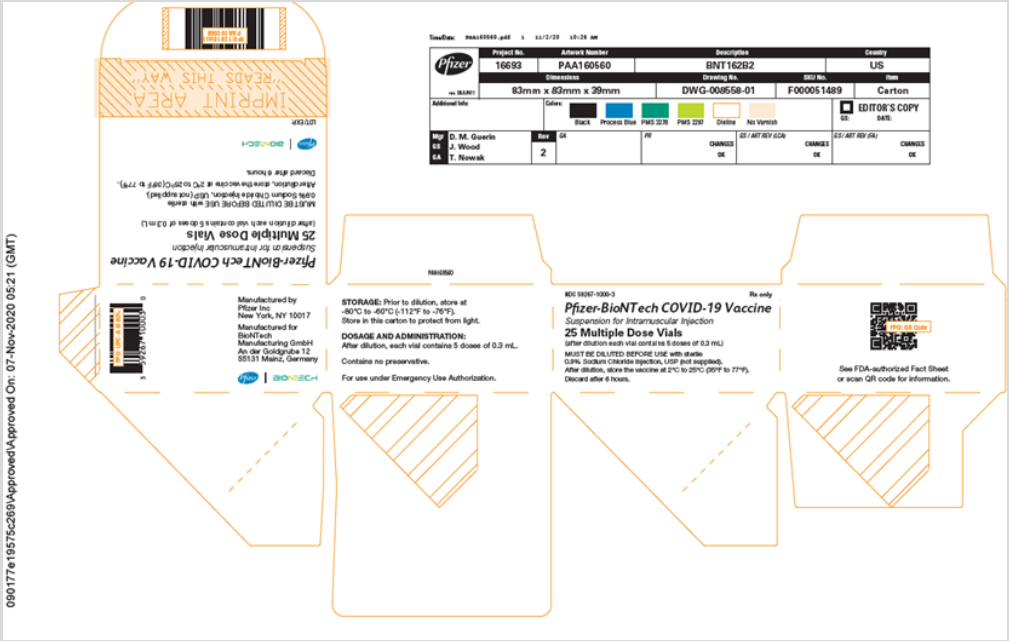
detailed report related to this phenomenon to continue assessing the safety of the product.

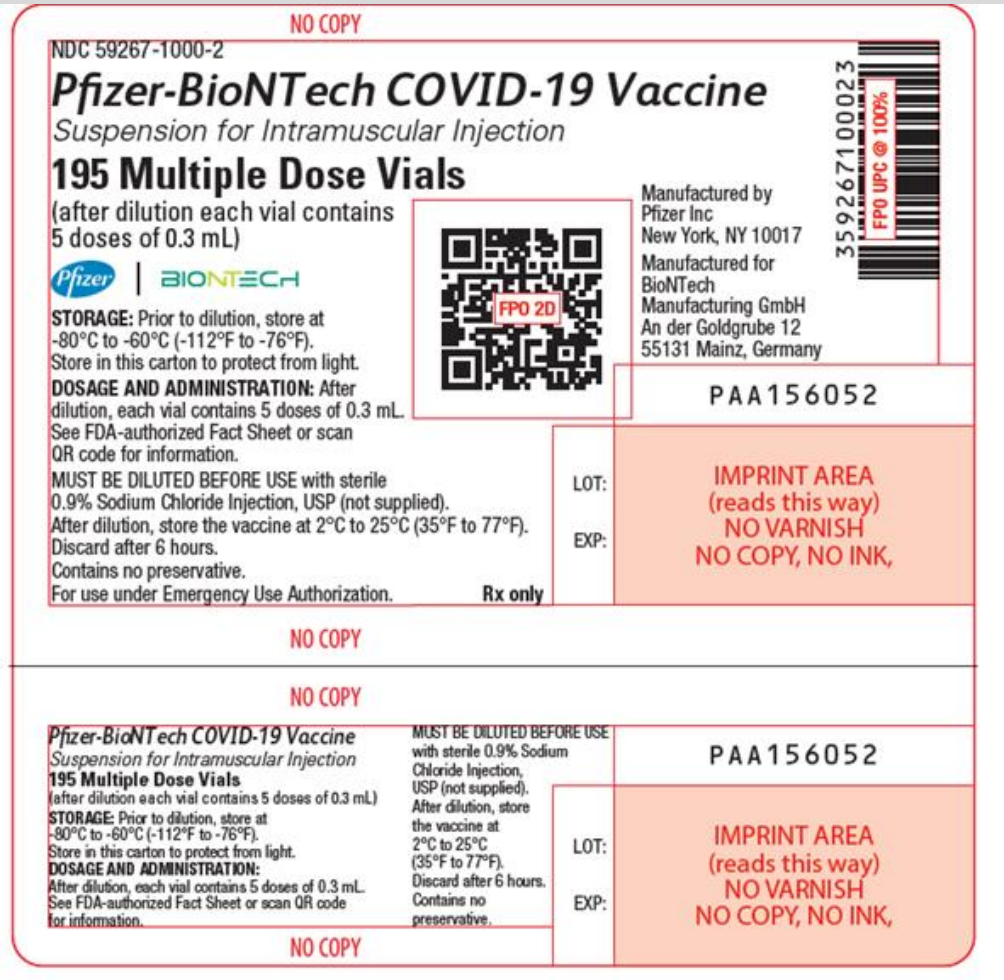
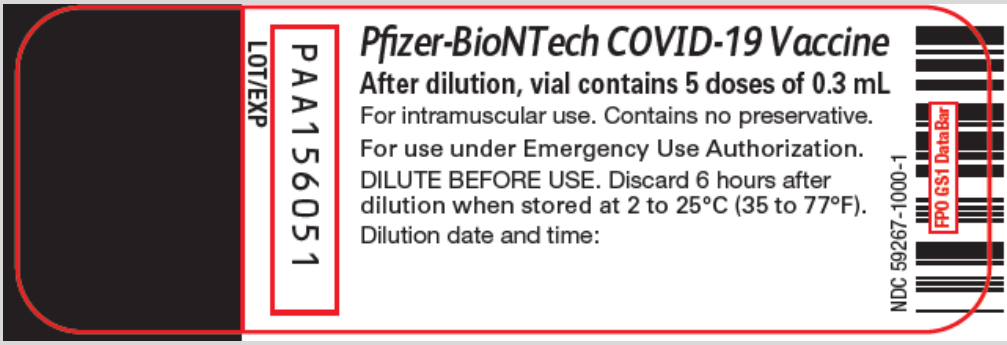
- In addition to the submitted document, SFDA requires the applicant to provide studies related to the Developmental and Reproductive toxicity (DART) study of BNT162 vaccine.
- SFDA would ask the applicant to provide safety data related to the novel excipients (ALC-0159 and ALC-0315) in addition to a genotoxicity study.
- SFDA would like to highlight the use of males only in the study (A Single Dose Pharmacokinetics Study of Alc-0315 And Alc-0159 Following Intravenous Bolus Injection of Pf-07302048 Nanoparticle Formulation In Wistar Han Rats). Please provide a justification regarding this matter.
- SFDA would like to raise a concern related to the use of only females in the Immunogenicity study of the LNP formulated modRNA encoding the viral S protein-V9). Please provide justification related to this matter.
- Submit the full clinical study report for study BNT162-01 including results for all age populations.
- Submit the full clinical study report for study C4591001 including results for all sub-populations.
- Submit the results of process 1 and process 2-group comparison in study C4591001 as it becomes available.
- Plan to monitor and report severe COVID-19 cases in study C4591001 (especially in the case where the applicant is considering un-blinding study participants and offering them the vaccine).
- Plan to monitor waning of immunity if available.
- Submit a risk management plan file following the Saudi Good Pharmacovigilance Practice guideline.
- Submit the interim and final reports of the three PASS that will be conducted in the USA.

- Submit a monthly safety update report for 6 months after receiving regulatory approval, which should include as a minimum:
    - Interval/ cumulative exposure of vaccine in Saudi Arabia and worldwide.
    - Interval / cumulative number of serious and non-serious case reports, overall and by age groups and in special populations (e.g. pregnant women).
    - Actions taken by regulatory agencies for safety reasons.
    - Changes to reference safety information.
    - New, ongoing and closed signals with signal evaluation.
    - Causality assessment evaluation of serious adverse events, including fatal cases.
    - Summary of efficacy and safety findings from clinical studies (completed or ongoing).
    - Benefit-risk evaluation.

7. Appendix

7.1 Artwork

Outer Carton 25 Multiple Doses	

Outer Carton 195 Multiple Doses	
5 Doses Vial label	

7.2 Educational Materials

- Vaccine recipient guide in English language
  https://sfda.gov.sa/en/node/66120
- Vaccine recipient guide in Arabic language
  https://sfda.gov.sa/ar/node/66120

- HCP guide in English language
  https://sfda.gov.sa/en/node/66120
- HCP guide in Arabic language
  https://sfda.gov.sa/ar/node/66120