# INVESTIGATOR'S BROCHURE

# BNT162/PF-07302048

**Version:** 8.0 **Date:** 27 OCT 2021

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Reference safety information for assessment of expectedness of serious adverse drug reactions for the investigational medicinal products (IMPs) is provided in Section 7.8.2.

## DOCUMENT HISTORY

| Use | Date | Version number |
|---|---|---|
| First sponsor approved version. | 25 MAR 2020 | 1.0 |
| With updated non-clinical content. | 09 APR 2020 | 2.0 |
| With updated non-clinical content. | 17 APR 2020 | 3.0 |
| With updated non-clinical and clinical content. | 03 JUL 2020 | 4.0 |
| With updated non-clinical and clinical content. | 12 AUG 2020 | 5.0 |
| With updated non-clinical and clinical content. | 29 JAN 2021 | 6.0 |
| With updated clinical content. | 14 JUL 2021 | 7.0 |
| With updated clinical content. | 27 OCT 2021 | 8.0 |

For a summary of the key changes introduced when preparing version 8.0, see Section 10.

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# LIST OF ABBREVIATIONS

| Abbreviation | Explanation |
|---|---|
| ~ | Approximately |
| A:G (ratios) | Albumin:globulin (ratio) |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| AR(s) | Adverse reaction(s) |
| BioNTech | BioNTech SE, Mainz, Germany |
| BMI | Body mass index |
| BNT162a | BNT162 RNA-LNP vaccine utilizing uridine-containing RNA (different variants of this platform are indicated as BNT162a1, BNT162a2, etc.) |
| BNT162b | BNT162 RNA-LNP vaccine utilizing nucleoside-modified RNA (different variants of this platform are indicated as BNT162b1, BNT162b2, etc.) |
| BNT162c | BNT162 RNA-LNP vaccine utilizing self-amplifying RNA (different variants of this platform are indicated as BNT162c1, BNT162c2, etc.) |
| CDC | Centers for Disease Control and Prevention |
| CI | Confidence intervals |
| COVID-19 | Coronavirus Disease 2019 |
| CRP | C-reactive protein |
| CSR | Clinical study report |
| d | Day(s) |
| DART | Developmental and reproductive toxicity (study) |
| Elderly | Individuals aged 65 yrs or older |
| ELISA | Enzyme-linked immunosorbent assay |
| ELISpot | Enzyme-linked immunosorbent-spot |
| FDA | US Food and Drug Administration |
| GCP | Good Clinical Practice |
| GD | Gestation day |
| GGT | Gamma ($\gamma$)-glutamyl transpeptidase |
| GHFI | Geometric mean fold increase |
| GLP | Good Laboratory Practice |
| GMC | Geometric mean concentration |
| GMFR | Geometric mean fold rise from baseline |
| GMR | Geometric mean ratio |
| GMT | Geometric mean titer |
| h | Hour(s) |
| HIV | Human immunodeficiency virus |
| IB | Investigator's brochure |
| ICH | International Council for Harmonisation |
| IgG | Immunoglobulin G |
| IL | Interleukin |
| IM | Intramuscular(ly) |
| IMM | Immunogenicity set |
| IMP | Investigational medicinal product |

| Abbreviation | Explanation |
|---|---|
| IFN | Interferon |
| IR | Incidence rate |
| IV | Intravenous(ly) |
| LNP | Lipid nanoparticle |
| LUC | Luciferase (from firefly *Pyractomena lucifera*) |
| MERS | Middle East respiratory syndrome |
| modRNA | Nucleoside-modified messenger RNA |
| mRNA | Messenger RNA |
| NAAT | Nucleic acid amplification test |
| NCT | ClinicalTrials.gov identifier |
| NHP | Non-human primates |
| NT50 | 50% neutralizing titer |
| Older adults | Individuals aged 56 to 85 yrs |
| ORF | Open reading frame |
| P/B | Prime/boost |
| PK | Pharmacokinetics |
| PT | Preferred term |
| PY | Person-years |
| RBC | Red blood cells |
| RBD | Receptor binding domain |
| RNA | Ribonucleic acid |
| S protein | SARS-CoV-2 spike protein |
| S1 | The subunit produced after the SARS-CoV-2 S protein is cleaved by host proteases |
| S9 | Supernatant fraction obtained from liver homogenate by centrifuging at 9,000 x g |
| SAE | Serious adverse event |
| SAF | Safety population |
| saRNA | Self-amplifying messenger RNA |
| SAR(s) | Serious adverse reaction(s) |
| SARS | Severe acute respiratory syndrome |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| SOC | System organ class |
| TEAE | Treatment-emergent adverse event |
| Th1 | Type 1 T helper cells |
| uRNA | Non-modified uridine-containing messenger RNA |
| US | United States (of America) |
| VAED | Vaccine-associated enhanced disease |
| VAERD | Vaccine-associated enhanced respiratory disease |
| VE | Vaccine efficacy |
| WBC | White blood cells |
| WHO | World Health Organization |
| Younger adults | Individuals aged 18 to 55 yrs |
| yr(s) | Year(s) |

# 2 SUMMARY

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The current COVID-19 outbreak is pandemic, hundreds of millions of people have been infected and almost 5 million deaths have been associated with COVID-19 to date.

This document summarizes available data for a group of ribonucleic acid (RNA)-based vaccines for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus. Each vaccine contains an RNA encoding a SARS viral antigen that is translated by the vaccinated organism to protein to induce a protective immune response. There are three different RNA platforms under development, namely non-modified uridine-containing mRNA (uRNA), nucleoside-modified mRNA (modRNA), and self-amplifying mRNA (saRNA). The BNT162 family of lipid nanoparticle (LNP) enveloped uRNA (BNT162a), modRNA (BNT162b), and saRNA (BNT162c) vaccine platforms encode SARS-CoV-2 antigens. The different vaccine candidates are identified by numbers, for example for BNT162b, the candidates are BNT162b1, BNT162b2, and BNT162b3.

The clinical program for these RNA-based vaccines started with the investigation of four BNT162 vaccine candidates (BNT162a1, BNT162b1, BNT162b2, BNT162c2). A fifth vaccine candidate, BNT162b3, was later added to the program.

One vaccine candidate, BNT162b2, has received temporary authorization for emergency supply in 46 countries and licenses or conditional marketing authorizations in 46 countries globally under tradename Comirnaty. Further clinical investigation of BNT162b2 is ongoing to expand the studied populations. With the emergence of new SARS-CoV-2 viral variants, several BNT162b2-based variant vaccines that target these viral variants were also added to the clinical program, e.g., BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), a 1:1 mixture of BNT162b2 (B.1.1.7) and BNT162b2 (B.1.617.2) called BNT162b2 (B.1.1.7 + B.1.617.2), and BNT162b2 (B.1.351) which is also referred to as BNT162b2s01 and BNT162b2$_{SA}$.

The available safety data for the BNT162 vaccine candidates, including BNT162b2, support the clinical investigation of these variant vaccine candidates (including BNT162b2-based variant vaccines) in the ongoing clinical studies. The available safety data include results from a developmental and reproductive toxicity (DART) study for the BNT162b vaccine candidates (including BNT162b2).

### Clinical data

For BNT162a1, BNT162b1, BNT162b3, and BNT162c2, all planned vaccine administration to study participants has been completed and the dosed participants are now in follow-up.

For BNT162b2 and the BNT162b2-based variant vaccines, enrollment and vaccine administration to study participants is ongoing and/or planned.

#### *Immunogenicity data for BNT162b1 and BNT162b2 in individuals ≥12 yrs of age*

Reported immunogenicity data in humans are available for BNT162b1 and BNT162b2 after prime (Dose 1)/boost (Dose 2) dosing, i.e., dosing twice, with ~21 days (d) between doses. Data are available from healthy participants aged 12 to 85 yrs and

immunocompromised (IC) participants (individuals with post-transplantation and human immunodeficiency virus-positive [HIV+] backgrounds). Immunogenicity data are also available for participants in Phase 1 (24 to 75 yrs of age) and Phase 3 (≥18 to 55 yrs of age) who received a booster dose (third dose) of BNT162b2 ~6 to 8 months after Dose 2.

In the BNT162-01 study, two doses of BNT162b1 or BNT162b2 induced strong SARS-CoV-2 S protein-specific immune responses in healthy participants aged 18 to 85 yrs, with no notable age-related differences, and no clear dose dependency. Compared to healthy and HIV+ participants given the same BNT162b2 30 µg dose, the immune responses in post-transplantation participants were non-existent or weak. The induced immune responses were directed against different epitopes of the SARS-CoV-2 S protein, including non-RBD sequences, indicating the induction of multi-epitopic responses by BNT162b2. The initial strong S-specific immune responses contracted but remained detectable at 28 d post-Dose 2 for HIV+ participants (the last time point assessed to date), and at 162 d post-Dose 2 for healthy younger and older participants.

Similar immunogenicity results were seen for BNT162b1 and BNT162b2 in Study C4591001/BNT162-02, and for BNT162b1 in the study BNT162-03 with Chinese participants. Phase 1 and Phase 3 booster data show that a third dose of BNT162b2 administered ~6 months after completing the 2-dose regimen induces a strong and broad immune response that is expected to confer extended protection against COVID-19, including COVID-19 caused by variants of concern. The observed kinetics of the BNT162b1 and BNT162b2 induced neutralizing antibody response after two doses were typical for antigen-activated B cells undergoing proliferation, followed by rebound contraction with a gradual decline in numbers before stabilization of the immune response.

### *Tolerability and safety data*

*BNT162a1 and BNT162c2 (preliminary data; individuals aged 18 to 55 yrs); BNT162b1 and BNT162b3 (reported data; individuals aged 18 to 85 yrs) - Phase 1:*

For BNT162a1, BNT162c2, BNT162b1, and BNT162b3, the observed reactogenicity was mostly mild or moderate. There were no potentially life-threatening events and, where tested, the frequency and severity of local and systemic reactogenicity events were generally comparable for younger and older participants. The reported treatment-emergent adverse events (TEAEs) were mostly mild or moderate, and all resolved without sequelae. Based on the totality of the safety data, all vaccine candidates were generally well tolerated and had acceptable safety profiles at the dose levels tested. For BNT162b1, twice dosing at 60 µg was not performed due to dose-related increases in reactogenicity at lower dose levels. For BNT162b3, dosing at 30 µg in younger participants was not performed due to dose-related increases in reactogenicity at lower dose levels, whereas dosing at BNT162b3 dose levels of ≤30 µg in older participants was performed and was considered acceptable.

*BNT162b2 (reported data) - Phase 1 (in individuals aged 18 to 85 yrs):*

In the BNT162-01 study, two doses of BNT162b2 were tested at dose levels of ≤30 µg in participants aged 18 to 85 yrs. At the doses tested, BNT162b2 was generally well tolerated

and had an acceptable safety profile in healthy and IC participants (individuals with post-transplantation and HIV+ backgrounds).

*BNT162b2 (reported data, 13 MAR 2021) - Phase 2/3 (in individuals ≥12 yrs of age):*

In Study C4591001/BNT162-02, ~46,000 participants 12 yrs of age and older were enrolled. Altogether, 25,651 participants (58.2%) ≥16 yrs of age were followed for ≥4 months after the second dose and from Dose 2 to the data cutoff date (13 MAR 2021), 12,006 participants (54.5%) in the BNT162b2 group had a total follow-up time of ≥6 months. In the Phase 2/3 part of the study, safety data from all participants enrolled through the 13 MAR 2021 data cutoff did not raise specific safety concerns. The most common solicited adverse reactions (ARs) were injection site pain (>80%), fatigue (>60%), headache (>50%), muscle pain (>40%), chills (>30%), joint pain (>20%), fever and injection site swelling (>10%). Severe AEs were reported by 1.2% and 0.7% in in the BNT162b2 and placebo groups respectively, and serious AEs (SAEs) were similar in the BNT162b2 (0.6%) and placebo (0.5%) groups during the blinded placebo-controlled follow-up period. With the exception of more frequent, generally mild to moderate reactogenicity in participants aged < 55 yrs, the safety profile of BNT162b2 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment. Among Phase 1 and Phase 3 participants who received a booster dose (Dose 3), the reactogenicity and AE profile was generally similar to that observed following Dose 2 of the initial 2-dose regimen, which suggests no potentiation of reactogenicity or any new safety concern arising from administration of a third dose.

### *Efficacy data*

*BNT162b2 (reported data, 13 MAR 2021) - Phase 2/3 (in individuals ≥12 yrs of age):*

Reported efficacy data is available from one clinical study with BNT162b2. In the Phase 2/3 part of Study C4591001/BNT162-02, the primary efficacy endpoint is incidence of COVID-19 in participants without evidence of SARS-CoV-2 infection before or during the 2-dose vaccination regimen. In an updated efficacy analysis up to 6 months post-Dose 2 (data cutoff date 13 MAR 2021) of 42,094 participants randomized 1:1 to vaccine or placebo who were included in the evaluable efficacy population of participants without evidence of SARS-CoV-2 infection before and during the vaccination regimen, the estimated efficacy in preventing confirmed COVID-19 occurring at least 7 d after the second dose of vaccine was 91.3%, with 77 COVID-19 cases in the vaccine group and 850 COVID-19 cases in the placebo group. Updated subgroup efficacy analyses showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for these outcomes did not allow for firm conclusions.

*Pediatric data (in individuals aged 5 to < 12 yrs)*

Based on Phase 1 observations of safety and tolerability and robust immune responses at the tested dose levels for each age group, the BNT162b2 doses selected for further evaluation in the Phase 2/3 part of pediatric Study C4591007 were 10 µg for the 5 to < 12 yrs of age group and 3 µg for the 6 months to < 2 yrs, and 2 to < 5 yrs of age groups.

Phase 2/3 data from ~2,250 children 5 to <12 yrs of age with a follow-up time of at least 2 months after Dose 2 showed BNT162b2 at 10 µg was safe and well tolerated.

### *Post-authorization experience*

Administration of BNT162b2 in the post-authorization setting has confirmed a favorable safety profile. The benefit-risk profile of BNT162b2 remains positive.

The following BNT162 vaccine candidates are under clinical investigation and have neither been approved for use nor been marketed in any country: BNT162a1, BNT162b1, BNT162b3, BNT162c2, BNT162b2 (B.1.351), BNT162b2 (B.1.617.2), BNT162b2 (B.1.1.7), and BNT162b2 (B.1.1.7 + B.1.617.2).

# 3 INTRODUCTION

## 3.1 Background

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. The current COVID-19 outbreak is pandemic, hundreds of millions of people have been infected and almost 5 million deaths have been associated with COVID-19 to date.

Most people infected with the virus experience mild to moderate respiratory illness and recover without requiring special treatment. However, some become seriously ill and require medical attention. Older people and those with underlying medical conditions like cardiovascular disease, diabetes, chronic respiratory disease, or cancer are more likely to develop serious illness. Anyone can get sick with COVID-19 and become seriously ill or die at any age.

All viruses, including SARS-CoV-2, change over time. These changes may have little to no impact on the virus' properties. However, some changes may affect the virus's properties, such as how easily it spreads, the associated disease severity, or the performance of vaccines, therapeutic medicines, diagnostic tools, or other public health and social measures.

An overview of the key SARS-CoV-2 variant strains tracked by the WHO as variants of concern (VOCs) and variants of interest (VOIs) is provided in Table 1.

**Table 1: SARS-CoV-2 variant strains tracked by the WHO**

| Variant of concern or interest | WHO label | Pango lineage | GISAID clade / lineage | Next strain clade |
|---|---|---|---|---|
| VOC | Alpha | B.1.1.7 | GRY | 20I (V1) |
| VOC | Beta | B.1.351 | GH/501Y.V2 | 20H (V2) |
| VOC | Gamma | P.1 | GR/501Y.V3 | 20J (V3) |
| VOC | Delta | B.1.617.2 | G/478K.V1 | 21A |
| VOI | Lambda | C.37 | GR/452Q.V1 | 21G |
| VOI | Mu | B.1.621 | GH | 21H |

VOC = A SARS-CoV-2 variant that meets the definition of a VOI (see below) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance: Increase in transmissibility or detrimental change in COVID-19 epidemiology; or increase in virulence or change in clinical disease presentation; or Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.

VOI = A SARS-CoV-2 variant with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; AND Identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.

Abbreviations: GISAID = Global Initiative on Sharing Avian Influenza Data; VOC = Variant of concern; VOI = Variant of interest; WHO World Health Organization.

Source: WHO webpage "SARS-CoV-2 Variants of Concern and Variants of Interest", accessed 29 SEP 2021. https://www.who.int/en/activities/tracking-SARS-CoV-2 -variants/

## 3.2 Introduction to BioNTech's RNA-based vaccines

The development of an RNA-based vaccine encoding a viral antigen that is translated in the vaccinated individual to protein to induce a protective immune response, provides significant advantages over more conventional vaccine approaches.

RNA-based vaccines can mimic antigen expression during natural infection by directing expression of virtually any pathogen antigen with high precision and flexibility of antigen design. RNA occurs naturally in the body, is metabolized and eliminated by the body's natural mechanisms, does not integrate into the genome, is transiently expressed, and therefore considered safe. Vaccination with RNA in general generates robust immune responses as RNA not only delivers the vaccine antigen, but also has intrinsic adjuvanticity.

Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (such as pregnant women and immunocompromised persons). RNA-based vaccines are manufactured using a cell-free *in vitro* transcription process, which allows easy and rapid production and the prospect of producing high numbers of vaccine doses within a shorter time period than possible with conventional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

BioNTech has three different RNA platforms for the development of BNT162 vaccine candidates for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus: RNA which contains the standard uRNA, modRNA, in which uridine is replaced by the nucleoside pseudouridine; and saRNA, which also contains uridine nucleosides. The three RNA platforms have complementary strengths: uRNA with high intrinsic adjuvanticity, modRNA with blunted innate immune sensor activating capacity and thus augmented expression, and saRNA from which higher amounts of protein per injected RNA template can be produced.

The structural elements of the vector backbones of BNT162 vaccine candidates are optimized for prolonged and strong translation of the antigen-encoding RNA component. The potency of BNT162 vaccine candidates is further optimized by encapsulation of the RNA component into LNPs, which protect the RNA from degradation by RNases and enable transfection of host cells after IM delivery (Figure 1). Due to RNA's inherent adjuvant activity mediated by binding to innate immune sensors such as toll-like receptors, RNA-LNP vaccines induce a robust neutralizing antibody response and a concomitant T-cell response resulting in protective immunization with minimal vaccine doses.

The different BNT162 vaccine candidates exhibit distinct antigen expression profiles after IM injection. All RNA encoded antigens are expressed transiently. While for BNT162a (uRNA) and BNT162b (modRNA) the antigen expression peaks shortly after injection, for BNT162c (saRNA) the antigen expression peaks later and is more prolonged due to self-amplification.

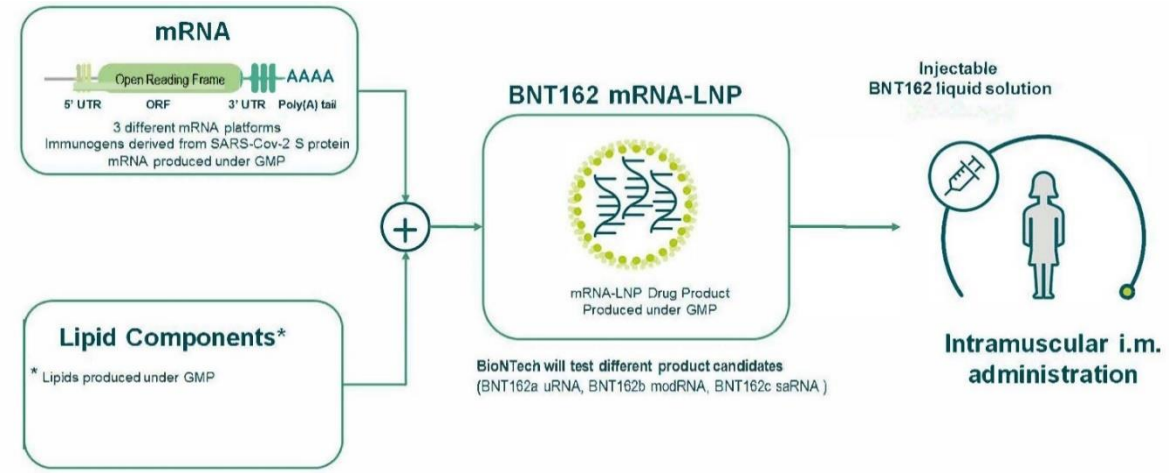



**Figure 1: RNA-LNP-based BNT162 vaccines**

The BNT162 vaccines are GMP-grade RNA drug substances that encode SARS-CoV-2 antigens. The RNA is formulated with lipids as RNA-LNP drug product. The vaccine candidates are supplied as buffered liquid solutions for intramuscular injection.

Abbreviations: GMP = good manufacturing practice; i.m. = intramuscular; mRNA = messenger RNA; ORF = open reading frame; RNA-LNP = RNA complexed with liposomes; S protein = SARS-CoV-2 sp ke protein; UTR = untranslated region.

## Coronavirus spike (S) protein as vaccine target

Coronaviruses like SARS-CoV-2 are a (+) ssRNA enveloped virus family that encode for a total of four structural proteins. Within these four structural proteins, the S protein is the key target for vaccine development. Similar to the influenza virus hemagglutinin (HA), the S protein is responsible for receptor-recognition, attachment to the cell, viral envelope fusion with a host cell membrane, and genomic release driven by the S protein conformation change leading to the fusion of viral and host cell membranes (Figure 2).

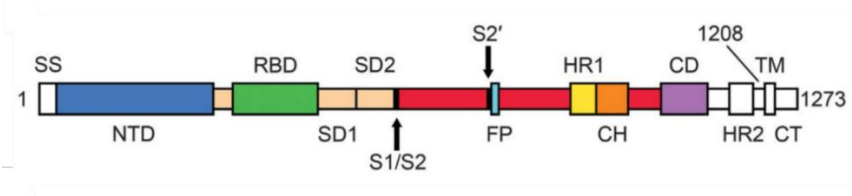



**Figure 2: Schematic overview of the organization of the SARS-CoV-2 S protein**

The sequence within the S1 fragment includes the signal sequence (SS) and the receptor binding domain (RBD), which is the key subunit within the S protein that is relevant for binding to the human cellular receptor ACE2. The S2 subunit contains the S2 protease cleavage site (S2') followed by a fusion peptide (FP) for membrane fusion, heptad repeats (HR1 and HR2) with a central helix (CH) domain, the transmembrane domain (TM) and a cytoplasmic tail (CT). NTD = N-terminal domain.

Source: modified from Wrapp et al. 2020.

The SARS-CoV-2 S protein is cleaved by host proteases into the S1 and S2 subunits. While S2, with its transmembrane domain, is responsible for membrane fusion, the S1 domain with its C-terminal RBD recognizes the host receptor and binds to the target host cell.

The S protein is pivotal for host cell recognition and entry, and thus, a primary target for virus neutralizing antibodies (Zakhartchouk et al. 2007; Yong et al. 2019). Some

monoclonal antibodies against the S protein, particularly those directed against the RBD, neutralize SARS-CoV and Middle East Respiratory Syndrome (MERS)-CoV infection *in vitro* and *in vivo* (Hulswit et al. 2016).

RNA-based vaccines can mimic antigen expression during natural infection by directing expression of the S protein, as well as its S1 cleavage fragment or the RBD alone, to induce virus neutralizing antibodies (Al-Amri et al. 2017). The RBD forms membrane distal "heads" on the S protein that are connected to the S protein body by a hinge. In the native S protein, when the RBD is in the "heads down" conformation, the neutralizing epitopes at the receptor binding site are occluded. When the RBD is in the "heads up" conformation (also referred to as the "pre-fusion conformation"), the neutralizing epitopes at the receptor binding site are exposed. Therefore, two mutations in the S2 domain within the central helix domain were included that lead to a "heads up" stabilized, pre-fusion conformation variant of S protein which can induce a stronger neutralizing antibody response than the native S protein (Pallesen et al. 2017; Wrapp et al. 2020).

### Lipid nanoparticle (LNP) formulation

The BNT162 vaccine candidate RNA is encapsulated into LNPs, which protect the RNA from degradation and enable transfection of the RNA into host cells after IM injection. The same LNP formulation is used for all of the BNT162 vaccine candidates. After injection, the RNA-LNPs are taken up by the cells, and the RNA is released into the cytosol. In the cytosol, the RNA is translated to the encoded viral antigen.

## 3.3 Clinical development

The clinical program started with the investigation of four BNT162 vaccine candidates (BNT162a1, BNT162b1, BNT162b2, BNT162c2). A fifth vaccine candidate, BNT162b3, was later added to the program. For an overview of the BNT162 vaccine candidates under clinical investigation, see Table 2.

One vaccine candidate, BNT162b2, has received temporary authorization for emergency supply in 46 countries and licenses or conditional marketing authorizations in 46 countries globally under tradename Comirnaty.

To date, BNT162b2 has been administered to hundreds of millions of individuals. Further clinical investigation of BNT162b2 is ongoing to expand the studied populations.

With the emergence of new SARS-CoV-2 variants, several BNT162b2-based variant vaccines that target these viral variants were also added to the clinical program, e.g., BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), BNT162b2 (B.1.1.7 + B.1.617.2), and BNT162b2 (B.1.351). For the variant vaccines, the code in brackets indicates the Pango lineage (see Section 3.1). For an overview of the BNT162 variant vaccines under clinical investigation, see Table 2.

**Table 2: Characteristics of the different BNT162 vaccine candidates in clinical investigation**

| RNA platform | BNT162 vaccine candidate (Product code) | SARS-CoV-2 variant [d] | Encoded antigen | Sequence variant [a] |
|---|---|---|---|---|
| uRNA | BNT162a1 | Wild type | SARS-CoV-2 RBD, a secreted variant | V5 |
| modRNA | BNT162b1 | Wild type | SARS-CoV-2 RBD, a secreted variant | V5 |
| | BNT162b2 | Wild type | Full length SARS-CoV-2 S protein bearing mutations preserving neutralization-sensitive sites | V8 and V9 [b] |
| | BNT162b2 (B.1.1.7)<br>BNT162b2 (B.1.617.2)<br>BNT162b2 (B.1.351) [c] | Alpha<br>Delta<br>Beta | Full length SARS-CoV-2 S protein for each viral strain bearing mutations preserving neutralization-sensitive sites | CCI<br>[redacted]<br>[redacted] |
| | BNT162b3 | Wild type | SARS-CoV-2 RBD, a membrane-bound variant | CCI [redacted] |
| saRNA | BNT162c2 | Wild type | Full length SARS-CoV-2 S protein bearing mutations preserving neutralization-sensitive sites | V9 |

a. Sequence variant refers to the nucleotide sequence of the RNA component encoding the antigen.
b. Note that there were two variants of the BNT162b2 vaccine tested. The RNA component of the two sequence variants, V8 and V9, have different nucleotide sequences, but both encode the same antigen.
c. Also referred to as BNT162b2s01 and BNT162b2$_{SA}$.
d. Wild type refers to the ancestral Wuhan strain; other designations follow the WHO variant of concern classification (Tracking SARS-CoV-2 variants [https://www.who.int/en/activities/tracking-SARS CoV 2 -variants/])

Abbreviations: modRNA = nucleoside-modified RNA; n.a. = not applicable; RBD = receptor binding domain; S protein = sp ke protein; saRNA = self-amplifying RNA; uRNA = uridine-containing RNA; WHO World Health Organization.

For BNT162a1, BNT162b1, BNT162b3, and BNT162c2, all planned vaccine administration to study participants has been completed and the dosed participants are now in follow-up.

For BNT162b2 and BNT162b2-based variant vaccines, enrollment and vaccine administration to study participants is ongoing and/or planned.

# 4 PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

This section gives general information about the physical, chemical and pharmaceutical properties of the BNT162 family of prophylactic RNA-based vaccine candidates. The RNA components of the RNA-LNP drug products of the three different RNA platforms for clinical investigation are the uRNA, modRNA, and saRNA, each encoding the full length or parts of the SARS-CoV-2 S protein. For an overview of the different BNT162 vaccine candidates under clinical investigation, see Table 2.

## 4.1 Physical, chemical and pharmaceutical properties of the drug substance

The RNA drug substances of BNT162 are highly purified single-stranded, 5'-capped messenger RNAs (mRNAs) produced by *in vitro* transcription from the corresponding DNA templates, each encoding full length or parts of the SARS-CoV-2 S protein.

### *4.1.1 Non-modified uridine-containing mRNA (uRNA)*

The active principle of the uRNA drug substance is a single-stranded, 5′-capped mRNA that is translated after entering the cell. In addition to the sequence encoding the SARS-CoV-2 antigen (i.e., open reading frame [ORF]), each uRNA contains common structural elements optimized for high efficacy of the RNA with respect to stability and translational efficiency (5′-cap, 5′-UTR, 3′-UTR, poly(A)-tail).

### *4.1.2 Nucleoside-modified mRNA (modRNA)*

The active principle of the modRNA drug substance is a single-stranded, 5′-capped mRNA that is translated after entering the cell. In addition to the sequence encoding the SARS-CoV-2 antigen (i.e., ORF), each modRNA contains common structural elements optimized for high efficacy of the RNA. Compared to uRNA, modRNA contains 1-methyl-pseudouridine instead of uridine and a different 5'-cap structure.

### *4.1.3 Self-amplifying mRNA (saRNA)*

The active principle of the saRNA drug substance is a single-stranded 5'-capped RNA, which self-amplifies after entering the cell, and the SARS-CoV-2 antigen is translated as the RNA self-amplifies. In addition to the sequence encoding the SARS-CoV-2 antigen (i.e., ORF) and the common structural elements in uRNA and modRNA, the saRNA vector contains an additional open reading frame, which encodes the Venezuelan equine encephalitis virus RNA-dependent RNA polymerase (RNA replicase) and a subgenomic promoter plus conserved sequence elements supporting replication and translation, but no other Venezuelan equine encephalitis virus coding sequences.

The physicochemical properties of the RNA drug substances are listed in Table 3.

**Table 3: General properties of uRNA, modRNA, and saRNA drug substances**

| Parameter | Value/Description |
|---|---|
| Appearance | Clear, colorless liquid |
| Concentration | 1.70 ± 0.17 mg/mL; 2.25 ± 0.25 mg/mL [a] |
| pH | 7.0 ± 1.0; 7.0 ± 0.5 [b] |

a. Depending on batch size.
b. Changed in later stages of development for BNT162b2 and the variants thereof, e.g., BNT162b2 (B.1.351).
Abbreviations: modRNA = nucleoside-modified RNA; saRNA = self-amplifying RNA; uRNA = uridine-containing RNA.

## 4.2 Description of the drug product

The drug product is a preservative-free, sterile dispersion of RNA formulated in LNP in aqueous cryoprotectant buffer for IM administration. The RNA drug substance is the only active ingredient in the drug product. The drug product with initial formulation is a concentrate for injection and filled at 0.5 ± 0.13 mg/mL in glass vials and closed with stoppers and flip-off crimping caps. The packaged drug product is stored between -90°C to -60°C. The formulation of the BNT162b2 modRNA drug product was further optimized during development. The drug product with Tris/Sucrose formulation is a preservative-free, sterile dispersion of LNPs in aqueous cryoprotectant buffer for IM administration. The Tris/Sucrose drug product is formulated at 0.1 mg/mL RNA supplied in a 2 mL glass vial sealed with a bromobutyl rubber stopper and an aluminum seal with flip-off plastic cap. There is no manufacturing overage.

### *4.2.1 Composition of the initial drug product formulation*

The composition of RNA drug products for use in the clinical studies and the function of the respective components are given in Table 4. The LNP composition is the same for all five BNT162 vaccine candidates.

**Table 4: Composition of the initial drug product formulation**

| Component | Quality standard | Function |
|---|---|---|
| Drug substance | In-house | Active |
| ALC-0315 [a] | In-house | Functional lipid |
| ALC-0159 [b] | In-house | Functional lipid |
| DSPC [c] | In-house | Structural lipid |
| Cholesterol | Ph. Eur. | Structural lipid |
| Sucrose | NF, Ph. Eur. [d] | Cryoprotectant |
| NaCl | USP-NF, Ph. Eur. [d] | Buffer |
| KCl | USP-NF, Ph. Eur. [d] | Buffer |
| $Na_2HPO_4$ | USP-NF, Ph. Eur. [d] | Buffer |
| $KH_2PO_4$ | USP-NF, Ph. Eur. [d] | Buffer |
| Water for injection | USP-NF, Ph. Eur. [d] | Solvent/Vehicle |

a. ALC-0315 = ([4-hydroxybutyl]azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
b. ALC-0159 = 2-[(polyethylene glycol)-2000]-*N,N*-ditetradecylacetamide
c. DSPC = 1,2-distearoyl-*sn*-glycero-3-phosphocholine

d. Grades of incoming materials are the same across sites as confirmed by the supplier Certificate of Analysis. However, incoming testing at each manufacturing site may initially be performed only in accordance with each site's local compendia.

Abbreviations: Ph. Eur. = European Pharmacopoeia (*Pharmacopoeia Europaea*); USP-NF = United States Pharmacopeia-National Formulary.

### 4.2.2 Composition of the Tris/Sucrose drug product formulation

The composition of BNT162b2 modRNA drug products for use in clinical studies was further optimized with respect to stability and handling. The LNP composition in the Tris/Sucrose formulation is given in Table 5.

**Table 5: Composition of the Tris/Sucrose drug product formulation**

| Name of ingredient | Quality standard | Function |
|---|---|---|
| BNT162b2 drug substance | In-house specification | Active ingredient |
| ALC-0315 [a] | In-house specification | Functional lipid |
| ALC-0159 [b] | In-house specification | Functional lipid |
| DSPC [c] | In-house specification | Structural lipid |
| Cholesterol | Ph. Eur. | Structural lipid |
| Sucrose | USP-NF, Ph. Eur. | Cryoprotectant |
| Tromethamine (Tris base) | USP-NF, Ph. Eur. | Buffer component |
| Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl) | In-house specification | Buffer component |
| Water for Injection | Ph. Eur. | Solvent |

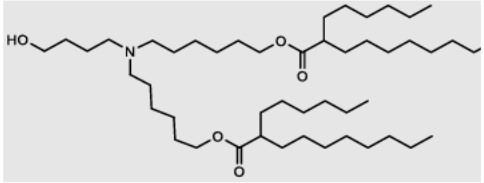
### 4.2.3 Description of the excipients

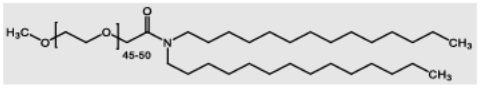
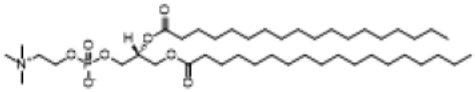
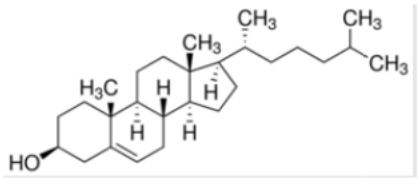
All excipients used in the formulation of the drug product are listed in Table 4 and Table 5.

The drug product contains the two functional lipids ALC-0315 and ALC-0159 and the two structural lipids DSPC (1,2-distearoyl-*sn*-glycero-3-phosphocholine) and cholesterol.

Physicochemical properties and the structures of the four lipids are shown in Table 6.

**Table 6: Lipid excipients in the drug product**

| Lipid (CAS number) | Molecular weight [Da] | Molecular formula | Physical state and storage condition | Chemical name (synonyms) and structure |
|---|---|---|---|---|
| ALC-0315 (2036272-55-4) | 766 | $C_{48}H_{95}NO_5$ | Liquid (oil) -20°C | ([4-hydroxybutyl]azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)  |

| Lipid (CAS number) | Molecular weight [Da] | Molecular formula | Physical state and storage condition | Chemical name (synonyms) and structure |
|---|---|---|---|---|
| ALC-0159 (1849616-42-7) | ~2400-2600 | $C_{30}H_{60}NO(C_2H_4O)_nOCH_3$ n=45-50 | Solid -20°C | 2-([polyethylene glycol]-2000)-*N,N*-ditetradecyclacetamide  |
| DSPC (816-94-4) | 790 | $C_{44}H_{88}NO_8P$ | Solid -20°C | 1,2-distearoyl-*sn*-glycero-3-phosphocholine  |
| Cholesterol (57-88-5) | 387 | $C_{27}H_{46}O$ | Solid -20°C |  |

CAS = Chemical Abstracts Service.

## 4.3 Description of the diluent

For the dilution of drug products for IM injection, isotonic NaCl solution (0.9%) is sourced as an approved medicinal product. The composition is according to the supplier's specifications.

## 4.4 Description of the IMP

| | |
|---|---|
| **IMP name:** | BNT162 vaccine candidates - Anti-viral RNA vaccines for active immunization against COVID-19. |
| **IMP type:** | RNA-LNP vaccine candidates utilizing different BioNTech RNA formats, i.e.,<br>uRNA (product code):<br>• BNT162a1<br>saRNA (product code):<br>• BNT162c2<br>modRNA (product codes):<br>• BNT162b1<br>• BNT162b3<br>• BNT162b2<br>• BNT162b2 (B.1.1.7)<br>• BNT162b2 (B.1.617.2)<br>• BNT162b2 (B.1.351) |
| **IMP administration route:** | IM injection. |
| **Dosage frequency:** | Depending on the vaccine, using either single- or multiple-dose regimens. |

## 4.5 Storage and handling of the IMP

### *4.5.1 Initial drug product formulation*

Drug product of BNT162 is provided as a frozen dispersion for injection at a concentration of 0.50 mg/mL. To prepare the dispersion for injection, the drug product is thawed and diluted with isotonic NaCl solution (0.9%). The one step dilution process is to be performed either in a syringe or directly in the drug product vial depending on the dose level. The concentration of the final dispersion for injection varies depending on the respective dose level to be administered.

After dilution, store the dispersion for injection at between 2 and 25°C (for commercial BNT162b2 [Comirnaty™] batches only, store the dispersion for injection at between 2 and 30°C) and use within 6 h. Discard any diluted dispersion for injection after 6 h. Do not refreeze.

For detailed instructions for storage and handling, see the respective study-specific Pharmacy Manual.

### *4.5.2 Tris/Sucrose drug product formulation*

BNT162 Tris/Sucrose drug product is provided as a frozen dispersion for injection at a concentration of 0.1 mg/mL. No dilution is required for administration.

After thawing, store the dispersion for injection at 2 to 8°C for up to 10 weeks. After first puncture of the stopper for administration, store between 2 and 30°C and use within 12 h. Discard any dispersion for injection after 12 h. Do not refreeze.

For detailed instructions for storage and handling, see the respective study-specific Pharmacy Manual.

# 5 NON-CLINICAL STUDIES

The primary pharmacology of the BNT162 vaccine candidates was evaluated in a range of non-clinical pharmacology studies *in vitro* and *in vivo*.

*In vitro*, the expression of the vaccine antigen was evaluated to confirm functionality of the RNA. *In vivo* studies were performed to benchmark the different vaccine antigens and to provide proof-of-concept, i.e., to demonstrate that BNT162 vaccines can induce an anti-SARS-CoV-2 immune response, supporting clinical investigation in humans. A SARS-CoV-2 challenge study in BNT162b2 (V9)-immunized NHPs was also conducted to assess protection against infection and to demonstrate lack of disease enhancement.

Platform properties were initially demonstrated with non-SARS-CoV-2 antigens. Non-GLP *in vivo* testing of an LNP-formulated modRNA encoding luciferase examined biodistribution in BALB/c mice and Wistar Han rats after IM injection and the PK of the two novel excipients in the LNP formulation, ALC-0315 and ALC-0159, in Wistar Han rats. In addition, the metabolism of ALC-0315 and ALC-0159 was evaluated in mouse, rat, monkey, and in human blood, liver microsomes, S9 fractions, and hepatocytes and *in vivo* in rat plasma, urine, feces, and liver samples from the PK study.

The BNT162 vaccines have been studied in GLP-compliant repeat-dose toxicity studies in rats. The study designs are based on WHO guidelines for vaccine development (WHO Technical Report Series No. 987, 2014). A DART study assessing BNT162b vaccines (modRNA-based variants) in rats has also been completed. IM administration was chosen for the toxicity studies as this is the intended route of administration. Rats were chosen for toxicity assessments as they are a commonly used animal species for the evaluation of toxicity, and they mount an antigen-specific immune response to vaccination with BNT162 vaccines. The repeat-dose toxicity studies and the DART study in rats were conducted in accordance with Good Laboratory Practice for Non-Clinical Laboratory Studies, Code of US Federal Regulations (21 CFR Part 58), in an OECD Mutual Acceptance of Data member state.

Table 2 summarizes the nomenclature used for the BNT162 vaccine candidates.

## 5.1 Non-clinical pharmacology

### *5.1.1 Primary pharmacodynamics*

Table 30 summarizes the primary pharmacodynamics studies.

#### 5.1.1.1 *In vitro* expression of BNT162 RNA encoded antigens

*In vitro* expression of BNT162 RNA encoded antigens was used to confirm that the two SARS-CoV-2 derived vaccine antigens V5 and V9 are robustly translated from the respective RNA drug substances.

*In vitro* expression and co-localization of the antigens with an endoplasmic reticulum marker was confirmed in HEK293T cells expressing BNT162b1 (modRNA encoding V5) RNA or BNT162b2 (modRNA encoding V9) RNA, respectively. Robust expression of the

trimerized RBD or P2 S was also confirmed in HEK293T cells expressing BNT162b1 RNA or BNT162b2 RNA.

BNT162b3 is a vaccine candidate with a modRNA encoding a membrane anchored trimerized variant of the RBD of the SARS-CoV-2 S protein (CCI ) was developed. CCI antigen expression and transport to the cell surface was confirmed.

#### 5.1.1.2 *In vivo* immunogenicity studies in rodents

##### *5.1.1.2.1 Immunogenicity of BNT162 vaccine candidates in mice*

Non-clinical immunogenicity studies were performed in mice for the BNT162 vaccine candidates BNT162a1 (V5), BNT162b1 (V5), BNT162b2 (V9), BNT162b3 (CCI ), and BNT162c2; for a summary of these studies, see Table 30.

In mice, the S-specific IgG antibody response was detected at a very early time point (7 d) post-immunization. The observed induction of an antibody response in mice by a very low immunization dose (0.2 µg) with BNT162b1, BNT162b2, BNT162b3, and BNT162c2, indicates a high vaccine potency. Also, (pseudovirus) neutralizing antibody responses were detectable 14 d post-immunization in mice immunized with intermediate doses. Overall, all BNT162b candidates were immunogenic with BNT162b3 inducing the highest virus neutralization titer in mice.

##### *5.1.1.2.2 Immunogenicity of BNT162 vaccine candidates after repeated dosing in rats (Study 38166)*

In a GLP-compliant repeat-dose toxicity study in rats (Section 5.3.1, Study 38166), the immunogenicity of the administered RNA vaccines BNT162a1 (uRNA encoding V5), BNT162b1 (modRNA encoding V5), BNT162b2 (modRNA encoding V8), and BNT162c1 (saRNA encoding V5) were investigated. The non-clinical evaluation of BNT162b2 included two variants of BNT162b2: V8 and V9. BNT162b2 (V9; the candidate assessed clinically), differs from BNT162b2 (V8) only in the presence of optimized codons to improve antigen expression, but the amino acid sequences of the encoded antigens are identical. Results presented here were obtained with BNT162b2 (V8) (Study 38166). However, results obtained with BNT162b2 (V9) obtained in a subsequent study (20GR142) are generally similar.

Serum samples were collected from 10 repeatedly dosed main study rats per group on Day 10 (BNT162c1) or Day 17 after first immunization (BNT162a1, BNT162b1, and BNT162b2) as well as from recovery cohorts consisting of five rats per group at the end of the study on Day 31 (BNT162c1) or Day 38 (BNT162a1, BNT162b1, and BNT162b2).

Treatment with all BNT162 vaccine candidates resulted in the formation of IgG antibodies against the S1 domain as well as the RBD subdomain of the SARS-CoV-2 S protein. There was a weak antibody immune response for BNT162c1 treated animals on Days 10 and 31, and a strong antibody response for BNT162b1 and BNT162b2 (V8) on Days 17 and 38. Antibody concentrations against S1 and RBD increased, for BNT162b1 in a dose-dependent manner, over time in animals.

Treatment of rats with each of the BNT162 vaccine candidates resulted in the formation of neutralizing antibodies protecting against pseudovirus infection (titer resulting in 50% pseudovirus neutralization).

Neutralizing antibody titers in vaccinated animals increased over time with the recorded neutralizing activity being consistent with the enzyme-linked immunosorbent assay (ELISA) data. CCI [redacted], a strong pseudovirus neutralization effect was mediated by sera obtained from BNT162b1- and BNT162b2-treated rats. For BNT162b1 and BNT162b2, the neutralizing antibody titers resulting in 50% pseudovirus neutralization ($pVN_{50}$) exceeded the upper limit of quantification of a reciprocal titer of 1,536 in at least 8 out of 10 rats per group on Day 38.

In another repeat-dose toxicity study, testing BNT162b2 (V9) and BNT162b3, as well as in the DART study, where BNT162b1, BNT162b2 (V9) and BNT162b3 were assessed, serum samples were collected from study animals prior to vaccine administration, at the end of the dosing phase on Day 17 (2 d after the third dose), and at the end of the 3-week recovery phase on recovery phase Day 21. Sera were analyzed for SARS-CoV-2 neutralizing antibodies. After immunization, BNT162b2 (V9) and BNT162b3 elicited SARS-CoV-2 neutralizing antibody responses in males and females at the end of the dosing and recovery phases of the repeat-dose toxicity study. SARS-CoV-2 neutralizing antibody responses were not observed in animals prior to vaccine administration or in saline-administered control animals. In the DART study, female rats were administered four total IM doses of the BNT162b1, BNT162b2 (V9), or BNT162b3, one dose at each of 21 and 14 d prior to mating and on gestation day (GD) 9 and GD 20. Serum samples were collected from females prior to vaccine administration, just prior to mating (M0), at the end of GD 21, and at the end of lactation (lactation day 21) and offspring (fetuses on GD 21 and pups on postnatal day 21). Sera were analyzed for SARS-CoV-2 neutralizing antibodies. After immunization, SARS-CoV-2 neutralizing titers were detected in the majority of maternal females as well as in most of their offspring (fetuses and pups). SARS-CoV-2 neutralizing antibody titers were not observed in animals prior to vaccine administration or in saline-administered control animals.

#### 5.1.1.3 *In vivo* immunogenicity and SARS-CoV-2 challenge in NHP

##### *5.1.1.3.1 Immunogenicity of BNT162b1 (modRNA encoding V5) and BNT162b2 (modRNA encoding V9) and BNT162b3 (CCI [redacted])*

In a study with rhesus macaques (i.e., NHP), six animals per group were immunized IM with CCI [redacted] of BNT162b1 (V5) or BNT162b2 (V9), CCI [redacted] of BNT162b3, or with saline (buffer) on Days 0 and 21.

First, sera were tested for IgG antibodies that bind to the SARS-CoV-2 S1 subunit. On Day 28 after the first dose, i.e., 7 d after the second immunization, titers were highest.

RBD-binding IgG was readily detectable by Day 14 after Dose 1, and levels increased further by 7 d after Dose 2 (Day 28). For comparison, the RBD-binding IgG geometric mean concentration (GMC) of a panel of 38 COVID-19 human convalescent sera was included and lower than the GMC of immunized rhesus macaques after one or two doses.

SARS-CoV-2 neutralizing antibody titers were determined in the NHP serum samples. Fifty percent geometric mean titers (GMTs), measured by a SARS-CoV-2 neutralization assay, were detectable in the sera of most BNT162b1-immunized rhesus macaques by Day 21 after Dose 1 and in all BNT162b2 and BNT162b3-immunized macaques by Day 14 after Dose 1. There was a strong boosting effect, with comparable GMTs elicited by BNT162b1 (768 for 30 µg and 1,714 for 100 µg) or BNT162b2 (962 for 30 µg and 1,689 for 100 µg), measured in sera drawn 7 or 14 d after Dose 2. For comparison, the neutralization GMT of the human convalescent serum was 94, substantially lower than the GMTs of rhesus macaque sera drawn 21 or 35 d after Dose 2.

The rhesus macaque immunogenicity data show strong neutralizing humoral responses to the BNT162b vaccine candidates that exceed those observed in COVID-19 convalescing humans.

For BNT162b2 immunized rhesus macaques, S-specific T-cell responses were analyzed using peripheral blood mononuclear cells collected 42 d after first immunization. Enzyme-linked immunosorbent-spot (ELISpot) assays demonstrated strong IFNγ but minimal IL-4 responses, indicating a Th1-biased response.

At 41 to 55 d after Dose 2, 6 rhesus macaques that had been immunized with 100 µg BNT162b1 and 6 that had been immunized with 100 µg BNT162b2 were challenged with $1.05 \times 10^6$ plaque forming units of SARS-CoV-2. In addition, nine age-matched macaques (controls) that had been mock immunized with saline received the same SARS-CoV-2 challenge, and 6 age-matched macaques (sentinels) were mock-challenged with cell culture medium. Bronchoalveolar lavage was performed, and samples were tested for SARS-CoV-2 RNA (genomic RNA and subgenomic transcripts) by reverse transcription quantitative polymerase chain reaction (RT-qPCR). Viral RNA was detected in bronchoalveolar lavage fluid from control macaques on Day 3, and to lesser extent in samples from BNT162b1 immunized animals. Viral RNA was not detected in bronchoalveolar lavage fluid from the BNT162b2-immunized and SARS-CoV-2 challenged macaques at no time point.

None of the challenged animals, whether immunized or not, showed clinical signs of illness. Radiographic abnormalities were generally minimal or mild and were not consistently associated with viral challenge. Histopathology of necropsy specimens obtained 7 to 8 d after challenge revealed localized areas of pulmonary inflammation that were limited in extent even in the control animals challenged after mock immunization with saline. These studies showed that the 2 to 4 yr old male rhesus macaque challenge model is primarily a SARS-CoV-2 infection model rather than a COVID-19 disease model.

### *5.1.2 Secondary pharmacodynamics*

No secondary pharmacodynamics studies were conducted.

### *5.1.3 Safety pharmacology*

No safety pharmacology studies were conducted for the BNT162 vaccine candidates as they are not considered necessary according to the WHO guideline (WHO Technical Report Series, No. 927, 2005).

### *5.1.4 Non-clinical pharmacology – Conclusions*

All tested BNT162 vaccine candidates were immunogenic to highly immunogenic in non-clinical models, including mice, rats, and NHPs.

In mice, the S-specific IgG antibody response was detected at a very early time point (7 d) post-immunization. The observed induction of an antibody response in mice by a very low immunization dose (0.2 µg) with BNT162b1, BNT162b2, BNT162b3, and BNT162c2, indicates a high vaccine potency. Also, (pseudovirus) neutralizing antibody responses were detectable 14 d post-immunization in mice immunized with intermediate doses.

After SARS-CoV-2 challenge in NHP (rhesus macaques) immunized with either BNT162b1 or BNT162b2, animals showed higher resistance against viral replication when immunized with BNT162b2. Read-out of challenged NHP after immunization with BNT162b3 was not performed.

Overall, all BNT162b candidates were immunogenic with BNT162b3 inducing the highest virus neutralization titer in both mice and NHPs. Both, BNT162b1 and BNT162b2 protected rhesus macaques from infectious SARS-CoV-2 challenge, with BNT162b2 immunization providing complete protection in the lower respiratory tract, as demonstrated by the absence of detectable SARS-CoV-2 RNA. No vaccine elicited disease enhancement was observed.

Results indicating immunogenicity were also obtained in the GLP-compliant repeat-dose toxicity and DART studies in rats with BNT162b2 and the other candidates.

## 5.2 Non-clinical pharmacokinetics and metabolism

Platform properties that support BNT162 vaccines were demonstrated with non-SARS-CoV-2 antigens. Non-GLP *in vivo* testing of an LNP-formulated modRNA encoding luciferase examined biodistribution in BALB/c mice and Wistar Han rats after IM injection (Section 5.2.3) and the PK of the two novel lipid excipients in the LNP formulation, ALC-0315 and ALC-0159, in Wistar Han rats (Section 5.2.2). In addition, the metabolism of ALC-0315 and ALC-0159 was evaluated in mouse, rat, monkey, and human blood, liver microsomes, S9 fractions, and hepatocytes and *in vivo* in rat plasma, urine, feces, and liver samples from the PK study (Section 5.2.4).

### *5.2.1 Methods of analysis*

No methods of analysis have been validated to support studies of components of BNT162b2; however, a qualified liquid chromatography-tandem mass spectrometry (LC/MS) method was developed to support quantitation of the two novel LNP excipients for the non-GLP IV PK study in rats (Study PF-07302048_06Jul20_072424).

### *5.2.2 Absorption and single dose pharmacokinetics*

The administration route for the BNT162 vaccines is IM, so no absorption studies were conducted.

An IV rat PK study (PF-07302048_06Jul20_072424) was performed using LNPs containing modRNA encoding the luciferase surrogate marker, with the identical lipid

composition as BNT162b2, to explore the disposition of ALC-0315 and ALC-0159. The findings are depicted in Table 7 and Figure 3.

**Table 7: PK of ALC-0315 and ALC-0159 in Wistar Han rats after IV administration of LNPs containing RNA encoding the luciferase surrogate marker at 1 mg/kg**

| Analyte | Dose of analyte (mg/kg) | Sex/N [b] | $t_{½}$ (h) | $AUC_{inf}$ (µg•h/mL) | $AUC_{last}$ (µg•h/mL) | Estimated fraction of dose distributed to liver (%) [a] |
|---|---|---|---|---|---|---|
| ALC-0315 | 15.3 | Male/3 [b] | 139 | 1,030 | 1,020 | 60 |
| ALC-0159 | 1.96 | Male/3 [b] | 72.7 | 99.2 | 98.6 | 20 |

a. Calculated as highest mean amount in the liver (µg)/total mean dose (µg) of ALC-0315 or ALC-0159.
b. 3 animals per timepoint; non-serial sampling.

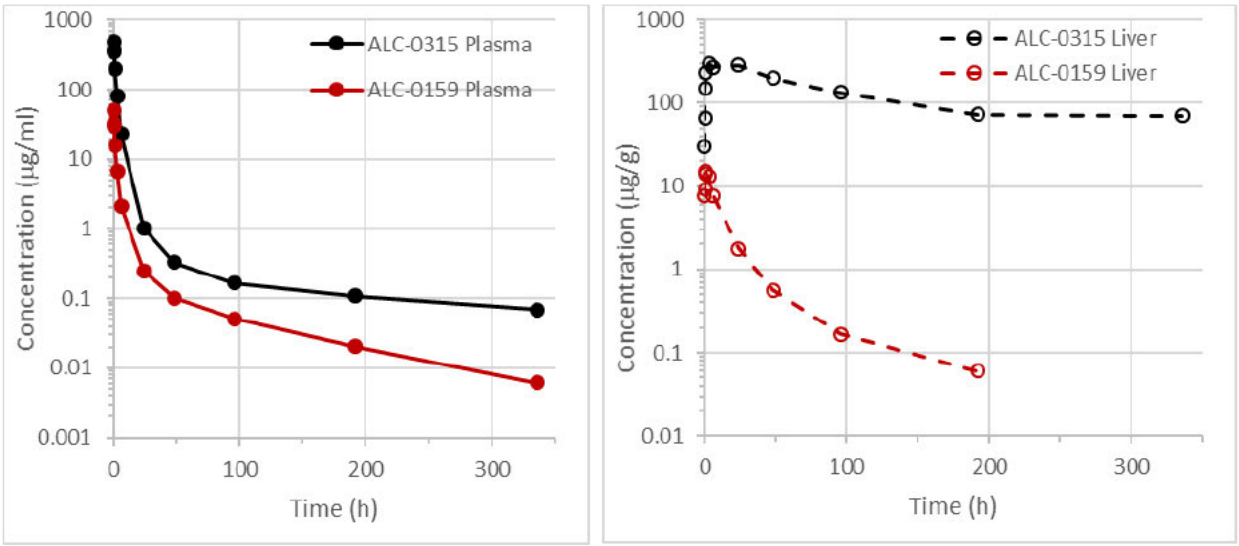



**Figure 3: Plasma and liver concentrations of ALC-0315 and ALC-0159 in Wistar Han rats after IV administration of 1 mg/kg LNPs containing RNA encoding the luciferase surrogate marker**

Pharmacokinetic studies have not been conducted with BNT162b2 and are generally not considered necessary to support the development and licensure of vaccine products for infectious diseases (WHO Technical Report Series No. 927, 2005; WHO Technical Report Series No. 987, 2014).

### *5.2.3 Distribution*

No biodistribution studies were performed with the BNT162 vaccine candidates. Instead, biodistribution of a comparable RNA-LNP formulation was assessed in mice using luciferase as a surrogate marker in place of the antigens encoded in the BNT162 vaccines (Study R-20-0072). Luciferase expression can be detected after injection of luciferin by measuring the luminescence *in vivo*. Using modRNA (BNT162b) as representative for all three RNA platforms, injection of RNA led to a high and long expression of luciferase *in vivo* in mice. Expression of the luciferase reporter was observed at the site of injection

and, to a lesser extent, in the liver. Distribution to the liver is considered to be mediated by LNPs entering the blood stream.

The distribution of a surrogate LNP with an identical lipid composition to BNT162 vaccines, but with a luciferase reporter (monitoring the $^{3}$H-CHE lipid label), was investigated in blood, plasma and selected tissues in male and female Wistar Han rats over 48 h after a single IM injection (Study 185350). The highest mean concentration of LNP was found at the injection site for each time point in both sexes. Outside the injection site, low levels of radioactivity were detected in most tissues, whereby the highest levels were seen in plasma at 1 to 4 h post-dose. Over 48 h, the LNP distributed mainly to liver, adrenal glands, spleen and ovaries, with maximum concentrations observed at 8 to 48 h post-dose.

For male and female animals together, the total recovery (% of injected dose) of radiolabeled LNP outside the injection site was ≤18% in the liver, ≤1.0% in the spleen, ≤0.11% in adrenal glands, ≤0.095% in ovaries. The mean concentrations and tissue distribution patterns were broadly similar between the sexes.

### *5.2.4 Metabolism and excretion*

RNA, including pseudouridine modified RNA, is degraded by cellular RNases and subject to nucleic acid metabolism. Nucleotide metabolism occurs continuously within the cell, with the nucleoside being degraded to waste products and excreted or recycled for nucleotide synthesis.

The antigens encoded by the RNA in the BNT162 vaccine candidates are proteolytically degraded, just like endogenous proteins. Therefore, no RNA or protein metabolism or excretion studies were conducted.

Of the four lipids used as excipients in the LNP formulation, two are naturally occurring (cholesterol and DSPC) and will therefore be metabolized and excreted like other endogenous lipids. The *in vitro* metabolic stability of the two novel lipids, ALC-0315 (amino lipid) and ALC-0159 (polyethylene glycol [PEG]-lipid), were evaluated in mouse, rat, monkey, and human liver microsomes, S9 fractions, and hepatocytes. ALC-0315 and ALC-0159 were stable (>82% remaining) over 2 h in liver microsomes and S9 fractions and over 240 min in hepatocytes in all species and test systems (Studies 01049-20008, 01049-20009, 01049-20010, 01049-20020, 01049-20021, and 01049-20022).

Further study of the metabolism of ALC-0315 and ALC-0159 *in vitro* and *in vivo* evaluating the plasma, urine, feces, and liver from the rat PK study (Section 5.2.2) determined ALC-0315 and ALC-0159 are metabolized slowly (Study PF 07302048_05Aug20_043725). ALC-0315 and ALC-0159 underwent hydrolytic metabolism of the ester and amide functionalities, respectively, and this hydrolytic metabolism was observed across the species evaluated (Figure 4 and Figure 5).

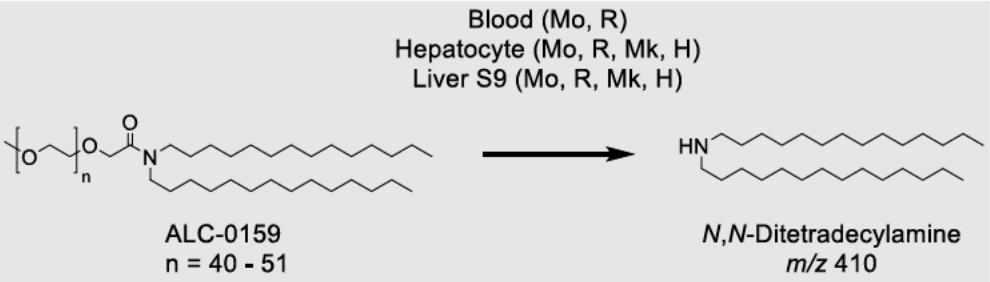



**Figure 4: Proposed biotransformation pathway of ALC-0159 in various species**

H = human; Mk = monkey; Mo = mouse; R = rat.

Metabolism of ALC-0315 occurs via two sequential ester hydrolysis reactions, first yielding the monoester metabolite (*m/z* 528) followed by the doubly deesterified metabolite (*m/z* 290). Subsequent metabolism of the doubly deesterified metabolite resulted in a glucuronide metabolite (*m/z* 466), which was only observed in urine from the rat PK study. Additionally, 6-hexyldecanoic acid (*m/z* 255), the acid product of both hydrolysis reactions of ALC-0315, was identified.

The primary route of metabolism identified for ALC-0159 involves amide bond hydrolysis yielding *N*, *N*-ditetradecylamine (*m/z* 410).

In the rat PK study (Section 5.2.2), there was no detectable excretion of ALC-0315 or ALC-0159 in urine after IV administration of LNPs containing modRNAs encoding the luciferase surrogate marker at 1 mg/kg. The percent excreted unchanged in feces was ~1% for ALC-0315 and ~50% for ALC-0159. Metabolites of ALC-0315 were detected in the urine of rats (Figure 5). No excretion studies have been conducted with BNT162b2.

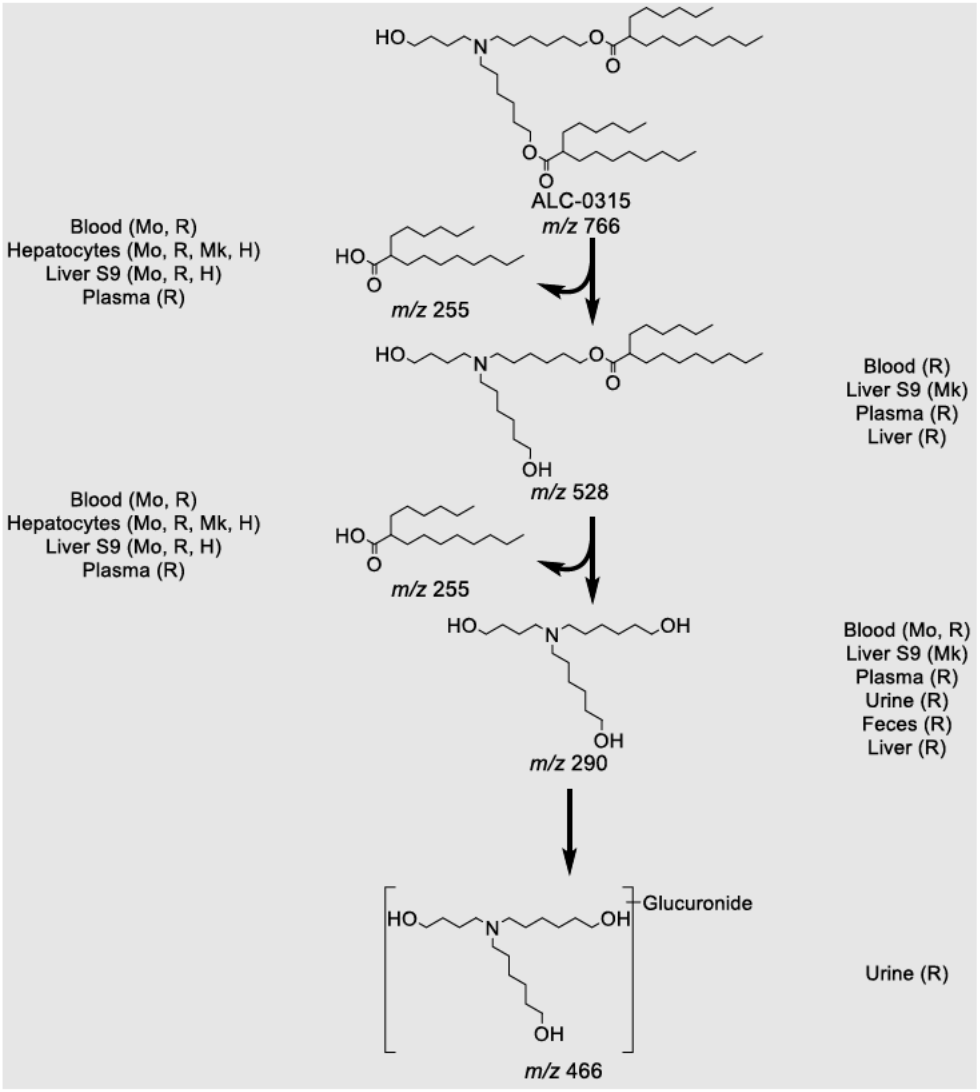



**Figure 5: Proposed biotransformation pathway of ALC-0315 in various species**

H = human; Mk = monkey; Mo = mouse; R = rat.

### *5.2.5 Pharmacokinetic drug interactions*

No pharmacokinetic drug interaction studies were performed.

### *5.2.6 Non-clinical pharmacokinetics and metabolism – Conclusions*

Distribution studies were conducted using an modRNA encoding luciferase. After IM injection *in vivo* in mice, expression of luciferase was observed at the site of injection and, to a lesser extent, in the liver. The distribution was also examined in male and female Wistar Han rats using a surrogate LNP with an identical lipid composition to BNT162b2 but with a modRNA encoding luciferase and containing trace amounts of radiolabeled [$^3$H]-CHE (radiolabeled [Cholesteryl-1,2-3H(N)]-Cholesteryl Hexadecyl Ether), a non-exchangeable, non-metabolizable lipid marker. The highest mean concentration of

LNP was found remaining in the injection site in both sexes. Total recovery (% of injected dose) of LNP outside the injection site was greatest in the liver and was much less in the spleen, adrenal glands, and ovaries.

The *in vitro* metabolism of ALC-0315 and ALC-0159 was evaluated 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. 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.

In summary, the non-clinical absorption, distribution, metabolism, excretion studies indicate that the LNP distributes to the liver. Approximately 50% of ALC-0159 is excreted unchanged in feces, while metabolism played a role in the elimination of ALC-0315.

## 5.3 Toxicology

The non-clinical toxicity assessment of BNT162 vaccines included two GLP-compliant repeat-dose toxicity studies and a DART study in Wistar Han rats. The non-clinical safety evaluation of BNT162b2 included two variants of BNT162b2: V8 and V9. BNT162b2 (V9; the candidate approved for conditional/emergency use), differs from BNT162b2 (V8) only in the presence of optimized codons to improve antigen expression, but the amino acid sequences of the encoded antigens are identical.

The potential toxicity of BNT162b2-based variant vaccines has not been tested in non-clinical safety studies. However, because of the high degree of similarity between the BNT162b2-based variant vaccine and the parent vaccine BNT162b2, the available non-clinical safety data for the BNT162 vaccine candidates, including BNT162b2, is believed to support the clinical investigation of these BNT162b2-based variant vaccine candidates.

The IM route of exposure was selected as it is the intended route of clinical administration. The selection of rats as the toxicology test species is consistent with the WHO guidance documents on non-clinical evaluation of vaccines (WHO Technical Report Series No. 927, 2005), which recommends that vaccine toxicity studies be conducted in a species in which an immune response is induced by the vaccine. Generation of an immune response to BNT162b2 has been confirmed in rats in both repeat-dose toxicity studies. The Wistar Han rat is used routinely for regulatory toxicity studies, and there is an extensive historical safety database on this strain of rat.

In both repeat-dose toxicity studies, administration of BNT162b2 by IM injection to male and female Wistar Han rats once every week for a total of 3 doses was tolerated without evidence of systemic toxicity. Expected reactions indicating an immune response to the vaccine were evident such as edema and erythema at the injection sites, transient elevation in body temperature, elevations in white blood cells (WBCs) and acute phase reactants and decreased albumin:globulin (A:G) ratios. Injection site reactions were common in all vaccine-administered animals and were greater after boost immunizations. Changes secondary to inflammation included slight and transient reductions in body weights and transient reductions in reticulocytes, platelets, and red blood cell (RBC) mass

parameters (Brooks et al. 2017; Kim et al. 2016; Kim et al. 2020). All changes in clinical pathology parameters were similar to control at the end of the recovery phase for BNT162b2 with the exception of higher red cell distribution width, higher globulins, and lower A:G ratios in animals administered BNT162b2 (V9). Macroscopic pathology and organ weight changes were also consistent with immune activation and inflammatory response and included increased size of draining iliac lymph nodes and increased size and weight of spleen. Vaccine-related microscopic findings at the end of dosing for BNT162b2 were evident in injection sites and surrounding tissues, in the draining iliac lymph nodes, bone marrow, spleen, and liver. Microscopic findings at the end of the dosing phase were partially (recovery in progress) or completely recovered in all animals at the end of the recovery phase for BNT162b2. A robust immune response was elicited to the BNT162b2 vaccine antigen.

### *5.3.1 Repeat-dose toxicology studies supporting the clinical investigation of BNT162 vaccine candidates*

#### 5.3.1.1 Repeat-dose toxicity study of BNT162a1, BNT162b1, BNT162b2 (V8), and BNT162c1 in Wistar Han rats

This repeat-dose toxicity study assessed different vaccines as a platform study. Overall, observations made were similar for all vaccines tested and results are presented for BNT162b2 (V8) representatively. The vaccine candidate BNT162b2 (V8), an LNP-formulated modRNA vaccine encoding SARS-CoV-2 P2 S, was assessed in a GLP-compliant repeat-dose toxicity study in Wistar Han rats (Study 38166). This study also included assessment of three other LNP-formulated RNA vaccines (BNT162a1, BNT162b1, BNT162c1), encoding RBD antigens. Only the study findings from the 100 µg BNT162b2 (V8) vaccine group are summarized; findings from the other vaccine candidates were generally similar.

Administration of BNT162b2 (V8) via IM injections once weekly for a total of 3 doses to male and female Wistar Han rats was tolerated without evidence of systemic toxicity. The vaccine elicited a robust antigen-specific immune response and produced non-adverse clinical pathology changes consistent with an immune response; macroscopic changes at the injection sites, spleen, and the draining lymph nodes; increased hematopoiesis in the bone marrow and spleen; and periportal hepatocyte vacuolation. The findings in this study were fully recovered or showed evidence of ongoing recovery at the end of the 3-week recovery phase, and consistent with those typically associated with the IM administration of LNP-encapsulated mRNA vaccines (Hassett et al. 2019).

Body weights were lower 24 h after each BNT162b2 (V8) vaccine administration compared with pre-dose values (down to 0.92x baseline) with evidence of weight gain (1.22x to 1.37x baseline) by the end of recovery. Body weight gain between the administrations was comparable to the buffer control group. There were no noteworthy effects on body weight at the end of the recovery phase. There were no effects on food consumption.

BNT162b2 (V8)-administered animals generally had higher body temperatures compared with buffer-injected control animals at 4 and 24 h post-dose. Group mean temperatures in rats administered the BNT162b2 (V8) vaccine were higher, but within ~1°C above the

group mean body temperature of buffer-administered animals. Rats administered BNT162b2 (V8) did not have body temperatures >40.0°C after administration.

Local reactions were observed in male and female animals dosed IM with BNT162b2 (V8). The incidence and severity of the reactions were higher after the second or third injections compared with the first injection. The majority of animals had very slight edema or rarely slight erythema after the first dose. After the second or third dose, the severity of edema and erythema increased up to moderate or rarely, severe grades. These observations resolved prior to the next injection or for recovery animals resolved during the 3-week recovery phase.

Most BNT162b2 (V8)-related changes in clinical pathology were consistent with an acute phase response and anticipated inflammation. Minor and variable alterations in other clinical pathology parameters were considered secondary effects of vaccination.

Expected immune responses to BNT162b2 (V8) were evident in hematology, such as elevations in mean neutrophil (up to 7.8x controls), eosinophil (up to 5.1x controls), basophil (1.47x controls) and LUC counts (up to 7.7x controls) and were highest on Day 17, 48 h after the last injection. The WBC counts were higher (up to 2.2x controls) in the BNT162b2 (V8) vaccinated group on Day 17. Platelets were slightly decreased on Day 17 (down to 0.66x controls). A transient reduction in reticulocyte counts (down to 0.28x controls) was only observed after the administration of the first dose on Day 4. Decreased reticulocytes were similarly observed in rats treated with the licensed LNP-siRNA pharmaceutical Onpattro™ (NDA # 210922), but have not been observed in humans treated with this biotherapeutic (Kozauer et al. 2018), suggesting this is a species-specific effect. A slight reduction in RBC mass (hemoglobin down to 0.87x controls) was observed on Day 17. Reticulocyte and RBC mass parameter decreases were likely secondary to the inflammation.

BNT162b2 (V8)-related changes in clinical chemistry included slightly higher gamma (γ)-glutamyl transpeptidase (GGT; a biomarker of biliary and not hepatocellular injury (Boone et al. 2005) on Days 4 [up to 4.6x controls] and 17 [up to 4.2x controls]) without evidence of microscopic changes in the biliary system or other hepatobiliary biomarkers. Additionally, higher GGT was not observed in the second repeat-dose toxicity study (Study 20GR142), conducted with the clinical candidate submitted for licensure. Thus, the slight and inconsistent increase in GGT in the first study was not considered biologically significant. Albumin was slightly lower on Days 4 (down to 0.87x controls) and 17 (down to 0.89x controls) and globulin slightly higher on Day 17 (up to 1.2x controls). This resulted in the A:G ratio being slightly lower on Days 4 (down to 0.84x controls) and 17 (down to 0.76x controls). The effect on albumin and globulin were related to the vaccine-mediated inflammatory response as part of the negative and positive acute phase response, respectively (Sellers et al. 2020).

The acute phase proteins alpha-1-acid glycoprotein (up to 21x controls on Day 17) and alpha-2 macroglobulin (up to 217x controls on Day 17) were elevated in both males and females in the BNT162b2 (V8)-administered group on Days 4 and 17. Fibrinogen was higher in the vaccine-administered group (up to 3.1x controls), consistent with an acute

phase response. Higher concentrations of acute phase proteins are an anticipated response to vaccination.

All changes in clinical pathology parameters and acute phase proteins were reversed at the end of the recovery phase.

Compared with the buffer control, there were no test article-related differences in the concentration of serum cytokines evaluated, in urinalysis parameters, or in ophthalmoscopic or auditory parameters.

BNT162b2 (V8)-related higher absolute and relative (to body) spleen weights (up to 1.62x controls) were evident and correlated with the macroscopic observation of increased spleen size and the increased hematopoiesis. This is likely secondary to immune responses induced by the BNT162b2 (V8) vaccine.

The most common macroscopic observation in the BNT162b2 (V8) group was a thickened injection site and/or induration noted for nearly all main study animals (16/20) at necropsy (Day 17). This finding correlated with microscopic inflammation at the injection site. Macroscopic findings at the injection site were resolved at the end of the recovery phase. Enlarged spleen and iliac lymph nodes were noted in several animals in the BNT162b2 (V8)-administered group. The effects on the lymphoid organs are consistent with immune responses to the BNT162b2 (V8).

Vaccine-related microscopic findings at the end of dosing were evident in injection sites and surrounding tissues, in the draining (iliac) lymph nodes, bone marrow, spleen, and liver.

The inflammation at the injection site was characterized by infiltrates of macrophages, granulocytes, and lymphocytes into the muscle, and variably into the dermis and subcutis. Injection site inflammation was associated with mostly mild myofiber degeneration, occasional muscle necrosis, and mostly mild fibrosis. Injection site findings were consistent with an immune/inflammatory response to an intramuscular vaccine administration.

In the draining (iliac) lymph node, increased cellularity of the follicular germinal centers and increased plasma cells (plasmacytosis) were variably present for all BNT162b2 (V8)-dosed animals. In addition, minimal to mild increases in the cellularity of bone marrow and hematopoiesis in the spleen likely related to increased granulopoiesis and correlated with increased circulating neutrophils (which correlated with increased spleen size and weight) were present in BNT162b2 (V8)-dosed animals.

Vacuolation of hepatocytes (minimal to mild) in the portal regions of the liver were present for all BNT162b2 (V8)-dosed animals. The liver findings were not associated with changes in markers of hepatocyte injury (e.g., alanine-aminotransferase or aspartate-aminotransferase). While GGT was elevated in vaccine-administered animals, it was not considered to be associated with the vacuolation of hepatocytes (Ennulat et al. 2010). The microscopic observation of liver vacuolation is believed to be associated with hepatocyte uptake of the LNP lipids (Sedic et al. 2018).

Microscopic findings at the end of the dosing phase were partially or completely resolved in all animals at the end of the recovery phase. Inflammation at the injection site and

surrounding tissues was less severe (minimal to mild) in animals administered BNT162b2 (V8) at the end of the 3-week recovery phase, indicating partial recovery. In the iliac lymph node, plasmacytosis was less severe, and macrophage infiltrates were present at the end of the 3-week recovery phase and reflect resolution of the inflammation noted at the end of the dosing phase.

All other observations in the bone marrow, spleen and liver were fully resolved at the end of the 3-week recovery phase.

The immune response to the vaccine antigen was evaluated by S1-binding IgG and RBD-binding IgG ELISAs, and a SARS-CoV-2 S pseudovirus-based neutralization assay (pVNT) assay at Days 17 and 38. The data demonstrate that BNT162b2 (V8) elicited a SARS-CoV-2 S-specific antibody response with high neutralizing activity.

In conclusion, administration of BNT162b2 (V8) by IM injection to male and female Wistar Han rats once every week for three doses, was tolerated at 100 µg RNA without evidence of systemic toxicity.

#### 5.3.1.2 17-day IM toxicity study of BNT162b2 (V9) and BNT162b3 in Wistar Han rats with a 3-week recovery

In this study, two vaccine candidates, BNT162b2 (V9) and BNT162b3 were tested. Here, the findings for BNT162b2 (V9) are summarized; the findings for BNT162b3 were generally similar. BNT162b2 (V9) was assessed in a GLP-compliant repeat-dose toxicity study in male and female Wistar Han rats (Study 20GR142). This study also included assessment of another BNT162b platform vaccine candidate (BNT162b3). BNT162b2 (V9) was administered IM at CCI once weekly for three doses (Days 1, 8, and 15) followed by a 3-week recovery phase.

Administration of BNT162b2 (V9) once weekly for three doses was tolerated without evidence of systemic toxicity. The vaccine elicited a robust antigen-specific immune response and produced non-adverse clinical pathology changes consistent with an immune response; macroscopic changes at the injection sites, spleen, and the draining lymph nodes; increased hematopoiesis in the bone marrow and spleen; and liver vacuolation. The findings in this study were either fully recovered or showed evidence of ongoing recovery at the end of the 3-week recovery phase, and were consistent with those typically associated with the IM administration of LNP-encapsulated mRNA vaccines (Hassett et al. 2019).

All animals administered BNT162b2 (V9) survived to scheduled necropsy. There were no test article-related clinical signs or body weight changes noted. Test article-related reduced mean food consumption was noted on Days 4 and 11 (down to 0.83x controls). Test article-related higher mean body temperature compared with control animals was noted on Day 1 (up to 0.54°C increase), Day 8 (up to 0.98°C increase), and Day 15 (up to 1.03°C increase) post-dose.

BNT162b2 (V9)-related injection site edema and erythema were noted after each dose administration on Days 1 (up to slight edema and very slight erythema), 8 (up to moderate edema and very slight erythema) and 15 (up to moderate edema and very slight erythema). The incidence and severity of the reactions were higher after the second or

third injections compared with the first injection. Test article-related erythema and edema fully resolved prior to dose administration on Days 8 and 15. Injection site erythema and edema were fully resolved at the end of the recovery phase.

All clinical pathology changes (type and magnitude) were generally consistent with expected immune responses to the vaccine or secondary to inflammation.

There were higher WBCs (up to 2.95x controls), primarily involving neutrophils (up to 6.60x controls), monocytes (up to 3.30x controls), and LUC (up to 13.2x controls) and slightly higher eosinophils and basophils on Days 4 and 17. The WBCs were higher on Day 17 as compared with Day 4. There were transiently lower reticulocytes on Day 4 (down to 0.27x controls) in both sexes and higher reticulocytes on Day 17 (up to 1.31x controls) in females only. Lower RBC mass parameters (down to 0.90x controls) were present on Days 4 and 17. All test article-related hematology and coagulation changes noted in the dosing phase were fully reversed after a 3-week recovery phase, with the exception of higher red cell distribution width (up to 1.21x controls) in animals administered BNT162b2(V9).

There were lower A:G ratios (down to 0.82x) on Days 4 and 17. Higher fibrinogen levels were observed on Day 17 (up to 2.49x) when compared with control animals, consistent with an acute phase response. The acute phase proteins alpha-1-acid glycoprotein (up to 39x on Day 17) and alpha-2 macroglobulin (up to 71x on Day 17) were elevated in both males and females in the BNT162b2 (V9)-administered group on Days 4 and 17 with higher concentrations generally observed in males. All other changes in clinical pathology parameters were considered incidental. All test article-related clinical chemistry changes noted in the dosing phase were fully reversed after a 3-week recovery phase, except higher globulins (up to 1.08x controls) in animals administered BNT162b2(V9) and lower A:G ratio (down to 0.91x controls) in females administered BNT162b2(V9), reflecting vaccine-related immune responses.

Test article-related higher group mean absolute and relative spleen weights (compared to body weight) were noted in males that had received BNT162b2 (V9) (up to 1.42x) and females (up to 1.59x) relative to control group means. There were no other test article-related changes in organ weights. At the end of the recovery phase, spleen weights were within normal limits.

Test article-related macroscopic findings included the observation of enlarged draining and inguinal lymph nodes (2/20 animals) and pale/dark (5/20 animals) or firm (6/20 animals) injection sites in animals administered BNT162b2 (V9). These changes fully recovered, except for partial recovery of enlarged draining lymph nodes, suggesting recovery in progress.

Test article-related microscopic pathology findings were observed at the injection site and in the draining and inguinal lymph nodes, spleen, bone marrow, and liver for both vaccine candidates, BNT162b2 and BNT162b3. All microscopic findings were non-adverse, as there was no evidence of systemic toxicity or clinical signs of illness or lameness.

At the end of the dosing phase, test article-related mixed cell inflammation (mild to moderate) and edema (mild to moderate) at the injection site were consistent with findings

typically associated with the IM administration of LNP-encapsulated RNA vaccines (Hassett et al. 2019). These findings correlated with macroscopic observations of abnormal color (dark/pale) and consistency (firm). At the end of the 3-week recovery phase, there was full recovery for injection site edema and partial recovery for injection site inflammation, suggesting recovery in progress.

At the end of the dosing phase, test article-related findings in the draining (iliac) and inguinal lymph nodes (up to moderately increased cellularity of plasma cells and germinal centers), spleen (minimally increased cellularity of hematopoietic cells and germinal centers), and the bone marrow (minimal increased cellularity of hematopoietic cells) were present. These changes are secondary to immune activation and/or inflammation at the injection site. The presence of plasma cells (interpreted as plasmablasts) in the draining (iliac) and inguinal lymph nodes is consistent with a robust immunological response to the vaccines. These observations correlated with macroscopic observations of abnormal size (enlarged) in the lymph nodes and spleen and increased spleen weights. At the end of the 3-week recovery phase, full recovery of increased cellularity of hematopoietic cells in the spleen and bone marrow, with partial recovery (recovery in progress) of increased cellularity of plasma cells and germinal centers in the draining and inguinal lymph nodes, and increased cellularity of the germinal centers in the spleen.

At the end of the dosing phase, the test article-related microscopic finding of minimal peri-portal hepatocyte vacuolation was not associated with hepatocellular damage or alterations in liver function tests. The liver vacuolation is believed to be associated with hepatocyte uptake of the LNP lipids (Section 5.2.3; Sedic et al. 2018). At the end of 3-week recovery phase, this finding was completely recovered.

Administration of three once weekly doses of BNT162b2 (V9) elicited SARS-CoV-2 neutralizing antibody responses in males and females at the end of the dosing (Day 17) and recovery phases (Day 21) of the study. SARS-CoV-2 neutralizing antibody responses were not observed in animals prior to vaccine administration or in saline-administered control animals.

In conclusion, administration of BNT162b2 (V9) via IM injections weekly for three administrations to male and female Wistar Han rats was tolerated without evidence of systemic toxicity. Dosing of BNT162b2 (V9) produced changes consistent with an inflammatory response and immune activation. The findings in this study are consistent with those typically associated with the IM administration of LNP-encapsulated RNA vaccines.

### *5.3.2 Genotoxicity*

The components of all BNT162 vaccines (lipids and RNA) are not expected to have genotoxic potential. No impurity or component of the delivery system warrants genotoxicity testing. Therefore, in accordance with the WHO guideline (WHO Technical Report Series No. 927, 2005), no genotoxicity studies were performed.

### *5.3.3 Carcinogenicity*

RNA itself, and the lipids used in the BNT162 vaccines have no carcinogenic or tumorigenic potential. Furthermore, according to ICH S1A (1995) no carcinogenicity studies are required for therapeutics that are not continuously administered. Therefore, no carcinogenicity studies were performed.

### *5.3.4 Reproductive and developmental toxicity*

#### 5.3.4.1 A combined fertility and developmental study (including teratogenicity and postnatal investigations) of BNT162b1, BNT162b2 and BNT162b3 by IM administration in the Wistar Han rat (Study 20256434)

This study assessed repeated administration of BNT162b1, BNT162b2 (V9) and BNT162b3. In general, results observed were comparable for all three candidates and results for BNT162b2 (V9) are presented representatively. BNT162b2 (V9) was administered by IM injection at the human clinical dose (30 µg RNA/dosing day) to 44 female Wistar Han rats (F0) 21 and 14 d prior to mating with untreated males and on GD 9 and GD 20, for a total of four dosing days. A separate control group of 44 F0 females received saline by the same route and regimen. This study also included assessment of two other BNT162b vaccine candidates (BNT162b1 and BNT162b3). Here, the study findings for BNT162b2 (V9) are summarized; the findings for BNT162b1 and BNT162b3 were generally similar.

Following completion of a mating phase with untreated males, 22 rats/group underwent cesarean-section on GD 21 and were submitted to routine embryo-fetal development evaluations. The remaining 22 rats/group were allowed to litter, and behavior of the mothers and development of the offspring was observed until postnatal Day 21.

There were no BNT162b2-related deaths during the study. IM administration of BNT162b2 before and during gestation to female Wistar rats resulted in non-adverse clinical signs and macroscopic findings localized to the injection site as well as transient, non-adverse body weight and food consumption effects after each dose administration. These maternal findings are all consistent with administration of a vaccine and an inflammatory/immune response and with those observed in the repeat-dose toxicity studies with BNT162b2.

There were no BNT162b2-related effects on any mating or fertility parameters. There were no BNT162b2-related effects on any ovarian, uterine, or litter parameters, including embryo-fetal survival, growth, or external, visceral, or skeletal malformations, anomalies, or variations. There were no effects of BNT162b2 administration on postnatal offspring (F1) development, including postnatal growth, physical development (pinna unfolding and eye opening), neurodevelopment (pre-weaning auditory and visual function tests), macroscopic observations, and survival.

All of F0 females administered BNT162b2 developed a SARS-CoV-2 neutralizing antibody response and these responses were detectable in all fetuses and pups from the cesarean and littering groups, respectively. The animals in the saline control group did not exhibit an immune response to BNT162b2.

In conclusion, administration of BNT162b2 to female rats twice before the start of mating and twice during gestation at the human clinical dose was associated with non-adverse effects (body weight, food consumption, and effects localized to the injection site) after each dose administration. However, there were no effects of BNT162b2 administration on mating performance, fertility, or any ovarian or uterine parameters in the F0 female rats nor on embryo-fetal or postnatal survival, growth, or development in the F1 offspring. An immune response was confirmed in F0 female rats following administration and these responses were also detectable in the F1 offspring (fetuses and pups).

### *5.3.5 Local tolerance*

Special attention was paid to the local tolerance of the vaccines in the repeat-dose toxicity studies (Section 5.3.1). The injection sites were assessed for erythema/eschar/edema formation and induration/hardening following palpation.

The majority of immunized animals developed very slight (grade 1) to slight (grade 2) edema at the injection site 24 h after first dose. Edema was more pronounced after the second and third injection, where moderate to severe edema formation was observed in some animals.

For a few animals, slight or well-defined erythema was also observed in test-item administered animals after the first, second, and/or third injection. In addition, after the second or third injection, transient observations of severe erythema were seen for all vaccines, except for 30 µg BNT162b1, starting at 96 h after administration. At the end of the recovery phase, any local skin reactions had subsided in all but one animal (immunized with 30 µg BNT162c1).

In summary, almost all animals showed local reactions after the first immunization with all vaccines, but mostly low grade edema and more rarely erythema. The occurrence of high-grade local reactions after boost immunizations was attributed to the short immunization interval. The induction of a local pro-inflammatory environment within the muscle, which promotes potent immune responses, can be considered a mode of action of BNT162 vaccines.

### *5.3.6 Immunotoxicology*

Stand-alone immunotoxicity studies with BNT162b2 have not been conducted. However, immunotoxicological endpoints were collected as part of the repeat-dose toxicity studies; there were no adverse effects observed and no significant effects on measured cytokines. (Section 5.3.1).

### *5.3.7 Toxicology – Conclusions*

Administration of BNT162b2 by IM injection to male and female Wistar Han rats once a week for 3 weeks was tolerated without evidence of systemic toxicity in GLP-compliant repeat-dose toxicity studies. Expected inflammatory responses to the vaccine were evident such as edema and erythema at the injection sites, transient elevation in body temperature, elevations in WBCs and acute phase reactants and lower A:G ratios. A transient elevation in GGT was noted in animals vaccinated with BNT162b2 (V8) in

Study 38166 without evidence of microscopic changes in the biliary system or other hepatobiliary biomarkers but was not recapitulated in Study 20GR142. Injection site reactions were common in all vaccine-administered animals and were greater after boost immunizations. Changes secondary to inflammation included slight and transient reduction in body weights and transient reduction in reticulocytes, platelets and RBC mass parameters. All changes in clinical pathology parameters and acute phase proteins were reversed at the end of the recovery phase for BNT162b2 with the exception of higher red cell distribution width, higher globulins, and lower A:G ratios in animals administered BNT162b2 (V9). Macroscopic pathology and organ weight changes were also consistent with immune activation and inflammatory response and included increased size of draining iliac lymph nodes and increased size and weight of spleen. Vaccine-related microscopic findings at the end of the dosing phase consisted of edema and inflammation in injection sites and surrounding tissues, increased cellularity in the draining iliac lymph nodes, bone marrow, and spleen and hepatocyte vacuolation in the liver. Mostly minimal periportal vacuolation of hepatocytes was not associated with any microscopic evidence of hepatic injury or alterations in liver function tests and is interpreted to reflect hepatocyte uptake of the LNP lipids (Sedic et al. 2018). Microscopic findings at the end of the dosing phase were partially or completely recovered in all animals at the end of the recovery phase for BNT162b2. A robust immune response was elicited to the BNT162b2 antigen.

Administration of BNT162b2 to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg RNA/dosing day) was associated with non-adverse effects (body weight, food consumption and effects localized to the injection site) after each dose administration. However, there were no effects of BNT162b2 administration on mating performance, fertility, or any ovarian or uterine parameters in the F0 female rats nor on embryo-fetal or postnatal survival, growth, or development in the F1 offspring. An immune response was confirmed in F0 female rats following administration of each vaccine candidate and these responses were also detectable in the F1 offspring (fetuses and pups).

The available non-clinical safety data for the BNT162 vaccine candidates, including BNT162b2, support the clinical investigation of BNT162 vaccine candidates including BNT162b2-based variant vaccines such as BNT162b2 (B.1.351).

# 6 EFFECTS IN HUMANS

The reference safety information for the BNT162 candidate vaccines is provided in Section 7.8.2.

## 6.1 Ongoing and planned clinical studies

For an overview of the ongoing and currently planned clinical studies, see Table 31.

### *6.1.1 BNT162-01 for BNT162b1 and BNT162b2 in healthy younger and older adults – Results (status 16 SEP 2021)*

This is a multi-site, Phase 1/2, dose escalation and expansion study investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA-based vaccines against COVID-19 using different dosing regimens in healthy and immunocompromised male and female participants.

The participants in this study are either younger adults (18 to 55 yrs of age), older adults (56 to 85 yrs of age), or immunocompromised (IC) participants 18 to 85 yrs of age. IC participants are individuals with post-transplantation and HIV+ backgrounds. Participants with a post-transplantation background are individuals who received solid organ transplant or peripheral blood stem cell transplantation at least 6 months prior to enrollment. HIV+ participants are individuals with HIV infection with a $CD4^+$ T-cell count of ≥200 x $10^6$/L who are without symptoms of advanced AIDS.

This study is ongoing clinically. The treatment phase has been completed for all dose escalation dose groups and the participants are now in the follow-up phase. Four expansion dose groups with BNT162b2 administration are ongoing. Dose Group 11 is testing an alternative posology cohort with a reduced Dose 1 (3 µg) and then a standard Dose 2 (30 µg) given ~21 d apart in healthy adults. The other dose groups use two 30 µg BNT162b2 doses given ~21 d apart. Dose Group 12 is investigating the adaptive immune response (including safety and long term immune response) in healthy adults. Dose Group 13 is investigating the safety and long term immune responses in immunocompromised adults. Dose Group 14 is investigating B cell immune responses induced by BNT162b2 in healthy adults.

This section presents BNT162b1 and BNT162b2 data from the interim clinical study report (CSR) dated 16 SEP 2021. Due to prioritization of BNT162b1 and BNT162b2 reporting, only preliminary and unaudited reactogenicity and tolerability data are available for BNT162a1 and BNT162c2. Data are available for BNT162b2 dose escalation dose groups in healthy participants and for the BNT162b2 Dose Group 13 with IC participants.

#### 6.1.1.1 Immunogenicity and cell-mediated responses in study BNT162-01 (status 16 SEP 2021)

The immunogenicity and cell-mediated response data for BNT162b2 and BNT162b1 were generally similar, therefore only BNT162b2 data are summarized here. The available data from the BNT162-01 study can be summarized as follows:

***Immune responses in healthy younger and older participants***

- Participants dosed with BNT162b2 showed strong IMP-induced SARS-CoV-2 neutralizing and S1- and RBD-binding antibody responses, which were dose-dependent, and which increased further after Dose 2, and persisted until ~28 d post-dose, and plateaued at a lower level (but above the pre-Dose 2 level). The decline was generally faster in older than younger participants.
- The observed kinetics of the BNT162b2 induced neutralizing antibody response is typical of antigen-activated B cells going through over proliferation, followed by rebound contraction with a gradual decline in numbers.
- Two doses of BNT162b2 induced strong SARS-CoV-2 S-specific $CD4^+$ and $CD8^+$ T-cell responses in healthy participants. There were no notable age-related differences and no clear dose dependency. In both age groups, the responses were directed against different epitopes of the SARS-CoV-2 S protein, indicating the induction of multi-epitopic responses.
- The induced responses decreased by 63 d after Dose 2, but remained detectable until 162 d after Dose 2 in almost all younger and older participants dosed with at least 10 µg BNT162b2.
- Two doses of BNT162b2 induced comparable poly-functional and pro-inflammatory $CD4^+$/$CD8^+$ T-cell responses in almost all younger and older participants. A favorable Th1 cytokine profile was observed, with T cells secreting IFN$\gamma$ and IL-2, but no IL-4 after vaccination.
- In most younger and older participants, the initial strong S-specific IFN$\gamma^+$ and IL-$2^+$ $CD8^+$ and Th1 $CD4^+$ T cell responses contracted by 21 d post-Dose 2 and plateaued at a lower level by 63 d after Dose 2. These responses remained detectable until the last available assessment point, i.e., until 162 d after Dose 2.

***Immune responses in IC participants (HIV+ and post-transplant participants)***

- The kinetics to peak neutralizing and binding antibody responses (based on SARS-CoV-2 neutralizing and S1- and RBD-binding antibody data) were similar between HIV+ and age comparable, HIV-uninfected participants dosed twice with 30 µg BNT162b2, but the magnitudes of the responses were lower. In contrast, the neutralizing and binding antibody responses were non-existent to weak and second-dose responses were delayed in post-transplant participants, and for those who seroconverted, the magnitude of response was even weaker than observed in the HIV+ participants.
- Two doses of BNT162b2 at 30 µg induced grossly comparable SARS-CoV-2 S protein-specific $CD4^+$ T-cell responses in frequency and magnitude in HIV+ compared to HIV- uninfected participants, but the responses were less frequent and weaker in post-transplant participants.
- As in healthy participants, the initial strong S-specific IFN$\gamma^+$ and IL-$2^+$ from $CD8^+$ and Th1 $CD4^+$ T cell responses contracted, but remained detectable at 28 d post-Dose 2 for HIV+ participants (the last time point assessed to date).

- In post-transplant participants, two doses of BNT162b2 induced less frequent and weaker $CD4^+$ and $CD8^+$ T cell responses than in age comparable healthy participants.

*6.1.1.1.1 Immunogenicity – functional antibody responses*

Only the study findings for BNT162b2 are summarized here because the results for BNT162b1 were generally similar.

***Healthy younger and older participants – BNT162b2***

Neutralizing antibody data from VisMederi Srl (Italy) is summarized here. Previously data from Pfizer was reported. Comparability of the data from the two sources has been confirmed. As of 28 APR 2021, SARS-CoV-2 virus neutralizing titers and neutralizing antibody data are available for younger participants, older participants, and IC participants dosed with BNT162b2.

Functional 50% SARS-CoV-2 neutralizing antibody titers ($VN_{50}$) for younger participants dosed with 1, 3, 10, 20, or 30 µg BNT162b2, and older participants dosed with 10, 20, or 30 µg BNT162b2 are shown in Figure 6.

For healthy younger and older participants dosed with BNT162b2, virus neutralizing GMTs (against a SARS-CoV-2 strain with the wild-type [Wuhan-Hu-1] S sequence) were detected by 21 d after Dose 1 and showed dose-dependent second-dose responses by 7 d after Dose 2. Across all dose ranging cohorts, peak titers were seen at Day 29 and Day 50 (7 d and 28 d after Dose 2).

At Day 50 (28 d after Dose 2), neutralizing GMTs were higher for the younger compared to the older participant dose groups 10, and 20 µg, whereas for the 30 µg dose level, neutralizing GMTs were higher for the older participant dose group (see Table 8).

For the younger participant dose groups, neutralizing GMTs slightly decreased by Day 85 (63 d after Dose 2). A more rapid decrease in titers was observed for the older participant dose groups. By Day 184 (162 d after Dose 2), neutralizing GMTs for the 30 µg dose groups decreased further, but were still higher than before Dose 2.

The geometric mean fold increase (GMFI) from baseline in $VN_{50}$ is shown in Figure 7.

Independent of age, all younger and older participants dosed with two doses of 30 µg BNT162b2 seroconverted by Day 29 (7 d after Dose 2) and remained at least 90.9% seropositive until Day 184 (162 d after Dose 2). The frequency of participants with seroconversion is displayed in Figure 8.

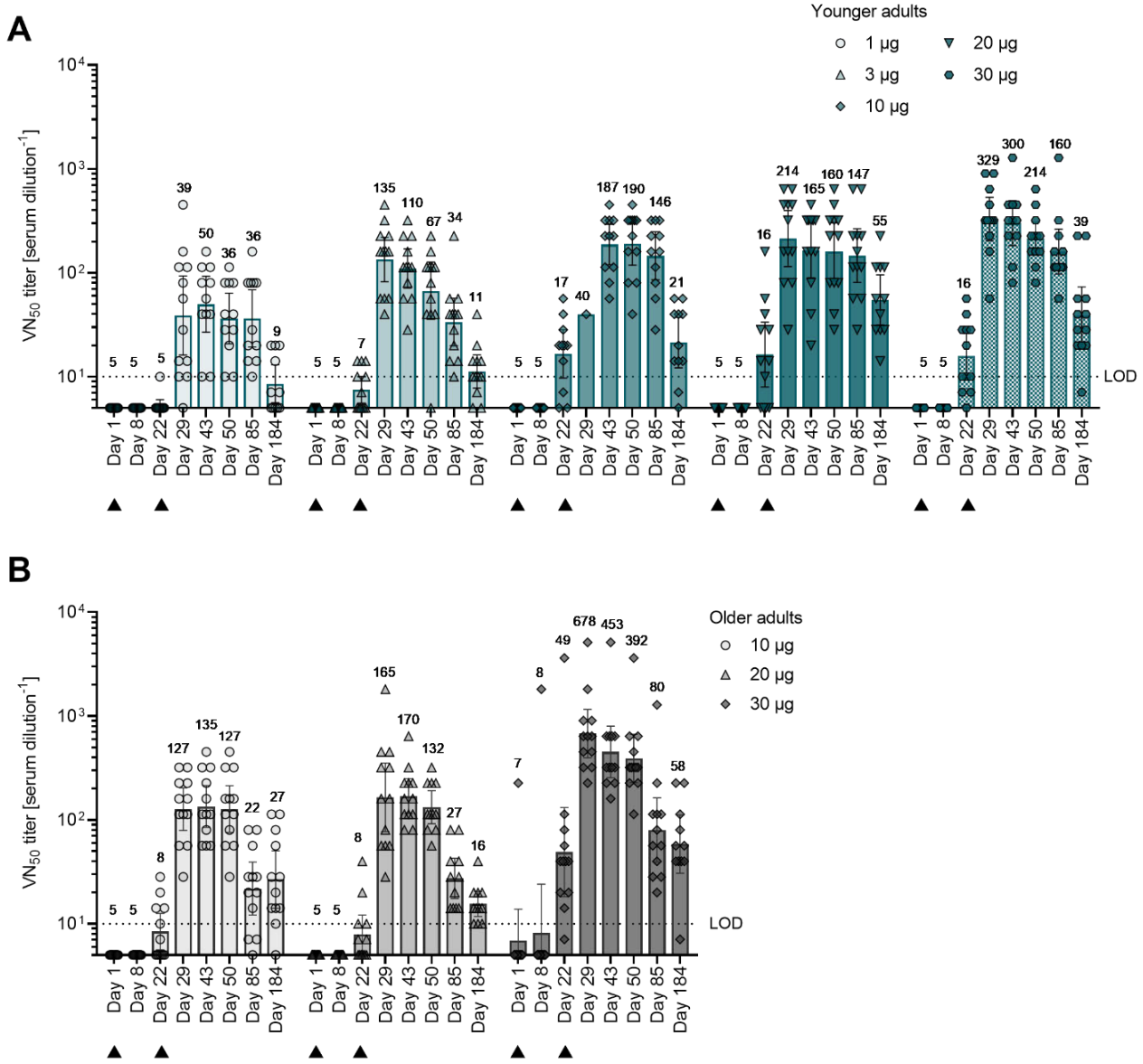



**Figure 6: BNT162b2 – Functional 50% SARS-CoV-2 neutralizing antibody titers ($VN_{50}$) – IMM**

This figure is based on the definitive functional neutralizing antibody analyses performed by VisMederi Srl (Italy). $VN_{50}$ geometric mean titers with 95% confidence intervals are shown for (**A**) younger adult (aged 18 to 55 years) dose groups 1, 3, 10, 20, and 30 µg BNT162b2, and (**B**) older adult (aged 56 to 85 years) dose groups 10, 20, and 30 µg BNT162b2. Values smaller than the LOD are plotted as 0.5*LOD. Arrowheads indicate pre-Dose 1 baseline (Day 1) and Dose 2 (Day 22). The dotted horizontal line shows the LOD.

IMM = Immunogenicity Set; LOD = limit of detection; $VN_{50}$ = 50% SARS-CoV-2 neutralizing antibody titers.

Source: Report R-21-0347.

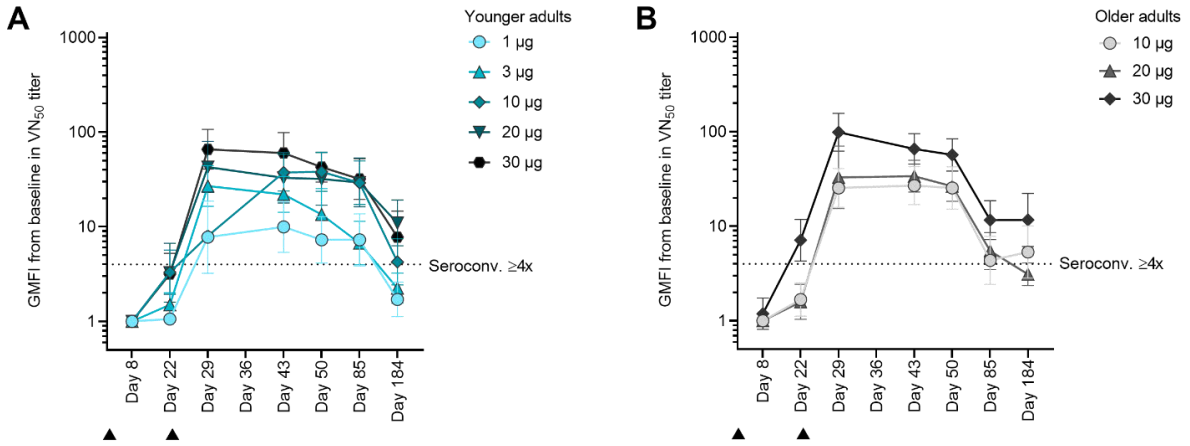



**Figure 7: BNT162b2 – Fold increase from baseline in functional 50% SARS-CoV-2 neutralizing antibody titers ($VN_{50}$) – IMM**

This figure is based on the definitive functional neutralizing antibody analyses performed by VisMederi Srl (Italy). GMFI from baseline in $VN_{50}$ titers with 95% confidence intervals are shown for (**A**) younger participants (aged 18 to 55 years) dosed with 1, 3, 10, 20, and 30 µg BNT162b2, and (**B**) older participants (aged 56 to 85 years) dosed with 10, 20, and 30 µg BNT162b2. Arrowheads indicate pre-Dose 1 baseline (Day 1) and Dose 2 (Day 22). The dotted horizontal line represents the threshold for seroconversion (fold increase ≥4).

Abbreviations: IMM = Immunogenicity Set; GMFI = Geometric means fold increase; $VN_{50}$ = 50% SARS-CoV-2 neutralizing antibody titers.

Source: Report R-21-0347.

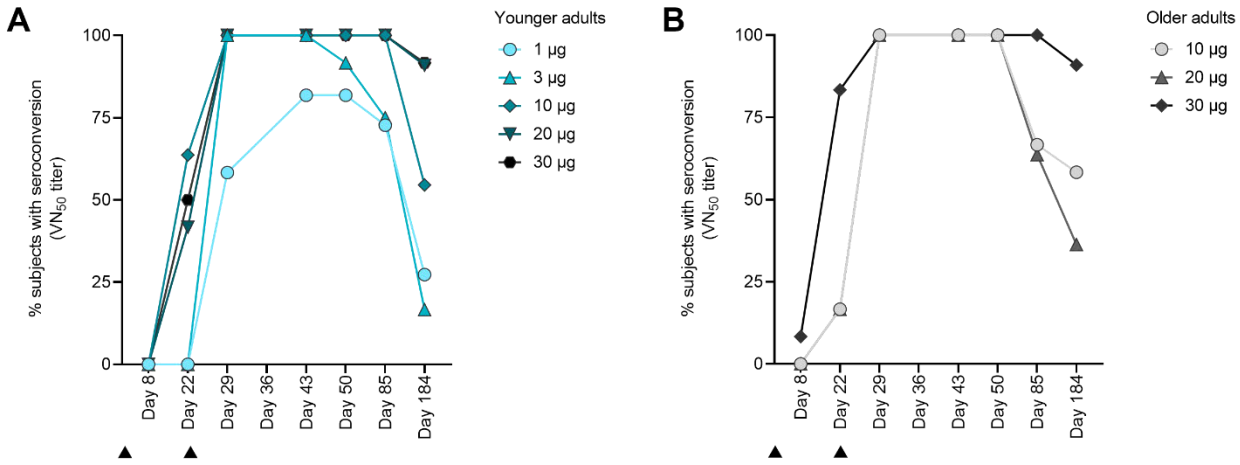



**Figure 8: BNT162b2 – Frequency of participants with SARS-CoV-2 GMT seroconversion – IMM**

This figure is based on the definitive functional neutralizing antibody analyses performed by VisMederi Srl (Italy). Seroconversion with regard to 50% SARSCoV2-neutralizing antibody titers ($VN_{50}$) is shown for (**A**) younger participants (aged 18 to 55 years) dosed with 1 µg, 3 µg, 10 µg, 20 µg, and 30 µg BNT162b2, and (**B**) older participants (aged 56 to 85 years) dosed with 10 µg, 20 µg, and 30 µg BNT162b2. Seroconversion is defined as a minimum of a 4-fold increase of functional antibody titers compared to baseline. Arrowheads indicate pre-Dose 1 baseline (Day 1) and Dose 2 (Day 22).

Abbreviations: GMT = geometric mean titer; IMM = Immunogenicity Set.

Source: Report R-21-0347.

### *BNT162b2 in IC participants (Dose Group 13)*

Functional neutralizing antibody analysis data from VisMederi Srl (Italy) is summarized here.

BNT162b2 (30 µg) induced virus neutralizing GMTs in HIV+ participants by 21 d after Dose 1 with a second-dose response by 7 d after Dose 2. Peak neutralizing GMTs were ≤0.63-fold that seen for the healthy younger and older participants dosed with 30 µg BNT162b2. Virus neutralizing GMTs decreased slightly by 28 d after Dose 2 (Day 50), but remained 27-fold above baseline (see Table 8).

**Table 8: Functional antibody responses at 28 d after Dose 2 (Day 50) in participants dosed twice with 30 µg BNT162b2**

| | | Younger participants aged 18 to 55 yrs (N=12) | Older participants aged 56 to 85 yrs (N=12) | HIV+ participants (N=15) | Post-transplant participants (N=15) |
|---|---|---|---|---|---|
| | n | 12 | 12 | 15 | 15 |
| Day 50 | GMT (95% CI) | 213.6 (148.8-306.6) | 391.7 (229.4-668.8) | 136.1 (76.2-243.0) | 11.0 (5.1-23.7) |
| | GMFR (95% CI) | 42.7 (29.8-61.3) | 57.0 (38.6-84.3) | 27.2 (15.2-48.6) | 2.2 (1.0-4.7) |

Geometric mean fold rise from baseline (GMFR) and geometric mean titer (GMT) with associated 95% confidence intervals (CI) are shown.
Abbreviations: N = number of participants in the analysis set; n = number of participants with data available; yrs = years.
Source: BNT162-01 CSR v5.0.

All HIV+ participants dosed twice with 30 µg BNT162b2 seroconverted by 7 d after Dose 2 and remained seropositive until 28 d after Dose 2 (Day 50; the last time point assessed to date). BNT162b2 induced only weak antibody responses in post-transplant participants. Except for in one participant, virus neutralizing GMTs were not detected at 21 d after Dose 1. At 7 d after Dose 2 neutralizing GMTs were detected for 7 of 15 post-transplant participants, but these GMTs decreased again by 28 d after Dose 2 (Day 50) and were only 2-fold above baseline (see Table 8).

The GMFI from baseline in functional 50% SARS-CoV-2 neutralizing antibody titers ($VN_{50}$) data for IC participants dosed with two doses of 30 µg BNT162b2 is shown in Figure 9.

Only 4 of 15 post-transplant participants dosed twice with 30 µg BNT162b2 seroconverted by 7 d after Dose 2 and were still seropositive at 28 d after Dose 2 (Day 50; the last time point assessed to date). The frequency of participants with seroconversion is displayed in Figure 10.

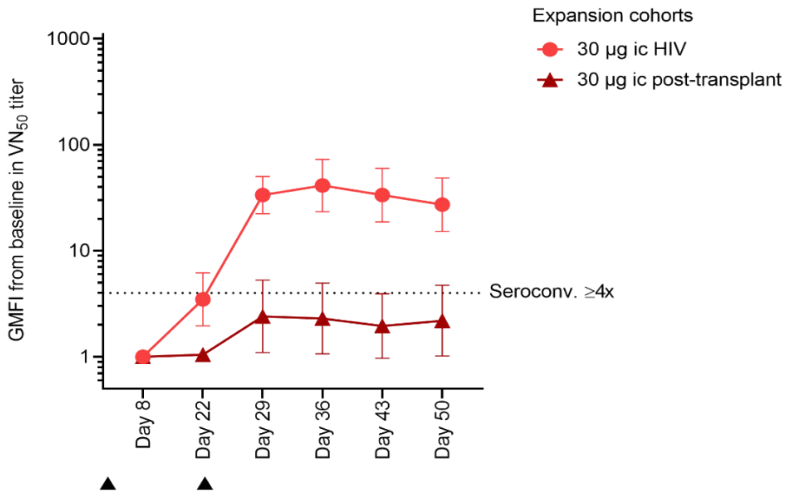



**Figure 9: BNT162b2 and IC participants – Fold increase from baseline in functional 50% SARS-CoV-2 neutralizing antibody titers ($VN_{50}$) – IMM**

This figure is based on the definitive functional neutralizing antibody analyses performed by VisMederi Srl (Italy). GMFI from baseline in $VN_{50}$ titers with 95% confidence intervals are shown for HIV+ participants and post-transplant participants dosed with 30 µg BNT162b2. Seroconversion is defined as a minimum of a 4-fold increase of functional antibody titers compared to baseline. Arrowheads indicate pre-Dose 1 baseline (Day 1) and Dose 2 (Day 22). The dotted horizontal line represents the threshold for seroconversion (fold increase ≥4).

Abbreviations: GMFI = Geometric means fold increase; ic = immunocompromised; ic HIV or HIV+ = human immunodeficiency virus-positive participants; ic post-transplant = participants with a post-transplantation backgrounds; IMM = Immunogenicity set; $VN_{50}$ = 50% SARS-CoV-2 neutralizing ant body titers.

Source: Report R-21-0347.

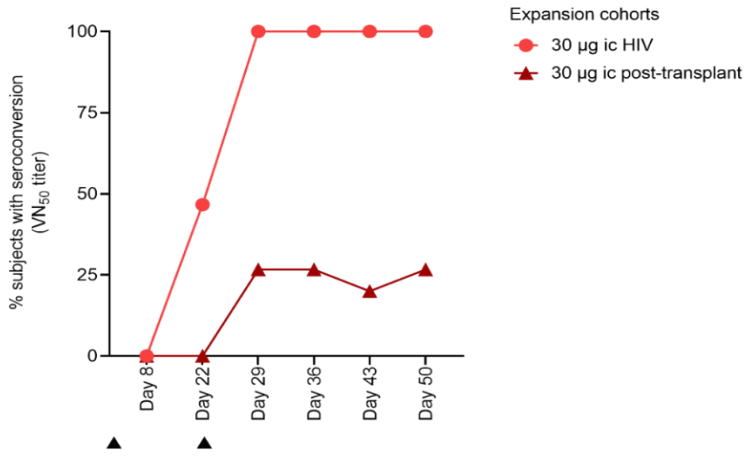



**Figure 10: BNT162b2 and IC participants – Frequency of participants with SARS-CoV-2 GMT seroconversion – IMM**

This figure is based on the definitive functional neutralizing antibody analyses performed by VisMederi Srl (Italy). Seroconversion with regard to $VN_{50}$ is shown for HIV+ participants and post-transplant participants (≥6 months after solid organ or peripheral blood stem cell transplants) dosed with 30 µg BNT162b2. Seroconversion is defined as a minimum of a 4-fold increase of functional ant body titers compared to baseline. Arrowheads indicate pre-Dose 1 baseline (Day 1) and Dose 2 (Day 22).

Abbreviations: ic = immunocompromised; ic HIV or HIV+ = human immunodeficiency virus-positive participants; ic post-transplant = participants with a post-transplantation backgrounds; IMM = Immunogenicity set; $VN_{50}$ = 50% SARS-CoV-2 neutralizing ant body titers.

Source: Report R-21-0347.

#### *6.1.1.1.2 Immunogenicity - binding antibody concentrations*

Only the study findings for BNT162b2 are summarized here because the results for BNT162b1 were generally similar.

***Healthy younger and older participants – BNT162b2***

Functional neutralizing antibody analysis data from VisMederi Srl (Italy) is summarized here. Previously data from Pfizer was reported. Comparability of the data from the two sources has been confirmed.

BNT162b2-dosed healthy participants showed strong BNT162b2-induced S1-binding IgG responses at 21 d after Dose 1 and substantial dose-dependent second-dose responses at 7 d after Dose 2. At 21 d after Dose 2 (Day 43), S1-binding GMTs were higher for the younger participants than for the older participants dosed with 10 and 20 µg BNT162b2, whereas they were comparable for the 30 µg dose groups. Across all dose levels, S1-binding GMTs slightly decreased by 28 d after Dose 2 (Day 50). Thereafter, GMTs decreased substantially up to 162 d after Dose 2 (Day 184) for all dose groups independent of age.

All participants dosed twice with 30 µg BNT162b2 seroconverted by 7 d after Dose 2 and remained seropositive until 162 d after Dose 2 (Day 184).

The GMFI from baseline in SARS-CoV-2 S1-binding IgG titer data after dosing with BNT162b2 is summarized in Figure 11.

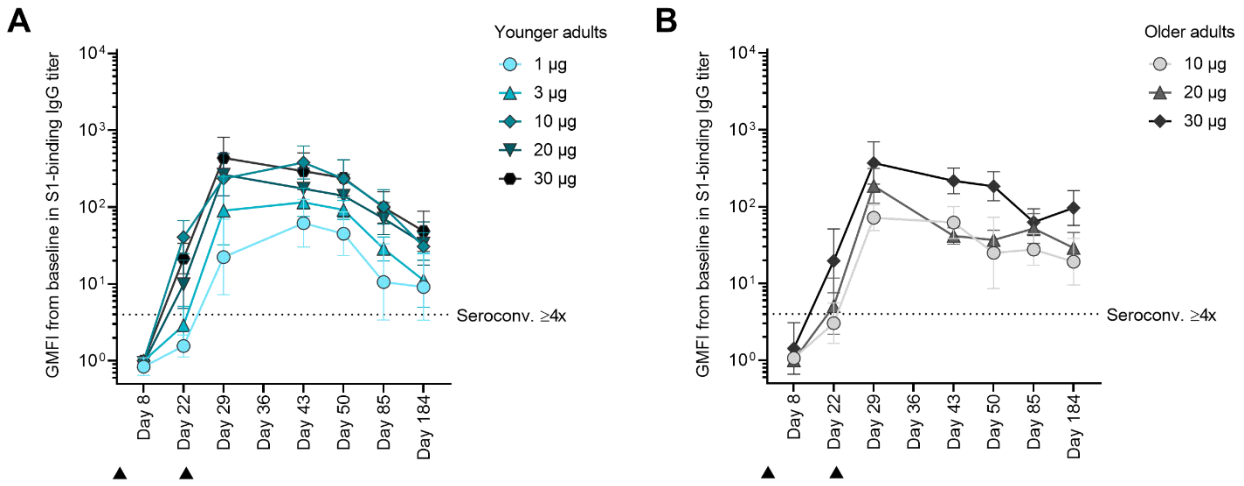



**Figure 11: BNT162b2 – Fold increase from baseline in S1-binding IgG titer – IMM**

This figure is based on the definitive binding antibody analyses performed by VisMederi Srl (Italy). GMFI from baseline in S1binding immunoglobulin G (IgG) antibody titers with 95% confidence intervals are shown for (**A**) younger participants (aged 18 to 55 years) dosed with 1, 3, 10, 20, or 30 µg BNT162b2, and (**B**) older participants (aged 56 to 85 years) dosed with 10, 20, or 30 µg BNT162b2. Arrowheads indicate pre-Dose 1 baseline (Day 1) and Dose 2 (Day 22). The dotted horizontal line represents the threshold for seroconversion (fold increase ≥4).

Abbreviations: GMFI = Geometric means fold increase; IMM = Immunogenicity set.

Source: Report R-21-0347.

The frequency of participants with seroconversion after dosing with BNT162b2 is summarized in Figure 12.

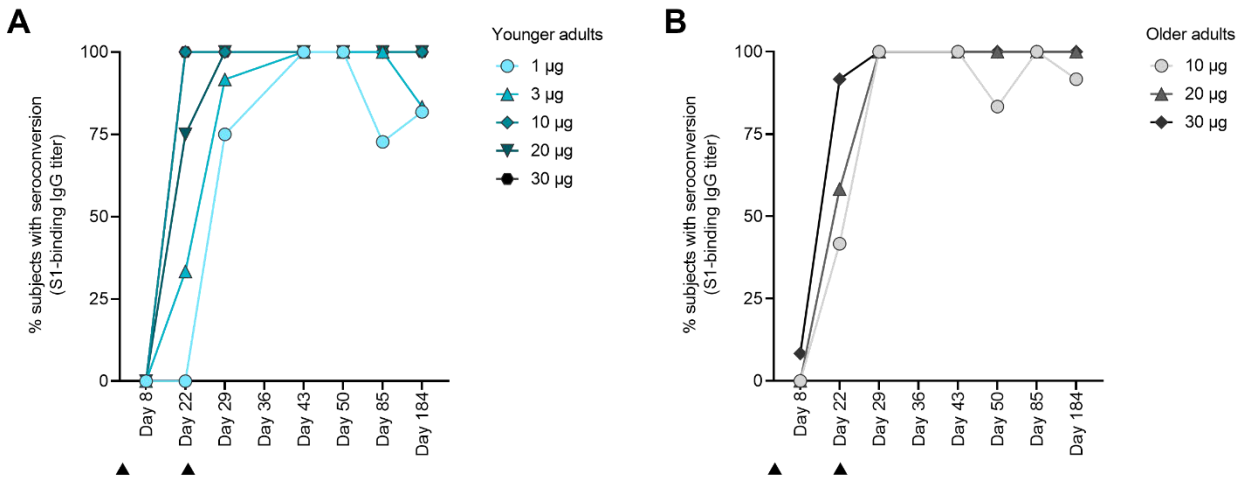



**Figure 12: BNT162b2 – Frequency of participants with S1-binding IgG GMT seroconversion – IMM**

This figure is based on the definitive binding antibody analyses performed by VisMederi Srl (Italy). Seroconversion with regard to S1-binding immunoglobulin G (IgG) GMT is shown for (**A**) younger participants (aged 18 to 55 years) dosed with 1, 3, 10, 20, or 30 µg BNT162b2, and (**B**) older participants (aged 56 to 85 years) dosed with 10, 20, or 30 µg BNT162b2. Seroconversion is defined as a minimum of a 4-fold increase of binding antibody titers compared to baseline. Arrowheads indicate pre-Dose 1 baseline (Day 1) and Dose 2 (Day 22).

Abbreviations: GMT = geometric mean titer; IMM = Immunogenicity set.

Source: Report R-21-0347.

Similar observations were made using only the RBD domain as the target antigen.

### *BNT162b2 in IC participants (Dose Group 13)*

Binding antibody analyses data from VisMederi Srl (Italy) is summarized here.

The fold increase from baseline in S1-binding IgG titers for IC participants after dosing with 30 µg BNT162b2 is displayed in Figure 13.

The frequency of IC participants with seroconversion after dosing with BNT162b2 is summarized in Figure 14.

HIV+ participants dosed with 30 µg BNT162b2 showed strong BNT162b2-induced S1-binding IgG responses at 21 d after Dose 1 and a substantial second-dose response at 7 d after Dose 2. Peak S1-binding GMTs were comparable to those observed for the healthy adult 30 µg BNT162b2 dose groups. S1-binding GMTs remained relatively stable up to 28 d after Dose 2 and were less prone to waning compared to the healthy adult 30 µg BNT162b2 dose groups. All HIV-positive participants dosed twice with 30 µg BNT162b2 seroconverted by 7 d after Dose 2 and remained seropositive until 28 d after Dose 2 (the last time point assessed to date).

Post-transplant participants dosed with 30 µg BNT162b2 showed only weak IMP-induced binding antibody responses. S1-binding IgG titers were below the lower limit of quantitation at 21 d after Dose 1 for 12 of 15 participants. A delayed but substantial second-dose

response was observed at 14 d after Dose 2. Nonetheless, peak binding GMTs were still markedly lower than those observed for healthy younger and older participants, as well as those observed for HIV+ participants. S1-binding antibody GMTs decreased only slightly by 28 d after Dose 2. Only 11 of 15 post-transplant participants dosed twice with 30 µg BNT162b2 seroconverted by 14 d after Dose 2. All 11 of 15 post-transplant participants remained seropositive until 28 d after Dose 2 (Day 50; the last time point assessed to date). Similar observations were made using only the RBD domain as the target antigen.

HIV+ participants dosed with 30 µg BNT162b2 showed strong BNT162b2-induced S1-binding IgG responses at 21 d after Dose 1 (Day 22) and a substantial second-dose response at 7 d after Dose 2 (Day 29). Peak S1-binding GMTs were comparable to those observed for the healthy adult 30 µg BNT162b2 dose groups. S1-binding GMTs remained relatively stable up to Day 50 and were less prone to waning compared to the healthy adult 30 µg BNT162b2 dose groups. Similar observations were made using only the RBD domain as the target antigen.

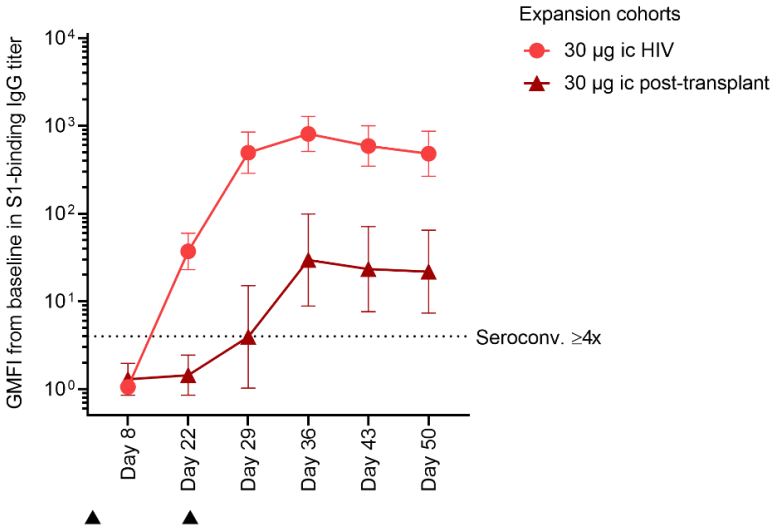



**Figure 13: BNT162b2 and IC participants – Fold increase from baseline in S1-binding IgG titer – IMM**

This figure is based on the definitive binding antibody analyses performed by VisMederi Srl (Italy). GMFI from baseline in S1-binding immunoglobulin G (IgG) antibody titers with 95% confidence intervals are shown for HIV+ participants and post-transplant participants dosed with 30 µg BNT162b2. Arrowheads indicate pre-Dose 1 baseline (Day 1) and Dose 2 (Day 22). The dotted horizontal line represents the threshold for seroconversion (fold increase ≥4).

Abbreviations: GMFI = Geometric means fold increase; ic = immunocompromised; ic HIV or HIV+ = human immunodeficiency virus-positive participants; ic post-transplant = participants with a post-transplantation backgrounds; IMM = Immunogenicity set.

Source: Report R-21-0347.

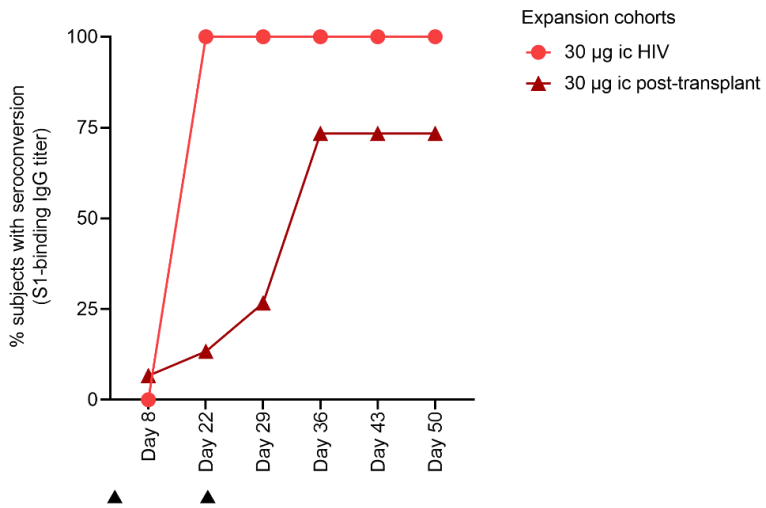



**Figure 14: BNT162b2 – Frequency of IC participants with S1-binding IgG GMT seroconversion – IMM**

This figure is based on the definitive binding antibody analyses performed by VisMederi Srl (Italy). Seroconversion with regard to S1-binding immunoglobulin G (IgG) GMT is shown for ic participants dosed with 30 µg BNT162b2. Seroconversion is defined as a minimum of a 4-fold increase of binding antibody titers compared to baseline. Arrowheads indicate pre-Dose 1 baseline (Day 1) and Dose 2 (Day 22).

Abbreviations: GMT = geometric mean titer; ic = immunocompromised; ic HIV = human immunodeficiency virus-positive participants; ic post-transplant = participants with post-transplantation backgrounds; IMM = Immunogenicity set.

Source: Report R-21-0347.

#### *6.1.1.1.3 SARS-CoV-2 -specific CD4⁺ and CD8⁺ T-cell responses*

Only the study findings for BNT162b2 are summarized here because the results for BNT162b1 were generally similar.

As of 27 JUL 2021, evaluable CD4⁺ and CD8⁺ T-cell response data were available from 76 participants that received BNT162b2 at dose levels of 1, 3, 10, 20, or 30 µg (47 younger adults), or 10, 20, or 30 µg (29 older adults). This included:

- Younger adults aged 18 to 55 yrs per dose group (n=47): 1 µg (n=9), 3 µg (n=10), 10 µg (n=9), 20 µg (n=9), and 30 µg (n=10).
- Older adults aged 56 to 85 yrs per dose group (n=29): 10 µg (n=10), 20 µg (n=9), and 30 µg (n=10).
- IC participants aged 18 to 85 yrs dosed with BNT162b2 30 µg (n=28).

Evaluable CD4⁺ and CD8⁺ T-cell response data are available for pre-Dose 1 and 7 d post-Dose 2. BNT162b2 induced strong SARS-CoV-2 S-specific CD4⁺ T-cell responses by 7 d post-Dose 2 in all of the dosed younger and older participants. CD8⁺ T cell responses were induced in 95.7% and 82.8% of the younger and older participants, respectively. Despite the slightly lower CD8⁺ immunogenicity rate in older participants, the magnitude of BNT162b2-induced responses was comparable to those induced in younger participants at the same BNT162b2 dose. In both age groups, the observed T cell responses were directed against different epitopes of the SARS-CoV-2 S protein, including non-RBD sequences, indicating the induction of multi-epitopic responses by BNT162b2.

Dosing twice with BNT162b2 led to a substantial increase in the incidence and magnitude of T-cell responses in both age groups. The magnitude of $CD4^+$ T-cell responses induced were similar across different dose levels, whereby the magnitude of $CD8^+$ T-cell responses was highest at the 30 µg dose level. At 28 d after Dose 2, the time of the peak response, the participants with the strongest $CD4^+$ T-cell responses had more than 10-fold of the memory responses observed in the same participants against immunodominant peptides from cytomegalovirus, Epstein-Barr virus, influenza virus, and tetanus toxoid. The same participants also had strong $CD8^+$ T-cell responses that were comparable to memory responses against the above mentioned viral antigens.

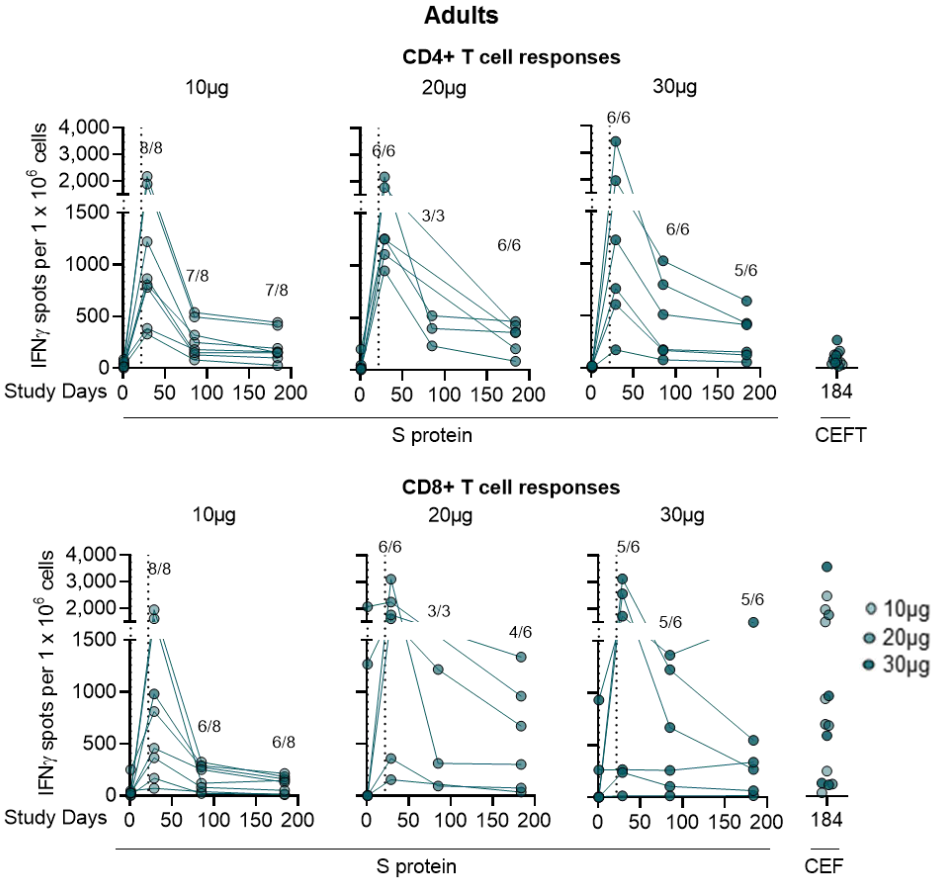



**Figure 15: Durability of BNT162b2-induced T-cell responses in younger participants**

PBMCs obtained on Day 1 (before Dose 1), Days 29, 85, and 184 (7, 63, and 162 d post-Dose 2, respectively), were analyzed in *ex vivo* IFNγ ELISpot (for details see GA-RB-022-01A). Common pathogen T-cell epitope pools CEF (CMV, EBV, and influenza virus HLA class I epitopes) and CEFT (CMV, EBV, influenza virus, and tetanus toxoid HLA class II epitopes) served to assess general T-cell reactivity, cell culture medium served as negative control. Each dot represents the sum of normalized mean spot count from duplicate wells stimulated with two peptide pools corresponding to the full length wild-type S protein for one study participant, after subtraction of the medium-only control. Ratios above post-vaccination data points are the number of participants with detectable $CD4^+$ or $CD8^+$ T-cell responses within the total number of tested participants per dose group and time point. Data for the 1 µg and 3 µg dose groups are not shown here because the data are not available for the same observation period.

Abbreviations: CMV = cytomegalovirus; EBV = Epstein-Barr virus; ELISpot = enzyme-linked immunosorbent-spot; HLA = human leukocyte antigen; IFN = interferon; PBMC = peripheral blood mononuclear cells; S protein = SARS-CoV-2 sp ke protein.

Source: Report R-20-0244.

BNT162b2-induced CD4$^+$ and CD8$^+$ T cell- responses decreased by 63 d post-Dose 2, but remained detectable (i.e., at levels higher than or in range of recall antigen memory responses) until 162 d post-Dose 2 in almost all younger and older participants dosed with at least 10 µg BNT162b2 (see Figure 15 and Figure 16).

RBD- and S-specific CD4$^+$ T-cell responses were induced *de novo* by BNT162b2 in 100% of participants. RBD- and S-specific CD8$^+$ T-cell responses were induced *de novo* by BNT162b2 in 96.6% of participants.

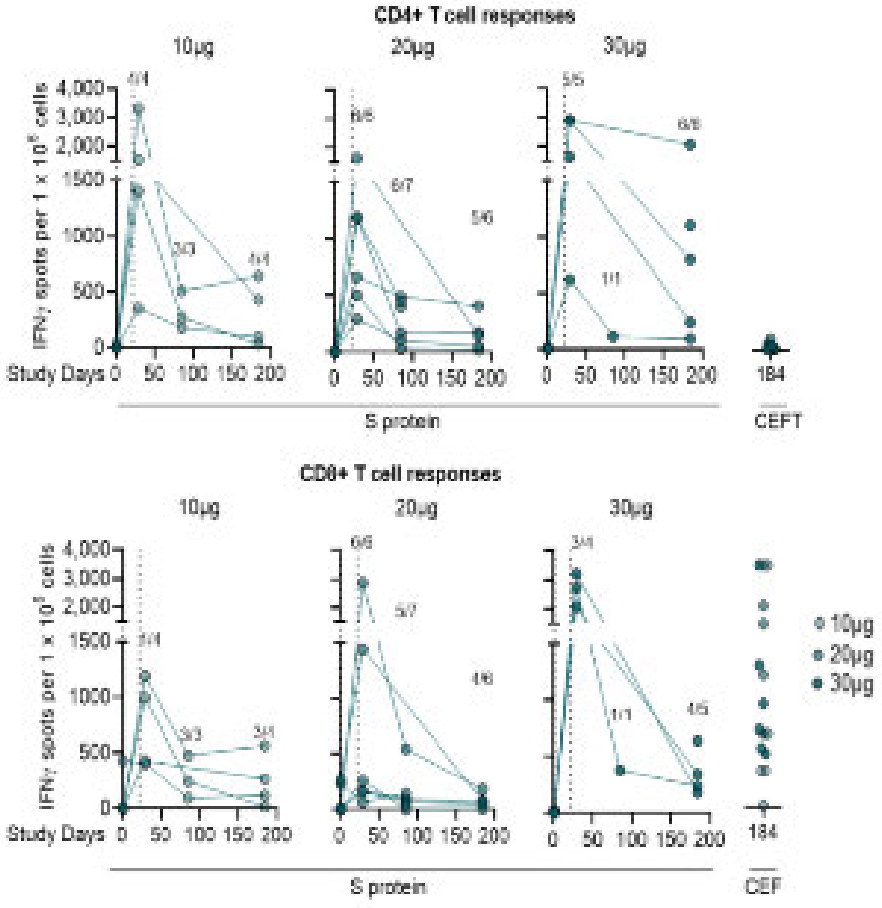



**Figure 16: Durability of BNT162b2-induced T-cell responses in older participants**

PBMCs obtained on Day 1 (before Dose 1), Days 29, 85, and 184 (7, 63, and 162 d post-Dose 2, respectively), were analyzed in *ex vivo* IFNγ ELISpot (for details see GA-RB-022-01A). Common pathogen T-cell epitope pools CEF (CMV, EBV, and influenza virus HLA class I epitopes) and CEFT (CMV, EBV, influenza virus, and tetanus toxoid HLA class II epitopes) served to assess general T-cell reactivity, cell culture medium served as negative control. Each dot represents the sum of normalized mean spot count from duplicate wells stimulated with two peptide pools corresponding to the full length wild-type S protein for 1 study participant, after subtraction of the medium-only control. Ratios above post-vaccination data points are the number of participants with detectable CD4$^+$ or CD8$^+$ T-cell responses within the total number of tested participants per dose group and time point. Cumulative spot count data from 2 participants (one from the 20 µg and one from the 30 µg cohort) are not shown here, as data from only one S pool was available. In addition, no CD8 data for Day 85 and Day 184 were available for 1 participant from the 30 µg cohort, therefore data from Day 1 and Day 28 are not included.

Abbreviations: CMV = cytomegalovirus; EBV = Epstein-Barr virus; ELISpot = enzyme-linked immunosorbent-spot; HLA = human leukocyte antigen; IFN = interferon; PBMC = peripheral blood mononuclear cells; S protein = SARS-CoV-2 sp ke protein.

Source: Report R-20-0244.

In HIV+ participants (n=14) dosed twice with 30 µg BNT162b2, both the frequency and magnitude of the $CD4^+$ and $CD8^+$ T-cell responses at 7 d post-Dose 2 were comparable to that seen in healthy younger and older participants. However, in post-transplant participants (n=12), two doses of BNT162b2 induced less frequent and weaker $CD4^+$ and $CD8^+$ T-cell responses at 7 d post-Dose 2 than in healthy younger and older participants (see Figure 17). Data for HIV+ and post-transplant participants at later times after Dose 2 was not available at the cutoff date for the CSR.

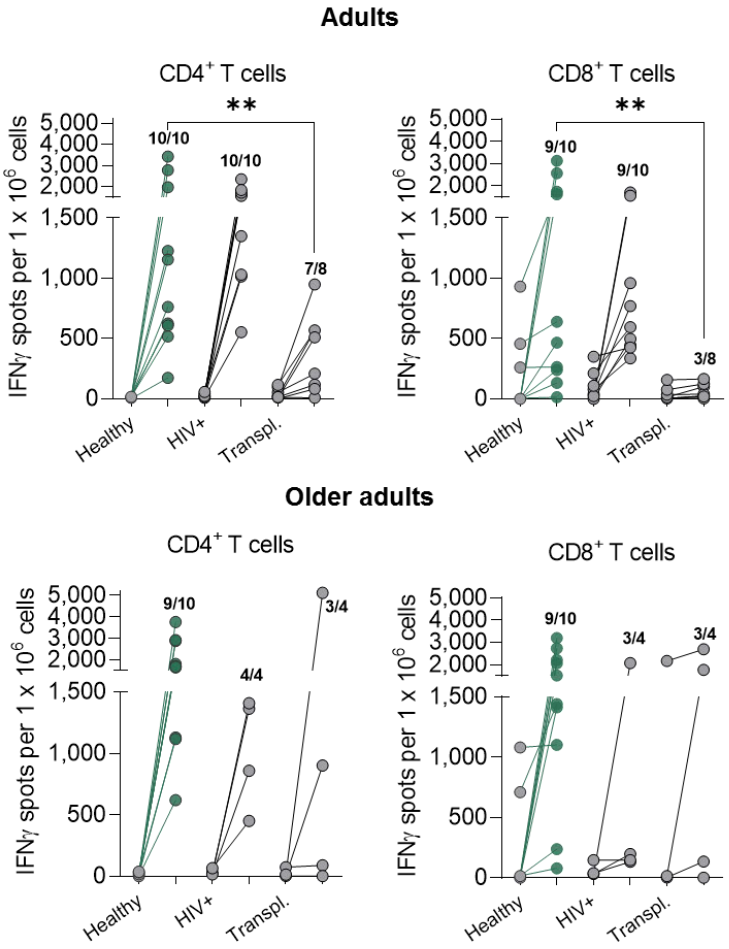



**Figure 17: BNT162b2-induced $CD4^+$ and $CD8^+$ T-cell responses in IC participants in comparison to in healthy participants**

PBMCs obtained on Day 1 (pre-Dose 1) and on Day 29 (7 d post-Dose 2) from healthy, HIV-positive (HIV+), and post-transplant participants (Transplant.) vaccinated with 30 µg BNT162b2 were analyzed using *ex vivo* IFNγ ELISpot assays (for details see GA-RB-022-01A). Each dot represents the sum of normalized mean spot counts from duplicate wells stimulated with two peptide pools corresponding to the full length wild-type S protein for 1 participant, after subtraction of the medium-only control. $CD4^+$ (left) and $CD8^+$ (right) T-cell response data from younger adults (18 to 55 yrs, upper panel) and older adults (56 to 85 yrs, lower panel) are shown. Ratios above post-vaccination data points are the number of participants with detectable $CD4^+$ or $CD8^+$ T-cell responses within the total number of tested participants per dose group. Note: CD4 data from 1 participant (276-05-0006) from the "adult" group could not be background subtracted and normalized and hence has not been included in the plots. Statistical comparison for spot counts was performed using two-tailed Mann-Whitney test, * $p < 0,05$; ** $p < 0,01$.

Abbreviations: ELISpot = enzyme-linked immunosorbent-spot; ic = immunocompromised; HIV+ = human immunodeficiency virus-positive participants; IFN = interferon; S protein = SARS-CoV-2 spike protein.

Source: Report R-20-0244.

#### *6.1.1.1.4 Functional and pro-inflammatory $CD4^+/CD8^+$ T-cell responses*

Only the study findings for BNT162b2 are summarized here because the results for BNT162b1 were generally similar.

The T helper type 1 (Th1; IFNγ and IL-2) and Th2 (IL4) cytokine profile of T cells specific to defined proteins/protein domains of SARS-CoV-2 as a result of two immunizations with 1 to 30 µg doses of BNT162b2 was assessed using intracellular cytokine staining.

As of 12 JUL 2021, evaluable functional and pro-inflammatory $CD4^+/CD8^+$ T-cell response data are available for:

- Healthy adults aged 18 to 55 yrs per dose cohort: 1 µg (n=8), 3 µg (n=9), 10 µg (n=11), 20 µg (n=11), and 30 µg (n=11).
- Healthy older adults aged 56 to 85 yrs per dose cohort: 10 µg (n=11), 20 µg (n=9), and 30 µg (n=9).
- IC study participants who received 30 µg: post-transplant participants (n=12) and stable HIV+ participants (n=15).

The functionality and polarization of vaccine-induced SARS-CoV-2 S-specific T cells were assessed by intracellular accumulation of cytokines IFNγ, IL-2, and IL4 in response to stimulation with overlapping peptides representing the full length sequence of the RBD and the wild-type SARS-CoV-2 S protein. For bench-marking, PBMCs from 18 virologically confirmed, convalescent COVID-19 patients were used.

Evaluable cell-mediated immune response data are available for 104 participants:

- Healthy adults aged 18 to 55 yrs per dose cohort: 1 µg (n=8), 3 µg (n=9), 10 µg (n=11), 20 µg (n=11), and 30 µg (n=10).
- Healthy older adults aged 56 to 85 yrs per dose cohort: 10 µg: (n=11), 20 µg (n=7), and 30 µg (n=9).
- IC participants received 30 µg (Day 43 only): post-transplant participants (n=13) and stable HIV+ participants (n=15).

Evaluable functional and pro-inflammatory $CD4^+/CD8^+$ T-cell response data for BNT162b2 are available at pre-Dose 1 and at 7 d and 21 d post-Dose 2 in younger and older participants, and in post-transplant or HIV+ participants. Data is also available for younger and older participants at 63 d and 162 d after Dose 2.

Vaccination with BNT162b2 induced S-specific cytokine-producing $CD4^+$ and $CD8^+$ T cells 7 d after Dose 2 whose fraction was substantially higher than that of convalescent COVID-19 patients. At 30 µg dose group, the cytokine responses elicited by BNT162b2 in healthy younger and older participants were mostly identical in response pattern and mirrored the aforementioned ELISpot results. For the majority of participants, the strong S-specific $CD8^+$ and $CD4^+$ T cell responses decreased by 21 d after Dose 2 and plateaued at a lower level until 63 d after Dose 2. This observation held true for dose groups at ≥3 µg BNT162b2, with varying response magnitudes likely depending on individual differences

between the healthy participants tested. For these participants, the cell-mediated immune responses remained detectable until 162 d after Dose 2.

S-specific CD4$^+$ T-cell responses were characterized by a Th1 cytokine profile secreting IFNγ, or IL-2, or both at 7 d after Dose 2. Almost no Th2 cytokine IL-4 secreting T cells were detectable in response to S peptide sub-pool stimulations. S-specific CD8$^+$ T cells secreted IFNγ in 65 of 79 healthy younger and older participants: in younger participants 43 of 50, in older participants 22 of 29. IL-2 secreting CD8$^+$ T cells were also detected.

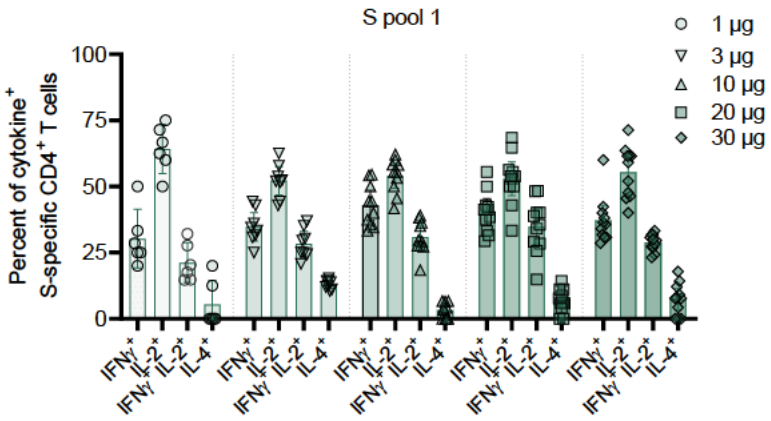



**Figure 18: S-specific CD4$^+$ T-cells producing the indicated cytokines in response to S protein pool 1 as a fraction of total cytokine-producing S-specific CD4$^+$ T cells (1 to 30 µg BNT162b2 younger participant dose groups)**

Bar charts show arithmetic means with 95% confidence interval at Day 29 (7 d after Dose 2). Cytokine production was calculated by summing up the fractions of all CD4$^+$ T cells positive for either IFNγ, IL-2, or IL-4, setting this sum to 100% and calculating the fraction of each specific cytokine-producing subset thereof. Two participants from the 1 µg cohort, 1 participant from the 3 µg cohort, and 1 participant from the 10 µg cohort were excluded from this analysis (frequency of total cytokine-producing CD4$^+$ T cells < 0.03%).
Abbreviations: IFN = interferon; IL = interleukin; younger participants = participants aged 18 to 55 yrs; S protein = SARS-CoV-2 spike protein.
Source: Interim report R-20-0241.

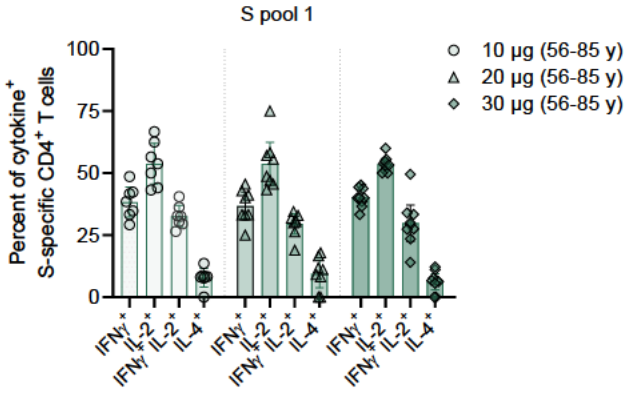



**Figure 19: S-specific CD4⁺ T-cells producing the indicated cytokines in response to S protein pool 1 as a fraction of total cytokine-producing S-specific CD4⁺ T cells (10 to 30 µg BNT162b2 older participant dose groups)**

Bar charts show arithmetic means with 95% CI at Day 29 (7 d after Dose 2). Cytokine production was calculated by summing up the fractions of all CD4⁺ T cells positive for either IFNγ, IL-2, or IL-4, setting this sum to 100%, and calculating the fraction of each specific cytokine-producing subset thereof. Four participants from the 10 µg cohort and 1 participant from the 20 µg cohort were excluded from this analysis (frequency of total cytokine-producing CD4⁺ T cells < 0.03%).

Abbreviations: IFN = interferon; IL = interleukin; older participants = participants aged 56 to 85 yrs; S protein = SARS-CoV-2 spike protein.

Source: Interim report R-20-0241.

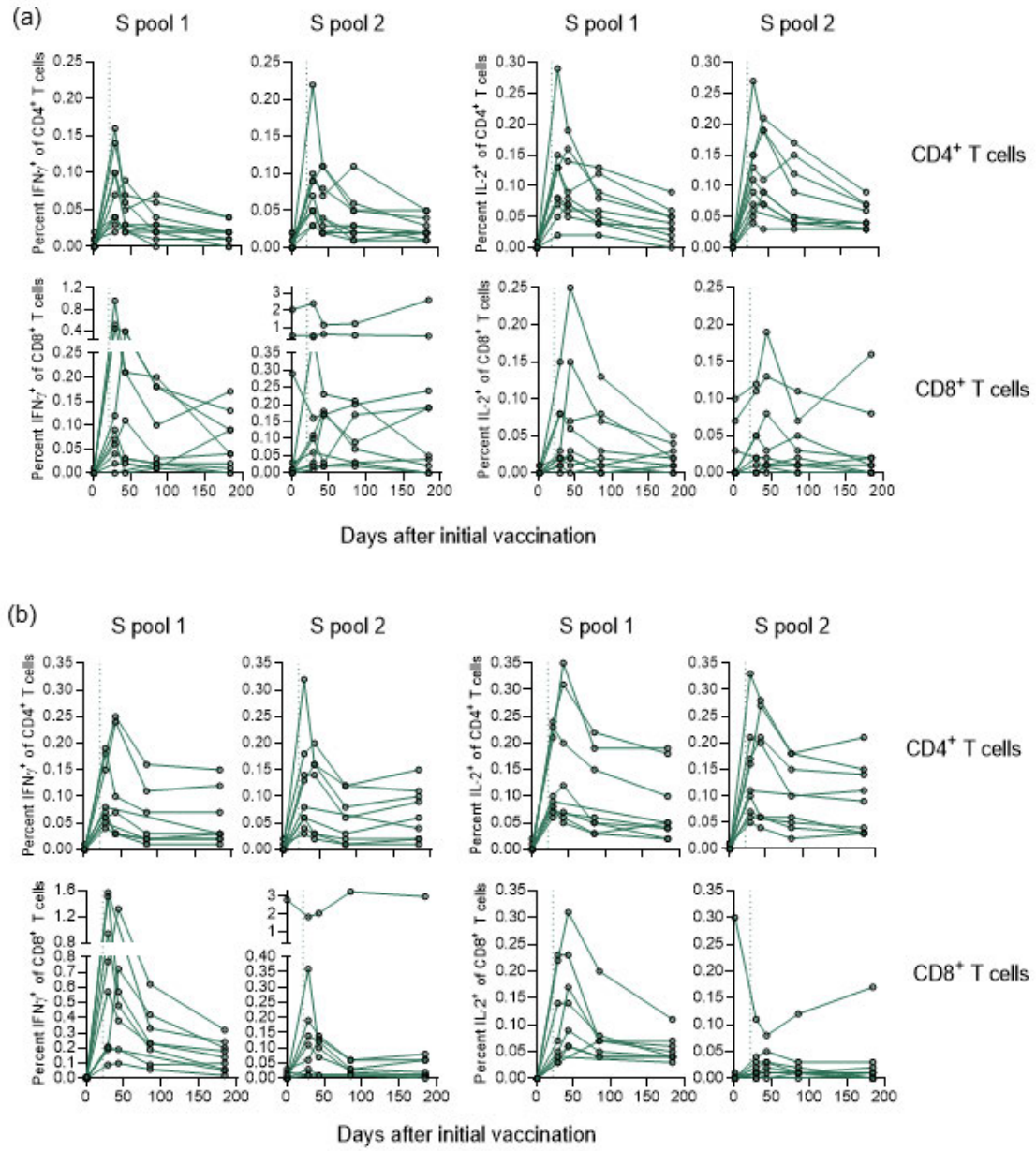



**Figure 20: Persistence of S-specific CD4⁺ and CD8⁺ T cells producing the indicated cytokines (IFNγ and IL-2) as a fraction of total circulating CD4⁺ and CD8⁺ T cells (30 µg dose groups, younger and older adults)**

Cytokine data are plotted for dosed participants from (a) the 30 µg adult (n=10) and (b) 30 µg older adult cohort (n=9) from Day 1 (pre-Dose 1), Days 29, 43, 85, and 184 (7, 21, 63 and 162 d after Dose 2) after the first vaccination. Green dotted lines indicate the time point of the second vaccination (Day 22). For the older adult dose groups, samples were not available for n=2 from Day 43 and n=1 from Day 85. Initial vaccination = Dose 1.

Abbreviations: IFN = interferon; IL = interleukin.

Source: Report R-20-0241.

BNT162b2-induced vaccine-specific CD4⁺ and CD8⁺ T-cell responses in IC participants, i.e., stable HIV+ participants and post-transplant participants, are shown in Figure 21. The responses in HIV+ participants receiving antiretroviral therapy (n=15) were similar in

magnitude and persistence compared to healthy participants up to 21 d after Dose 2; data for later time points was not yet available at the time of this interim CSR. The responses in post-transplantation participants (n=12) were significantly reduced at Days 29 and 43 in comparison to healthy participants, as would be expected for participants using immunosuppressive therapies to avoid transplant rejection.

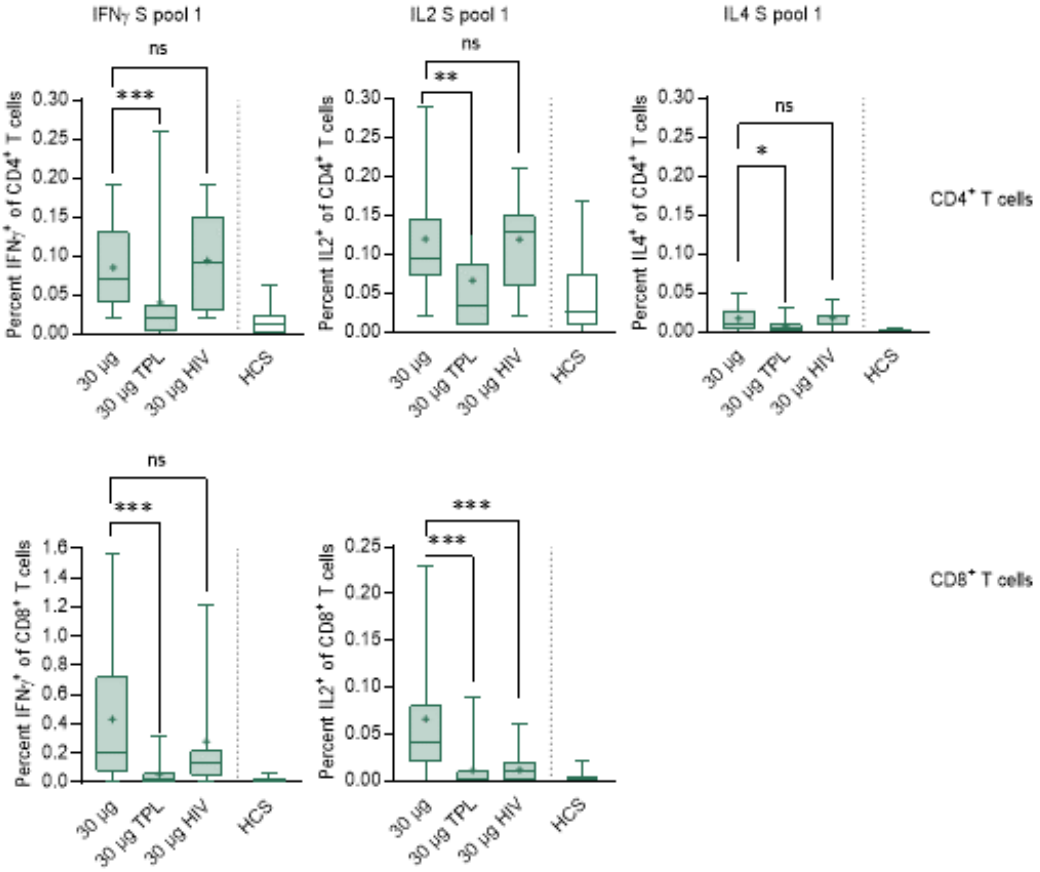



**Figure 21: Frequency of S-specific CD4⁺ and CD8⁺ T cells producing the indicated cytokines (IFNγ, IL-2 or IL-4) as a fraction of total circulating CD4⁺ and CD8⁺ T cells in response to S pool 1 stimulation (30 µg healthy participants vs. IC participants)**

Cytokine data are plotted for 30 µg dosed healthy participants (n=20), stable HIV-positive (n=15), and post-transplant (n=13) IC participants from Day 29 (7 d after Dose 2). Box-Whisker plots indicating the min and max values, lines in the boxes indicate the median values, + indicates the mean values.

Abbreviations: HCS = human convalescent sample (n=18); IC = immunocompromised; IFN = interferon; IL = interleukin; TPL = post-transplant participants; HIV = human immunodeficiency virus-positive participants; Mann-Whitney test, ns = not significant, * p< 0.05, ** p< 0.01.

Source: Report R-20-0241.

BNT162b2 induced poly-functional and pro-inflammatory CD4⁺/CD8⁺ T-cell responses in almost all healthy and HIV+ participants. The induced cytokine responses were directed against different epitopes of the SARS-CoV-2 S protein, including non-RBD sequences, indicating the induction of multi-epitopic responses by BNT162b2. These responses persisted in the majority of healthy participants until 162 d after Dose 2. The Th1

polarization of the helper T-cell response was characterized by a robust IFNγ/IL-2 and only minor IL-4 production upon antigen-specific (wild-type SARS-CoV-2 S protein peptide pools) re-stimulation, which was still observed, although with a reduced magnitude, at later time points.

#### 6.1.1.2 Safety in study BNT162-01 (status 28 NOV 2020)

In the study BNT162-01, younger adults aged 18 to 55 yrs were dosed with one of four BNT162 vaccine candidates (BNT162a1, BNT162b1, BNT162b2, and BNT162c2). Older adults aged 56 to 85 yrs were dosed with one of two BNT162b vaccine candidates (BNT162b1 and BNT162b2).

The presented data from the BNT162-01 study can be summarized as follows:

- The majority of the TEAEs reported were reactogenicity symptoms which were anticipated for IM administered vaccines. The observed reactogenicity was mild or moderate in severity.
- BNT162a1 and BNT162c2 showed acceptable tolerability in younger participants aged 18 to 55 yrs.
- BNT162b1 and BNT162b2 are well tolerated and have an acceptable safety profile in younger participants aged 18 to 55 yrs and older participants aged 56 to 85 yrs.
- The frequency of local and systemic reactogenicity was generally slightly lower for BNT162b2 compared to BNT162b1. BNT162b2 generally had a slightly milder and therefore more favorable reactogenicity profile than BNT162b1 across dose levels.

##### *6.1.1.2.1 BNT162a1 - Summary of safety*

The overall assessment of safety data following dosing with BNT162a1 has not changed since issue of the previous investigator's brochure (IB) version.

The treatment phase has been completed for all dose escalation cohorts for BNT162a1. The dosed participants are now in the follow-up phase until ~162 d post-Dose 2. No further clinical investigation of BNT162a1 is currently planned.

BNT162a1 has been tested at doses of 0.1, 0.3, and 3 µg (starting dose level). In the first six participants treated (sentinel and subgroup 2), the frequency and duration of systemic reactogenicity (predominantly of moderate intensity) led to a recommendation to de-escalate the dose. This was a precautionary measure by the study Safety Review Committee, although formal dose limiting toxicity criteria were not met. In the resultant 0.1 µg cohort minimal evidence of reactogenicity was found and a further cohort was treated at 0.3 µg BNT162a1. Across both these dose levels, most participants reported only injection site reactions (pain and tenderness, almost exclusively of mild intensity) and no systemic reactions.

In the first six participants treated with a single dose 3 µg dose of BNT162a1, the frequency and duration of systemic reactogenicity (predominantly of moderate intensity) led to a decision not to administer the planned 3 µg second dose and to defer further

dosing with this vaccine candidate. Despite this deferral, there were no SAEs, AESIs, or participants withdrawn due to related AEs after dosing with BNT162a1.

#### *6.1.1.2.2 BNT162b1 - Summary of safety*

At the time of preparation of this summary, the overall assessment of safety data following dosing with BNT162b1 has not changed since issuance of the previous IB version.

The treatment phase has been completed for all dose escalation cohorts for BNT162b1. The dosed participants are now in the follow-up phase until ~162 d post-Dose 2. No further clinical investigation of BNT162b1 is currently planned.

***Local reactions after BNT162b1 dosing in younger participants aged 18 to 55 yrs (across all dose groups)***

- Dose 2 for the 60 µg dose group was not administered after reviewing the totality of the data available, including the local and systemic reactogenicity data such as the increasing number of severe (Grade 3) systemic reactions reported with ascending dose.
- Within 7 d after Dose 1, the most frequently reported local reactions by severity were (n [%]): mild events were tenderness (59 [70%]) and pain (55 [65%]); moderate events were tenderness (29 [35%]) and pain (12 [14%]); severe events were pain (9 [11%]) and tenderness (6 [7%]).
- Within 7 d after Dose 2, the most frequently reported local reactions by severity were (n [%]): mild local reactions were tenderness (46 [67%]) and pain (40 [58%]); moderate local reactions were tenderness (24 [35%]) and pain (23 [33%]); severe local reactions were tenderness and pain in (5 [7%]).
- Within 7 d after Dose 1 and Dose 2, there were no potentially life-threatening local reactions reported.

***Local reactions after BNT162b1 dosing in older participants aged 56 to 85 yrs (across all dose groups)***

- Within 7 d after Dose 1, the most frequently reported local reactions given by severity were (n [%]): mild local reactions were tenderness in (24 [67%]) and pain (22 [61%]); moderate local reactions were tenderness in (7 [19%]) and pain (2 [6%]).
- Within 7 d after Dose 2, the most frequently reported local reactions given by severity were (n [%]): mild local reactions were tenderness in (24 [69%]) and pain in (21 [60%]); moderate local reactions were tenderness in (11 [31%]) and pain (7 [20%]).
- Within 7 d after Dose 1 and Dose 2, there were no severe or no potentially life-threatening local reactions reported.

***Systemic reactions after BNT162b1 dosing in younger participants aged 18 to 55 yrs (across all dose groups)***

- Dose 2 for the 60 µg dose group was not administered after reviewing the totality of the data available, including the local and systemic reactogenicity data such as the increasing number of severe (Grade 3) systemic reactions reported with ascending dose.
- Within 7 d after Dose 1, the most frequently reported events given by severity were (n [%]): mild events were fatigue (55 [65%]), headache (42 [50%]), and malaise (33 [39%]); moderate events were headache and fatigue (22 [26%] each) and myalgia and malaise (14 [17%] each); severe events were headache (9 [11%]), chills (8 [10%]), and malaise (7 [8%]).
- Within 7 d after Dose 1, two (2%) participants in the 30 µg and 50 µg dose groups (one each) had clinically significant mild or moderate elevated body temperature at 48 h after Dose 1, which resolved by the next visit after medication. These events were reported as TEAEs and assessed as related to the IMP.
- Within 7 d after Dose 2, the most frequently reported events given by severity were (n [%]): mild events were fatigue (37 [54%]), headache (35 [51%]), and malaise (30 [43%]); moderate events were headache (29 [42%]), fatigue (27 [39%]), and myalgia (20 [29%]), and severe events were headache (13 [19%]), chills (12 [17%]), and malaise (11 [16%]).
- Within 7 d after Dose 1 and Dose 2, there were no potentially life-threatening events reported.

***Systemic reactions after BNT162b1 dosing in older participants aged 56 to 85 yrs (across all dose groups)***

- Within 7 d after Dose 1, the most frequently reported events given by severity were (n [%]): mild events were fatigue (18 [50%]), myalgia (12 [33%]), and headache (11 [31%]); moderate events were headache (11 [31%]), myalgia (4 [11%]), and fatigue, arthralgia, and chills (3 [8%] each); severe events were headache and fatigue (3 [8%] each), and malaise (2 [6%]).
- Within 7 d after Dose 2, the most frequently reported events given by severity were (n [%]): mild events were headache and fatigue (21 [60%]) each, and malaise (16 [46%]); moderate events were headache in (9 [26%]), and myalgia and chills in (7 [20%] each); severe events were fatigue and chills (3 [9%] each) and myalgia, arthralgia, and headache (2 [6%]) each.
- Within 7 d after Dose 1 and Dose 2, there were no potentially life-threatening events reported.

***Unsolicited TEAEs after BNT162b1 dosing***

For a summary of unsolicited TEAEs in younger see Table 9 and for in older participants see Table 10.

**Table 9: Summary of TEAEs without AEs based on solicited reporting via diaries – BNT162b1 – Younger participants aged 18 to 55 yrs (Safety Set)**

| Time interval | | 1 µg (N=12) n (%) E | 3 µg (N=12) n (%) E | 10 µg (N=12) n (%) E | 20 µg (N=12) n (%) E | 30 µg (N=12) n (%) E | 50 µg (N=12) n (%) E | 60 µg (N=12) n (%) E | Total [a] (N=84) n (%) E |
|---|---|---|---|---|---|---|---|---|---|
| Dose 1 up to Dose 2 or 28 d after Dose 1 (whatever comes first) | Any TEAE | 1 (8) 6 | 0 (0) 0 | 4 (33) 11 | 3 (25) 4 | 4 (33) 5 | 3 (25) 4 | 6 (50) 9 | 21 (25) 39 |
| | Related TEAE | 1 (8) 1 | 0 (0) 0 | 3 (25) 7 | 3 (25) 4 | 3 (25) 3 | 1 (8) 1 | 6 (50) 8 | 17 (20) 24 |
| | Grade ≥3 TEAE | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 |
| | Related Grade ≥3 TEAE | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 |
| | Any TESAE | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 |
| | Related TESAE | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 |
| Dose 1 up to 28 d after Dose 2 or after Dose 1 (if no Dose 2) | Any TEAE | 6 (50) 21 | 0 (0) 0 | 7 (58) 16 | 5 (42) 12 | 6 (50) 8 | 8 (67) 17 | 6 (50) 9 | 38 (45) 83 |
| | Related TEAE | 4 (33) 10 | 0 (0) 0 | 6 (50) 10 | 4 (33) 9 | 4 (33) 4 | 6 (50) 10 | 6 (50) 8 | 30 (36) 51 |
| | Grade ≥3 TEAE | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 2 (17) 4 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 2 (2) 4 |
| | Related Grade ≥3 TEAE | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 1 (8) 3 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 1 (1) 3 |
| | Any TESAE | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 |
| | Related TESAE | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 |

a. The sum across all dose levels.

Abbreviations: AE = adverse event; E = number of events; N = number of participants in the analysis set (the denominator for the percentage calculation); n = number of participants with the specified characteristic; TE(S)AE = treatment-emergent (serious) adverse event.

Source: BNT162-01 CSR v2.0.

**Table 10: Summary of TEAEs without AEs based on solicited reporting via diaries – BNT162b1 – Older participants and the All Total participants (Safety Set)**

| | | Older participants aged 56 to 85 yrs | | | | All |
|---|---|---|---|---|---|---|
| Time interval | | 10 µg (N=12) n (%) E | 20 µg (N=12) n (%) E | 30 µg (N=12) n (%) E | Total [a] (N=36) n (%) E | Total [b] (N=120 n (%) E |
| Dose 1 up to Dose 2 or 28 d after Dose 1 (whatever comes first) | Any TEAE | 0 (0) 0 | 0 (0) 0 | 5 (42) 9 | 5 (14) 9 | 21 (18) 33 |
| | Related TEAE | 0 (0) 0 | 0 (0) 0 | 4 (33) 6 | 4 (11) 6 | 20 (17) 29 |
| | Grade ≥3 TEAE | 0 (0) 0 | 0 (0) 0 | 1 (8) 1 | 1 (3) 1 | 1 (1) 1 |
| | Related grade ≥3 TEAE | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 |
| | Any TESAE | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 |
| | Related TESAE | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 |
| Dose 2 up to 28 d after Dose 2 | Any TEAE | 3 (25) 3 | 2 (17) 4 | 7 (58) 13 | 12 (33) 20 | 33 (28) 59 |
| | Related TEAE | 0 (0) 0 | 0 (0) 0 | 4 (33) 6 | 4 (11) 6 | 21 (18) 30 |
| | Grade ≥3 TEAE | 1 (8) 1 | 1 (8) 1 | 1 (8) 1 | 3 (8) 3 | 3 (3) 3 |
| | Related Grade ≥3 TEAE | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 |
| | Any TESAE | 0 (0) 0 | 1 (8) 1 | 0 (0) 0 | 1 (3) 1 | 1 (1) 1 |
| | Related TESAE | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 | 0 (0) 0 |

a. The sum across all dose levels.

b. The sum of younger and older participants across all dose levels.

Abbreviations: AE = adverse event; E = number of events; N = number of participants in the analysis set (the denominator for the percentage calculation); n = number of participants with the specified characteristic; TE(S)AE = treatment-emergent (serious) adverse event.

Source: BNT162-01 CSR v2.0.

*Clinical laboratory and vital signs parameters after BNT162b1 dosing (younger and older participants) (across all dose groups)*

Two (2%) participants in the 30 and 50 µg younger dose groups (one in each) had clinically significant high C-reactive protein (CRP) values at 48 h after Dose 1. These values returned to normal without clinical consequence by the next visit. Otherwise, there were no clinically significant findings in the clinical laboratory parameters.

Apart from two (2%) younger participants with elevated body temperature after Dose 1 (see the reactogenicity reporting), there were no clinically significant findings in vital signs parameters.

#### *6.1.1.2.3 BNT162b2 - Summary of safety*

At the time of preparation of this IB, the overall assessment of safety data following dosing with BNT162b2 in the BNT162-01 study has not changed since issuance of the previous IB version.

The treatment phase has been completed for all dose escalation cohorts for BNT162b2 in younger and older adults. The dosed participants are now in the follow-up phase until ~162 d post-Dose 2.

Three expansion cohorts ("dose groups") are clinically ongoing:

- Dose Group 11 is testing an alternative posology cohort with a reduced Dose 1 (3 µg) and then a standard Dose 2 (30 µg) given ~21 d apart.
- Dose Group 12 is investigating the adaptive immune response (including safety and long term immune response) in adults after two 30 µg BNT162b2 doses given ~21 d apart.
- Dose Group 13 is investigating safety and long term immune responses in immunocompromised adults after two 30 µg BNT162b2 doses given ~21 d apart.
- Dose Group 14 is investigating B cell immune responses induced by BNT162b2 after two 30 µg BNT162b2 doses given ~21 d apart.

Given the availability of safety data from the Phase 2/3 part of Study C4591001/BNT162-02, where ~46,000 participants aged ≥16 yrs were randomized 1:1 to vaccine or placebo, see Section 6.1.2 for a summary of the safety data for BNT162b2, including follow-up for a median of 2 months after the second dose. These data suggest a favorable safety profile, with no specific safety concerns identified for emergency use. The data for BNT162b2 in the BNT162-01 study were consistent with those of Study C4591001/BNT162-02 at the same dose levels.

#### *6.1.1.2.4 BNT162c2 - Summary of safety*

The overall assessment of safety data following dosing with BNT162c2 has not changed since issue of the previous IB version.

The treatment phase has been completed for all dose escalation cohorts for BNT162c2. The dosed participants are now in the follow-up phase until ~162 d post-Dose 2 (2-dose regimen) / ~184 d post-dose (one dose regimen). No further clinical investigation of BNT162c2 is currently planned.

In the BNT162-01 study in participants aged 18 to 55 yrs, single BNT162c2 doses ≤1 µg and two BNT162c2 doses between ≤3 µg showed generally acceptable tolerability, with a similar or weaker reactogenicity than seen with BNT162b1 or BNT162b2 at the same doses. All reported events were self-limiting or simply managed. To date, except for one SAE after COVID-19 infection, there were no SAEs, AESIs, or participants withdrawn due to related AEs after dosing with BNT162c2.

### *6.1.2 C4591001/BNT162-02 – Results*

#### 6.1.2.1 Overview of study

The Study C4591001/BNT162-02 is the ongoing, randomized, placebo-controlled, observer-blind, dose-finding Phase 1/2/3 registration study that is evaluating the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals (Mulligan et al. 2020; Walsh et al. 2020; Polack et al. 2020; Frenck et al. 2021).

Study C4591001/BNT162-02 was started as a Phase 1/2 study in adults in the US and was then amended to expand the study to a global Phase 2/3 study planning to enroll ~44,000 participants to accrue sufficient COVID-19 cases to conduct a timely efficacy assessment. The protocol was also amended to include older and younger adolescents 16 to 17 yrs of age, and 12 to 15 yrs of age, respectively.

Data from the Phase 1 part of the study, which evaluated BNT162b1 and BNT162b2 at different dose levels, were the basis for selection of the vaccine candidate and dose level for Phase 2/3. The Phase 2/3 part of the study evaluated the safety, immunogenicity, and efficacy of the selected vaccine candidate and dose level, BNT162b2 30 µg as a 2-dose series, and is intended to support licensure globally.

The protocol was amended to evaluate the immune response and safety profile of a third dose (booster dose) of BNT162b2 30 µg administered to participants who received a 2-dose series of either BNT162b1 or BNT162b2 during Phase 1, or participants who received BNT162b2 30 µg as a 2-dose series in Phase 3 of the study.

**Phase 1**

In Phase 1, two age groups were studied separately, younger adults (18 to 55 yrs of age) and older adults (65 to 85 yrs of age). The study population includes male and female participants deemed healthy as determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

For each of the two vaccine candidates evaluated (BNT162b1 and BNT162b2), younger participants received escalating dose levels (N=15 per dose level, 4:1 randomization ratio between vaccine and placebo) with progression to subsequent dose levels and the older

age group (N=15 per dose level, 4:1 randomization ratio between vaccine and placebo) based on recommendation from an Internal Review Committee.

The vaccine candidates, administered IM in the upper arm in a 2-dose regimen separated by ~21 d, were:

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

Note: The Independent Review Committee recommended that a second dose of BNT162b1 at 100 µg not be administered and discontinued due to reactogenicity after the first dose in the younger age group.

Based upon review of safety and immunogenicity from the Phase 1 part of the study, and available non-clinical data, BNT162b2 at 30 µg was selected as the final candidate and dose level to proceed into Phase 2/3 of the study. BNT162b2 at 30 µg provided the optimum combination of a favorable reactogenicity profile and a robust immune response likely to afford protection against COVID-19 in younger and older adults.

Phase 1 participants who were randomized to either BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg were offered booster vaccination (Dose 3) with BNT162b2 at 30 µg, ~6 to 12 months after their second dose of BNT162b1 or BNT162b2.

**Phase 2/3**

In Phase 2/3, participants were randomized 1:1 (active vaccine or placebo) and enrolled with stratification of younger adults (18 to 55 yrs of age) and older adults (>55 yrs of age) to achieve ~40% enrollment in the older adult group. Adolescents were added later by a protocol amendment: older adolescents (16 to 17 yrs of age) are included in the younger adult stratum, and younger adolescents (12 to 15 yrs of age) were added as a separate age stratum. Eligibility in Phase 2/3 included higher risk for acquiring COVID-19 in the investigator's judgment. Participants with immunocompromizing conditions or treatments were excluded.

The Phase 2 portion of the study evaluated reactogenicity and immunogenicity for 360 adult participants enrolled into the study who also contribute to the overall efficacy and safety assessments in the Phase 3 portion of the study.

Phase 3 (which is ongoing) included planned interim analyses of the first primary efficacy endpoint, ongoing efficacy and safety evaluations including reactogenicity assessment in a subset of participants, and exploratory vaccine immunogenicity evaluation in a subset of participants. Participants were stratified by age group (16 to 55 yrs and >55 yrs). The final efficacy analysis was to be conducted when at least the prespecified total number of 164 efficacy events accrued. An updated analysis of 1,165 confirmed cases in blinded placebo-controlled follow-up from Dose 1 to a data cutoff date of 13 MAR 2021 has been conducted. Safety and long term persistence of efficacy follow-up will continue for at least 2 yrs following the second dose and/or end of study. Safety and efficacy analyses included the 360 participants who were analyzed for Phase 2.

Cases of COVID-19 for primary and secondary efficacy endpoints were evaluated as described by Polack et al. 2020.

**Booster and variant strain evaluation**

For further evaluation of booster effects and protection against emerging SARS-CoV-2 VOC, a subset of existing Phase 3 participants 18 to 55 yrs of age have been randomized 1:1 to receive either a third dose of BNT162b2 or a third dose of a variant vaccine based upon the beta variant (first detected in South Africa), BNT162b2 (B.1.351) (~5 to 7 months after their second dose of BNT162b2. An additional subset of existing Phase 3 participants 18 to 55 yrs of age have been enrolled to receive a third and fourth dose of BNT162b2 (B.1.351). A new cohort has been recruited who are COVID-19 vaccine-naïve (i.e., have not received BNT162b2) and have not experienced COVID-19 to receive BNT162b2 (B.1.351) as a 2-dose series 21 d apart. Data from Phase 3 participants who received a booster dose of BNT162b2 are summarized in Sections 6.1.2.3.5 and 6.1.2.4.4. Data from Phase 3 participants who received BNT162b2 (B.1.351) will be reported at a later time.

### 6.1.2.2 Summary of efficacy (Phase 3)

In the pivotal study C4591001/BNT162-02, Phase 3 efficacy analyses were event driven. The prespecified interim analysis was conducted on an accrued 94 evaluable COVID-19 cases (interim analysis data cutoff date: 04 NOV 2020), and the final analysis was conducted on an accrued 170 evaluable COVID-19 cases (final analysis data cutoff date: 14 NOV 2020). Results of both analyses demonstrated 95% vaccine efficacy (VE) against COVID-19. An updated analysis of 1,165 confirmed cases in blinded placebo-controlled follow-up from Dose 1 to a data cutoff date of 13 MAR 2021 evaluated duration of protection and is summarized below.

Efficacy was assessed based on confirmed cases of COVID-19, where the case onset date was the date that symptoms were first experienced by the participant and the cases met evaluable criteria.

#### *6.1.2.2.1 Updated analysis of primary efficacy endpoints*

For the first primary efficacy endpoint, VE against confirmed COVID-19 was evaluated in participants without prior evidence of SARS-CoV-2 infection, on cases occurring at least 7 d after Dose 2. For the second primary efficacy endpoint, VE against confirmed COVID-19 was evaluated in participants with or without prior evidence of SARS-CoV-2 infection at least 7 d after Dose 2.

In the updated efficacy analysis up to 6 months post-Dose 2 (data cutoff date: 13 MAR 2021), among participants in the evaluable efficacy population without evidence of SARS-CoV-2 infection before and during the vaccination regimen, the estimated VE against confirmed COVID-19 occurring at least 7 d after Dose 2 was 91.3% (2-sided 95% CI: 89.0%, 93.2%), with 77 cases in the BNT162b2 group and 850 cases in the placebo group (Table 11).

Among participants with or without evidence of SARS-CoV-2 infection before and during the vaccination regimen, the estimated VE against confirmed COVID-19 occurring at least

7 d after Dose 2 was 91.1% (2-sided 95% CI: 88.8%, 93.0%), with 81 and 873 cases in the BNT162b2 and placebo groups, respectively (Table 11).

**Table 11: Vaccine efficacy – First COVID-19 occurrence from 7 d after Dose 2 – Blinded placebo-controlled follow-up period - Participants without and participants with or without evidence of infection prior to 7 d after Dose 2 – Evaluable Efficacy (7 d) Population**

| | Vaccine group (as randomized) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | BNT162b2 (30 µg) | | | Placebo | | | | | |
| Efficacy Endpoint | N[a] | n1[b] | Surveillance Time[c] (n2[d]) | N[a] | n1[b] | Surveillance Time[c] (n2[d]) | VE (%) | (95% CI[e]) | Pr (VE >30% \| data)[f] |
| First COVID-19 occurrence from 7 d after Dose 2 (Participants without evidence of infection)[g] | 20,998 | 77 | 6.247 (20,712) | 21,096 | 850 | 6.003 (20,713) | 91.3 | (89.0, 93.2) | >0.9999 |
| First COVID-19 occurrence from 7 d after Dose 2 (Participants with or without evidence of infection) | 22,166 | 81 | 6.509 (21,642) | 22,320 | 873 | 6.274 (21,689) | 91.1 | (88.8, 93.0) | >0.9999 |

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 person-yrs for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 d after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. 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.
g. Participants who had no serological or virological evidence (prior to 7 d after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding ant body [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 d after Dose 2 were included in the analysis.

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.

PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (19:19) Source Data: adc19ef Table Generation: 27MAR2021 (01:59) (Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File:./nda2_unblinded/C4591001_BLA/adc19ef_ve_cov_7pd2_wo_eval and :./nda2_unblinded/C4591001_BLA/adc19ef_ve_cov_7pd2_eval

All reports of COVID-19, with onset at any time after Dose 1 regardless of evidence of infection before or during the vaccination regimen, are accounted for in Table 12. In this analysis, the estimated VE against all cases occurring at any time after Dose 1 was 87.8% (2-sided- 95% CI: 85.3%, 89.9%), with 131 cases in the BNT162b2 group and 1,034 cases in the placebo group.

Between Dose 1 and Dose 2, 46 cases occurred in the BNT162b2 group and 110 cases occurred in the placebo group, corresponding to an estimated VE of 58.4% (95% CI: 40.8%, 71.2%), indicating early protection by BNT162b2, starting ~11 d after Dose 1 (Figure 22).

From ≥7 d after Dose 2 to < 2 months after Dose 2, estimated VE was 96.2% (95% CI: 93.3, 98.1); from ≥2 months after Dose 2 to < 4 months after Dose 2, VE was 90.1% (95% CI: 86.6, 92.9); and from ≥4 months after Dose 2, VE was 83.7% (95% CI: 74.7, 89.9).

**Table 12: Vaccine efficacy – First COVID-19 occurrence after Dose 1 – Blinded placebo-controlled follow-up period – Dose 1 All-Available Efficacy Population**

| | Vaccine group (as randomized) | | | | | |
|---|---|---|---|---|---|---|
| | BNT162b2 (30 µg) (N[a]=23,040) | | Placebo (N[a]=23,037) | | | |
| Efficacy Endpoint Subgroup | n1[b] | Surveillance Time[c] (n2[d]) | n1[b] | Surveillance Time[c] (n2[d]) | VE (%) (95% CI[e]) | |
| First COVID-19 occurrence after Dose 1 | 131 | 8.412 (22,505) | 1,034 | 8.124 (22,434) | 87.8 | (85.3, 89.9) |
| After Dose 1 to before Dose 2 | 46 | 1.339 (22,505) | 110 | 1.331 (22,434) | 58.4 | (40.8, 71.2) |
| After Dose 1 to < 11 d after Dose 1 | 41 | 0.677 (22,505) | 50 | 0.675 (22,434) | 18.2 | (-26.1, 47.3) |
| ≥11 Days after Dose 1 to before Dose 2 | 5 | 0.662 (22,399) | 60 | 0.656 (22,369) | 91.7 | (79.6, 97.4) |
| Dose 2 to 7 d after Dose 2 | 3 | 0.424 (22,163) | 35 | 0.422 (22,057) | 91.5 | (72.9, 98.3) |
| ≥7 Days after Dose 2 | 82 | 6.649 (22,132) | 889 | 6.371 (22,001) | 91.2 | (88.9, 93.0) |
| ≥7 d after Dose 2 to < 2 Months after Dose 2 | 12 | 2.923 (22,132) | 312 | 2.884 (22,001) | 96.2 | (93.3, 98.1) |
| ≥2 Months after Dose 2 to < 4 Months after Dose 2 | 46 | 2.696 (20,814) | 449 | 2.593 (20,344) | 90.1 | (86.6, 92.9) |
| ≥4 Months after Dose 2 | 24 | 1.030 (12,670) | 128 | 0.895 (11,802) | 83.7 | (74.7, 89.9) |

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 person-yrs for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method (adjusted for surveillance time for overall row).

Abbreviations: VE = vaccine efficacy.

PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (19:19) Source Data: adc19ef Table Generation: 19APR2021 (17:34) (Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File:./nda2_unblinded/C4591001_BLA/adc19ef_ve_cov_pd1_aai

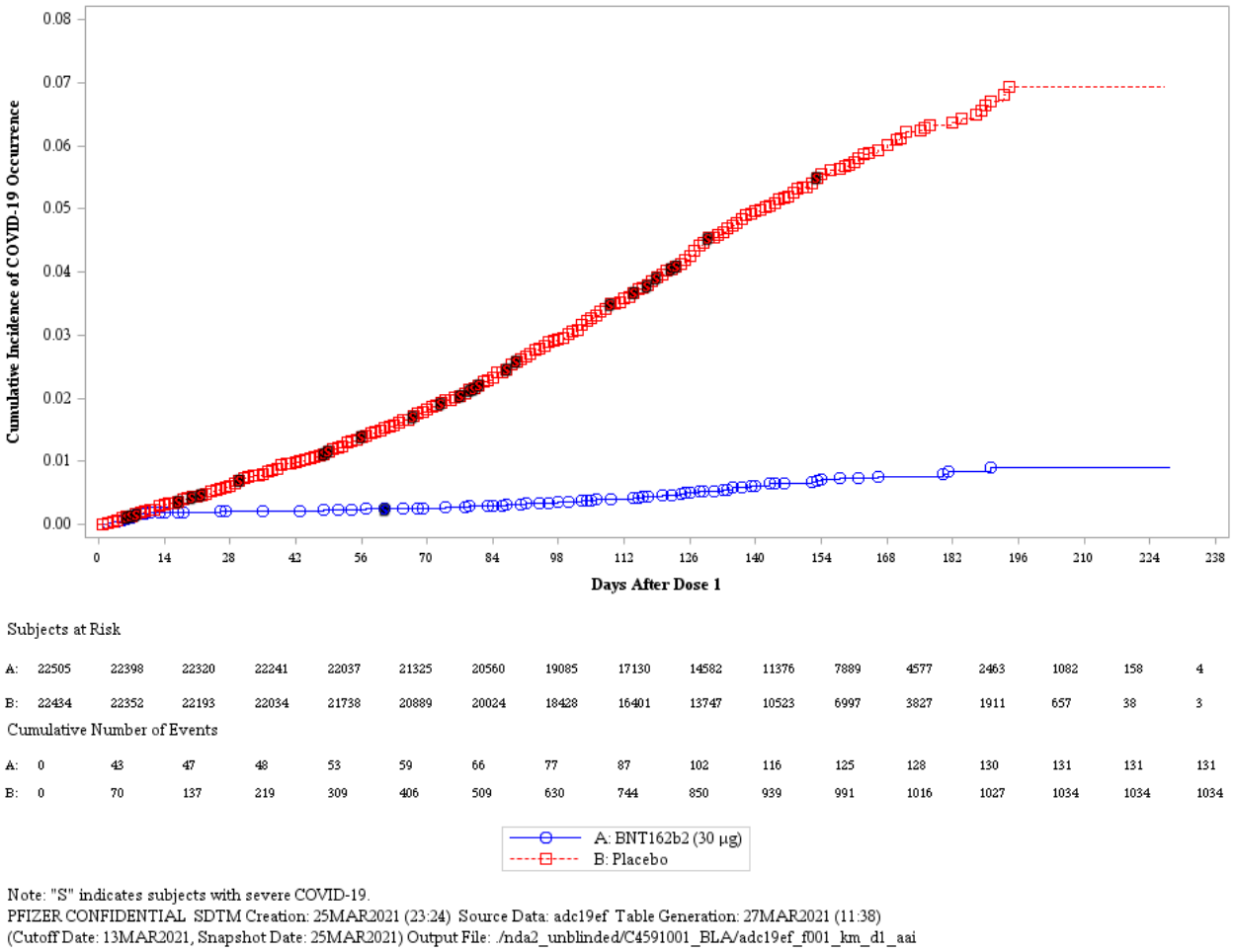



**Figure 22: Cumulative incidence curves for the first COVID-19 occurrence after Dose 1 – Blinded placebo-controlled follow-up period - Dose 1 All-Available Efficacy Population – Updated analysis**

### *6.1.2.2.2 Vaccine efficacy by subgroup*

Among participants without evidence of SARS-CoV-2 infection before and during the vaccination regimen, the estimated VE was ≥90% in most subgroups (Table 13), similar to the estimated 91.3% overall VE with the exception of VE among race/ethnicity groups (VE was 87.6% among Asian participants and 88.5% among Hispanic/Latino participants) and by country (VE was 86.5% in Argentina and 86.2% in Brazil). Similar results were observed for subgroup analyses among participants with or without evidence of SARS-CoV-2 infection before and during the vaccination regimen.

**Table 13: Vaccine efficacy – First COVID-19 occurrence from 7 d after Dose 2, by subgroup – Blinded placebo-controlled follow-up period – Participants without evidence of infection prior to 7 d after Dose 2 – Evaluable Efficacy (7 d) Population**

| | Vaccine group (as randomized) | | | | | |
|---|---|---|---|---|---|---|
| | BNT162b2 (30 µg) (N[a]=20,998) | | Placebo (N[a]=21,096) | | | |
| Efficacy Endpoint Subgroup | n1[b] | Surveillance Time[c] (n2[d]) | n1[b] | Surveillance Time[c] (n2[d]) | VE (%) | (95% CI[e]) |
| **First COVID-19 occurrence from 7 d after Dose 2** | | | | | | |
| Overall | 77 | 6.247 (20,712) | 850 | 6.003 (20,713) | 91.3 | (89.0, 93.2) |
| **Age group (years)** | | | | | | |
| 12 to 15 | 0 | 0.154 (1,001) | 16 | 0.147 (972) | 100.0 | (75.3, 100.0) |
| 16 to 55 | 52 | 3.593 (11,517) | 568 | 3.439 (11,533) | 91.2 | (88.3, 93.5) |
| >55 | 25 | 2.499 (8,194) | 266 | 2.417 (8,208) | 90.9 | (86.3, 94.2) |
| ≥65 | 7 | 1.233 (4,192) | 124 | 1.202 (4,226) | 94.5 | (88.3, 97.8) |
| ≥75 | 1 | 0.239 (842) | 26 | 0.237 (847) | 96.2 | (76.9, 99.9) |
| **Sex** | | | | | | |
| Male | 42 | 3.246 (10,637) | 399 | 3.047 (10,433) | 90.1 | (86.4, 93.0) |
| Female | 35 | 3.001 (10,075) | 451 | 2.956 (10,280) | 92.4 | (89.2, 94.7) |
| **Race** | | | | | | |
| White | 67 | 5.208 (17,186) | 747 | 5.026 (17,256) | 91.3 | (88.9, 93.4) |
| Black or African American | 4 | 0.545 (1,737) | 48 | 0.527 (1,737) | 91.9 | (78.0, 97.9) |
| American Indian or Alaska Native | 0 | 0.041 (186) | 3 | 0.037 (176) | 100.0 | (-119.0, 100.0) |
| Asian | 3 | 0.260 (946) | 23 | 0.248 (934) | 87.6 | (58.9, 97.6) |
| Native Hawaiian or other Pacific Islander | 0 | 0.015 (54) | 1 | 0.008 (30) | 100.0 | (-1961.2, 100.0) |
| Multiracial | 3 | 0.151 (518) | 22 | 0.128 (476) | 88.5 | (61.6, 97.8) |
| Not reported | 0 | 0.026 (85) | 6 | 0.030 (104) | 100.0 | (2.8, 100.0) |
| All others [f] | 6 | 0.494 (1,789) | 55 | 0.451 (1,720) | 90.0 | (76.9, 96.5) |
| **Ethnicity** | | | | | | |
| Hispanic/Latino | 29 | 1.786 (5,161) | 241 | 1.711 (5,120) | 88.5 | (83.0, 92.4) |
| Non-Hispanic/non-Latino | 47 | 4.429 (15,449) | 609 | 4.259 (15,484) | 92.6 | (90.0, 94.6) |
| Not reported | 1 | 0.032 (102) | 0 | 0.033 (109) | -∞ | (NA, NA) |
| **Country** | | | | | | |
| Argentina | 15 | 1.012 (2,600) | 108 | 0.986 (2,586) | 86.5 | (76.7, 92.7) |
| Brazil | 12 | 0.406 (1,311) | 80 | 0.374 (1,293) | 86.2 | (74.5, 93.1) |
| Germany | 0 | 0.047 (236) | 1 | 0.048 (242) | 100.0 | (-3874.2, 100.0) |
| South Africa | 0 | 0.080 (291) | 9 | 0.074 (276) | 100.0 | (53.5, 100.0) |
| Turkey | 0 | 0.027 (228) | 5 | 0.025 (222) | 100.0 | (-0.1, 100.0) |
| USA | 50 | 4.674 (16,046) | 647 | 4.497 (16,094) | 92.6 | (90.1, 94.5) |

Note: Participants who had no serological or virological evidence (prior to 7 d after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 d after Dose 2 were included in the analysis.

a. N = number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 d after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. All others = American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

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.

PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (19:22) Source Data: adc19ef Table Generation: 30MAR2021 (22:37) (Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File:./nda2_unblinded/C4591001_BLA/adc19ef_ve_cov_7pd2_wo_sg_eval

Analyses of efficacy by risk status were performed. For these analyses, at risk participants were defined as those who had at least one Charlson Comorbidity Index condition or who were obese (defined as BMI ≥30 kg/m$^2$). Among participants without evidence of SARS-CoV-2 infection before and during the vaccination regimen, the estimated VE was similar for participants at risk (91.6%) and for participants not at risk (91.0%) (Table 14). The estimated VE for participants ≥65 yrs of age and at risk was 91.8%, as compared with 98.1% for those ≥65 yrs of age and not at risk. The estimated VE was similar in obese (91.6%) and non-obese (91.1%) participants.

Results were similar among participants with or without evidence of SARS-CoV-2 infection before and during the vaccination regimen.

**Table 14: Vaccine efficacy – First COVID-19 occurrence from 7 d after Dose 2, by risk status – Blinded Placebo-controlled follow-up period - Participants without evidence of infection prior to 7 d after Dose 2 – Evaluable Efficacy (7 d) Population**

| | Vaccine group (as randomized) | | | | | |
|---|---|---|---|---|---|---|
| | BNT162b2 (30 µg) (N[a]=20,998) | | Placebo (N [a]=21,096) | | | |
| Efficacy Endpoint Subgroup | n1 [b] | Surveillance Time[c] (n2 [d]) | n1 [b] | Surveillance Time[c] (n2 [d]) | VE (%) | (95% CI [e]) |
| **First COVID-19 occurrence from 7 d after Dose 2** | | | | | | |
| Overall | 77 | 6.247 (20,712) | 850 | 6.003 (20,713) | 91.3 | (89.0, 93.2) |
| **At risk [f]** | | | | | | |
| Yes | 35 | 2.797 (9,167) | 401 | 2.681 (9,136) | 91.6 | (88.2, 94.3) |
| No | 42 | 3.450 (11,545) | 449 | 3.322 (11,577) | 91.0 | (87.6, 93.6) |
| **Age group (years) and at risk** | | | | | | |
| 12-15 and not at risk | 0 | 0.121 (788) | 11 | 0.116 (769) | 100.0 | (61.9, 100.0) |
| 12-15 and at risk | 0 | 0.034 (213) | 5 | 0.032 (203) | 100.0 | (-2.0, 100.0) |
| 16-64 and not at risk | 41 | 2.776 (8,887) | 385 | 2.661 (8,886) | 89.8 | (85.9, 92.8) |
| 16-64 and at risk | 29 | 2.083 (6,632) | 325 | 1.993 (6,629) | 91.5 | (87.5, 94.4) |
| ≥65 and not at risk | 1 | 0.553 (1,870) | 53 | 0.546 (1922) | 98.1 | (89.2, 100.0) |
| ≥65 and at risk | 6 | 0.680 (2,322) | 71 | 0.656 (2,304) | 91.8 | (81.4, 97.1) |
| **Obese [g]** | | | | | | |
| Yes | 27 | 2.103 (6,796) | 314 | 2.050 (6,875) | 91.6 | (87.6, 94.6) |
| No | 50 | 4.143 (13,911) | 536 | 3.952 (13,833) | 91.1 | (88.1, 93.5) |

| Efficacy Endpoint Subgroup | Vaccine group (as randomized) BNT162b2 (30 µg) (N[a]=20,998) n1 [b] | Surveillance Time[c] (n2 [d]) | Placebo (N [a]=21,096) n1 [b] | Surveillance Time[c] (n2 [d]) | VE (%) | (95% CI [e]) |
|---|---|---|---|---|---|---|
| **Age group (years) and obese** | | | | | | |
| 12-15 and not obese | 0 | 0.135 (878) | 13 | 0.131 (867) | 100.0 | (68.3, 100.0) |
| 12-15 and obese | 0 | 0.019 (123) | 3 | 0.016 (105) | 100.0 | (-104.8, 100.0) |
| 16-64 and not obese | 46 | 3.178 (10,212) | 444 | 3.028 (10,166) | 90.1 | (86.6, 92.9) |
| 16-64 and obese | 24 | 1.680 (5,303) | 266 | 1.624 (5,344) | 91.3 | (86.7, 94.5) |
| ≥65 and not obese | 4 | 0.829 (2,821) | 79 | 0.793 (2,800) | 95.2 | (87.1, 98.7) |
| ≥65 and obese | 3 | 0.404 (1,370) | 45 | 0.410 (1,426) | 93.2 | (78.9, 98.7) |

Note: Participants who had no serological or virological evidence (prior to 7 d after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 d after Dose 2 were included in the analysis.

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 d after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. Includes participants who had at least one of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m$^2$ [≥16 Years of age] or BMI ≥95$^{th}$ percentile [12-15 yrs of age]).
g. Participants (≥16 yrs of age) who had BMI ≥30 kg/m$^2$. For 12 through 15 yrs age group, obesity is defined as a BMI at or above the 95$^{th}$ percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

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.

PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (19:22) Source Data: adc19ef Table Generation: 30MAR2021 (22:35) (Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File:./nda2_unblinded/C4591001_BLA/adc19ef_ve_cov_7pd2_wo_rg_eval

#### *6.1.2.2.3 Vaccine efficacy for severe COVID-19 cases*

Among participants without evidence of SARS-CoV-2 infection, and among participants with or without evidence of SARS-CoV-2 infection before and during vaccination, the estimated VE against severe COVID-19 as defined by US Food and Drug Administration (FDA) occurring at least 7 d after Dose 2 was 95.3% with 1 and 21 cases in the BNT162b2 and placebo groups, respectively, in analyses of both populations (Table 15).

***All confirmed cases of severe COVID-19 after Dose 1***

Following Dose 1 there was one case of severe COVID-19 as defined by FDA in the BNT162b2 group compared to 30 cases in the placebo group, corresponding to an estimated VE against severe COVID-19 occurring after Dose 1 of 96.7% (2-sided 95% CI: 80.3%, 99.9%).

**Table 15: Vaccine efficacy for severe COVID-19 cases**

| | Vaccine group (as randomized) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | BNT162b2 (30 µg) | | | Placebo | | | | | |
| Efficacy Endpoint | N[a] | n1[b] | Surveillance Time (n2[d]) | N[a] | n1[b] | Surveillance Time[c] (n2[d]) | VE (%) | (95% CI[e]) | Pr (VE >30% \| data)[f] |
| First severe COVID-19 occurrence from 7 d after Dose 2 (Participants without evidence of infection) [g] | 20,998 | 1 | 6.257 (20,712) | 21,096 | 21 | 6.120 (20,713) | 95.3 | (71.0, 99.9) | >0.9999 |
| First severe COVID-19 occurrence from 7 d after Dose 2 (Participants with or without evidence of infection) | 22,166 | 1 | 6.522 (21,649) | 22,320 | 21 | 6.404 (21,730) | 95.3 | (70.9, 99.9) | >0.9999 |

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 d after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. 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.
g. Participants who had no serological or virological evidence (prior to 7 d after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding ant body [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 d after Dose 2 were included in the analysis.

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; VE = vaccine efficacy.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (19:19) Source Data: adc19ef Table Generation: 27MAR2021 (02:26) (Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File:./nda2_unblinded/C4591001_BLA/adc19ef_ve_sev_cov_7pd2_wo_eval
./nda2_unblinded/C4591001_BLA/adc19ef_ve_sev_cov_7pd2_eval

#### *6.1.2.2.4 Efficacy in adolescents (12 through 15 yrs of age)*

Efficacy was assessed in an updated analysis of data from Study C4591001/BNT162-02 for the 12 to 15 yrs of age group based on all cases of COVID-19 accrued for this group in blinded follow-up to a data cutoff date of 13 MAR 2021. Data were derived from ~2,200 participants 12 to 15 yrs of age among who a majority had follow-up time to at least 2 months after Dose 2.

Among adolescent participants without evidence of SARS-CoV-2 infection before and during vaccination, there were no COVID-19 cases with onset from at least 7 d after Dose 2 in the BNT162b2 group, and 16 COVID-19 cases in the placebo group, corresponding to an observed VE of 100% (2-sided 95% CI: 75.3%,100.0%) (Table 16).

Among adolescent participants with or without evidence of SARS-CoV-2 infection before and during vaccination, there were no COVID-19 cases with onset from at least 7 d after

Dose 2 in the BNT162b2 group, and 18 COVID-19 cases in the placebo group, corresponding to an observed VE of 100% (2-sided 95% CI: 78.1%,100.0%) (Table 16).

The observed VE for first occurrence of COVID-19 after Dose 1 was 91.6% (2-sided 95% CI: 73.5%, 98.4%) with three cases of COVID-19 in the BNT162b2 group and 35 cases in the placebo group (Dose 1 all-available [modified intention-to-treat] population). After Dose 1 and before Dose 2, there were three cases of COVID-19 in the BNT162b2 group and 12 cases in the placebo group. The three cases in the BNT162 group all occurred within the period from after Dose 1 to < 11 d after Dose 1 and all three of these cases occurred in participants who had baseline SARS-CoV-2 negative status. No cases of COVID-19 were reported in the BNT162b2 group starting from ≥11 d after Dose 1.

No severe COVID-19 cases (per protocol definition or CDC criteria) were reported in adolescents (12 to 15 yrs of age) as of the data cutoff date (13 MAR 2021).

**Table 16: Vaccine efficacy – First COVID-19 occurrence from 7 d after Dose 2 – Blinded placebo-controlled follow-up period – Adolescent participants without, and adolescent participants with or without evidence of infection prior to 7 d after Dose 2 – Evaluable Efficacy (7 d) Population**

| | Vaccine Group (as Randomized) | | | | | |
|---|---|---|---|---|---|---|
| | BNT162b2 (30 µg) (N[a]=1,005) | | Placebo (N[a]=978) | | | |
| Efficacy Endpoint | n1[b] | Surveillance Time[c] (n2[d]) | n1[b] | Surveillance Time[c] (n2[d]) | VE (%) | (95% CI[e]) |
| First COVID-19 occurrence from 7 d after Dose 2 (participants without evidence of infection)[f] | 0 | 0.154 (1,001) | 16 | 0.147 (972) | 100.0 | (75.3, 100.0) |
| First COVID-19 occurrence from 7 d after Dose 2 (participants with or without evidence of infection) | 0 | 0.170 (1,109) | 18 | 0.163 (1,094) | 100.0 | (78.1, 100.0) |

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 d after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. Participants who had no serological or virological evidence (prior to 7 d after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding ant body [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 d after Dose 2 were included in the analysis.

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.

PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (19:19) Source Data: adc19ef Table Generation: 30MAR2021 (22:23) (Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File:./nda2_unblinded/C4591001_BLA/adc19ef_ve_cov_7pd2_peds_wo_eval and ./nda2_unblinded/C4591001_BLA/adc19ef_ve_cov_7pd2_peds_eval

#### *6.1.2.2.5 Efficacy conclusions from Study C4591001/BNT162-02*

Updated efficacy results up to 6 months post-Dose 2, show that BNT162b2 at 30 µg provided protection against COVID-19 in participants ≥16 yrs of age regardless of evidence of past infection with SARS-CoV-2, including across demographic and risk subgroups, with severe cases observed predominantly in the placebo group. In adolescents 12 to 15 yrs of age, efficacy data suggest highly effective protection against COVID-19 in a broad population across demographic characteristics including age and prior SARS-CoV-2 infection.

### 6.1.2.3 Summary of immunogenicity in Study C4591001/BNT162-02

#### *6.1.2.3.1 Phase 1 immunogenicity after 2 doses*

**BNT162b1 – Summary of immunogenicity**

SARS-CoV-2 neutralizing titers and IgG responses (as measured by RBD-binding IgG levels) for BNT162b1 were similar to those observed in BNT162-01 (Sahin et al. 2020a; Walsh et al. 2020).

**BNT162b2 – Summary of immunogenicity**

***Persistence of immune response up to 6 months after Dose 2 of BNT162b2 30 µg***

Neutralizing titers and S1-binding IgG concentrations were evaluated up to 6 months after Dose 2 for the Phase 1 groups of participants who received BNT162b2 at 30 µg and corresponding placebo recipients.

Among participants who received the 30 µg dose level of BNT162b2, in both age groups, the observed SARS-CoV-2 serum 50% neutralizing GMTs peaked 1 month after Dose 2 (Day 52) and then declined at 6 months after Dose 2 (Day 202). In the younger age group, GMTs were 179.2 at 1 month after Dose 2 and 54.7 at 6 months after Dose 2; in the older age group GMTs declined from 151.6 to 29.0. Observed S1-binding IgG GMCs followed a similar time course.

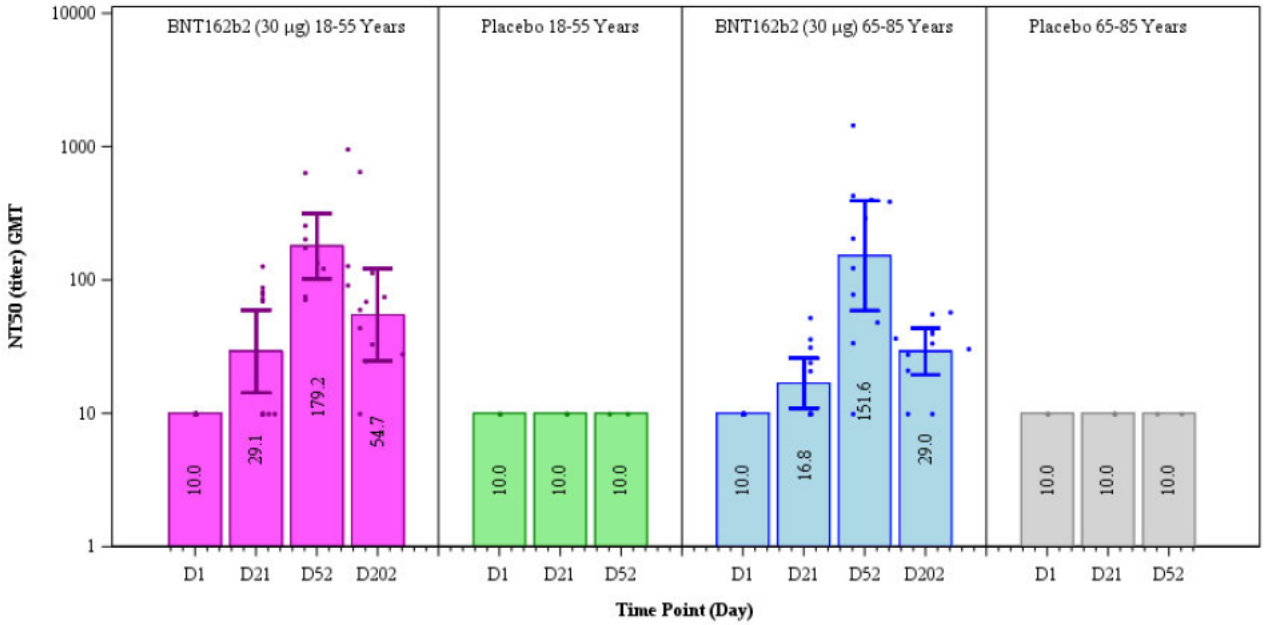
At 6 months after Dose 2, both neutralizing antibody GMTs and S1-binding IgG GMCs remained higher than pre-vaccination and placebo control levels.

For Phase 1 data available up to 6 months after Dose 2, neutralizing antibody GMTs are shown in Figure 23 and S1-binding IgG GMCs are shown in Figure 24.

***Number (%) of participants achieving a ≥4-fold rise from baseline***

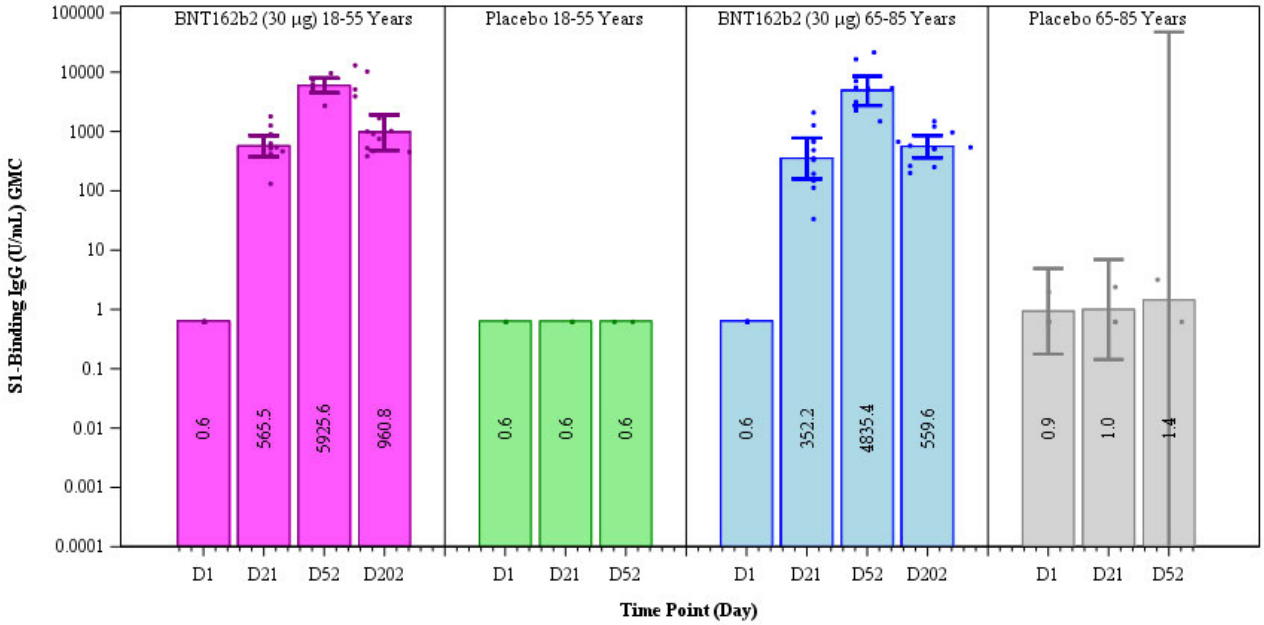
In the younger age group, the proportions of participants achieving a ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination to each time point were: 50.0% (6/12) at Day 21; 100.0% (11/11) at 1 month after Dose 2; and 60.0% (6/10) at 6 months after Dose 2 of BNT162b2 30 µg. In the older age group, these proportions were 9.1% (1/11) at Day 21; 81.8% (9/11) at 1 month after Dose 2; and 27.3% (3/11) at 6 months after Dose 2 of BNT162b2 30 µg.

With respect to S1-binding IgG concentrations, 100% of participants in both age groups had a ≥4-fold rise from baseline at Day 21, at 1 month after Dose 2, and at 6 months after Dose 2.




Abbreviations: D = day; GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Blood samples from the Day 7 and Day 14 post–Dose 2 visits are not included since these samples were not retested with the 6-month post–Dose 2 samples.
Note: Dots represent individual antibody levels.
Note: Number within each bar denotes geometric mean titer.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:25) Source Data: adva Table Generation: 01APR2021 (02:17)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA1/adva_f002_sars_50_b2_p1

**Figure 23: GMTs and 95% CI: SARS-CoV-2 neutralization assay – NT50 – Phase 1, 2 Doses, 21 d apart – BNT162b2 (30 µg)/Placebo – Evaluable Immunogenicity Population**



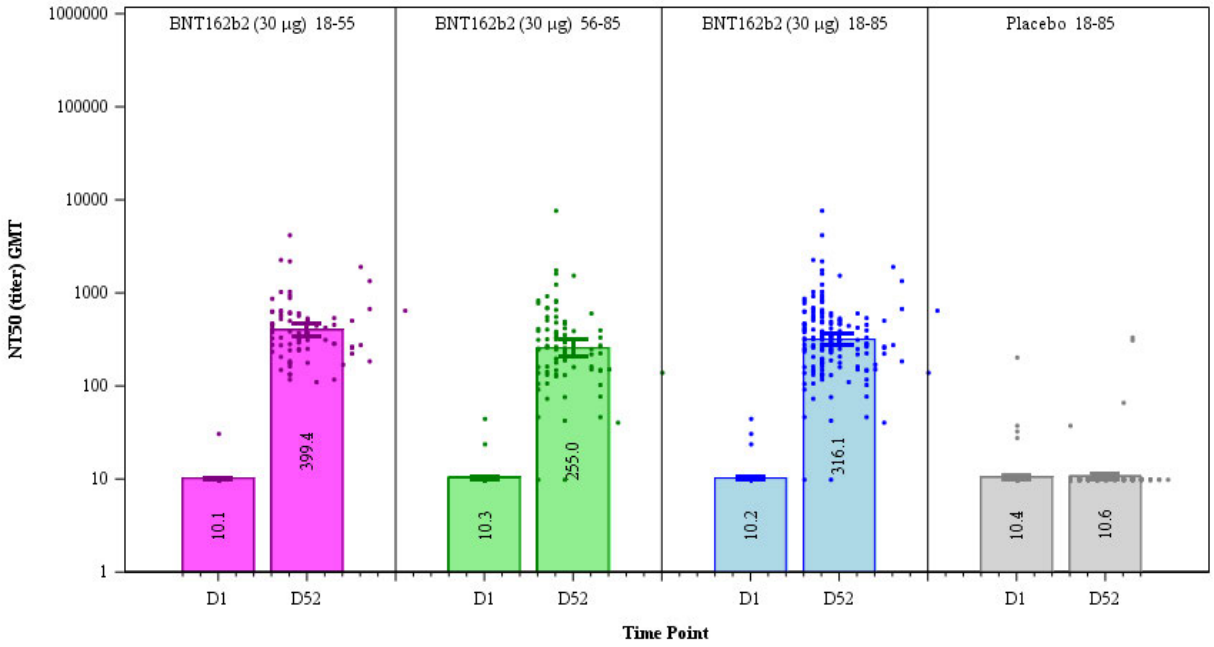

Abbreviations: D = day; GMC = geometric mean concentration; IgG = immunoglobulin G; S1 = spike protein S1 subunit.
Note: Blood samples from the Day 7 and Day 14 post–Dose 2 visits are not included since these samples were not retested with the 6-month post–Dose 2 samples.
Note: Dots represent individual antibody levels.
Note: Number within each bar denotes geometric mean titer.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:25) Source Data: adva Table Generation: 01APR2021 (02:19)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA1/adva_f002_s1_b2_p1

**Figure 24: GMCs and 95% CI: S1-Binding IgG Level Assay – Phase 1, 2 doses, 21 d apart – BNT162b2 (30 µg)/Placebo – Evaluable Immunogenicity Population**

#### *6.1.2.3.2 Phase 2 immunogenicity after 2 doses*

In the Phase 2 portion of the study, 360 participants were enrolled and randomized 1:1 to BNT162b2 and placebo. Immunogenicity results are currently available for the pre-vaccination and 1-month post-Dose 2 time point for the immunogenicity-evaluable population.

BNT162b2 elicited robust SARS-CoV-2 immune responses at 1 month after Dose 2 defined by SARS-CoV-2 50% neutralizing titers (GMTs) (Figure 25). GMTs were higher in younger participants (18 to 55 yrs of age) than in older participants (56 to 85 yrs of age). Of note, 50% neutralizing GMTs at 1-month post-Dose 2 for both younger (GMT = 399.4) and older participants (GMT = 255.0) in the evaluable immunogenicity population were similar to the GMTs of a comparative panel of human convalescent sera (GMT = 319) (Sahin et al. 2020a; Walsh et al. 2020).




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

**Figure 25: GMTs: SARS-CoV-2 neutralization assay – NT50 – Evaluable Immunogenicity Population – Phase 2**

#### *6.1.2.3.3 Phase 3 immunogenicity*

In Phase 3, exploratory immunogenicity assessments are planned at time points up to 24 months, to be reported at a later time.

#### *6.1.2.3.4 Immunogenicity in adolescents 12 through 15 yrs of age after 2 doses*

An analysis of SARS-CoV-2 50% neutralizing titers 1 month after Dose 2 in a randomly selected subset of participants demonstrated non-inferior immune responses (within 1.5-fold) comparing adolescents 12 through 15 yrs of age to participants 16 through 25 yrs of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2 (Table 17).

**Table 17: Summary of GMR for 50% neutralizing titers – Comparison of adolescents 12 through 15 yrs of age (Immunogenicity Subset) – Participants without evidence of infection up to 1 month after Dose 2 – Dose 2 Evaluable Immunogenicity Population**

| | | BNT162b2 | | | |
|---|---|---|---|---|---|
| | | 12 through 15 years n[a]=190 | 16 through 25 years n[a]=170 | 12 through 15 years/ 16 through 25 years | |
| Assay | Time Point[b] | GMT[c] (95% CI[c]) | GMT[c] (95% CI[c]) | GMR[d] (95% CI[d]) | Met noninferiority objective [e] (Y/N) |
| SARS-CoV-2 neutralization assay - NT50 (titer)[f] | 1 month after Dose 2 | 1,239.5 (1,095.5, 1402.5) | 705.1 (621.4, 800.2) | 1.76 (1.47, 2.10) | Y |

Note: Participants who had no serological or virological evidence (up to 1 month after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. Protocol-specified timing for blood sample collection.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1 [12 through 15 yrs of age] – Group 2 [16 through 25 yrs of age]) and the corresponding CI (based on the Student t distr bution).
e. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
f. SARS-CoV-2 50% neutralization titers (NT50) were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2.

#### *6.1.2.3.5 Immunogenicity following a booster dose (third dose, BNT162b2)*

**Phase 1 booster data**

Phase 1 participants (N=23; 18 to 55 yrs of age and 65 to 85 yrs of age) who had received two doses of BNT162b2 received a booster dose (third dose) of BNT162b2 30 µg, which was administered to most participants ~8 months after their second vaccination (mean = 8.3 months).

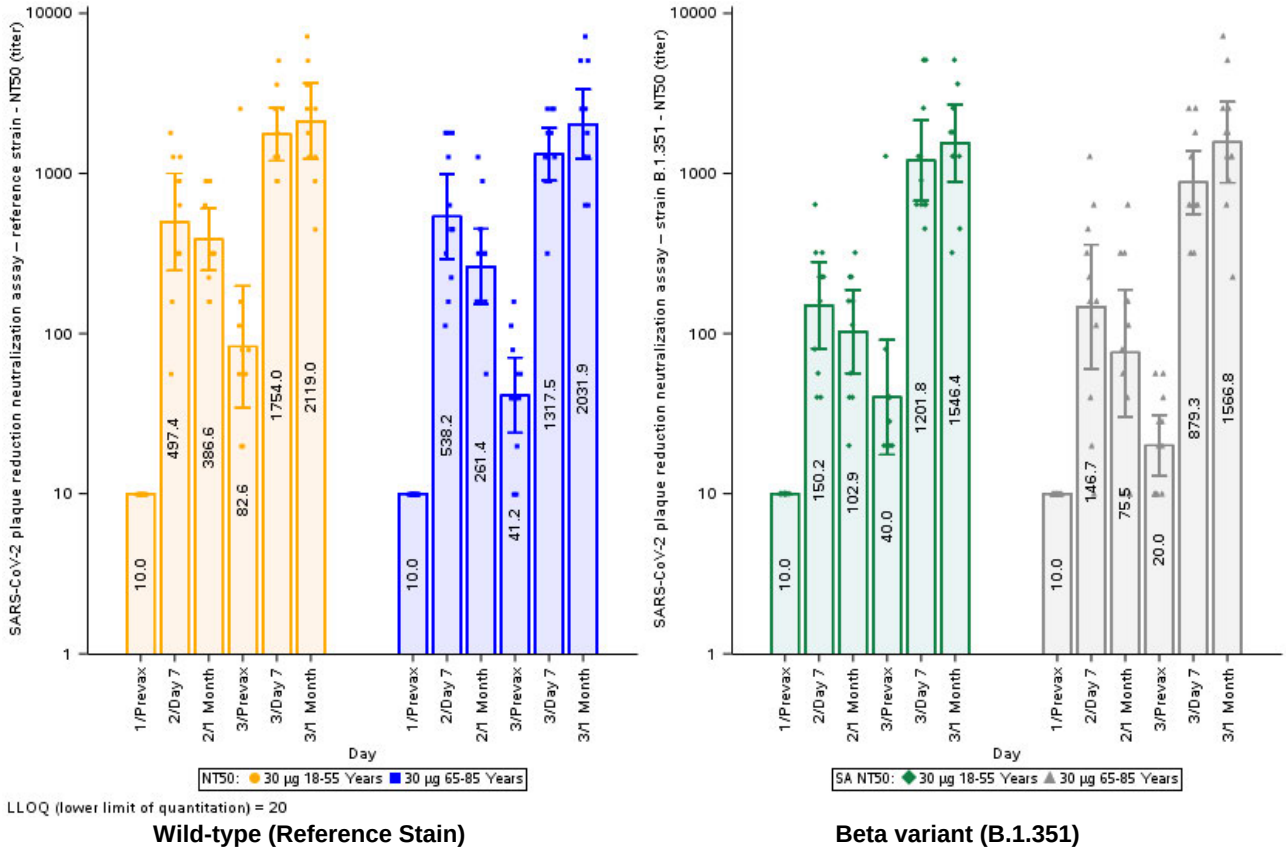
***Neutralization titers against wild-type***

SARS-CoV-2 neutralization GMTs against the wild-type USA-WA1/2020 strain substantially increased after Dose 3. GMTs at 1 month after Dose 3 were 2,119 (95% CI: 1,229.1, 3,653.4) for younger participants 18 to 55 yrs of age, and 2,032 (95% CI: 1,232.6, 3,349.3) for older participants 65 to 85 yrs of age, which were >5-fold and >7-fold, respectively, the GMTs observed at 1 month after Dose 2 (Figure 26, left side). Geometric mean fold rises (GMFR) against the wild-type strain from before Dose 3 to 1 month after Dose 3 were 25.7 (95% CI: 12.4, 53.3) for younger adults, and 49.4 (95% CI: 29.2, 83.3) for older adults. From 7 d to 1 month after the second dose, neutralizing GMTs decreased – in younger adults (from 497.4 to 386.6) and in older adults (from 538.2 to 261.4). In

contrast, from 7 d to 1 month after the third dose, neutralizing GMTs increased – in younger adults (from 1,754.0 to 2,119.0) and in older adults (from 1,317.5 to 2,031.9).

***Neutralization titers against the beta variant***

A third dose also increased the neutralizing titers against recombinant SARS-CoV-2 with the beta variant spike protein. At 1 month after Dose 3, GMTs were 1,546 (95% CI: 888.1, 2,692.4) for younger participants, and 1,567 (95% CI: 875.2, 2,804.7) for older participants, which were >15-fold and >20-fold, respectively, the GMTs observed at 1 month after Dose 2 (Figure 26, right side). GMFRs from before Dose 3 to 1 month after Dose 3 were 38.7 (95% CI: 19.8, 75.5) for younger adults, and 78.3 (95% CI: 40.7, 150.6) for older adults. From 7 d to 1 month after the second dose, neutralizing GMTs decreased – in younger adults (from 150.2 to 102.9) and in older adults (from 146.7 to 75.5). In contrast, from 7 d to 1 month after the third dose, neutralizing GMTs increased – in younger adults (from 1,201.8 to 1,546.4) and in older adults (from 879.3 to 1,566.8).




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

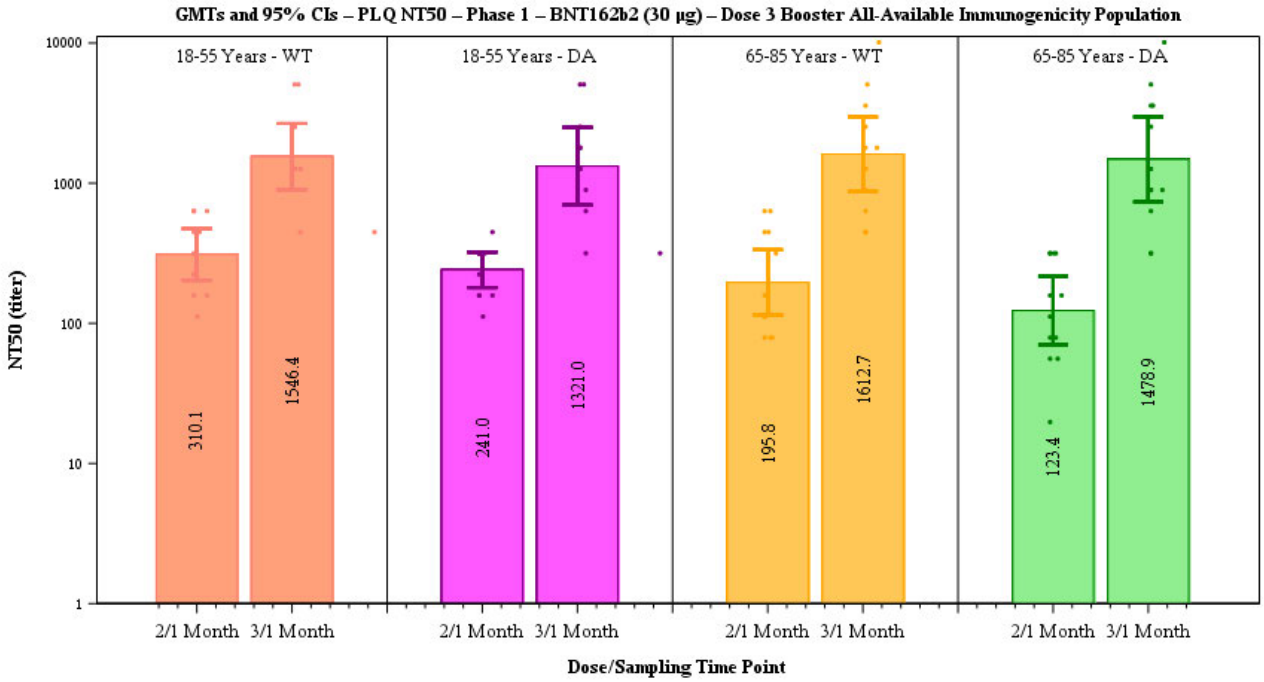
**Figure 26: GMTs and 95% CI: SARS-CoV-2 neutralizing titers (NT50) for wild-type (reference strain) and B.1.351 (Beta) Variant – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster All-Available Immunogenicity Population (18 to 55 yrs of age and 65 to 85 yrs of age)**

The difference between neutralizing titers against the wild-type virus and the beta variant observed after Dose 2 narrowed after BNT162b2 Dose 3 (Figure 26). Specifically, at 1 month after Dose 2, the GMRs of neutralizing titers against the beta variant to

neutralizing titers against the wild-type virus were 0.27 (95% CI: 0.18, 0.39) for younger adults and 0.29 (95% CI: 0.17, 0.49) for older adults; at 1 month after Dose 3, the corresponding GMRs increased to 0.73 (95% CI: 0.52, 1.02) and 0.77 (95% CI: 0.51, 1.16).

***Neutralization titers against the delta variant***

A third dose of BNT162b2 also increased the neutralizing titers against recombinant SARS-CoV-2 with the delta variant spike protein. At 1 month after Dose 3, GMTs were 1,321 (95% CI: 698.5, 2,498.3) for younger adults, and 1,479 (95% CI: 734.9, 2,975.8) for older adults, which were ~5-fold and 12-fold, respectively, the GMTs observed at 1 month after Dose 2 (Figure 27).




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

**Figure 27: GMTs and 95% CIs for SARS-CoV-2 plaque reduction neutralization assay (NT50) for wild-type (reference strain) and B.1.617.2 (delta) variant – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster All-Available Immunogenicity Population (18 to 55 yrs of age and 65 to 85 yrs of age)**

The difference between neutralizing titers against the wild-type virus and the delta variant observed after Dose 2 narrowed after BNT162b2 Dose 3 (Figure 27). Specifically, at 1 month after Dose 2, the GMRs of neutralizing titers against the delta variant to neutralizing titers against the wild-type virus were 0.78 (95% CI: 0.63, 0.96) for younger adults and 0.63 (95% CI: 0.46, 0.86) for older adults; at 1 month after Dose 3, the

corresponding GMRs increased to 0.85 (95% CI: 0.71, 1.03) and 0.92 (95% CI: 0.71, 1.18), respectively.

**Phase 3 booster data**

A booster dose (Dose 3) of BNT162b2 30 µg was administered to 306 Phase 3 participants (18 to 55 yrs of age) without prior evidence of SARS-CoV-2 infection ~6 months after completing the 2-dose regimen. The immune response was evaluated at 1 month after Dose 3.

***Noninferiority of the booster response (Dose 3 relative to Dose 2)***

*GMR for neutralization titers (Dose 3 relative to Dose 2)*

Based on SARS-CoV-2 50% neutralizing titers, the immune response to BNT162b2 30 µg at 1 month after the booster (Dose 3) was non-inferior to that observed at 1 month after Dose 2 in the same participants (Table 18). The SARS-CoV-2 neutralizing GMT ratio of 1 month after Dose 3 to 1 month after Dose 2 was 3.29 (2-sided 97.5% CI: 2.76, 3.91), which meets the 1.5-fold noninferiority criterion (i.e., lower bound of the 2-sided 97.5% CI for GMR >0.67) and point estimate of GMR ≥0.8.

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

*Difference in seroresponse rate (Dose 3 relative to Dose 2)*

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after the booster (Dose 3), a high proportion of participants (99.5%) had a seroresponse at 1 month after Dose 3, compared with 98.0% at 1 month after Dose 2 (Table 18).

**Table 18: GMRs – Comparison of 1 month after booster Dose to 1 month after Dose 2 – Phase 3 – BNT162b2-experienced participants without evidence of infection up to 1 month after booster dose who were rerandomized to receive 1 booster dose of BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population**

| | | | | | Sampling time point | | |
|---|---|---|---|---|---|---|---|
| | | | | | 1 mon after booster dose | 1 mon after Dose 2 (BNT162b2) | 1 mon after booster Dose/1 mon after Dose 2 |
| Objective [a] | Assay at 1 mon after booster dose | Assay at 1 mon after Dose 2 | Vaccine group (as randomized) | n[b] | GMT[c] (95% CI[c]) | GMT[c] (95% CI[c]) | GMR[d] (97.5% CI[e]) |
| E1a | SARS-CoV-2 neutralization assay - reference strain - NT50 (titer) | SARS-CoV-2 neutralization assay - reference strain - NT50 (titer) | BNT162b2 (30 µg) | 210 | 2,476.4 (2,210.1, 2774.9) | 753.7 (658.2, 863.1) | 3.29 (2.76, 3.91) |

Note: Participants who had no serological or virological evidence (up to 1 month after receipt of booster vaccination) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visits 1, 3, 301, and 303 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1, 2, and 301) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster vaccination were included in the analysis.

a. The first primary objective to be evaluated in Phase 3 booster portion of the study, where 'E' represents BNT162b2-experienced participants and 'a' represents GMR estimands.
b. n = Number of participants with valid and determinate assay results for both the specified assays at the given dose/sampling time point within specified window.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
e. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8.

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; mon = month(s); N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2.

The difference in proportions of participants with a seroresponse 1 month after the booster (Dose 3) and 1 month after Dose 2 (Dose 3 – Dose 2) was 1.5% (2-sided 97.5% CI: -0.7, 3.7%), which meets the 10% noninferiority margin (i.e., lower bound of the 2-sided 97.5% CI was greater than 10%) (Table 19).

**Table 19: Percentage difference of participants achieving seroresponse – Comparison of 1 month after booster dose to 1 month after Dose 2 – Phase 3 – BNT162b2-experienced participants without evidence of infection up to 1 month after booster dose who were rerandomized to receive 1 booster dose of BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population**

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

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a post-vaccination assay result ≥4 × LLOQ is considered a seroresponse.
Note: Participants who had no serological or virological evidence (up to 1 month after receipt of booster vaccination) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visits 1, 3, 301, and 303 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1, 2, and 301) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster vaccination were included in the analysis.

a. The first primary objective to be evaluated in Phase 3 booster portion of the study, where 'E' represents BNT162b2-experienced participants and 'b' represents seroresponse rate estimands.
b. N = number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
f. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
g. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is greater than -10.

Abbreviations: LLOQ = lower limit of quantitation; mon = month(s); N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2.

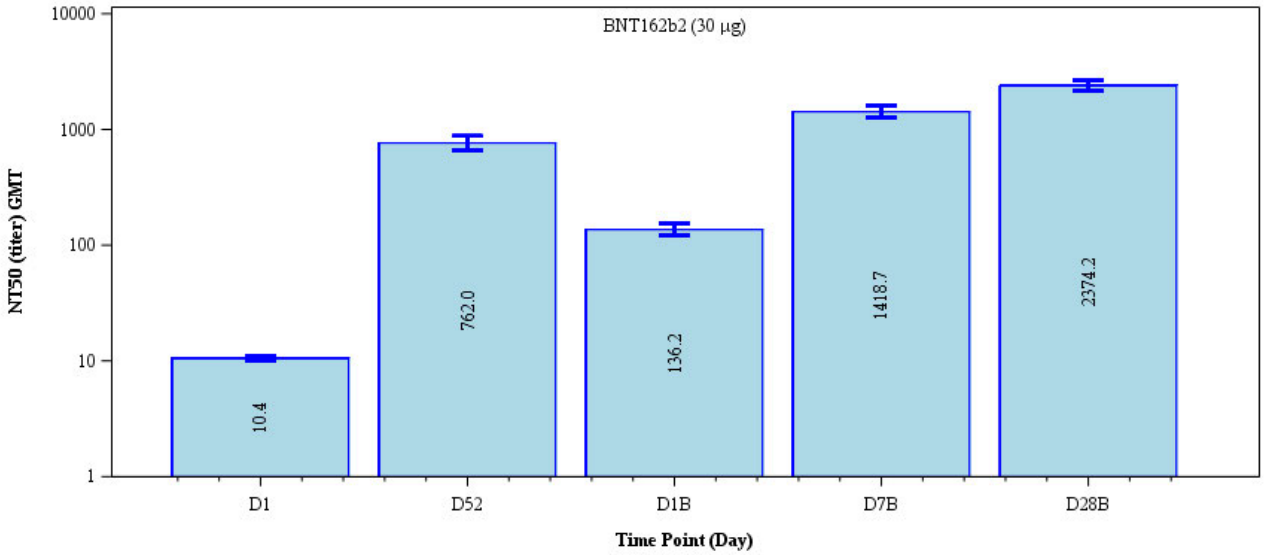
### *SARS-CoV-2 neutralizing titers and fold rises*

*Geometric mean titers (GMTs)*

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after the booster (third) dose, the SARS-CoV-2 50% neutralizing GMT increased substantially after the booster vaccination, from 136.2 before Dose 3 to 2,374.2 1 month after Dose 3 (Figure 28). The GMT after the booster dose was 3 times those observed 1 month after Dose 2, showing a strong boost of the neutralizing antibody response.

From baseline (prior to receipt of Dose 1) to 1 month after Dose 2, the GMT substantially increased to 73-times the pre-vaccination GMT, from 10.4 (2-sided 95% CI: 10.0, 10.9) to 762.0 (2-sided 95% CI: 663.3, 875.5). The median duration between receipt of Dose 2 and the booster with Dose 3 was 6.8 months. The GMT had declined by the time the booster (Dose 3) was administered: from 762.0 (2-sided 95% CI: 663.3, 875.5) 1 month after Dose 2 to 136.2 (2-sided 95% CI: 121.5, 152.6) at the time of booster administration. Following the booster (third) dose, the GMT increased to 1,418.7 (95% CI: 1,263.3,

1,593.3) at 7 d post-Dose 3. By 1 month after Dose 3, the GMT increased further to 2,374.2 (95% CI: 2,134.1, 2,641.3).




Abbreviations: B = booster vaccination; D = day; GMT = geometric mean titer; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subjects who had no serological or virological evidence (up to 1 month after receipt of booster vaccination) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1, 3, 301, and 303 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1, 2, and 301) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster vaccination were included in the analysis.
Note: Number within each bar denotes geometric mean titer.
PFIZER CONFIDENTIAL SDTM Creation: 16AUG2021 (09:19) Source Data: adva Table Generation: 18AUG2021 (22:21)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adva_f002_nt50_p3_g1

**Figure 28: GMTs and 95% confidence intervals, reference strain SARS-CoV-2 neutralization assay – NT50 – Phase 3 – BNT162b2-experienced participants without evidence of infection up to 1 month after booster dose who were rerandomized to receive 1 booster dose of BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population**

### *GMFR in titers*

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

### *Seroresponse rate*

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

(Dose 3) the seroresponse rate increased further to 99.5% (2-sided 95% CI: 97.4%, 100.0%).

#### *6.1.2.3.6 Immunogenicity conclusions from Study C4591001/BNT162-02*

In Study C4591001, BNT162b2 elicited robust SARS-CoV-2 neutralizing antibody response starting from 7 d after Dose 2 in younger and older adults. Responses were generally stronger in younger adults than in older adults. For the groups that received BNT162b2 at 30 µg, persistence of the immune response was observed through 6 months after Dose 2. SARS-CoV-2 serum neutralizing titers and serum S1-binding IgG concentrations at 6 months after Dose 2 had decreased relative to those observed at 1 month after Dose 2 but remained above pre-vaccination and placebo levels.

Immunogenicity results from ~360 participants in Phase 2 of Study C4591001 showed BNT162b2 at 30 µg elicited robust SARS-CoV-2 neutralization and S1-binding IgG antibody responses at 1 month after Dose 2 similar to those previously observed in Phase 1 of the study.

In adolescents 12 to 15 yrs of age, the immune response was non-inferior to that observed in young adults 16 to 25 yrs of age based on SARS-CoV-2 50% neutralizing titers.

Phase 1 and Phase 3 booster data show that a third dose of BNT162b2 administered ~6 months after completing the 2-dose regimen induces a strong and broad immune response that is expected to confer extended protection against COVID-19, including variants of concern.

### 6.1.2.4 Summary of safety in Study C4591001/BNT162-02

#### *6.1.2.4.1 Phase 1 safety after 2 doses*

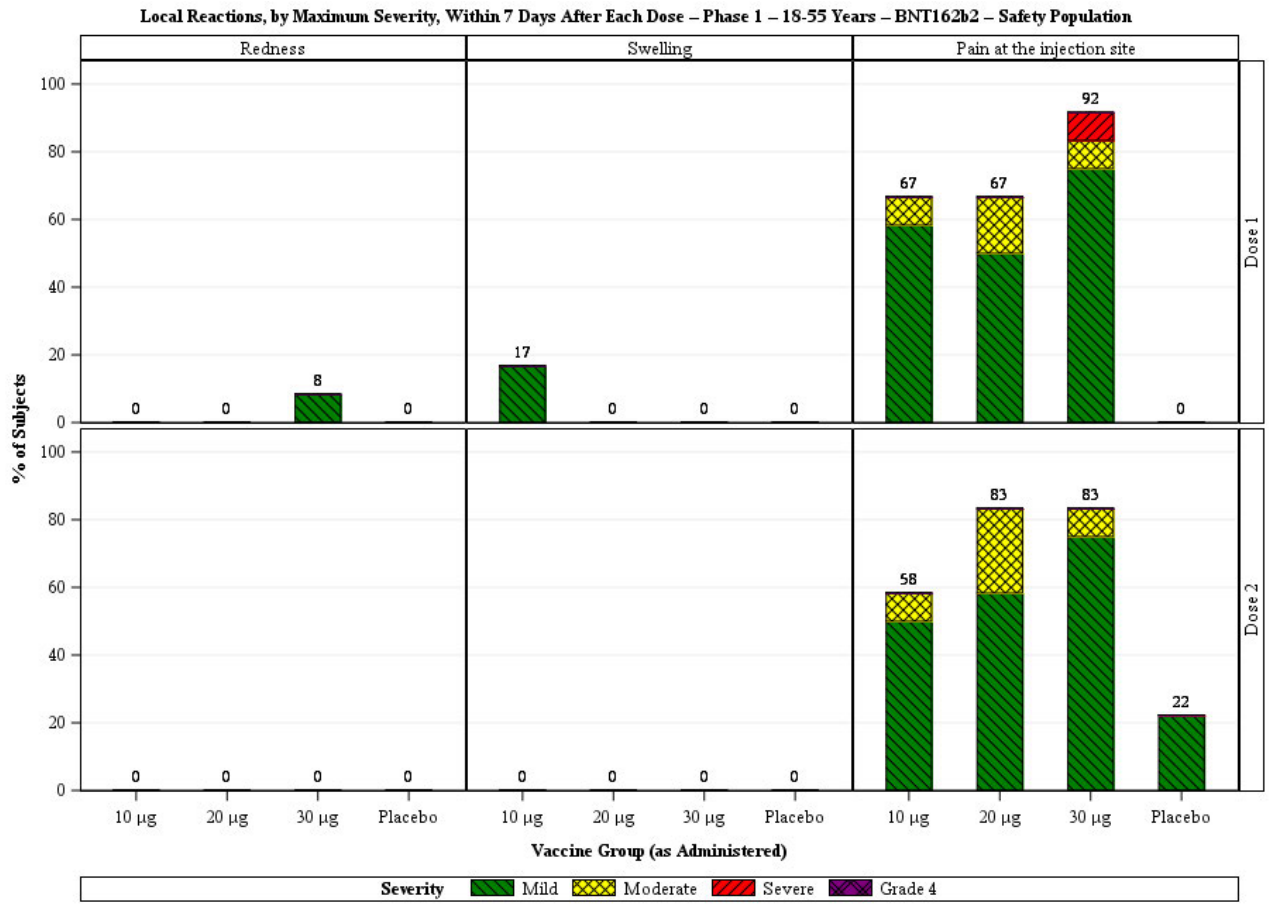
Overall, the dose levels 10, 20, and 30 µg of BNT162b1 and BNT162b2 exhibited a consistent tolerability and safety profile. The tolerability in older adults appears to be better than seen in younger adults at the same doses. Based on the tolerability profile observed with the BNT162b1 100 µg dose level after Dose 1, an internal decision was made not to give Dose 2 at 100 µg.

The available safety and tolerability data for younger and older adults dosed with BNT162b1 were broadly comparable to those in study BNT162-01.

Safety results are summarized in Mulligan et al. 2020 and Walsh et al. 2020.

***Local reactions – BNT162b2***

For BNT162b2 recipients, the frequency of local reactions was lower for the older group compared to the younger group (Figure 29 and Figure 30). Local reactions were generally infrequent in placebo recipients. The majority of local reactions in the BNT162b2 groups were mild or moderate in severity and resolved within several days of onset. No grade 4 (potentially life-threatening) reactions were reported. Pain at the injection site was the most frequent prompted local reaction across number of doses and dose levels in both age groups (33% to 92%), and redness (0% to 8%) and swelling (0% to 17%) were infrequent.




Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
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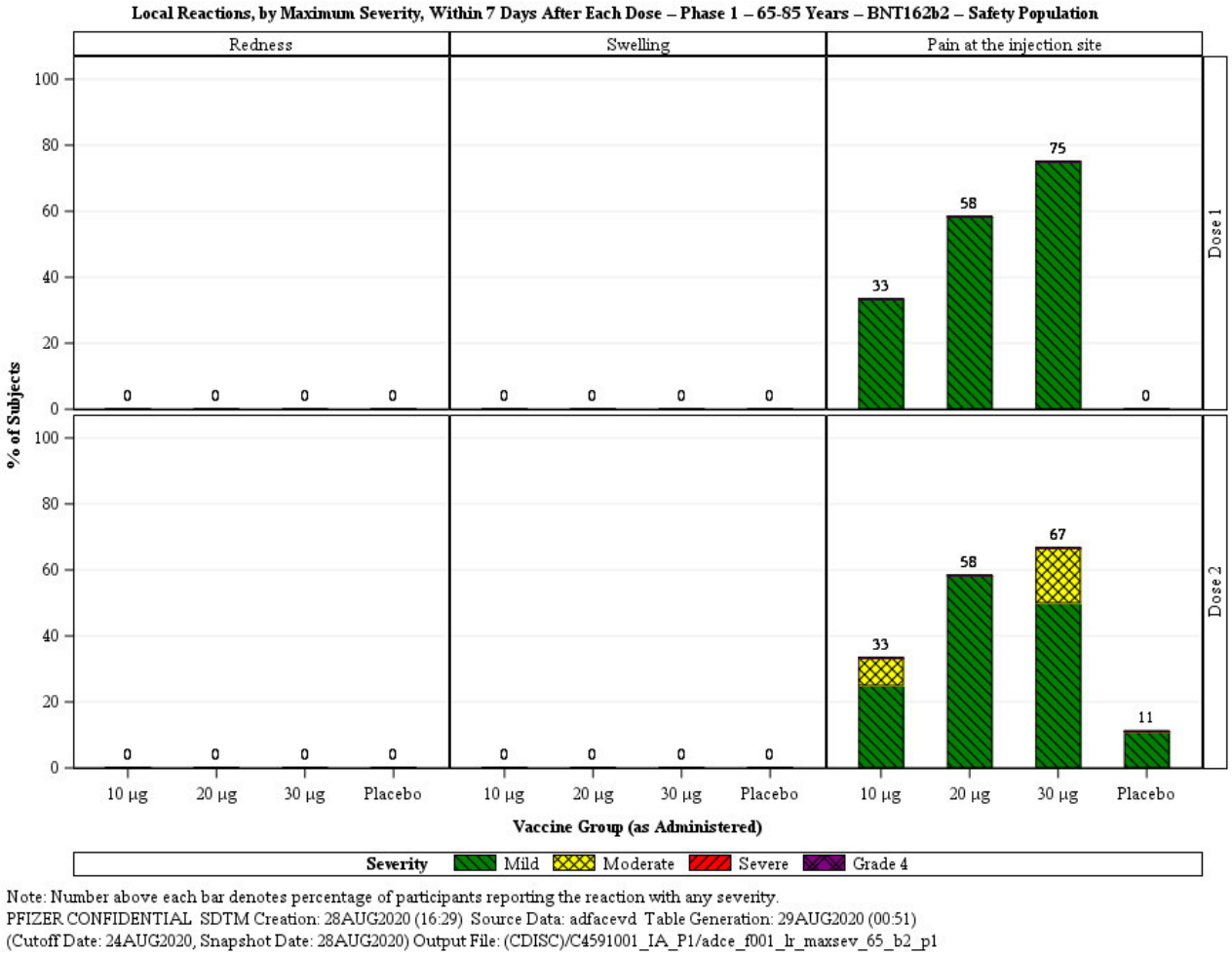
(Cutoff Date: 24AUG2020, Snapshot Date: 28AUG2020) Output File: (CDISC)/C4591001_IA_P1/adce_f001_lr_maxsev_18_b2_p1

**Figure 29: Participants reporting local reactions, by maximum severity, within 7 d after each dose – Phase 1, 2 Doses, 21 d apart – 18 to 55 yrs of age – BNT162b2 – Safety Population**

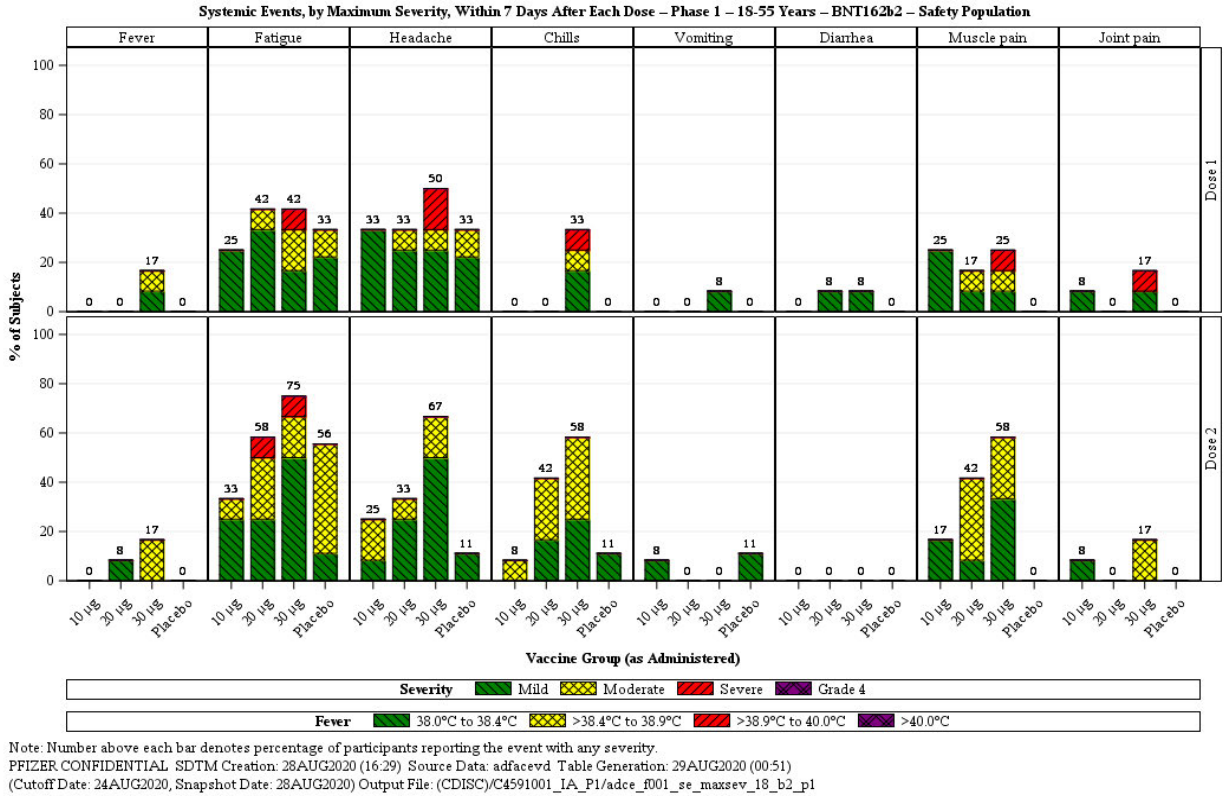



Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 28AUG2020 (16:29) Source Data: adfacevd Table Generation: 29AUG2020 (00:51)
(Cutoff Date: 24AUG2020, Snapshot Date: 28AUG2020) Output File: (CDISC)/C4591001_IA_P1/adce_f001_lr_maxsev_65_b2_p1

**Figure 30: Participants reporting local reactions, by maximum severity, within 7 d after each dose – Phase 1, 2 Doses, 21 d apart – 65 to 85 yrs of age – BNT162b2 – Safety Population**

### *Systemic events – BNT162b2*

The frequency of systemic events was lower for the older group compared to the younger group (Figure 31 and Figure 32). Notably, in the older group, frequencies of systemic events after the first dose were similar between BNT162b2 and placebo recipients. Systemic events were generally infrequent in placebo recipients. Prompted systemic events generally increased in frequency and/or severity with increasing dose level and number of doses of BNT162b2. Use of antipyretic/pain medication also increased in frequency with increasing dose level and number of doses. Most systemic events were mild or moderate, arose within the first 1 to 4 d after dosing, and resolved within 1 to 3 d of onset. No grade 4 (potentially life-threatening) events were reported. The most frequent prompted systemic events across number of doses and dose levels in both age groups were fatigue (8% to 75%), headache (0% to 67%), chills (0% to 58%), and muscle pain (0% to 58%). Fever was infrequent (0% to 17%).




Note: Number above each bar denotes percentage of participants reporting the event with any severity.
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(Cutoff Date: 24AUG2020, Snapshot Date: 28AUG2020) Output File: (CDISC)/C4591001_IA_P1/adce_f001_se_maxsev_18_b2_p1

**Figure 31: Participants reporting systemic events, by maximum severity, within 7 d after each dose – Phase 1, 2 doses, 21 d apart – 18 to 55 yrs of age – BNT162b2 – Safety Population**

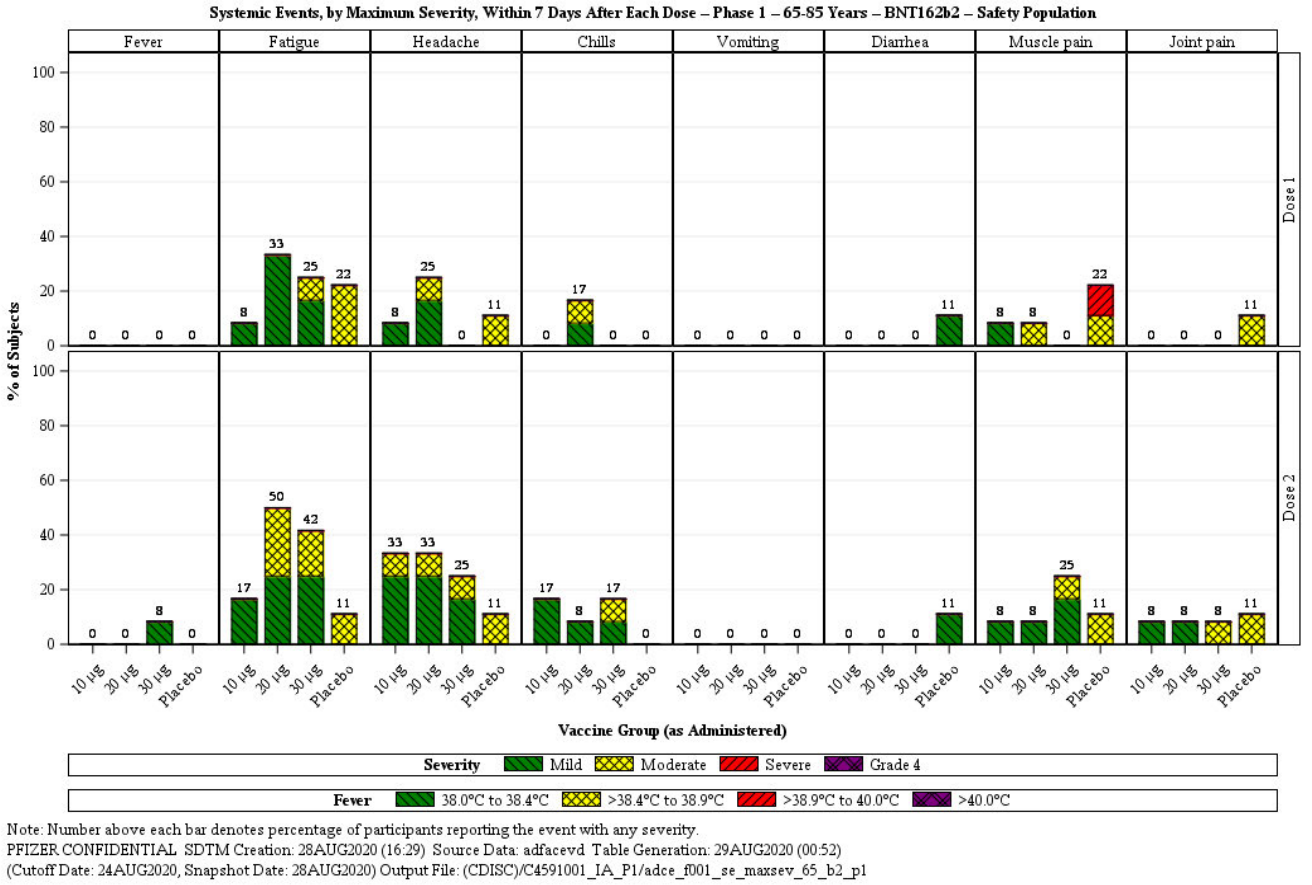



**Figure 32: Participants reporting systemic events, by maximum severity, within 7 d after each dose – Phase 1, 2 doses, 21 d apart – 65 to 85 yrs of age – BNT162b2 – Safety Population**

***Adverse events – BNT162b2***

All participants in each age group randomized to receive BNT162b2 completed the visit at 6 months after Dose 2, with most of these 6-month visits occurring during the open-label follow-up period. All participants in each age group randomized to the placebo group received both doses of BNT162b2 (Dose 3 and Dose 4 in the study) during the open-label period and completed the visit at 1 month after Dose 4, as of the data cutoff date of 13 MAR 2021. No participants were withdrawn from the study up to the data cutoff date.

In the Phase 1 portion of Study C4591001/BNT162-02, the majority of participants who received both BNT162b1 and BNT162b2 across age groups and dose levels reported one or more AEs after vaccine dosing (from Dose 1 onwards). AEs were reported at higher frequencies in BNT162b1 and BNT162b2 vaccine groups compared with placebo, across age groups and dose levels. AE incidences were generally lower in the older age groups compared with the younger age groups. Across BNT162b1 dose levels, 42% to 50% of younger participants and 25% to 58% of older participants reported AEs. Across BNT162b2 dose levels, 33% to 42% of younger participants and 8% to 25% of older participants reported AEs. Placebo recipients, in both the younger and older groups, reported AEs in 22% to 44% of participants.

Overall, most AEs reported were considered by the investigator as not related to study intervention. Most AEs were mild to moderate in severity. No SAEs, deaths, or discontinuations due to AEs were reported in the Phase 1 part of the study up to 1 month after Dose 2.

**Safety follow-up to at least 6 months after Dose 2 in BNT162b2 30 µg groups**

From Dose 1 of BNT162b2 30 µg to the unblinding date, 6 (50.0%) participants in the younger age group and 3 (25.0%) participants in the older age group reported at least 1 AE. Two (16.7%) participants in the BNT162b2 30 µg younger age group and 1 (8.3%) participant in the BNT162b2 30 µg older age group reported at least 1 severe AE. In the BNT162b2 30 µg younger age group, 3 (25.0%) participants reported at least 1 related AE and 1 (8.3%) participant reported 1 severe SAE.

No AEs were reported in either the younger or older participants in the placebo group. No SAEs or related AEs were reported in the BNT162b2 30 µg older age group. No AEs leading to withdrawal, life-threatening AEs, or deaths were reported in either the younger or older participants in the BNT162b2 30 µg group.

From Dose 1 of BNT162b2 30 µg to the unblinding date, AEs were most commonly reported in the system organ class (SOC) of nervous system disorders (3 [25.0%] participants in the younger age group and 1 [8.3%] participant in the older age group), followed by musculoskeletal and connective tissue disorders (1 [8.3%] participant in each age group). All AEs by preferred term (PT) were reported by no more than 1 participant.

There were no Phase 1 participants randomized to BNT162b2 30 µg or corresponding placebo who died through the data cutoff date of 13 MAR 2021. From Dose 1 to the unblinding date, 1 participant in the BNT162b2 30 µg younger age group reported a severe SAE (neuritis) that was assessed by the investigator as not related to study

intervention. No Phase 1 participants randomized to BNT162b2 30 µg or corresponding placebo reported any AEs leading to withdrawal from the study from Dose 1 to the unblinding date. AEs of special interest were not defined for Phase 1 of this study. Pregnancy was not reported in any Phase 1 participants through the data cutoff date of 13 MAR 2021.

***Laboratory assessments - BNT162b2***

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

The most commonly observed hematology laboratory changes were transient decreases in lymphocytes (< 0.8 × lower limit of normal [LLN]) noted 1 to 3 d after Dose 1. These decreases returned to normal by the next measurement, within 6 to 8 d of the first dose. Most decreases in lymphocyte counts were grade 1 or 2. RNA vaccines are known to induce type I interferon (Kranz et al. 2016), and type I interferons regulate lymphocyte recirculation and are associated with transient migration and/or redistribution of lymphocytes (Kamphuis et al. 2006). This rapid rebound of lymphocytes supports that the lymphocytes were not depleted, but temporarily migrated out of the peripheral blood, and subsequently re-entered the bloodstream by the time of the next assessment.

*6.1.2.4.2 Phase 2/3 safety (individuals ≥16 yrs of age) after 2 doses*

Safety data are collected cumulatively in Study C4591001/BNT162-02. Some participants ≥16 yrs of age have been unblinded to treatment assignment as they became locally eligible for receipt of BNT162b2, therefore safety data are presented separately for blinded placebo-controlled and open-label periods.

Safety data (reactogenicity and AE analyses) for participants in the Phase 2/3 portion of Study C4591001/BNT162-02 are included up to the most recent data cutoff date of 13 MAR 2021.

***Safety populations***

The safety population included a total of ~44,000 participants: 22,026 participants in the BNT162b2 group and 22,021 participants in the placebo group as of the cutoff date (13 MAR 2021). During the blinded placebo-controlled follow-up period, 51.1% of participants in the BNT162b2 group and 51.4% of participants in the placebo group had follow-up time between ≥4 months to < 6 months after Dose 2. In total, 8.1% of participants in the BNT162b2 group and 5.9% of participants in the placebo group had ≥6 months of blinded placebo-controlled follow-up. Altogether, 25,651 participants (58.2%) ≥16 yrs of age were followed for ≥4 months after the second dose. From Dose 2 to the cutoff date, 54.5% of participants originally randomized to BNT162b2 had a cumulative follow-up time of ≥6 months after the second dose. During the open-label follow-up period, 47.5% of original placebo participants had follow-up time between ≥1 month to < 2 months after Dose 1 of BNT162b2. A subset of Phase 2/3 participants ≥16 yrs of age with stable HIV (N=200) were analyzed separately per protocol.

The Phase 2/3 reactogenicity subset was comprised of 9,839 participants (≥16 yrs of age).

**Reactogenicity**

Reactogenicity data were collected by participants in an e-diary for 7 d after each dose.

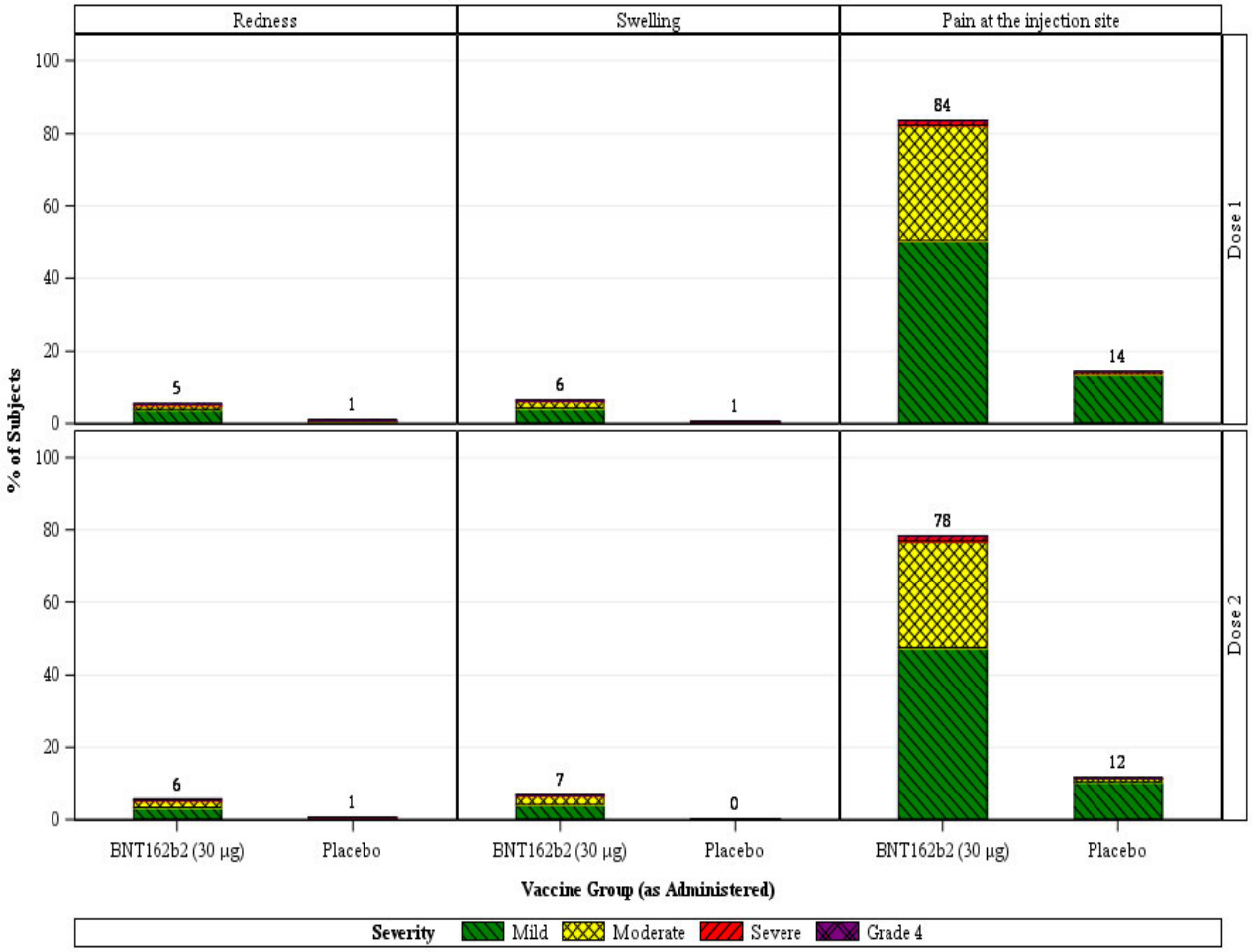
***Local reactions***

In the BNT162b2 group, pain at the injection site was reported more frequently in the younger group (includes participants 16 to 55 yrs of age) than in the older group (>55 yrs of age), and frequency was similar after Dose 1 compared with Dose 2 of BNT162b2 in the younger group (83.7% vs 78.3%) and in the older group (70.1% vs 66.1%) (Figure 33 and Figure 34, respectively).

In the BNT162b2 group, frequencies of redness and swelling were similar in the younger and older age group after Dose 1 and Dose 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 redness and swelling were reported infrequently and were similar in the younger and older age groups (≤0.7%) after any dose. Severe pain at the injection site occurred more frequently in the younger age group compared to the older age group (2.5% vs 0.7%). After the first and second dose and in both age groups, the majority of local reactions were mild or moderate in severity, and no grade 4 local reactions were reported.

The median onset for local reactions after either dose of BNT162b2 was between Day 1.0 and Day 2.0 in the younger age group and between Day 1.0 and Day 3.0 in the older age group (Day 1 was the day of vaccination). Local reactions resolved with median durations between 1.0 and 2.0 d in both age groups.




Note: Number above each bar denotes percentage of subjects reporting the reaction with any severity.
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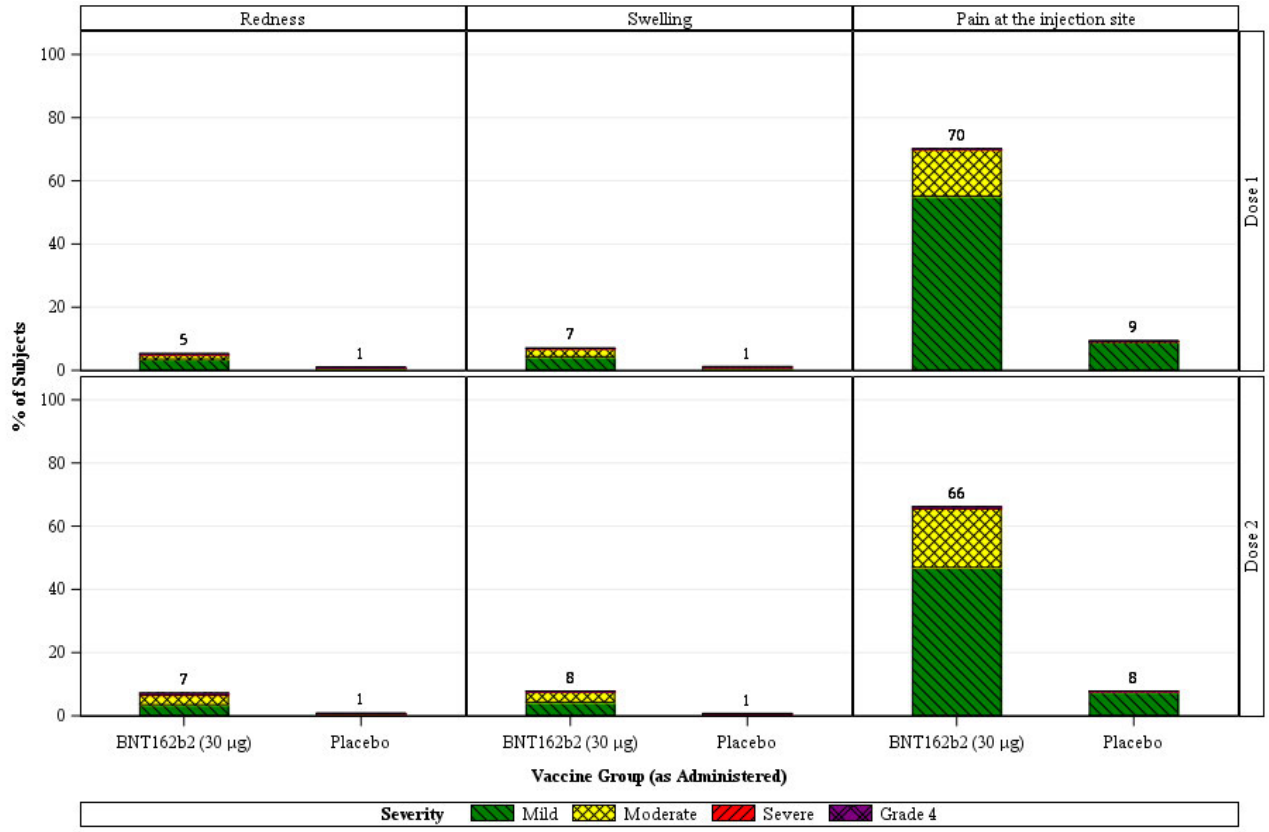
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adce_f001_lr_max_age_p3

**Figure 33: Participants reporting local reactions, by maximum severity, within 7 d after each dose, by age group – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population Age Group: 16 to 55 yrs**




Note: Number above each bar denotes percentage of subjects reporting the reaction with any severity.
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(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adce_f001_lr_max_age_p3

**Figure 34: Participants reporting local reactions, by maximum severity, within 7 d after each dose, by age group – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population Age Group: >55 yrs**

### *Systemic events*

Systemic events were generally increased in frequency and severity in the younger group (Figure 35) compared with the older group (Figure 36) with frequencies and severity increasing with number of doses (Dose 1 vs Dose 2). Vomiting and diarrhea were exceptions, with vomiting reported similarly infrequently in both age groups and diarrhea reported at similar incidences after each dose.

Systemic events were generally reported less frequently in the placebo group than in the BNT162b2 group, for both age groups and doses, with some exceptions. In the younger age group, vomiting and diarrhea (after Dose 1 and Dose 2) were reported at similar frequencies in the placebo group and the BNT162b2 group (Figure 35). In the older age group, vomiting and diarrhea (after Dose 1 and Dose 2) were reported at similar frequencies in the placebo group and the BNT162b2 group (Figure 36).

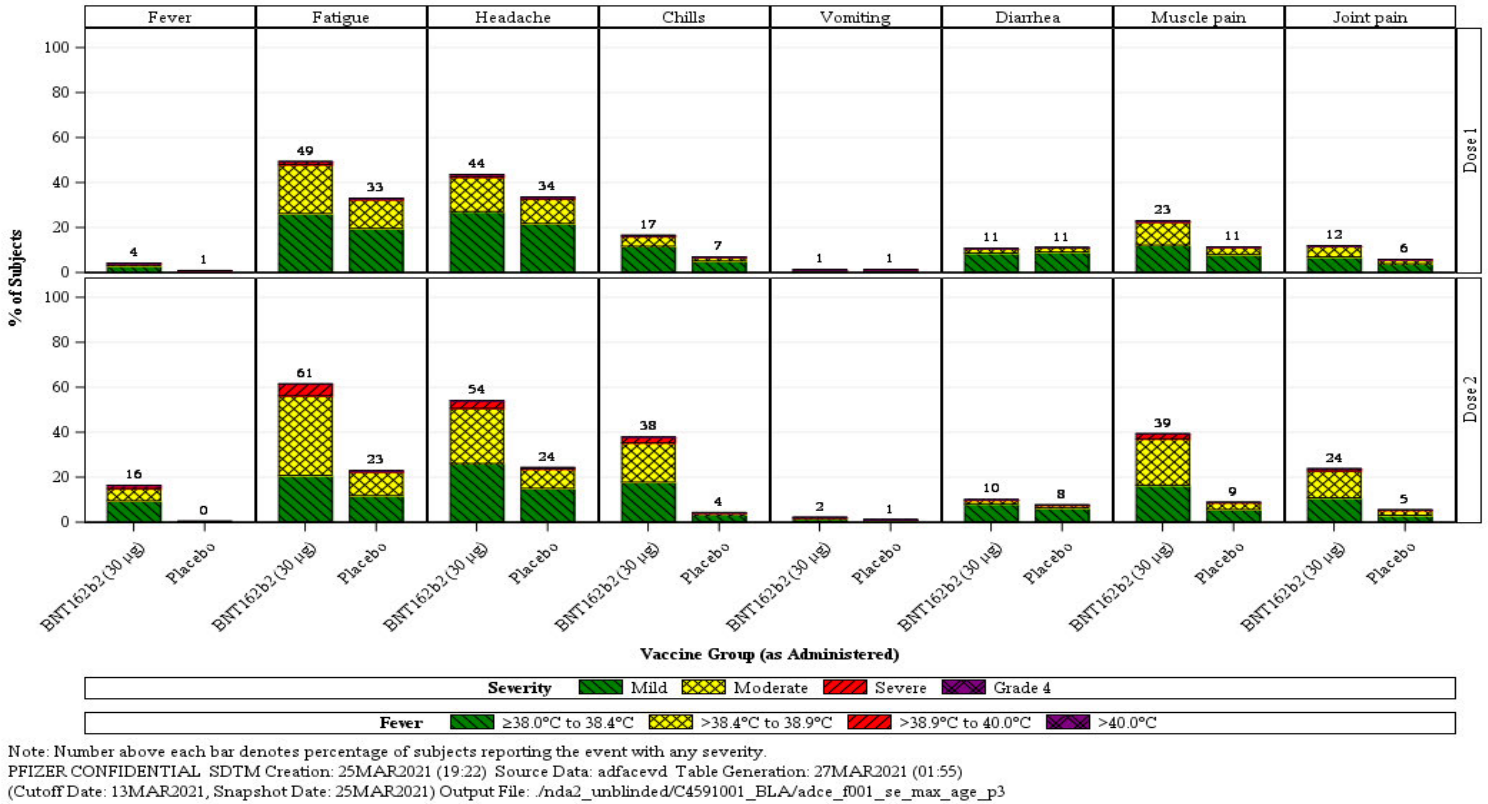
Following both Dose 1 and Dose 2, use of antipyretic/pain medication was slightly less frequent in the older age group (19.0% vs 37.0%) than in the younger age group (27.8% vs 45.2%) after both doses, and medication use increased in both age groups after Dose 2

as compared with after Dose 1. Use of antipyretic/pain medication was less frequent in the placebo group than in the BNT162b2 group and was similar after Dose 1 and Dose 2 in the younger and older placebo groups (9.3% to 13.7%).

Severe fever (>38.9°C to 40.0°C) increased in frequency with the number of doses (Dose 1 vs Dose 2) in younger (0.3% vs 1.5%) and older (0.0% vs 0.4%) participants who received BNT162b2 and was reported in 0.1% of participants who received placebo in both age group after both doses. One participant in the younger BNT162b2 group reported fever of 41.2°C only on Day 2 after Dose 2 and was nonfebrile for all other days of the reporting period. Grade 4 fever was not reported in the older BNT162b2 group or in any placebo participants.

After the first and second dose and in both age groups, most systemic events were mild or moderate in severity.

Systemic events in the younger and older age groups after either dose of BNT162b2 had a median onset day between Days 2.0 and 4.0 (Day 1.0 was the day of vaccination) and resolved with a median duration of 1 d in both age groups.




Note: Number above each bar denotes percentage of subjects reporting the event with any severity.
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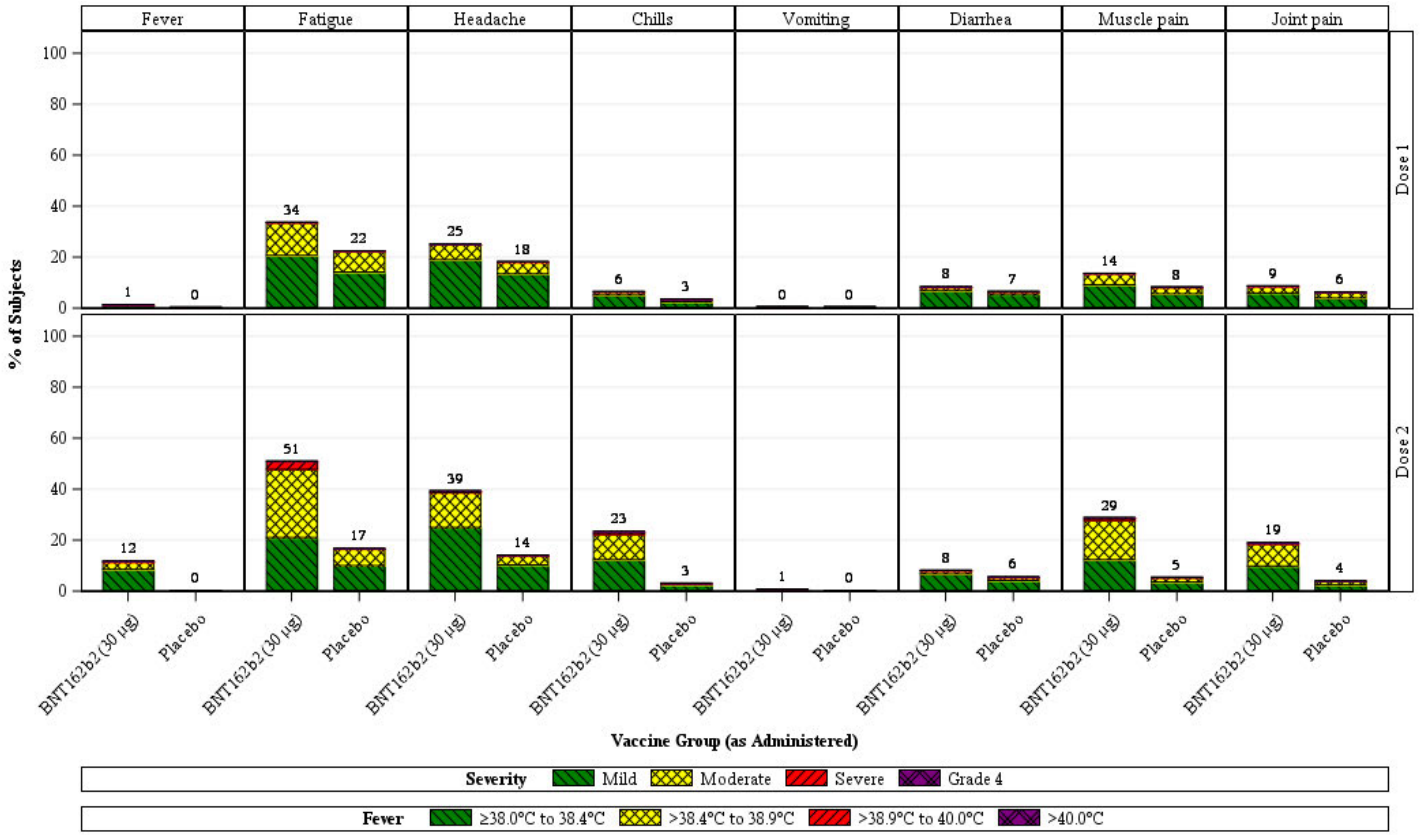
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adce_f001_se_max_age_p3

**Figure 35: Participants reporting systemic events, by maximum severity, within 7 d after each dose, by age group – reactogenicity subset for Phase 2/3 analysis – Safety Population Age Group: 16 to 55 yrs**




Note: Number above each bar denotes percentage of subjects reporting the event with any severity.
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(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adce_f001_se_max_age_p3

**Figure 36: Participants reporting systemic events, by maximum severity, within 7 d after each dose, by age group – reactogenicity subset for Phase 2/3 analysis – Safety Population Age Group: >55 yrs**

***Reactogenicity in HIV+ participants***

For the subset of HIV+ participants, local reactions and systemic events showed generally similar trends as the overall safety population.

***Reactogenicity by baseline SARS-CoV-2 status***

Reactogenicity subgroup analyses included 177 BNT162b2 and 187 placebo participants with baseline positive SARS-CoV-2 status, and 4,701 BNT162b2 and 4,690 placebo participants with baseline negative SARS-CoV-2 status. Differences observed in local reactions and systemic events by baseline SARS-CoV-2 status were not clinically meaningful. Note that the baseline SARS-CoV-2 positive subgroup included far fewer participants than the negative subgroup, so their results should be interpreted with caution.

**Adverse events**

Adverse events are presented separately for the blinded and open-label follow-up periods as follows (and as shown in Figure 37).

**Blinded placebo-controlled follow-up**: participants randomized to BNT162b2 and placebo:

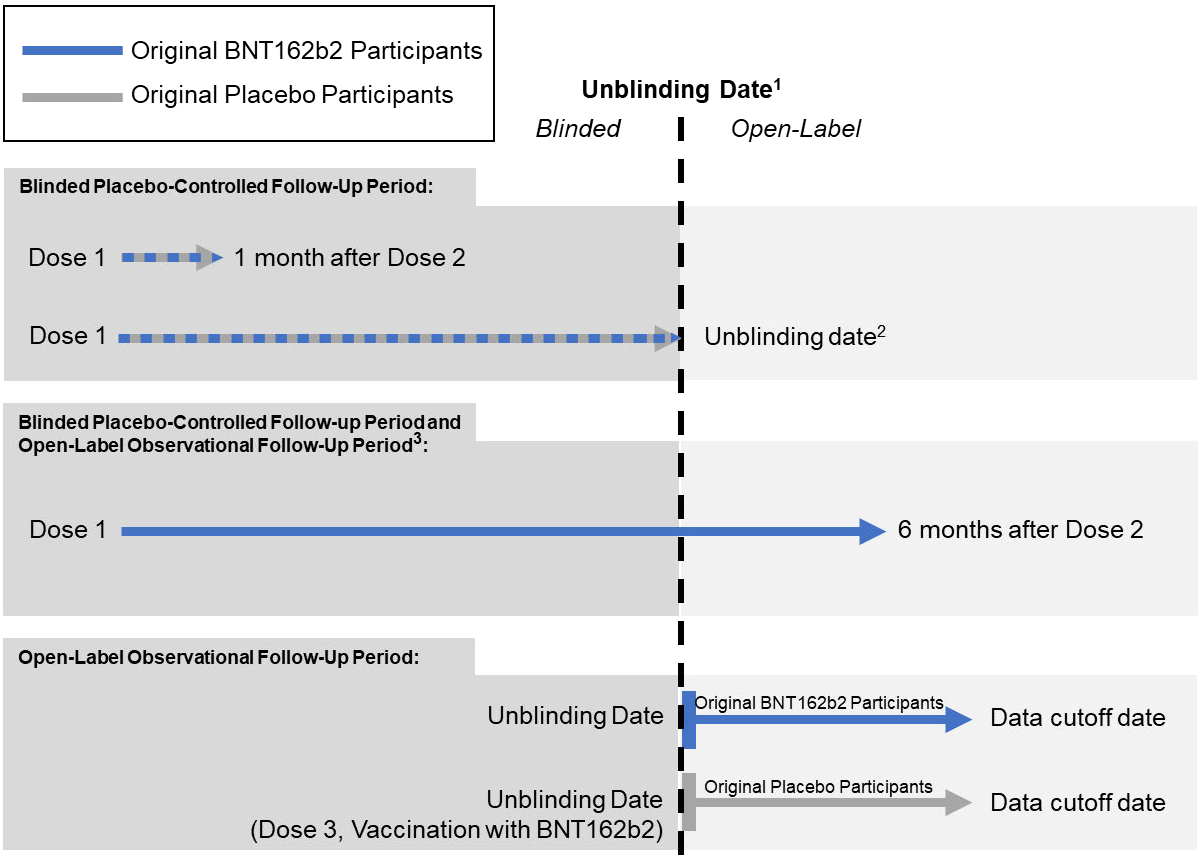
- Younger (16 to 55 yrs of age) and older (>55 yrs of age) groups, including HIV+ subset
    - from Dose 1 up to 1 month after Dose 2
    - from Dose 1 up to end of blinded follow-up (date of unblinding)

**Open-label follow-up for BNT162b2**: participants originally randomized to BNT162b2, from date of unblinding through the data cutoff date (13 MAR 2021).

**Cumulative blinded and open-label follow-up for BNT162b2**: participants originally randomized to BNT162b2, inclusive of blinded and post-unblinding open-label periods, from Dose 1 up to at least 6 months after Dose 2 (at least 3,000 participants per age group).

**Open-label follow-up for placebo after receiving BNT162b2**: participants originally randomized to placebo from time of unblinding/BNT162b2 vaccination (Dose 3) through the data cutoff date.

Note that due to individual study participant unblinding to treatment assignment (per protocol), safety data were calculated as IRs to adjust for variable exposure time in analyses of time intervals either up to, or starting from, the unblinding date.




[1] AE data analyzed from Dose 1 to unblinding date (on or after 14 DEC 2020) or from unblinding date to data cutoff date (13 MAR 2021) reported as IRs per 100 PY adjusted for exposure time; varies per participant.

[2] Blinded placebo-controlled follow-up period duration up to ~6 months after Dose 2.

[3] Cumulative BNT162b2 follow-up to ≥6 months after Dose 2, N ≥3,000/age group (16 to 55, >55 yrs of age).

**Figure 37: Study C4591001/BNT162-02 Phase 2/3 safety analyses: Time periods and analysis groups**

## Blinded placebo-controlled follow-up period

### *Blinded placebo-controlled follow-up period from Dose 1 to 1 month after Dose 2*

An overview of AEs reported during the blinded placebo-controlled follow-up period from Dose 1 to 1 month after Dose 2 is presented in Table 20.

**Table 20: Number (%) of participants reporting at least one AE from Dose 1 to 1 month after Dose 2 – Blinded placebo-controlled follow-up period – Phase 2/3 participants ≥16 yrs of age – Safety Population**

| | Vaccine group (as administered) | |
|---|---|---|
| | BNT162b2 (30 µg) (N[a]=21,926) | Placebo (N[a]=21,921) |
| Adverse Event | n[b] (%) | nb (%) |
| Any event | 6,617 (30.2) | 3,048 (13.9) |
| Related [c] | 5,241 (23.9) | 1,311 (6.0) |
| Severe | 262 (1.2) | 150 (0.7) |
| Life-threatening | 21 (0.1) | 26 (0.1) |
| Any serious adverse event | 127 (0.6) | 116 (0.5) |
| Related [c] | 3 (0.0) | 0 |
| Severe | 71 (0.3) | 66 (0.3) |
| Life-threatening | 21 (0.1) | 26 (0.1) |
| Any adverse event leading to withdrawal | 32 (0.1) | 36 (0.2) |
| Related [c] | 13 (0.1) | 11 (0.1) |
| Severe | 10 (0.0) | 10 (0.0) |
| Life-threatening | 3 (0.0) | 7 (0.0) |
| Death | 3 (0.0) | 5 (0.0) |

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least one occurrence of the specified event category. For "any event", n = the number of participants reporting at least one occurrence of any event.
c. Assessed by the investigator as related to investigational product.

PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (20:15) Source Data: adae Table Generation: 27MAR2021 (02:09) (Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File:./nda2_unblinded/C4591001_BLA/adae_s091_all_pd2_p3_saf1

Most AEs from Dose 1 to 1 month after Dose 2 were mild or moderate in severity. The percentages of overall participants who reported at least 1 AE and at least 1 related AE were higher in the BNT162b2 group (30.2% and 23.9%, respectively) as compared with the placebo group (13.9% and 6.0%, respectively). This was attributable to reactogenicity events reported as AEs within 7 d after each dose. Severe AEs were reported by 1.2% and 0.7% in in the BNT162b2 and placebo groups respectively, and life-threatening AEs were similar (0.1% in both groups).

Most reported AEs were in SOCs with reactogenicity events. The most frequently reported AEs in the BNT162b2 group by PT overall were injection site pain, pyrexia, fatigue, chills, headache, and myalgia. From Dose 1 to 1 month after Dose 2, most of these AEs were reported during the e-diary 7-day reporting period. The frequency of AEs in the SOC of investigations was higher in the BNT162b2 group as compared with the placebo group (mainly due to the higher frequency of the PT body temperature increased). A number of events were identified as occurring at a higher frequency than placebo within the 7-day period after either dose of BNT162b2 when reactogenicity is expected to be reported such as pain in extremity, decreased appetite, lethargy, asthenia, malaise, night sweats, and hyperhidrosis. These events are interpreted as attributable to the experience of local reactions and systemic events after vaccination with BNT162b2.

In the skin and subcutaneous tissue disorders SOC, 17 participants in the BNT162b2 group reported night sweats (vs 3 in the placebo group), with all but 1 occurring within the first 7 d after Dose 1 or 2; and 31 participants in the BNT162b2 group reported hyperhidrosis (vs 9 in the placebo group), with all but 3 occurring within the first 7 d after Dose 1 or 2.

Nineteen study participants reported events in the hepatobiliary disorders SOC (14 BNT162b2 recipients and 5 placebo recipients). Of the 19 total participants, 3 participants had hepatic events: 1 in the BNT162b2 group (alcoholic cirrhosis) and 2 in the placebo group (hepatic cirrhosis and nonalcoholic fatty liver disease). The remaining 16 participants reported biliary events: 13 participants in the BNT162b2 group and 3 participants in the placebo group.

- In the BNT162b2 group, 8 participants reported cholelithiasis (1 reported an event each of cholelithiasis and cholecystitis), 1 participant reported cholecystitis acute, 2 participants reported biliary colic, and 1 participant each reported bile duct stone/biliary dyskinesia.
- In the placebo group, 3 participants reported the following: 1 participant reported an event each of cholecystitis acute and cholelithiasis, 1 participant reported cholecystitis acute, and 1 participant reported cholelithiasis.

Most related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions, reported by 4,650 (21.2%) BNT162b2 recipients and 883 (4.0%) placebo recipients. Among the BNT162b2 participants who had AEs of lymphadenopathy, 62 of 83 participants had events assessed by the investigator as related to study intervention; the majority of lymphadenopathy events occurred in the arm and neck region and were reported within 1 to 4 d after vaccination.

SAEs were similar in the BNT162b2 (0.6%) and placebo (0.5%) groups. There were 3 SAEs reported in the BNT162b2 group that were assessed by the investigator as related to study intervention (lymphadenopathy; shoulder injury related to vaccine administration, erroneously administered into or near the shoulder joint capsule; and ventricular arrhythmia).

Few participants in the BNT162b2 group (0.1%) and placebo group (0.2%) were withdrawn because of AEs. There were 3 deaths in the BNT162b2 group and 5 deaths in the placebo group; none of the deaths were assessed as related to study intervention.

### *HIV+ Participants*

For the subset of HIV+ participants, AEs from Dose 1 up to 1 month after Dose 2 showed generally similar trends as the overall safety population.

### Blinded placebo-controlled follow-up period from Dose 1 to unblinding date

An overview of AEs reported during the blinded placebo-controlled follow-up period from Dose 1 to the participant unblinding date is presented in Table 21. AE data were calculated as incidence rates (IRs) per 100 person-years (PY) to adjust for variable exposure time due to individual participants unblinding.

**Table 21: Incidence rates of at least 1 adverse event from Dose 1 to unblinding date – Phase 2/3 participants ≥16 yrs of age – Safety Population**

| | Vaccine Group (as Administered) | | | | | |
|---|---|---|---|---|---|---|
| | BNT162b2 (30 µg) (N[a]=2,1926, TE[b]=83.4) | | | Placebo (N[a]=2,1921, TE[b]=82.2) | | |
| Adverse Event | n[c] | IR (/100 PY)[d] | (95% CI[e]) | n[c] | IR (/100 PY)[d] | (95% CI[e]) |
| Any event | 6,947 | 83.2 | (81.3, 85.2) | 3,568 | 43.4 | (42.0, 44.9) |
| Related [f] | 5,246 | 62.9 | (61.2, 64.6) | 1,313 | 16.0 | (15.1, 16.9) |
| Severe | 356 | 4.3 | (3.8, 4.7) | 256 | 3.1 | (2.7, 3.5) |
| Life-threatening | 48 | 0.6 | (0.4, 0.8) | 54 | 0.7 | (0.5, 0.9) |
| Any serious adverse event | 268 | 3.2 | (2.8, 3.6) | 268 | 3.3 | (2.9, 3.7) |
| Related [f] | 4 | 0.0 | (0.0, 0.1) | 1 | 0.0 | (0.0, 0.1) |
| Severe | 148 | 1.8 | (1.5, 2.1) | 156 | 1.9 | (1.6, 2.2) |
| Life-threatening | 48 | 0.6 | (0.4, 0.8) | 54 | 0.7 | (0.5, 0.9) |
| Any adverse event leading to withdrawal | 45 | 0.5 | (0.4, 0.7) | 51 | 0.6 | (0.5, 0.8) |
| Related [f] | 13 | 0.2 | (0.1, 0.3) | 12 | 0.1 | (0.1, 0.3) |
| Severe | 10 | 0.1 | (0.1, 0.2) | 12 | 0.1 | (0.1, 0.3) |
| Life-threatening | 15 | 0.2 | (0.1, 0.3) | 16 | 0.2 | (0.1, 0.3) |
| Death | 15 | 0.2 | (0.1, 0.3) | 14 | 0.2 | (0.1, 0.3) |

a) N = number of participants in the specified group.

b) TE = total exposure time in 100 person-years (PY) across all participants in the specified group. Exposure time for a participant is the time from Dose 1 to the end of blinded follow-up. This value is the denominator for the incidence rate calculation.

c) n = Number of participants reporting at least 1 occurrence of the specified event category. For "any event," n = number of participants reporting at least 1 occurrence of any event.

d) Incidence rate (IR) is calculated as number of participants reporting the event/total exposure time in 100 person-years (PY) across all participants in the specified group.

e) 2-sided CI based on Poisson distr bution.

f) Assessed by the investigator as related to investigational product.

PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (20:15) Source Data: adae Table Generation: 27MAR2021 (02:11) (Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File:./nda2_unblinded/C4591001_BLA/adae_s092_all_unb_p3_saf

Most AEs from Dose 1 to the unblinding date were mild or moderate in severity. The IR of at least 1 AE in the BNT162b2 group (83.2 per 100 PY) was greater as compared with the placebo group (43.4 per 100 PY), which upon analysis, was attributed to reactogenicity events reported as AEs within 7 d after each dose. IRs of severe AEs, SAEs, and AEs leading to withdrawal were ≤4.3, ≤3.3, and ≤0.6 per 100 PY, respectively, in both groups. IRs for discontinuations because of related AEs were 0.2 per 100 PY in the BNT162b2 group and 0.1 per 100 PY in the placebo group. AEs with the highest IRs in the BNT162b2 group by PT overall were injection site pain, pyrexia, fatigue, chills, headache, and myalgia. The IR of AEs in the SOC of investigations was higher in the BNT162b2 group than in the placebo group mainly due to the higher IR of body temperature increased in the BNT162b2 group.

In the nervous systems disorder SOC, four participants reported facial paralysis in the BNT162b2 group compared to one in the placebo group; one case of facial paresis was also reported in the placebo group. Cases of facial paralysis/paresis therefore totaled four in the BNT162b2 group and two in the placebo group during blinded follow-up.

IRs for hepatobiliary disorders was 0.3 per 100 PY and 0.2 per 100 PY in the BNT162b2 and placebo group, respectively. There were 24 participants in the BNT162b2 group with AEs in the SOC of hepatobiliary disorders compared to 16 participants in the placebo group.

A total of 11 cases of reported PTs associated with deafness included: deafness, deafness unilateral, deafness neurosensory, hypoacusis, and sudden hearing loss. Six participants were randomized to the BNT162b2 group and five were randomized to placebo. None of the reported events were SAEs.

In addition to the 3 related SAEs reported from Dose 1 to 1 month after Dose 2, there were two additional related SAEs reported after 1 month post-Dose 2 up to the unblinding date that were assessed by the investigator as related to study intervention: paraesthesia (BNT162b2 group) and psoriatic arthropathy (placebo).

IRs of participants withdrawn because of AEs were 0.5 per 100 PY in the BNT162b2 group and 0.6 per 100 PY in the placebo group. From Dose 1 to the unblinding date, there were 15 deaths in the BNT162b2 group and 14 in the placebo group (from 1 month post-Dose 2 to the unblinding date, this included 12 in the BNT162b2 group and 9 in the placebo group); none of the deaths were assessed as related to study intervention.

### *HIV+ Participants*

For the subset of HIV+ participants, IRs of AEs from Dose 1 to the participant unblinding date showed generally similar trends as the overall safety population.

### *Subgroup analyses*

Subgroup analyses for baseline SARS-CoV-2 status and demographics (race, ethnicity, and sex) were performed for AEs and SAEs reported from Dose 1 to the unblinding date. Overall, no clinically meaningful differences in IRs of SAEs were observed by baseline SARS-CoV-2 status, ethnicity, race, or sex subgroups. IRs were similar in the BNT162b2 and placebo groups for each of the subgroups.

### *Baseline SARS-CoV-2 status*

For the subset of participants who were SARS-CoV-2 positive at baseline, IR of AEs followed similar trends found in the overall AE analysis. Given the differences in exposure (2.5 vs 80.4) by baseline SARS-CoV-2 positive and negative status, respectively, direct comparisons should be interpreted with caution. The overall rate of AEs is 70.7 per 100 PY (95% CI: 60.7, 81.9) (baseline positive) compared with 83.6 per 100 PY (95% CI: 81.7, 85.7) (baseline negative). For other SOCs, the IR were either numerically lower or similar for the baseline positive group compared to the baseline negative group. Overall, there is no evidence that individuals who are positive at baseline report AEs at a higher frequency than those who are negative at baseline.

### *Race/ethnicity*

In the BNT162b2 group, overall IRs for participants reporting at least 1 AE were highest for participants of all other races (120.1 per 100 PY) compared to White participants (83.1 per

100 PY), with Black or African American participants having the lowest IR (53.5 per 100 PY).

In the BNT162b2 group, IRs for reporting at least 1 AE were higher in non-Hispanic/non-Latino participants (85.4 per 100 PY BNT162b2 and 41.6 per 100 PY placebo) and Hispanic/Latino participants (78.4 per 100 PY BNT162b2 and 47.9 per 100 PY placebo) and lowest in the group where ethnicity was not reported (49.4 per 100 PY BNT162b2 and 43.3 per 100 PY placebo).

***Sex***

Overall, female participants reported a higher IR of AEs (91.0 per 100 PY BNT162b2, 46.8 per 100 PY placebo) than male participants (76.0 per 100 PY BNT162b2, 40.1 per 100 PY placebo), with a greater difference in BNT162b2 groups than placebo groups. Higher IRs in female participants were due to reactogenicity AEs (vomiting, chills, fatigue, pyrexia, myalgia, and headache) in addition to lymphadenopathy, nausea, pain, increased body temperature, and pain in extremity. There were also sex-appropriate differences such as higher IR in the SOC of cardiac disorders in male (1.2 per 100 PY) versus female (0.9 per 100 PY) participants and lower IR in the SOC of reproductive system and breast disorders in male (0.3 per 100 PY) versus female (0.9 per 100 PY) participants.

**Open-label follow-up period – Original BNT162b2 group**

During open-label follow-up for the original BNT162b2 group from unblinding date through the data cutoff date, AE data were calculated as IRs per 100 PY to adjust for variable exposure time due to individual participants unblinding. Most AEs were mild or moderate in severity. The IRs for any AE, at least 1 related AE, and severe AE were 8.8 per 100 PY, 0.7 per 100 PY, and 1.6 per 100 PY, respectively, which is markedly reduced relative to those from Dose 1 to the unblinding date (83.2, 62.9, 4.3 respectively). The IR of life-threatening AEs was 0.4 per 100 PY (95% CI: 0.2, 0.8), which is similar to the IR from Dose 1 to the unblinding date, 0.6 per 100 PY (95% CI: 0.4, 0.8). Overall, the rates in all SOCs after the unblinding date decreased or remained similar to those in the blinded placebo-controlled period. The IR for the SOC of injury, poisoning and procedural complications was 1.4 per 100 PY, with the PT fall had the highest IR (0.4 per 100 PY). The IR for the SOC of vascular disorders was 0.8 per 100 PY, with the PT hypertension having the highest IR (0.6 per 100 PY).

The IRs of related AEs were highest for reactogenicity events and in the SOC of general disorders and administration site conditions reflecting AEs from their initial vaccinations.

One participant in the younger age group had 1 SAE of myocardial infarction assessed by the investigator as related to study intervention.

The IR of participants withdrawn because of AEs was 0.1 per 100 PY. There were 3 deaths reported in this period; none of the deaths were assessed as related to study intervention.

**Cumulative blinded and open-label follow-up periods from Dose 1 to 6 months after Dose 2 – BNT162b2 Group**

An analysis of AEs reported by participants in the original randomized BNT162b2 group from Dose 1 through 6 months after Dose 2 (inclusive of blinded placebo-controlled follow-up and open-label follow-up after participant unblinding) was conducted.

For the 12,006 participants with at least 6 months of follow-up time, most AEs were mild or moderate in severity from Dose 1 to 6 months after Dose 2. There were 28.8% of participants who reported at least 1 AE, and 18.7% of participants reported at least 1 related AE. The most frequently reported AEs in the BNT162b2 group were reactogenicity events. Severe AEs and SAEs were reported by 2.1% and 1.6%, respectively. One participant discontinued because of an AE (not related).

Most related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions. The AE of lymphadenopathy in 29 (0.2%) participants was assessed by the investigator as related to study intervention.

The number of participants with SAEs increased from 0.5% (Dose 1 to 1 month after Dose 2) to 1.1% (1 month after Dose 2 to 6 months after Dose 2). However, the number of related SAEs remained low. There were 2 participants with related SAEs reported: shoulder injury related to vaccine administration, erroneously administered into or near the shoulder joint capsule reported from Dose 1 to 1 month after Dose 2; and paraesthesia, reported from 1 month after Dose 2 to 6 months after Dose 2.

There were no deaths during this period for this group of participants.

AE frequencies decreased over time from 1 month after the second dose to 6 months after the second dose, without an increase by SOC. SAEs increased from 1 month after the Dose 2 to 6 months after Dose 2; however, the number of related SAEs remained low.

Overall, BNT162b2 at 30 µg was well tolerated with at least 6 months of follow-up after Dose 2.

**Open-label follow-up period – Original placebo participants who received BNT162b2**

An analysis of AEs reported by participants in the original randomized placebo group who were unblinded to receive BNT162b2 (Doses 3 and 4 in the study) during the open-label follow-up period from the date of participant unblinding through the data cutoff date (13 MAR 2021) was conducted. AE data were calculated as IRs per 100 PY to adjust for variable exposure time due to individual participants unblinding.

For the 19,525 original placebo participants who received BNT162b2 after unblinding, most AEs were mild or moderate in severity from Dose 3 through the data cutoff date. The IR of at least 1 AE was 205.4 per 100 PY, which was greater than the IR in original BNT162b2 participants (83.2 per 100 PY), due to the shorter exposure time in original placebo participants compared with original BNT162b2 participants (23.8 per 100 PY vs 83.4 per 100 PY). However, the IRs for life-threatening AE, SAE, AEs leading to withdrawal, and deaths were similar (0.5 per 100 PY, 2.7 per 100 PY, 0.8 per 100 PY, 0.1 per 100 PY vs 0.6 per 100 PY, 3.2 per 100 PY, 0.5 per 100 PY, 0.2 per 100 PY, respectively). The IR of related AEs was 189.5 per 100 PY and IRs of related AEs were

highest for reactogenicity events and in the SOC of general disorders and administration site conditions. Immediate AEs were low in frequency (0.6%) and most were in the SOC of general disorders and administration site conditions, primarily injection site reactions, with injection site pain (0.4%) most frequently reported. From Dose 3 (first dose of BNT162b2) to the data cutoff date, the severe AE IR was 6.0 per 100 PY in original placebo participants.

One participant had an SAE of anaphylactoid reaction 2 d after receiving BNT162b2 (Dose 3) that was assessed as related to study intervention. This participant had an ongoing medical history of drug hypersensitivity and food and seasonal allergies.

The IR of participants withdrawn because of AEs was 0.8 per 100 PY. There were 2 deaths; neither of these deaths were assessed as related to study intervention.

Overall, AEs after receipt of BNT162b2 in placebo participants showed a similar safety profile as that observed in the participants originally randomized to BNT162b2.

### AEs of clinical interest in Study C4591001 Phase 2/3 (Participants ≥16 yrs of age)

No AESIs were prespecified in the Study C4591001/BNT162-02 protocol.

Safety evaluations were conducted for AEs of clinical interest based on feedback from the FDA: anaphylaxis, Bell's Palsy, lymphadenopathy, and appendicitis. CDC-defined AESIs associated with COVID-19 vaccination were evaluated in the blinded placebo-controlled period of the study.

#### *Lymphadenopathy*

Lymphadenopathy was reported in 87 participants (1.0 per 100 PY) in the BNT162b2 group compared to 8 participants (0.1 per 100 PY) in the placebo group. The majority of events were mild to moderate; only 3 severe events of lymphadenopathy were reported (all in the BNT162b2 group). The median onset of lymphadenopathy after Dose 1 and before Dose 2 was 5.5 d in the BNT162b2 group and 5.0 d in the placebo group; median onset after Dose 2 was shorter in the BNT162b2 group versus the placebo group (2.0 d vs 7.0 d). The median duration of lymphadenopathy was 5.5 d in the BNT162b2 group and 4.0 d in the placebo group. One case was a related SAE.

#### *Appendicitis*

There were 14 cases of appendicitis and 1 case of appendicitis perforated in the BNT162b2 group, and 9 cases of appendicitis, 2 cases of complicated appendicitis, and 1 appendicitis perforated in the placebo group. Appendicitis cases were all reported as SAEs, and none of the cases were considered related to study intervention.

#### *Bell's Palsy/Facial paralysis*

AESI evaluations were performed for blinded placebo-controlled follow-up. There were 4 cases of Bell's palsy reported in the BNT162b2 group (previously reported in the submission to support the current US Emergency Use Authorization granted on 11 DEC 2020). Since then, 2 additional cases were reported in the placebo group during blinded follow-up, and an additional 4 cases of Bell's Palsy were reported during the open-

label follow-up period and are included for completeness: 3 cases in placebo participants who became unblinded and were then vaccinated with BNT162b2, and 1 participant originally randomized to BNT162b2 who was unblinded and developed Bell's palsy 154 d after the second dose of BNT162b2. At this time there is insufficient information to be certain of a causal link with the vaccine.

***Anaphylaxis/Hypersensitivity***

The allergic reaction evaluation did not identify anaphylaxis reactions associated with the vaccine. However, there was 1 anaphylactoid reaction reported 2 d after receiving BNT162b2 in a participant with an ongoing medical history of medicinal, seasonal, and food allergies. For angioedema the frequencies were low and very similar in the BNT162b2 (0.14%) and placebo (0.13%) groups. For hypersensitivity reactions most of the reactions were due to rash, rash maculopapular, and rash papular and were not reported within 7 d after either dose. Overall, the evaluation of cases reporting allergic reactions supports standard precautions for allergic reactions should be taken in the clinic when vaccinating.

Overall, there was no imbalance in PTs in non-anaphylactic allergic reactions (123 in the BNT162b2 group and 109 in the placebo group).

**Severe COVID-19 cases in Study C4591001/BNT162-02 Phase 2/3**

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

## Pregnancies in Study C4591001/BNT162-02

At the time of the data cutoff in Study C4591001/BNT162-02 (13 MAR 2021), a total of 50 participants who had received BNT162b2 had reported pregnancies, including 42 participants randomized to the BNT162b2 and 8 participants originally randomized to the placebo group who then received BNT162b2. In total, 12 participants (n=6 each in the randomized BNT162b2 and placebo groups) withdrew from the blinded placebo-controlled vaccination period of the study due to pregnancy, and 4 participants originally randomized to placebo who then received BNT162b2 withdrew from the open-label vaccination period due to pregnancy. These participants continue to be followed for pregnancy outcomes.

#### *6.1.2.4.3 Safety in adolescents 12 to 15 yrs of age after 2 doses*

In Study C4591001/BNT162-02, based on data up to the cutoff date of 13 MAR 2021, 2,260 adolescents (1,131 BNT162b2; 1,129 placebo) were 12 through 15 yrs of age. Of these, 1,308 (660 BNT162b2 and 648 placebo) adolescents have been followed for at least 2 months after the second dose of BNT162b2.

## Solicited local and systemic ARs

Local reactions within 7 d after each dose in adolescents 12 to 15 yrs of age are presented in Table 22. The mean duration of pain at the injection site after Dose 1 was 2.4 d (range 1 to 10 d), for redness 2.4 d (range 1 to 16 d), and for swelling 1.9 d (range 1 to 5 d) for adolescents in the BNT162b2 group. Systemic events within 7 d after each dose in adolescents 12 to 15 yrs of age are presented in Table 23.

**Table 22: Frequency and percentages of adolescents with solicited local reactions, by maximum severity, within 7 d after each dose – Adolescents 12 through 15 yrs of age – Safety Population***

| | BNT162b2 Dose 1 N[a]=1,127 n[b] (%) | Placebo Dose 1 N[a]=1,127 n[b] (%) | BNT162b2 Dose 2 N[a]=1,097 n[b] (%) | Placebo Dose 2 N[a]=1,078 n[b] (%) |
|---|---|---|---|---|
| **Redness** [c] | | | | |
| Any (>2 cm) | 65 (5.8) | 12 (1.1) | 55 (5.0) | 10 (0.9) |
| Mild | 44 (3.9) | 11 (1.0) | 29 (2.6) | 8 (0.7) |
| Moderate | 20 (1.8) | 1 (0.1) | 26 (2.4) | 2 (0.2) |
| Severe | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Swelling** [c] | | | | |
| Any (>2 cm) | 78 (6.9) | 11 (1.0) | 54 (4.9) | 6 (0.6) |
| Mild | 55 (4.9) | 9 (0.8) | 36 (3.3) | 4 (0.4) |
| Moderate | 23 (2.0) | 2 (0.2) | 18 (1.6) | 2 (0.2) |
| Severe | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Pain at the injection site** [d] | | | | |
| Any | 971 (86.2) | 263 (23.3) | 866 (78.9) | 193 (17.9) |
| Mild | 467 (41.4) | 227 (20.1) | 466 (42.5) | 164 (15.2) |
| Moderate | 493 (43.7) | 36 (3.2) | 393 (35.8) | 29 (2.7) |
| Severe | 11 (1.0) | 0 (0.0) | 7 (0.6) | 0 (0.0) |

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

**Table 23: Frequency and percentages of adolescents with solicited systemic reactions, by maximum severity, within 7 d after each dose – Adolescents 12 through 15 yrs of age – Safety Population***

| | BNT162b2 Dose 1 N[a]=1,127 n[b] (%) | Placebo Dose 1 N[a]=1,127 n[b] (%) | BNT162b2 Dose 2 N[a]=1,097 n[b] (%) | Placebo Dose 2 N[a]=1,078 n[b] (%) |
|---|---|---|---|---|
| **Fever** | | | | |
| ≥38.0°C | 114 (10.1) | 12 (1.1) | 215 (19.6) | 7 (0.6) |
| ≥38.0°C to 38.4°C | 74 (6.6) | 8 (0.7) | 107 (9.8) | 5 (0.5) |
| >38.4°C to 38.9°C | 29 (2.6) | 2 (0.2) | 83 (7.6) | 1 (0.1) |
| >38.9°C to 40.0°C | 10 (0.9) | 2 (0.2) | 25 (2.3) | 1 (0.1) |
| >40.0°C | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Fatigue [c]** | | | | |
| Any | 677 (60.1) | 457 (40.6) | 726 (66.2) | 264 (24.5) |
| Mild | 278 (24.7) | 250 (22.2) | 232 (21.1) | 133 (12.3) |
| Moderate | 384 (34.1) | 199 (17.7) | 468 (42.7) | 127 (11.8) |
| Severe | 15 (1.3) | 8 (0.7) | 26 (2.4) | 4 (0.4) |
| **Headache [c]** | | | | |
| Any | 623 (55.3) | 396 (35.1) | 708 (64.5) | 263 (24.4) |
| Mild | 361 (32.0) | 256 (22.7) | 302 (27.5) | 169 (15.7) |
| Moderate | 251 (22.3) | 131 (11.6) | 384 (35.0) | 93 (8.6) |
| Severe | 11 (1.0) | 9 (0.8) | 22 (2.0) | 1 (0.1) |
| **Chills [c]** | | | | |
| Any | 311 (27.6) | 109 (9.7) | 455 (41.5) | 73 (6.8) |
| Mild | 195 (17.3) | 82 (7.3) | 221 (20.1) | 52 (4.8) |
| Moderate | 111 (9.8) | 25 (2.2) | 214 (19.5) | 21 (1.9) |
| Severe | 5 (0.4) | 2 (0.2) | 20 (1.8) | 0 (0.0) |
| **Vomiting [d]** | | | | |
| Any | 31 (2.8) | 10 (0.9) | 29 (2.6) | 12 (1.1) |
| Mild | 30 (2.7) | 8 (0.7) | 25 (2.3) | 11 (1.0) |
| Moderate | 0 (0.0) | 2 (0.2) | 4 (0.4) | 1 (0.1) |
| Severe | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Diarrhea [e]** | | | | |
| Any | 90 (8.0) | 82 (7.3) | 65 (5.9) | 43 (4.0) |
| Mild | 77 (6.8) | 72 (6.4) | 59 (5.4) | 38 (3.5) |
| Moderate | 13 (1.2) | 10 (0.9) | 6 (0.5) | 5 (0.5) |
| Severe | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **New or worsened muscle pain [c]** | | | | |
| Any | 272 (24.1) | 148 (13.1) | 355 (32.4) | 90 (8.3) |
| Mild | 125 (11.1) | 88 (7.8) | 152 (13.9) | 51 (4.7) |
| Moderate | 145 (12.9) | 60 (5.3) | 197 (18.0) | 37 (3.4) |
| Severe | 2 (0.2) | 0 (0.0) | 6 (0.5) | 2 (0.2) |

| | BNT162b2 Dose 1 N[a]=1,127 n[b] (%) | Placebo Dose 1 N[a]=1,127 n[b] (%) | BNT162b2 Dose 2 N[a]=1,097 n[b] (%) | Placebo Dose 2 N[a]=1,078 n[b] (%) |
|---|---|---|---|---|
| **New or worsened joint pain [c]** | | | | |
| Any | 109 (9.7) | 77 (6.8) | 173 (15.8) | 51 (4.7) |
| Mild | 66 (5.9) | 50 (4.4) | 91 (8.3) | 30 (2.8) |
| Moderate | 42 (3.7) | 27 (2.4) | 78 (7.1) | 21 (1.9) |
| Severe | 1 (0.1) | 0 (0.0) | 4 (0.4) | 0 (0.0) |
| **Use of antipyretic or pain medication [f]** | 413 (36.6) | 111 (9.8) | 557 (50.8) | 95 (8.8) |

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
b. n = Number of participants with the specified reaction.
c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.
e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.
f. Severity was not collected for use of antipyretic or pain medication.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

### *Unsolicited AEs*

In Study C4591001/BNT162-02, among adolescents 12 through 15 yrs of age (1,131 of whom received BNT162b2 and 1,129 of whom received placebo), 98.3% of study participants had at least 30 d of follow-up after Dose 2.

### *Serious AEs*

Serious adverse events from Dose 1 through up to 30 d after Dose 2 in ongoing follow-up were reported by 0.4% of BNT162b2 recipients and by 0.1% of placebo recipients. There were no notable patterns or numerical imbalances between treatment groups for specific categories of SAEs that would suggest a causal relationship to BNT162b2.

### *Non-Serious AEs*

Non-serious adverse events from Dose 1 through up to 30 d after Dose 2 in ongoing follow-up were reported by 5.8% of BNT162b2 recipients and by 5.8% of placebo recipients. From Dose 1 through 30 d after Dose 2, reports of lymphadenopathy plausibly related to the study intervention were imbalanced, with notably more cases in the BNT162b2 group (7) vs. the placebo group (1). There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events that would suggest a causal relationship to BNT162b2.

#### *6.1.2.4.4 Safety following a booster dose (third dose, BNT162b2)*

**Phase 1 safety data following a booster dose**

Phase 1 data from 23 participants 24 to 75 yrs of age (11 in the younger 18 to 55 yrs of age group and 12 in the older 65 to 85 yrs of age group) who received a booster (Dose 3)

of BNT162b2 30 µg showed that the third dose was safe and well tolerated, based on the reactogenicity profile for 7 d after Dose 3 and the AE profile up to 1 month after Dose 3.

**Phase 3 safety data following a booster dose**

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

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

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

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

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

#### *6.1.2.4.5 Safety conclusions from Study C4591001/BNT162-02*

Based on Phase 2/3 data from ~44,000 participants ≥16 yrs of age with up to at least 6 months of follow-up after Dose 2 in Study C4591001/BNT162-02, BNT162b2 at 30 µg was safe and well tolerated across age groups. Reactogenicity and AEs were generally milder and less frequent in participants in the older group (>55 yrs of age) compared with the younger group (≤55 yrs of age). Reactogenicity was mostly mild to moderate and short-lived after dosing for both younger and older age groups (i.e., median onset between 1 to 4 d after dosing and resolution within 1 to 2 d after onset), and the AE profile did not suggest any serious safety concerns. The incidence of SAEs and deaths were low in the context of the number of participants enrolled and comparable in BNT162b2 and placebo. The incidence of discontinuations due to AEs was also generally low and similar between BNT162b2 and placebo groups.

Cumulative safety follow-up to at least 6 months after Dose 2 for ~12,000 Phase 2/3 participants originally randomized to BNT162b2, comprising the combined blinded and open-label periods, showed no new safety signals or suggested and new safety concerns arising from this period of follow-up.

Similarly, open-label follow-up of participants originally randomized to placebo from the time of unblinding to receive BNT162b2 until the data cutoff date showed no new safety signals or concerns.

Safety analysis results for subgroups based on demographics (age, race, ethnicity, and sex) and by baseline SARS-CoV-2 status (positive vs negative) have not shown any clinically important differences in the BNT162b2 safety profile. Analysis of the subset of individuals with stable HIV did not suggest any safety concerns in this population. Analysis of participants originally randomized to placebo who then received BNT162b2 (Dose 3) by demographic subgroups and based on prior evidence of SARS-CoV-2 infection or prior COVID-19 illness did not suggest any safety concerns.

Phase 3 data from ~2,200 adolescents 12 to 15 yrs of age with a median follow-up time of at least 2 months after Dose 2 showed BNT162b2 at 30 µg was safe and well tolerated.

Safety data from participants in Phase 1 and Phase 3 who received a booster dose of BNT 162b2 30 µg ~6 to 8 months after completing the 2-dose regimen of 30 µg BNT162b2 showed that post-Dose 3 reactogenicity and AE profiles did not show new safety concerns.

#### 6.1.2.5 Overall conclusions in Study C4591001/BNT162-02

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

The potential risks are based on the observed safety profile to date, which shows mostly mild reactogenicity, low incidence of severe or serious events, and no clinically concerning safety observations or safety concerns. The vaccine appears to be safe and well tolerated across the safety population comprising ~44,000 study participants ≥16 yrs of age, among whom ~12,000 have been followed for at least 6 months after completing the 2-dose regimen. Safety analyses have also included demographic subgroups based on age, sex, race, ethnicity, and baseline SARS-CoV-2 status and the subset with stable HIV. The confinement of severe cases of COVID-19 predominantly to the placebo group versus the BNT162b2 group suggests no evidence of VAED.

Vaccine efficacy was remarkably high (≥95%) in participants without evidence of prior SARS-CoV-2 infection, and >94% for those with and without prior infection, in the prespecified interim and/or final analyses. Updated analyses with all confirmed cases accrued up to ~6 months after Dose 2 showed persistence of protection with estimated VE of ≥91.1%. Overall, observed VE was >90% across subgroups identified by age, sex, race, ethnicity, country, and risk factors and remained high in the updated analysis.

Severe cases have been confined overwhelmingly to the placebo group in all efficacy analyses. Efficacy data suggest highly effective protection against COVID-19 in a broad population of individuals across demographic characteristics with durable immune responses and protection from COVID-19 disease observed up to ~6 months after completing the vaccination regimen.

Phase 1 and Phase 3 booster data show that a third dose of BNT162b2 administered ~6 months after completing the 2-dose regimen induces a strong and broad immune

response that is expected to confer extended protection against COVID-19, including VOCs. The reactogenicity and adverse event profile observed after the booster (Dose 3) was generally similar to that observed following Dose 2 of the initial 2-dose regimen, which suggests no potentiation of reactogenicity or any new safety concern arising from administration of a third dose.

BNT162b2 administered 21 d apart to 12 to 15-year-old adolescents was safe, immunogenic, and resulted in an observed VE of 100% against COVID-19 from 7 d post-Dose 2.

### *6.1.3 BNT162-03 for BNT162b1 in healthy Chinese younger and elderly adults (status 08 FEB 2021)*

This is a Phase 1, randomized, placebo-controlled, observer-blind study investigating the safety and immunogenicity of SARS-CoV-2 RNA vaccine (BNT162b1) in healthy Chinese participants aged 18 to 55 yrs (younger adults) and participants aged 65 to 85 yrs (elderly).

Clinical conduct of the study is ongoing. All planned vaccine administration to study participants has been completed and the dosed participants are now in follow-up.

Currently, only preliminary reactogenicity, safety, and tolerability data is available for up to 28 d after Dose 2.

A total of 72 younger adults were enrolled in this study: 24 participants each in the 10 µg group, 30 µg group, and placebo group. All younger adults received Dose 1 and Dose 2 as planned.

A total of 72 elderly adults were enrolled in this study: 24 participants each in the 10 µg group, 30 µg group, and placebo group. All elderly adults received dose 1 as planned; all but two elderly adult received Dose 1 (one elderly adult in each of the 10 µg and 30 g dose groups dropped out before receiving Dose 2).

There were no protocol deviations considered to affect GCP compliance, participant safety, or the statistical analysis.

In younger adults, the IR of solicited local reactions was 93.8% for Days 0 to 7 and Days 0 to 14, including injection site pain (91.7%), redness (29.2%) and swelling (25.0%), all of which belong to Grade 1 and Grade 2. The IR of solicited systemic AEs, including headache (62.5%), fatigue (58.3%) and fever (56.3%), was 79.2% for Days 0 to 7. The IR of solicited systemic reactions, including fever (73.0%), headache (62.5%) and fatigue (58.3%), was 81.3% for Days 0 to 14. The IR of unsolicited AEs related to vaccination was 39.6%. The IR of unsolicited AEs related to vaccination in 10 µg group, 30 µg group and placebo group were 37.5%, 41.7% and 4.2% respectively, and the severity was Grade 1.

In elderly adults, the IR of solicited local reaction for Days 0 to 7 and Days 0 to 14 was 81.3%, including injection site pain (77.1%), redness (14.6%) and swelling (10.4%), all of which were Grade 1 or Grade 2. The IR of solicited systemic reaction, including fever (35.4%), fatigue (20.8%) and malaise (12.5%), was 45.8% for Days 0 to 7. The IR of solicited systemic AEs, including fever (54.2%), fatigue (22.9%) and malaise (12.5%), was 58.3% for Days 0 to 14. The IR of unsolicited AEs related to vaccination was 27.1%. The IRs of unsolicited AEs related to vaccination were 16.7%, 37.5% and 8.3% in 10 µg group,

30 µg group and placebo group, respectively. The severity was mostly Grade 1 and rarely Grade 2 to Grade 3 (National Medical Products Administration [NMPA] guideline: 2 participants with Grade 2 [4.2%], 1 participant with Grade 3 [2.1%]; FDA guideline: 3 participants with Grade 2 [6.3%]).

The observed reactogenicity to BNT162b1 was dose-dependent and a higher frequency of AEs was generally observed after the second dose. Compared with the younger adults, the elderly adults had a lower IR and severity of solicited local reactions and solicited systemic reactions.

The IR of total AEs (including solicited and unsolicited events) related to vaccination in adult group is 95.8%. The IRs of AE related to vaccination in 10 µg group, 30 µg group and placebo groups were 91.7%, 100.0% and 20.8%, respectively. According to FDA guideline, the IR of AE related to vaccination at Grade 3 and above was 10.4%. The IRs of AEs in 10 µg, 30 µg and placebo groups were 4.2%, 16.7% and 0.0%, respectively. According to NMPA guideline, the IR was 25.0%, and the IRs in 10 µg group, 30 µg group and placebo group were 12.5%, 37.5% and 0.0%, respectively. The IR of AEs related to vaccination in elderly group was 93.8%. The IRs of AEs related to vaccination in 10 µg group, 30 µg group and placebo group were 93.8%; 91.7%, 95.8% and 16.7%, respectively. According to FDA guideline, the IR of AE related to vaccination at Grade 3 and above is 4.2%. The IRs of AE in 10 µg, 30 µg and placebo groups were 0.0%, 8.3% and 0.0%, respectively. According to NMPA guideline, the IR of AE related to vaccination at Grade 3 and above was 4.2%, and the IRs in 10 µg group, 30 µg group and placebo group were 0.0%, 8.3% and 0.0%, respectively. The occurrence of AEs was dose-dependent.

Until 28 d after Dose 2, there were no SAEs in younger adults who received two doses of BNT162b1 or placebo. In the elderly adults, there were two SAEs (both in one elderly adult who was hospitalized due to joint dislocation and humeral fracture after a car accident on Day 13 after dose 1; this SAE was considered not related to IMP by the investigator).

Until 28 d after Dose 2, no AESIs, and two participants were withdrawn due to related AEs. One elderly adult was withdrawn due to AEs considered related to IMP by the investigator (after Dose 1 [30 µg BNT162b1], solicited local reactions [flush, pain, and induration] and unsolicited AEs [fever, erythema, and pruritus at vaccination site]). Another participant was withdrawn due to AEs considered not related to IMP by the investigator.

At 24 h after dose 1, younger and elderly adults reported decreases in the number of lymphocytes and the increases in CRP as compared to the baseline mean. The change for CRP was stronger in 30 µg group than in the 10 µg group; this effect is believed to be related to the distribution of peripheral lymphocytes to immune organs after BNT162b1 administration. The investigators rated the changes in CRP to be not clinically significant, but some changes in lymphocytes to be clinically significant. The changes in both CRP and lymphocytes were transient, and returned to normal during the follow-up visits without any clinical consequences.

In summary, as investigated in this study, 10 µg and 30 µg of BNT162b1 was safe and well tolerated in younger and elderly Chinese adults.

Dosing with 10 µg and 30 µg BNT162b1 elicited specific humoral and cellular immune responses, with a clear boost effect of the second vaccination on antibody titers observed in both adult and elderly Chinese adults.

Overall, in this study two doses of 10 µg or 30 µg BNT162b1 in younger and elderly healthy Chinese adults showed a tolerability, safety and immunogenicity profile consistent with that reported for the same BNT162b1 doses in the studies BNT162-01 and C4591001/BNT162-02.

### *6.1.4 BNT162-04 for BNT162b3 in healthy younger and older adults (status 25 AUG 2021)*

This is a multi-site, Phase 1/2, dose escalation study investigating the safety and immunogenicity of a prophylactic SARS-CoV-2 RNA vaccine (BNT162b3) against COVID-19 using different dosing regimens in healthy adults.

This study is ongoing clinically. Except for at the 30 µg dose level, all planned vaccine administration to study participants has been completed and the dosed participants are now in follow-up. Interim safety and immunogenicity data reported on 25 AUG 2021 is summarized here.

BNT162b3 had an acceptable safety profile at the 3 µg and 10 µg doses in younger participants aged 18 to 55 yrs but the reactogenicity of the 20 µg Dose 2 in younger participants was less favorable than the lower doses, therefore Dose 2 at 30 µg was not administered. In older participants aged 56 to 85 yrs, BNT162b3 had an acceptable safety profile at the 3, 10, 20, and 30 µg doses. The majority of events reported were reactogenicity symptoms and consistent with the findings for other COVID-19 vaccines or candidate vaccines. Reactogenicity in older participants, in particular systemic reactogenicity, was generally milder and less frequent than that observed in younger participants for a given dose level.

Both younger and older participants dosed with BNT162b3 showed strong BNT162b3-induced antibody responses. Virus neutralizing GMTs were detected after Dose 1 and showed a substantial, second-dose response by 7 d after Dose 2 (Day 29). Day 43 neutralizing GMTs were comparable between the younger and older participants in the 3, 10, and 20 µg dose groups, with a trend to slightly higher GMTs in the older participants. Neutralizing GMTs remained stable up to Day 50 (with exception of the 10 µg-dosed younger participants group). All participants who received two doses of ≥10 µg BNT162b3 seroconverted either by 7 d or 14 d after Dose 2 (Day 29 or Day 36). All participants dosed with ≥10 µg BNT162b3 remained seropositive throughout the follow-up until Day 50.

### *6.1.5 C4591005/BNT162-05 for BNT162b2 in Japanese adults*

This is an observer-blinded, placebo-controlled study of BNT162b2 compared to placebo, randomized in a 3:1 ratio in 160 Japanese adults.

All planned vaccine administration has been completed and the dosed participants are now in follow-up.

### 6.1.6 BNT162-06 for BNT162b2 in healthy Chinese adults

This is a Phase 2, randomized, placebo-controlled, observer-blinded study of the safety and immunogenicity of BNT162b2 in healthy Chinese younger and older adults.

This study is ongoing clinically. Currently, only preliminary unaudited reactogenicity and tolerability data are available. Younger and older adults dosed once or twice at dose levels up 30 µg, showed acceptable tolerability, there were no AESIs, and no participants were withdrawn due to related AEs. There were six SAEs (two participants with cerebral infarction, and one participant each with lung carcinoma cell type unspecified stage 0, cholecystitis acute, diabetic neuropathy, or lower limb fracture) after administration of Dose 1 (non-of these participants received Dose 2).

### 6.1.7 BNT162-07/C4591007 for BNT162b2 in healthy children and young adults

Study C4591007 is an ongoing Phase 1/2/3 study in healthy children and young adults. Phase 1 is comprised of an open-label dose-finding portion that evaluated the safety, tolerability, and immunogenicity of BNT162b2 administered on a 2-dose schedule to participants in up to 3 age groups (participants 5 to < 12 yrs, 2 to < 5 yrs, and 6 months to < 2 yrs of age). Phase 2/3 is comprised of a selected-dose portion that will evaluate the safety, tolerability, and immunogenicity in each age group at the selected dose level from the Phase 1 open-label dose-finding portion of the study.

For the Phase 1 open-label dose-finding portion of the study, the number of participants who have received Dose 1 and Dose 2 of BNT162b2 and completed the 1-month post-Dose 2 visit is shown in Table 24.

**Table 24: Number of participants vaccinated in Phase 1 Study C4591007 (as of 16 JUL 2021)**

| | Age group | | |
|---|---|---|---|
| | **5 to < 12 years (N)** | **2 to < 5 years (N)** | **6 months to < 2 years (N)** |
| 3 µg dose group | Not available | 16 | 16 |
| 10 µg dose group | 16 | 32 | Not available |
| 20 µg dose group | 16 | Not available | Not available |
| 30 µg dose group | 16 [a] | Not available | Not available |
| **Total** | **48** | **48** | **16** |

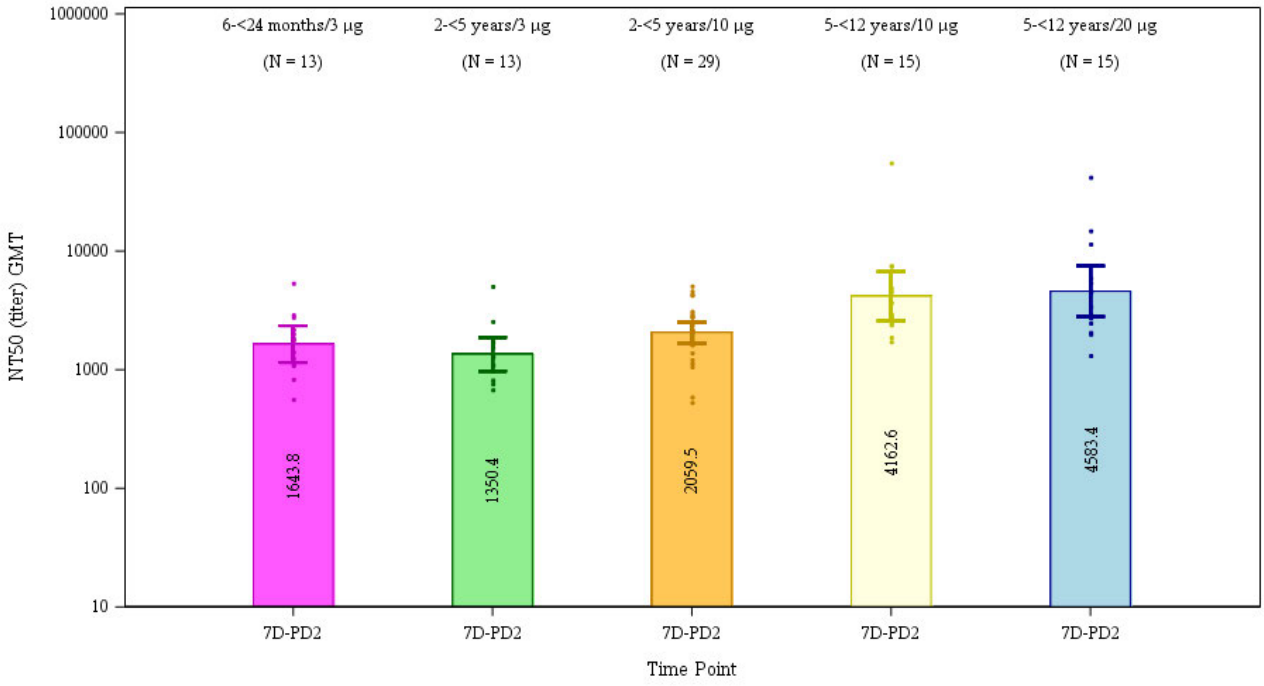
a. Of the 16 participants who received 30 µg at Dose 1, 4 participants received 30 µg at Dose 2 and 12 participants received 10 µg at Dose 2.

In the 5 to < 12 yrs group, due to observed reactogenicity in the initial 4/16 participants of the assigned 30 µg dose level group after receiving both doses, an Internal Review Committee decision was made for the remaining 12/16 participants in the dose level group to receive the same dose that was to be selected for Phase 2/3 (10 µg) at Dose 2, and the 30 µg dose level was discontinued in the study.

### 6.1.7.1 Summary of Immunogenicity in C4591007

#### *6.1.7.1.1 Phase 1 Immunogenicity – Children 6 months to < 12 yrs of age*

Phase 1 participants in the evaluable immunogenicity population had no prior evidence of SARS-CoV-2 infection. Phase 1 participants were without serological or virological evidence of SARS-CoV-2 infection up to 7 d post-Dose 2. Figure 38 illustrates that vaccination of children in all pediatric age groups with BNT162b2 at the dose levels indicated elicited high-titer serum neutralization of SARS-CoV-2. The neutralizing GMTs of sera drawn 7 d post-Dose 2 from children immunized with 3-, 10-, or 20-µg of BNT162b2 were comparable to or often higher than the GMTs of sera drawn 1-month post-Dose 2 from immunized adolescents 12 to 15 yrs of age and from immunized young adults 16 to 25 yrs age (data not shown).




Abbreviations: 7D-PD2 = 7 days after Dose 2; GMT = geometric mean titer; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Dot presents individual antibody levels.
Note: Number within each bar denotes geometric mean.
Note: Participants who had no serological or virological evidence (prior to the Visit 3 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visits 1, 2, and 3, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the Visit 3 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: adva Table Generation: 17AUG2021 (06:18)
(Cutoff Date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: ./nda3/C4591007_Phase1_EUA/adva_f002_gmt_p1_50

**Figure 38: GMT and 95% CI for neutralizing levels – 7 d post-Dose 2 for C4591007, Phase 1, 6 months to < 12 yrs of age – Evaluable Immunogenicity Population**

#### *6.1.7.1.2 Phase 2/3 Immunogenicity – Children 5 to < 12 yrs of age*

An analysis of SARS-CoV-2 50% neutralizing titers 1 month after Dose 2 in a subset of participants demonstrated effectiveness by immunobridging of immune responses

comparing children 5 through less than 12 yrs of age in the Phase 2/3 part of the study to randomly selected participants 16 through 25 yrs of age in the Phase 2/3 part of Study C4591001 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the GMR and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 50% neutralizing titers from baseline (before Dose 1).

The ratio of the SARS-CoV-2 50% neutralizing titers in children 5 through < 12 yrs of age to that of young adults 16 to 25 yrs of age was 1.04 (2-sided 95% CI: 0.93, 1.18), as presented in Table 25.

**Table 25: Summary of GMRs for 50% neutralizing titer – Comparison of children 5 through less than 12 yrs of age (Study C4591007) to participants 16 through 25 yrs of age (study C4591001) – Participants without evidence of infection up to 1 month after Dose 2 – Dose 2 Evaluable Immunogenicity Population**

| | | BNT162b2 | | | |
|---|---|---|---|---|---|
| | | 10 µg/Dose 5 through < 12 years n[a]=264 | 30 µg/Dose 16 through 25 years n[a]=253 | 5 through < 12 years/ 16 through 25 years | |
| Assay | Time Point[b] | GMT[c] (95% CI[c]) | GMT[c] (95% CI[c]) | GMR[d] (95% CI[d]) | Met Immunobridging Objective[e] (Y/N) |
| SARS-CoV-2 neutralization assay - NT50 (titer)[f] | 1 month after Dose 2 | 1,197.6 (1,106.1, 1296.6) | 1,146.5 (1,045.5, 1257.2) | 1.04 (0.93, 1.18) | Y |

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. Protocol-specified timing for blood sample collection.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1[5 through <12 yrs of age] - Group 2 [16 through 25 yrs of age]) and the corresponding CI (based on the Student t distr bution).
e. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8.
f. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2.

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 through less than 12 yrs of age and 99.2% of participants 16 through 25 yrs of age had a seroresponse from before vaccination to 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%) (Table 26).

**Table 26: Difference in percentages of participants with seroresponse – Participants without evidence of infection up to 1 month after Dose 2 – Immunobridging Subset – Phase 2/3 – Comparison of 5 through <12 yrs of age to Study C4591001 Phase 2/3 16 through 25 yrs of age – Evaluable Immunogenicity Population**

| | | BNT162b2 | | 5 through <12 years-16 through 25 years | |
|---|---|---|---|---|---|
| | | Study C4591007 10 µg /Dose 5 through < 12 years N[a]=264 | Study C4591001 30 µg /Dose 16 through 25 years N[a]=253 | | |
| Assay | Time Point[b] | n[c] (%) (95% CI[d]) | n[c] (%) (95% CI[d]) | Difference %[e] (95% CI[f]) | Met Immunobridging Objective[g] (Y/N) |
| SARS-CoV-2 neutralization assay - NT50 (titer)h | 1 month after Dose 2 | 262 (99.2) (97.3, 99.9) | 251 (99.2) (97.2, 99.9) | 0.0 (-2.0, 2.2) | Y |

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

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. N = number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. Protocol-specified timing for blood sample collection.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (Group 1 [5 through < 12 yrs of age] – Group 2 [16 through 25 yrs of age]).
f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
g. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0%.
h. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titer 50; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2.

### 6.1.7.2 Summary of safety in C4591007

#### *6.1.7.2.1 Phase 1 Safety - Children 6 months to < 12 yrs of age*

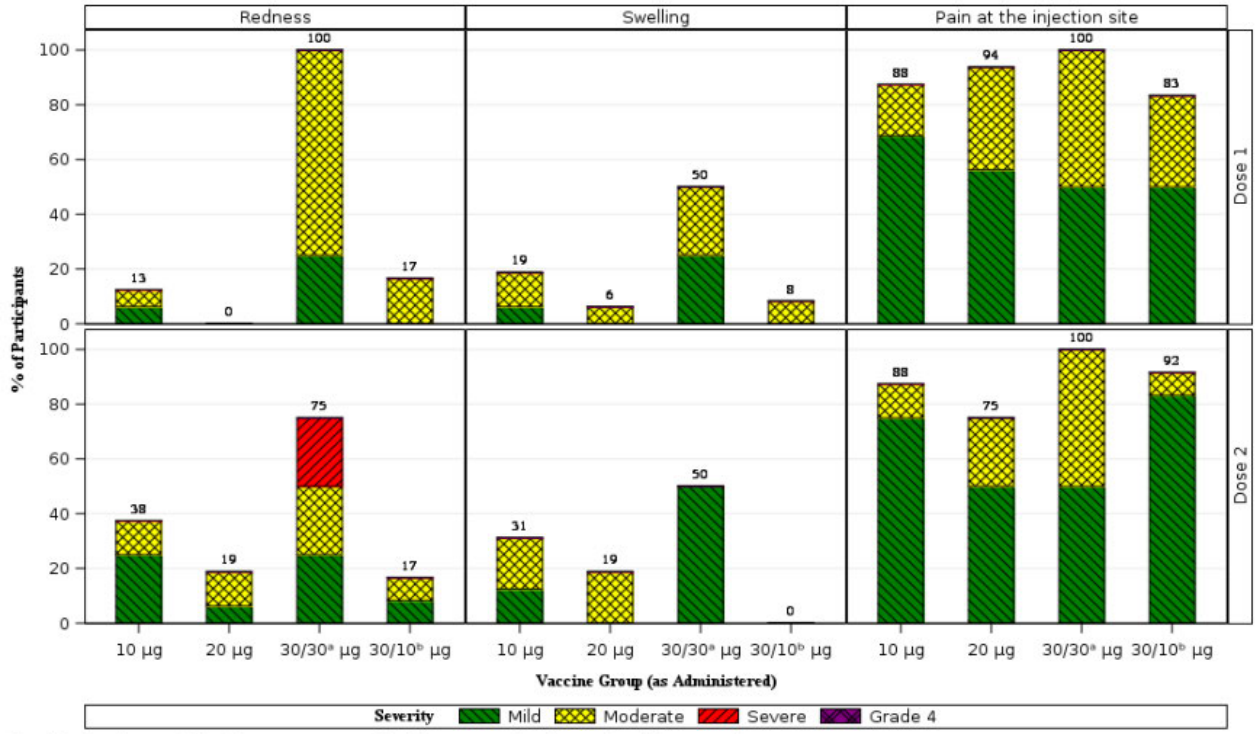
Available reactogenicity and AE data from participants enrolled in the Phase 1 part of Study C4591007 are summarized by age group. Available AE data includes AEs reported up to 1 month after Dose 2 for BNT162b2 (all dose levels) and supplemental AE data up to the data cutoff date (16 JUL 2021), which represents up to ~3 months of follow-up after Dose 2.

#### ***5 to < 12 yrs of age group***

*Reactogenicity*

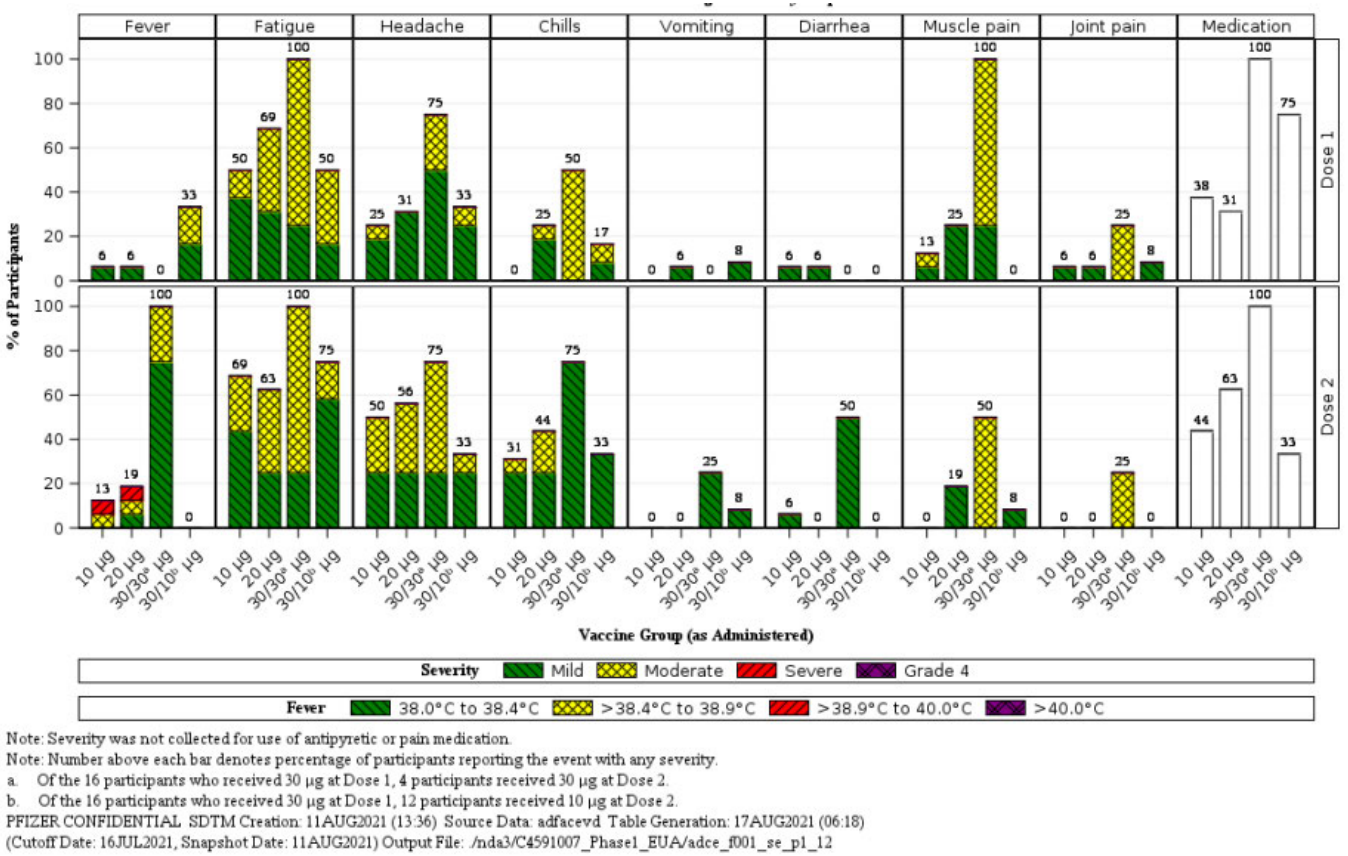
Overall, reactogenicity in the 5 to < 12 yrs of age group tended to increase in a dose level- and dose number-dependent manner with regard to the incidence and/or severity of local reactions (Figure 39) and systemic events (Figure 40) at 10, 20, and 30 µg dose

levels. Local reactions and systemic events were mostly mild to moderate and short-lived. For the 10 and 20 µg groups, pain at the injection site was the most commonly reported local reaction within 7 d after any dose (range: 87.5% to 93.8%) and fatigue was the most commonly reported systemic event within 7 d after any dose (87.5% and 81.3%, respectively).




Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
a. Of the 16 participants who received 30 µg at Dose 1, 4 participants received 30 µg at Dose 2.
b. Of the 16 participants who received 30 µg at Dose 1, 12 participants received 10 µg at Dose 2.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: adfacevd Table Generation: 17AUG2021 (06:18)
(Cutoff Date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: /nda3/C4591007_Phase1_EUA/adce_f001_lr_p1_12

**Figure 39: Participants reporting local reactions, by maximum severity, within 7 d after each dose – Phase 1 – 5 to < 12 yrs of age - Safety Population**




Note: Severity was not collected for use of antipyretic or pain medication.
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
a. Of the 16 participants who received 30 µg at Dose 1, 4 participants received 30 µg at Dose 2.
b. Of the 16 participants who received 30 µg at Dose 1, 12 participants received 10 µg at Dose 2.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: adfacevd Table Generation: 17AUG2021 (06:18)
(Cutoff Date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: /nda3/C4591007_Phase1_EUA/adce_f001_se_p1_12

**Figure 40: Participants reporting systemic events, by maximum severity, within 7 d after each dose – Phase 1 – 5 to < 12 yrs of age – Safety Population**

### *Adverse events*

From Dose 1 to 1 month after Dose 2, AEs were reported by 7 participants (43.8%) who received BNT162b2 at 10 µg and 5 participants (31.3%) who received 20 µg. Of these, the AEs were considered related to study intervention for 4 (25.0%) and 2 (12.5%) participants in the 10 µg and 20 µg dose groups, respectively.

In 4/16 participants who received both doses in the 30-µg group as assigned, AEs were reported by 2 participants with both considered by the investigator as related to study intervention (lymphadenopathy and arthralgia, n=1 each). In the remaining 12/16 participants who received the 30/10-µg dose regimen, 3 participants reported 4 AEs (injection site pain, n=2; injection site erythema and vomiting, n=1). Of these, the 3 AEs localized to the injection site were considered related to study intervention.

No SAEs, deaths, or AEs leading to withdrawal were reported in Phase 1 participants 5 to < 12 yrs of age as of the data cutoff date. Overall, no change in AE profile was reported in any dose level group up to the data cutoff date.

All AEs through the data cutoff date were mild to moderate, with the exception of 1 severe AE (Grade 3 pyrexia) reported in the 20-µg group on Day 1 post-Dose 2 (also recorded as a systemic event). This participant had a high temperature of 39.7°C on Day 2 that fell to < 38°C and resolved by Day 3. The investigator considered the event related to study intervention.

Immediate AEs (reported within 30 minutes post-dose) after Dose 1 included injection site discomfort and presyncope in 1 participant each in the 10-µg group and injection site pain in 2 participants in the 30/10-µg dose group. After Dose 2, 1 participant in the 10-µg group reported immediate injection site pain.

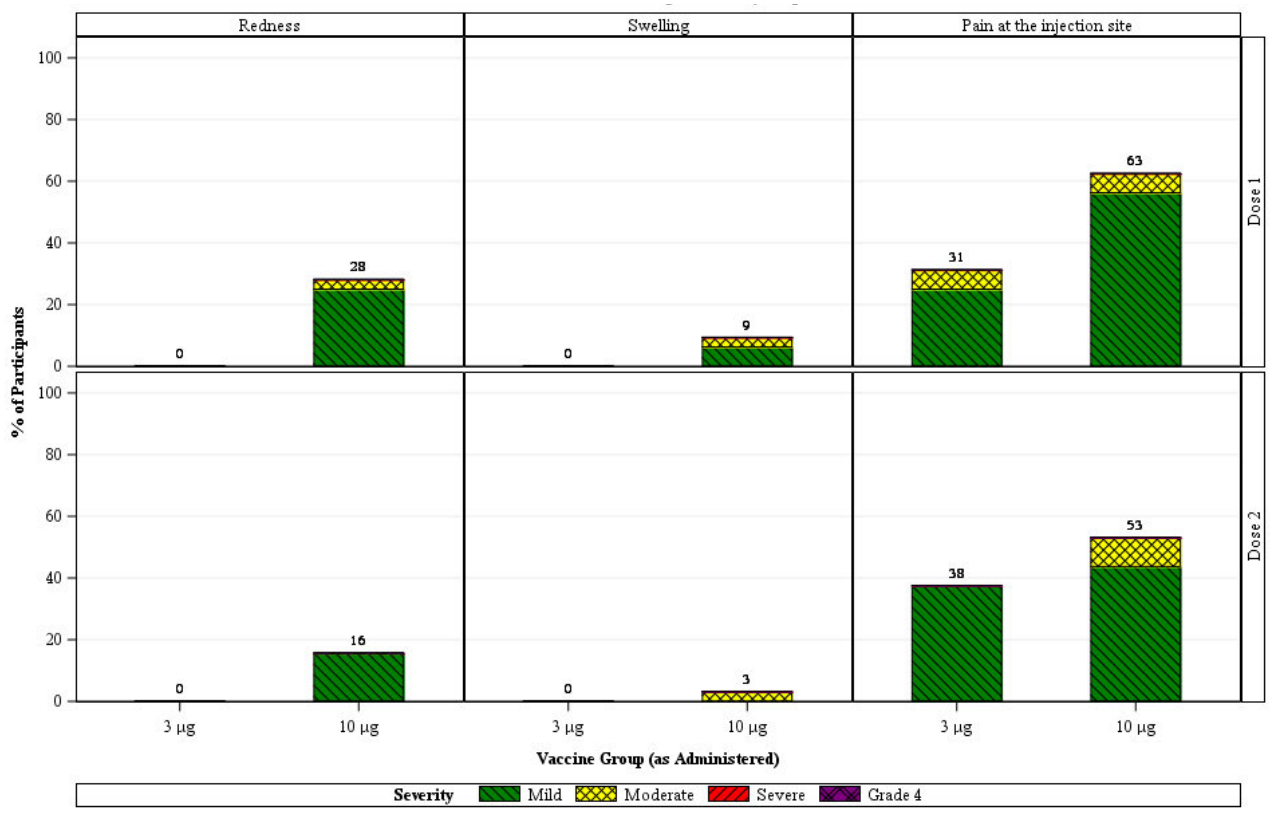
One (1) participant who received 2 doses of BNT162b2 30 µg as assigned had an AE of Grade 2 arthralgia (right hip pain) that was judged by the investigator as related to study intervention. Lymphadenopathy, identified as related to BNT162b2 in individuals ≥12 yrs of age, was observed in 2 pediatric participants 5 to < 12 yrs of age (assessed as related to study intervention for 1/2 participants).

## 2 to < 5 yrs of age group

### *Reactogenicity*

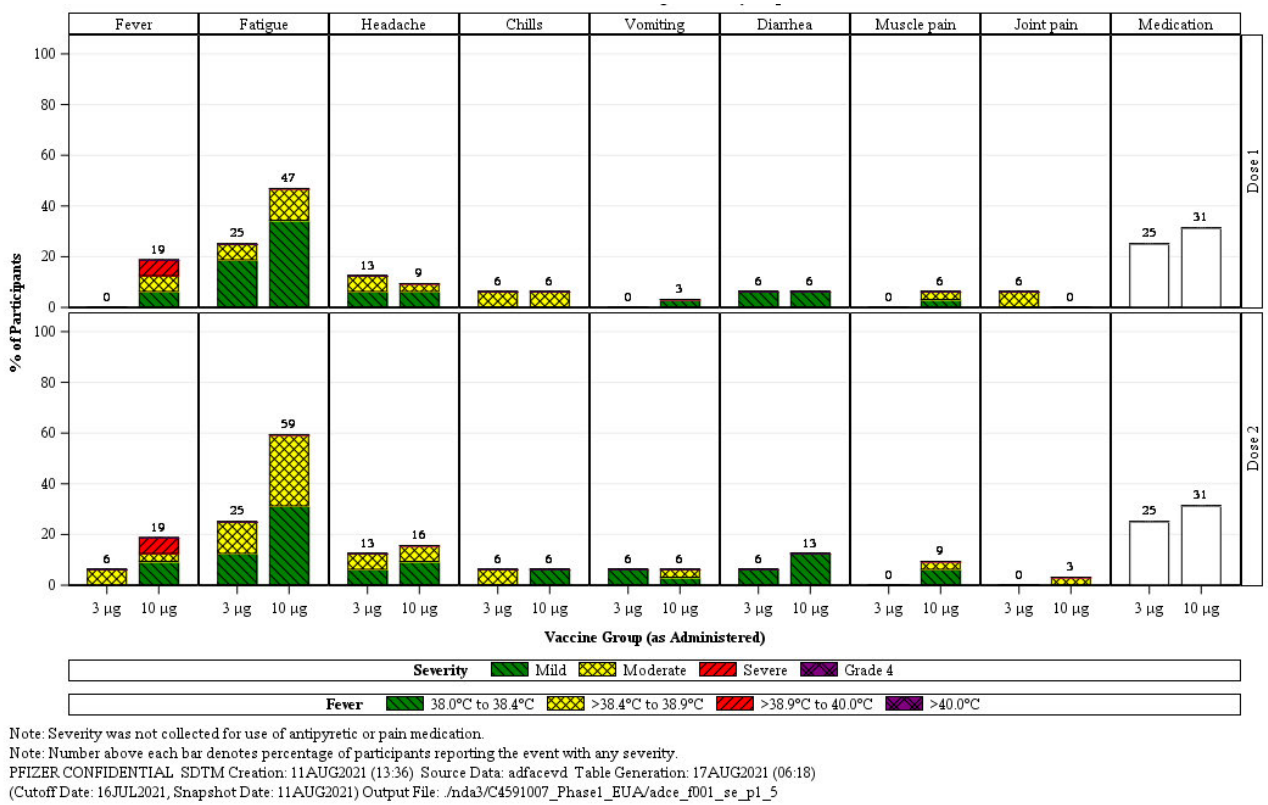
Overall, reactogenicity in the 2 to < 5 yrs of age group tended to increase in a dose level - dependent manner with regard to the incidence and/or severity of local reactions (Figure 41). Reactogenicity generally increased in a dose level- and/or dose number-dependent manner with regard to incidence and/or severity of systemic events (Figure 42). Local reactions and systemic events were mostly mild to moderate and resolved within 1 or 2 d. For the 3 and 10 µg groups, within 7 d after any dose, pain at the injection site was the most commonly reported local reaction (43.8% and 65.6%, respectively) and fatigue was the most commonly reported systemic event (31.3% and 71.9%, respectively). Fever was more common in the 10 µg dose level group than in the 3 µg dose level group after

Dose 1 and Dose 2 (10 µg: 18.8% and 18.8%, respectively; 3 µg: 0% and 6.3%, respectively). Severe fever was reported in the 10-µg dose level group by 2 (6.3%) participants within 7 d after Dose 1 and 2 (6.3%) participants within 7 d after Dose 2 and none in the 3-µg dose group.




Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: adfacevd Table Generation: 17AUG2021 (06:18)
(Cutoff Date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: ./nda3/C4591007_Phase1_EUA/adce_f001_lr_p1_5

**Figure 41: Participants reporting local reactions, by maximum severity, within 7 d after each dose – Phase 1 – 2 to < 5 yrs of age – Safety Population**




Note: Severity was not collected for use of antipyretic or pain medication.
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: adfacevd Table Generation: 17AUG2021 (06:18)
(Cutoff Date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: ./nda3/C4591007_Phase1_EUA/adce_f001_se_p1_5

**Figure 42: Participants reporting systemic events, by maximum severity, within 7 d after each dose – Phase 1 – 2 to < 5 yrs of age – Safety Population**

### *Adverse events*

From Dose 1 to 1 month after Dose 2, AEs were reported by 4 participants (25.0%) who received BNT162b2 at 3 µg and 12 participants (37.5%) who received 10 µg. Of these, the AEs were considered related to study intervention for 2 (12.5%) and 7 (21.9%) participants in the 3 µg and 10 µg dose groups, respectively. No severe AEs were reported.

No SAEs, deaths, or AEs leading to withdrawal were reported in Phase 1 participants 2 to < 5 yrs of age as of the data cutoff date. Overall, no change in AE profile was reported in any dose level group up to the data cutoff date.

After Dose 1, 1 participant in the 3 µg group and 1 participant in the 10 µg group reported immediate injection site pain (i.e., reported within 30 minutes post-dose). After Dose 2, 1 participant in the 10 µg group reported immediate injection site pain.

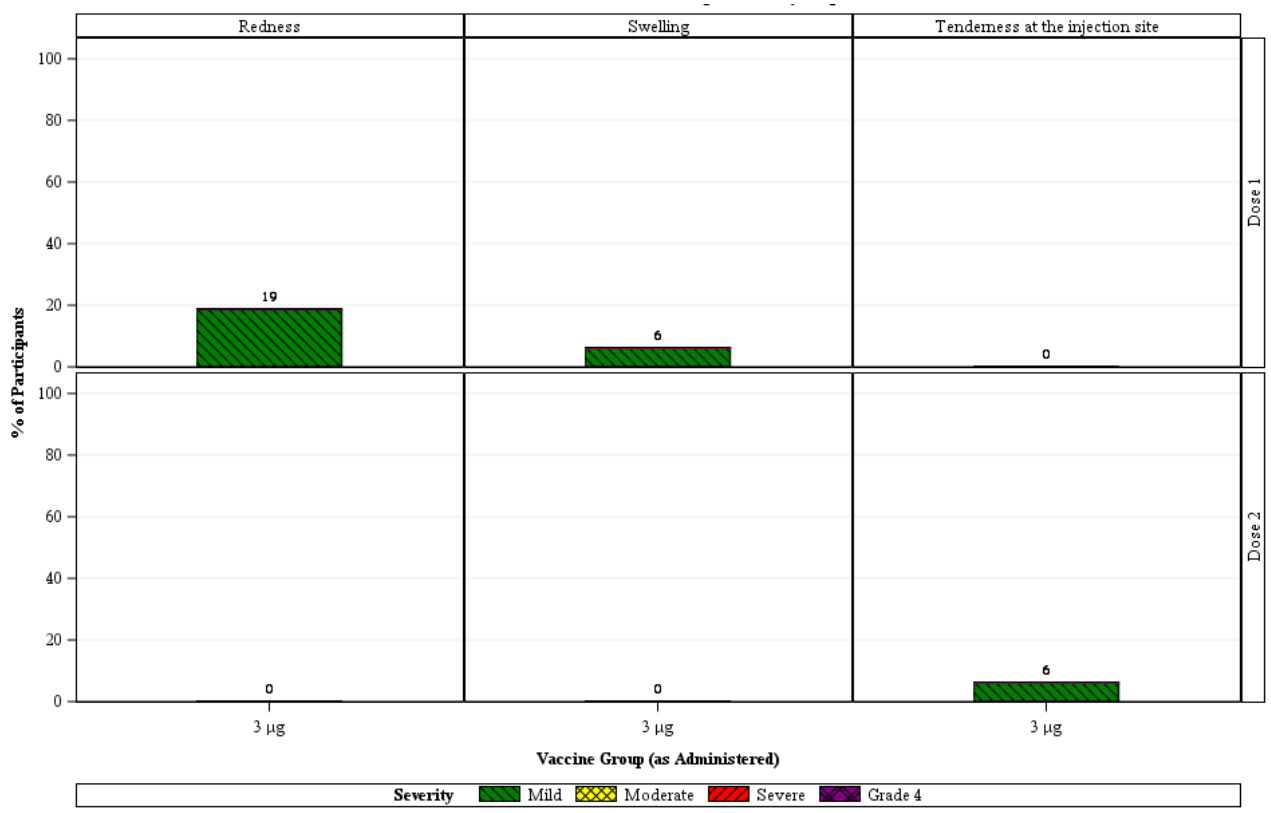
Lymphadenopathy, identified as related to BNT162b2 in individuals ≥12 yrs of age, was observed in 1 pediatric participant 2 to < 5 yrs of age in the 10 µg group (assessed as related to study intervention). Rash was observed in two participants (one each in the 3 µg and 10 µg groups; both were assessed as not related to study intervention).

## 6 months to < 2 yrs of age group

### *Reactogenicity*

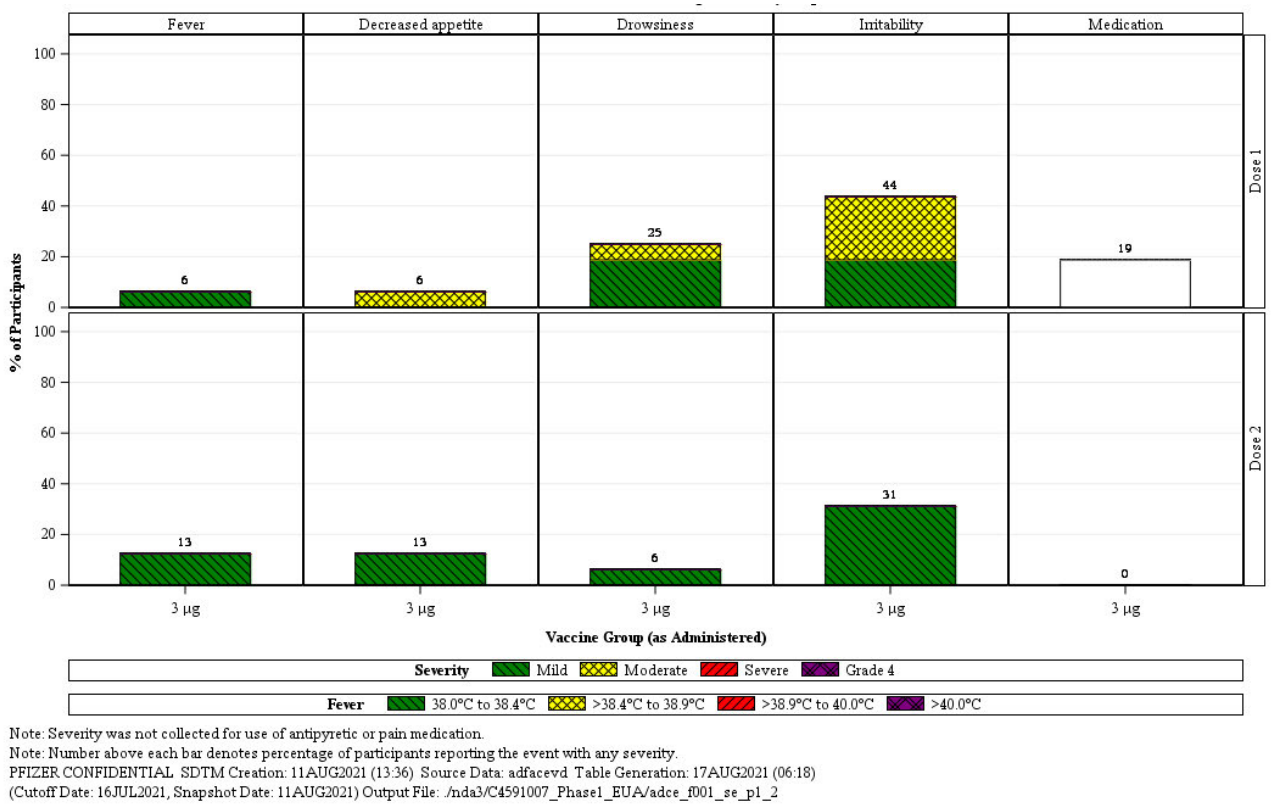
Overall, reactogenicity in the 6 months to < 2 yrs of age group shows that the 3 µg dose level was well tolerated with regard to incidence and severity of local reactions (Figure 43) and systemic events (Figure 44). Within 7 d after Dose 1, redness and swelling were the most commonly reported local reactions (18.8% and 6.3%, respectively). Within 7 d after Dose 2, tenderness at the injection site was the only reported local reaction (6.3%). Local reactions were all mild and the majority of events resolved within 1 d.

Within 7 d after Dose 1, irritability and drowsiness were the most commonly reported systemic events (43.8% and 25.0%, respectively). Within 7 d after Dose 2, irritability, fever, and decreased appetite were the most commonly reported systemic events (31.3%, 12.5%, and 12.5%, respectively). Systemic events were mostly mild, and the majority of events resolved within 1 or 2 d.




Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: adfacevd Table Generation: 17AUG2021 (06:18)
(Cutoff Date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: ./nda3/C4591007_Phase1_EUA/adce_f001_lr_p1_2

**Figure 43: Participants reporting local reactions, by maximum severity, within 7 d after each Dose – Phase 1 – 6 months to < 2 yrs of age - Safety Population**




Note: Severity was not collected for use of antipyretic or pain medication.
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: adfacevd Table Generation: 17AUG2021 (06:18)
(Cutoff Date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: ./nda3/C4591007_Phase1_EUA/adce_f001_se_p1_2

**Figure 44: Participants reporting systemic events, by maximum severity, within 7 d after each dose – Phase 1 – 6 months to < 2 yrs of age – Safety Population**

### *Adverse events*

From Dose 1 to 1 month after Dose 2, AEs were reported by 2 participants (12.5%) who received BNT162b2 at 3 µg. Of these, 1 of the AEs was considered related to study intervention. No severe AEs were reported.

No SAEs, deaths, or AEs leading to withdrawal were reported in Phase 1 participants 6 months to < 2 yrs of age as of the data cutoff date. Overall, no change in AE profile was reported in any dose level group up to the data cutoff date.

No participants reported immediate AEs (i.e., reported within 30 minutes post-dose) after either Dose 1 or Dose 2. One (1) participant reported with urticaria which was assessed as related to study intervention.

#### *6.1.7.2.2 Phase 2/3 Safety – Children 5 to < 12 yrs of age*

In Phase 2/3 of Study C4591007, based on data up to the cutoff date of 06 SEP 2021, 2,268 participants (1,518 BNT162b2 10 µg; 750 placebo) were 5 through less than 12 yrs of age. Of these, 2,158 (95.1%) (1,444 BNT162b2 10 µg and 714 placebo) participants have been followed for at least 2 months after the second dose of BNT162b2 10 µg. The safety evaluation in Study C4591007 is ongoing.

Demographic characteristics in Study C4591007 were generally similar with regard to age, gender, race, and ethnicity among participants 5 through less than 12 yrs of age who received BNT162b2 10 µg and those who received placebo. Among the 1,518 participants 5 through less than 12 yrs of age who received at least 1 dose of BNT162b2 10 µg, 52.6% were male and 47.4% were female, 79.3% were White, 5.9% were Black or African American, 21.0% were Hispanic/Latino, 5.9% were Asian, and 0.8% were American Indian/Alaska Native.

### Solicited local and systemic ARs

Local reactions within 7 d after each dose in children 5 to < 12 yrs of age are presented in Table 27. The mean duration of pain at the injection site after Dose 1 was 2.0 d (range 1 to 10 d), for redness 2.0 d (range 1 to 10 d), and for swelling 1.9 d (range 1 to 8 d) for children in the BNT162b2 10 µg group.

**Table 27: Frequency and percentages of participants with solicited local reactions, by maximum severity, within 7 d after each dose – Children 5 through less than 12 yrs of age – Safety Population***

| | BNT162b2 Dose 1 N[a]=1,511 n[c] (%) | Placebo Dose 1 N[a,b]=748 n[c] (%) | BNT162b2 Dose 2 N[a]=1,501 n[c] (%) | Placebo Dose 2 N[a,b]=740 n[c] (%) |
|---|---|---|---|---|
| **Redness** [d] | | | | |
| Any (≥0.5 cm) | 222 (14.7) | 43 (5.7) | 278 (18.5) | 40 (5.4) |
| Mild | 143 (9.5) | 37 (4.9) | 143 (9.5) | 31 (4.2) |
| Moderate | 79 (5.2) | 6 (0.8) | 132 (8.8) | 9 (1.2) |
| Severe | 0 | 0 | 3 (0.2) | 0 |
| **Swelling** [d] | | | | |
| Any (≥0.5 cm) | 158 (10.5) | 20 (2.7) | 229 (15.3) | 20 (2.7) |
| Mild | 85 (5.6) | 13 (1.7) | 117 (7.8) | 15 (2.0) |
| Moderate | 72 (4.8) | 7 (0.9) | 112 (7.5) | 5 (0.7) |
| Severe | 1 (0.1) | 0 | 0 | 0 |
| **Pain at the injection site** [e] | | | | |
| Any | 1,119 (74.1) | 234 (31.3) | 1,065 (71.0) | 218 (29.5) |
| Mild | 890 (58.9) | 204 (27.3) | 793 (52.8) | 192 (25.9) |
| Moderate | 225 (14.9) | 30 (4.0) | 267 (17.8) | 26 (3.5) |
| Severe | 4 (0.3) | 0 | 5 (0.3) | 0 |

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. The denominators (N) used in the percentage calculations for redness and swelling were 749 after Dose 1 and 741 after Dose 2 in the placebo group, due to an e-diary error.
c. n = Number of participants with the specified reaction.
d. Mild: ≥0.5 to ≤2.0 cm; Moderate: >2.0 to ≤7.0 cm; Severe: >7.0 cm.
e. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.
* Randomized participants who received at least 1 dose of the study intervention.

Systemic events within 7 d after each dose in children 5 to < 12 yrs of age are presented in Table 28.

**Table 28: Frequency and percentages of participants with solicited systemic reactions, by maximum severity, within 7 d after each dose – Children 5 through less than 12 yrs of age – Safety Population ***

| | BNT162b2 Dose 1 N[a]=1,511 n[c] (%) | Placebo Dose 1 N[a,b]=748 n[c] (%) | BNT162b2 Dose 2 N[a]=1,501 n[c] (%) | Placebo Dose 2 N[a,b]=740 n[c] (%) |
|---|---|---|---|---|
| **Fever** | | | | |
| ≥38.0°C | 38 (2.5) | 10 (1.3) | 98 (6.5) | 9 (1.2) |
| ≥38.0°C to 38.4°C | 23 (1.5) | 4 (0.5) | 51 (3.4) | 5 (0.7) |
| >38.4°C to 38.9°C | 12 (0.8) | 5 (0.7) | 38 (2.5) | 3 (0.4) |
| >38.9°C to 40.0°C | 3 (0.2) | 1 (0.1) | 8 (0.5) | 1 (0.1) |
| >40.0°C | 0 | 0 | 1 (0.1) | 0 |
| **Fatigue [d]** | | | | |
| Any | 508 (33.6) | 234 (31.3) | 592 (39.4) | 180 (24.3) |
| Mild | 333 (22.0) | 150 (20.1) | 321 (21.4) | 96 (13.0) |
| Moderate | 171 (11.3) | 83 (11.1) | 260 (17.3) | 83 (11.2) |
| Severe | 4 (0.3) | 1 (0.1) | 11 (0.7) | 1 (0.1) |
| **Headache [d]** | | | | |
| Any | 339 (22.4) | 180 (24.1) | 420 (28.0) | 138 (18.6) |
| Mild | 249 (16.5) | 131 (17.5) | 281 (18.7) | 93 (12.6) |
| Moderate | 88 (5.8) | 45 (6.0) | 136 (9.1) | 45 (6.1) |
| Severe | 2 (0.1) | 4 (0.5) | 3 (0.2) | 0 |
| **Chills [d]** | | | | |
| Any | 70 (4.6) | 35 (4.7) | 147 (9.8) | 32 (4.3) |
| Mild | 54 (3.6) | 30 (4.0) | 105 (7.0) | 24 (3.2) |
| Moderate | 16 (1.1) | 5 (0.7) | 40 (2.7) | 7 (0.9) |
| Severe | 0 | 0 | 2 (0.1) | 1 (0.1) |
| **Vomiting [e]** | | | | |
| Any | 33 (2.2) | 11 (1.5) | 28 (1.9) | 6 (0.8) |
| Mild | 26 (1.7) | 11 (1.5) | 27 (1.8) | 6 (0.8) |
| Moderate | 7 (0.5) | 0 | 1 (0.1) | 0 |
| Severe | 0 | 0 | 0 | 0 |
| **Diarrhea [f]** | | | | |
| Any | 89 (5.9) | 31 (4.1) | 79 (5.3) | 35 (4.7) |
| Mild | 79 (5.2) | 31 (4.1) | 72 (4.8) | 32 (4.3) |
| Moderate | 10 (0.7) | 0 | 7 (0.5) | 3 (0.4) |
| Severe | 0 | 0 | 0 | 0 |

| | BNT162b2 Dose 1 N[a]=1,511 n[c] (%) | Placebo Dose 1 N[a,b]=748 n[c] (%) | BNT162b2 Dose 2 N[a]=1,501 n[c] (%) | Placebo Dose 2 N[a,b]=740 n[c] (%) |
|---|---|---|---|---|
| **New or worsened muscle pain [d]** | | | | |
| Any | 137 (9.1) | 51 (6.8) | 175 (11.7) | 55 (7.4) |
| Mild | 96 (6.4) | 35 (4.7) | 116 (7.7) | 38 (5.1) |
| Moderate | 40 (2.6) | 16 (2.1) | 58 (3.9) | 17 (2.3) |
| Severe | 1 (0.1) | 0 | 1 (0.1) | 0 |
| **New or worsened joint pain [d]** | | | | |
| Any | 50 (3.3) | 41 (5.5) | 78 (5.2) | 27 (3.6) |
| Mild | 34 (2.3) | 31 (4.1) | 57 (3.8) | 20 (2.7) |
| Moderate | 16 (1.1) | 10 (1.3) | 21 (1.4) | 7 (0.9) |
| Severe | 0 | 0 | 0 | 0 |
| **Use of antipyretic or pain medication [g]** | 217 (14.4) | 62 (8.3) | 296 (19.7) | 60 (8.1) |

Note: Events and use of antipyretic or pain medication were collected in the electronic diary from Day 1 to Day 7 after each dose.

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
b. The denominators (N) used in the percentage calculations for fever and use of antipyretic or pain medication were 749 after Dose 1 and 741 after Dose 2 in the placebo group, due to an e-diary error.
c. n = Number of participants with the specified reaction.
d. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
e. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.
f. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.
g. Severity was not collected for use of antipyretic or pain medication.
* Randomized participants who received at least 1 dose of the study intervention.

### *Unsolicited AEs*

In Study C4591007, among children 5 through less than 12 yrs of age (1,518 of whom received BNT162b2 10 µg and 750 of whom received placebo), 99.5% of participants had at least 30 d of follow-up after Dose 2.

### *Serious AEs*

Serious adverse events from Dose 1 through up to 30 d after Dose 2 in ongoing follow-up were reported by no participants in the BNT162b2 10 µg group and in 1 (0.1%) participant in the placebo group.

### *Non-serious adverse events*

Non-serious adverse events from Dose 1 through up to 30 d after Dose 2 in ongoing follow-up were reported by 10.9% of BNT162b2 10 µg recipients and by 9.1% of placebo recipients. From Dose 1 through 30 d after Dose 2, lymphadenopathy was reported in 13 (0.9%) participants in the BNT162b2 10 µg group vs. 1 (0.1%) in the placebo group. Rash (including pruritic, macular, injection site rash) was reported in 8 participants in the BNT162b2 group vs. 1 in the placebo group. Of the rashes in the BNT162b2 group, 4 were considered by the investigator as related to study intervention and all were Grade 1. Rash is considered an adverse reaction to vaccine and reports of rash in Study C4591007 are

consistent with those from prior analyses of Phase 2/3 participants ≥12 yrs of age in Study C4591001. There were no other notable patterns between treatment groups for specific categories of non-serious adverse events that would suggest a causal relationship to BNT162b2.

There were no cases up to the data cutoff date, representing at least 2 months of follow-up after Dose 2, of myocarditis/pericarditis.

#### *6.1.7.2.3 Safety conclusions*

BNT162b2 was best tolerated at a dose level of 10 µg in healthy children 5 to < 12 yrs of age, and at 3 µg in healthy children 6 months to < 2 yrs and 2 to < 5 yrs of age. Reactogenicity and AEs were generally milder and less frequent in participants who received the lower dose levels than in those who received higher dose levels. Reactogenicity was mostly mild to moderate and short-lived after dosing, and the AE profile did not suggest any safety concerns.

BNT162b2 elicited robust SARS-CoV-2 50% neutralizing titers at all tested dose levels administered to healthy children across all age groups in Study C4591007. GMTs increased with increasing dose levels within age groups.

Based on these Phase 1 observations of safety and tolerability and robust immune responses at the tested dose levels for each age group, the BNT162b2 doses selected for further evaluation in the Phase 2/3 part of Study C4591007 were 10 µg for the 5 to < 12 yrs of age group and 3 µg for the 6 months to < 2 yrs and 2 to < 5 yrs of age groups.

Phase 2/3 data from ~2,250 children 5 to < 12 yrs of age with a follow-up time of at least 2 months after Dose 2 showed BNT162b2 at 10 µg was safe and well tolerated. An additional 2,250 children 5 to < 12 yrs of age completed enrollment on 10 SEP 2021 to further expand the safety database.

## 6.2 Marketing experience

BNT162b2 has received temporary authorization for emergency supply in 46 countries and licenses or conditional marketing authorizations in 46 countries globally under the tradename Comirnaty. Full approval of a 2-dose regimen of BNT162b2 30 µg in individuals ≥16 yrs of age was granted by the US FDA on 23 AUG 2021.

The safety profile of BNT162b2 based on available data in the ongoing Phase 2/3 C4591001/BNT162-02 study is favorable. Since its first marketing authorization in December 2020, BNT162b2 has been administered to hundreds of millions of individuals worldwide.

Notable post-authorization updates to the safety profile of BNT162b2 include:

- Anaphylactic reactions, which were not observed in association with the vaccine in the clinical study (Section 7.4), and
- Myocarditis and pericarditis (Section 7.4)

However, the benefit-risk profile of BNT162b2 remains positive.

The following BNT162 vaccine candidates are under clinical investigation and have neither been approved for use nor been marketed in any country: BNT162a1, BNT162b1, BNT162b3, BNT162c2, BNT162b2 (B.1.351), BNT162b2 (B.1.617.2), BNT162b2 (B.1.1.7), and BNT162b2 (B.1.1.7 + B.1.617.2).

# 7 SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

For a summary of the relevant non-clinical and clinical information, see Section 2.

The clinical program started with the investigation of four BNT162 vaccine candidates (BNT162a1, BNT162b1, BNT162b2, BNT162c2). Further vaccine candidates (e.g., BNT162b3) were later added to the program.

BNT162b2 was selected for further development and has received temporary authorization for emergency supply in 46 countries and licenses or conditional marketing authorizations in 46 countries globally under the tradename Comirnaty. Full approval of a 2-dose regimen of BNT162b2 30 µg in individuals ≥16 yrs of age was granted by the US FDA on 23 AUG 2021. To date, BNT162b2 has been administered to hundreds of millions of individuals worldwide. Further clinical investigation of BNT162b2 is ongoing to expand the studied populations.

With the emergence of new SARS-CoV-2 variants, several BNT162b2-based variant vaccines that target these viral variants were also added to the clinical program, e.g., BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), BNT162b2 (B.1.1.7 + B.1.617.2), and BNT162b2 (B.1.351).

Refer to local prescribing information for additional details regarding the use of BNT162b2.

## 7.1 Mode of action and intended indications

The BNT162 vaccine candidates use an LNP to deliver RNA to cells, where it is used to express proteins for the therapeutic effect.

The intended indication for the BNT162 vaccine candidates is "for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus".

**BNT162b2**

The approved/authorized indication for BNT162b2 is for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus in individuals 5 yrs of age and older.

## 7.2 Posology and method of administration

### *7.2.1 Posology*

BNT162 vaccines are intended for IM administration after dilution and are being evaluated as a course of two doses at least 21 d apart. Evaluation of later booster doses are also under clinical investigation. BNT162c2 was also evaluated as a single dose.

**BNT162b2**

***Individuals 12 yrs of age and older***

BNT162b2 is administered IM after dilution as a series of two doses (0.3 mL each) at greater than or equal to 21 d (preferably 3 weeks) apart. One dose (0.3 mL) contains 30 µg of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

A booster dose (third dose) of BNT162b2 may be administered IM ~6 months after the second dose in individuals 16 yrs of age and older.

The interchangeability of BNT162b2 with other COVID-19 vaccines to complete the primary vaccination series or the booster dose (third dose) has not been established. Individuals who have received 1 dose of BNT162b2 should receive a second dose of BNT162b2 to complete the primary vaccination series and for any additional doses.

***Individuals 5 through <12 yrs of age***

BNT162b2 (for age 5 yrs to <12 yrs) is administered IM after dilution as a primary series of 2 doses (0.2 mL) at greater than or equal to 21 d (preferably 3 weeks) apart.

Individuals may not be protected until at least 7 d after their second dose of the vaccine.

***Pediatric population***

The safety and efficacy of BNT162b2 in individuals under 5 yrs of age have not yet been established. The safety and effectiveness of a booster dose (third dose) of BNT162b2 in individuals 16 through 17 yrs of age is based on safety and effectiveness data in adults at least 18 through 55 yrs of age.

***Geriatric population***

Clinical studies of BNT162b2 include participants 65 yrs of age and older and their data contributes to the overall assessment of safety and efficacy. Of the total number of BNT162b2 recipients (16 yrs of age and older) in Study C4591001/BNT162-02 (N = 22,026), 16.5% (n = 3,627) were 65 through 74 yrs of age and 4.2% (n = 925) were 75 yrs of age and older. The safety and effectiveness of a booster dose (third dose) of BNT162b2 in individuals 65 yrs of age and older is based on safety and effectiveness data in adults at least 18 through 55 yrs of age.

### *7.2.2 Method of administration*

BNT162 vaccines should be administered IM in the deltoid muscle after dilution.

Do not inject the vaccines intravascularly, intradermally, or subcutaneously.

The BNT162 vaccines should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see Section 7.4.

## 7.3 Contraindications

No contraindications have been defined for BNT162a1, BNT162b1, BNT162c2, BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), BNT162b2 (B.1.1.7 + B.1.617.2), and BNT162b2 (B.1.351), all of which are vaccine candidates under development. All contraindications listed below for BNT162b2 should be applied for the BNT162b2-based variant vaccines.

**BNT162b2**

Hypersensitivity to the active substance or to any of the excipients listed in Section 4.2.

## 7.4 Special warnings and precautions for use

At the time of issue of this IB version, all planned administration of BNT162a1, BNT162b1, BNT162b3, and BNT162c2 to study participants has been completed and all dosed participants are now in follow-up.

For BNT162b2 and BNT162b2-based variant vaccines, enrollment and vaccine administration to study participants is ongoing and/or planned. All special warnings and precautions for use listed below for BNT162b2 should be also followed for the BNT162b2-based variant vaccines.

**BNT162b2**

***Traceability***

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

***Anaphylaxis***

Events of anaphylaxis have been reported for BNT162b2 during post-authorization surveillance. As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

***Myocarditis and pericarditis***

Very rare cases of myocarditis and pericarditis have been reported following vaccination with BNT162b2. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 d after vaccination. These are generally mild cases and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.

***Acute severe febrile illness***

The administration of BNT162b2 should be postponed in individuals suffering from acute severe febrile illness.

***Coagulation disorders***

Individuals receiving anticoagulant therapy or those with a bleeding disorder that would contraindicate intramuscular injection, should not be given the vaccine unless the potential benefit clearly outweighs the risk of administration.

***Immunocompromised individuals***

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.

***Stress-related responses***

Some individuals may have stress-related responses associated with the process of vaccination itself. Stress-related responses are temporary and resolve on their own. They may include dizziness, fainting, palpitations, increases in heart rate, alterations in blood pressure, feeling short of breath, tingling sensations, sweating and/or anxiety. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation and precautions should be in place to avoid injury from fainting.

***Limitations of vaccine effectiveness***

As with any vaccine, vaccination with BNT162b2 may not protect all vaccine recipients.

## 7.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed for any of the BNT162 vaccines.

Do not mix BNT162b2 with other vaccines/products in the same syringe.

Due to the novel mode of action, using RNA to deliver genetic information to cells, where it is used to express proteins for the therapeutic effect, pharmacokinetic interactions of BNT162 vaccines with other medicinal products are considered unlikely.

## 7.6 Fertility, pregnancy, and lactation

**Fertility**

It is unknown whether BNT162b2 has an impact on fertility. Animal studies with BNT162 vaccines do not indicate direct or indirect harmful effects with respect to female fertility or reproductive toxicity (see Section 5.3.4).

**Pregnancy**

There are limited amounts of data from the use of BNT162b2 in pregnant women from controlled clinical studies. In the ongoing Study C4591001/BNT162-02, there have been reports of pregnancy (Section 6.1.2.4.2). In addition, Study C4591015/BNT162-10 is an ongoing randomized clinical study that is evaluating the safety, tolerability, and immunogenicity of BNT162b2 in pregnant women.

There is no experience with use of the other BNT162 candidate vaccines in pregnant women.

Animal studies with BNT162 vaccines do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or postnatal development (see Section 5.3.4).

Administration of BNT162b2 in pregnancy should be considered when the potential benefits outweigh any potential risks for the mother and fetus.

**Lactation**

It is unknown whether BNT162 vaccines are excreted in human milk.

## 7.7 Effects on ability to drive and use machines

BNT162b2 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under Section 7.8 may temporarily affect the ability to drive or use machines.

The other BNT162 vaccine candidates are also expected to have no or negligible influence on the ability to drive and use machines.

## 7.8 Undesirable effects

### *7.8.1 Adverse reactions*

This section contains ARs which are AEs for which there is a reason to conclude that the vaccine caused the event(s). The sponsor determines ARs following a thorough assessment of available evidence from non-clinical, clinical and post-authorization information. Factors considered in the determination of ARs may include (but not be limited to) temporal relationship, frequency of occurrence, mechanism of action, biological plausibility, dose response, class effects, lack of confounding factors, dechallenge and rechallenge information, and an investigator's assessment of relatedness. The ARs in this section may be non-serious or serious.

The safety profile of the vaccine candidates other than BNT162b2 has not been established in powered clinical studies.

**Summary of safety profile of BNT162b2 in Study C4591001/BNT162-02 and Study C4591007**

The safety of BNT162b2 was evaluated in participants 5 yrs of age and older. Study C4591001/BNT162-02 enrolled ~46,000 participants 12 yrs of age or older. Study C4591007 enrolled ~2,300 participants 5 through less than 12 yrs of age.

Additionally, 306 existing Phase 3 participants at least 18 through 55 yrs of age received a booster dose (third dose) of BNT162b2 ~6 months after the second dose. The overall safety profile for the booster dose (third dose) was similar to that seen after two doses.

***Participants 16 yrs of age and older – after 2 doses***

In Study C4591001/BNT162-02, a total of 22,026 participants 16 yrs of age or older received at least 1 dose of BNT162b2 and a total of 22,021 participants 16 yrs of age or older received placebo (as of the data cutoff date of 13 MAR 2021). Safety populations are discussed in Section 6.1.2.4.2.

The most frequent ARs in participants 16 yrs of age and older that received 2 doses were injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants receiving BNT162b2, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Study C4591001/BNT162-02 also included 200 participants with confirmed stable HIV infection. The safety profile of the participants receiving BNT162b2 (n = 100) in the individuals with stable HIV infection was similar to that seen in the general population.

### *Adolescents 12 through 15 yrs of age*

In an analysis of Study C4591001/BNT162-02, 2260 adolescents (1,131 BNT162b2; 1,129 placebo) were 12 through 15 yrs of age. Of these, 1,308 adolescents (660 BNT162b2 and 648 placebo) have been followed for at least 2 months after the second dose of BNT162b2.

The most frequent ARs in adolescents 12 through 15 yrs of age that received 2 doses were injection site pain (>90%), fatigue and headache (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%).

### *Children 5 through <12 yrs of age – after 2 doses*

In an analysis of Study C4591007 Phase 2/3, 2,268 participants (1,518 BNT162b2 10 µg; 750 placebo) were 5 through < 12 yrs of age. Of these, 2,158 (95.1%) (1,444 BNT162b2 10 µg and 714 placebo) participants have been followed for at least 2 months after the second dose. The safety evaluation in Study C4591007 is ongoing.

The most frequent ARs in children 5 through < 12 yrs of age that received 2 doses included injection site pain (>80%), fatigue (>50%), headache (>30%), injection site redness and swelling (>20%), myalgia and chills (>10%).

### *Participants 18 yrs of age and older – after booster dose (third dose)*

A subset from Study C4591001 Phase 2/3 participants of 306 adults at least 18 through 55 yrs of age who completed the primary BNT162b2 2-dose course, received a booster dose (third dose) of BNT162b2 ~6 months (range of 4.8 to 8.0 months) after receiving Dose 2.

The most frequent ARs in participants 18 through 55 yrs of age were injection site pain (>80%), fatigue (>60%), headache (>40%), myalgia (>30%), chills and arthralgia (>20%).

### Tabulated list of ARs from clinical studies

The ARs observed during clinical studies are listed below according to the following frequency categories:

- Very common (≥1/10),

- Common (≥1/100 to < 1/10),
- Uncommon (≥1/1,000 to < 1/100),
- Rare (≥1/10,000 to < 1/1,000),
- Very rare (< 1/10,000),
- Not known (cannot be estimated from the available data).

**Table 29: Adverse reactions from BNT162b2 clinical studies**

| System organ class | Very common (≥1/10) | Common (≥1/100 to < 1/10) | Uncommon (≥1/1,000 to < 1/100) | Rare (≥1/10,000 to < 1/1,000) | Not known (cannot be estimated from the available data) |
|---|---|---|---|---|---|
| Blood and lymphatic system disorders | | | Lymphadenopathy [a] | | |
| Immune system disorders | | | Urticaria; [b,c,e] Rash; [b,c] Pruritus [b,c,d,e] | Angioedema [b,c,d,e,f] | Anaphylaxis [b] |
| Metabolism and Nutrition disorders | | | Decreased appetite[d] | | |
| Nervous system disorders | Headache | | Lethargy [d,e,f] | | |
| Gastrointestinal disorders | Diarrhea [b] | Vomiting; [b] Nausea | | | |
| Skin and subcutaneous Tissue disorders | | | Hyperhidrosis; [d,e,f] Night sweats [d,e,f] | | |
| Musculoskeletal and connective tissue disorders | Arthralgia; myalgia | | Pain in extremity (arm) [b] | | |
| General disorders and administration site conditions | Injection site pain; Fatigue; Chills; Pyrexia; Injection site swelling | Injection site redness | Asthenia; [d,e,f] Malaise [d,e] | | |

a) A higher frequency of lymphadenopathy (5.2% vs. 0.4%) was observed in participants receiving a booster dose (third dose) compared to participants receiving 2 doses.
b) These adverse reactions were identified in the post-authorization period.
c) The following events are categorized as hypersensitivity reactions: urticaria, pruritus, rash, and angioedema.
d) Event has not been reported in individuals 12 through 15 yrs of age in Study C4591001 (13 MAR 2021 Data Cutoff date).
e) Event was not reported in individuals who received a booster dose (third dose) of BNT162b2 in Study C4591001 (17 JUN 2021 data cutoff date).
f) Event was not reported in participants 5 to <12 yrs of age in Study C4591007 (06 SEP 2021 data cutoff date)

### *7.8.2 Reference safety information for assessment of expectedness of serious adverse drug reactions*

The reference safety information is used for the assessment of expectedness for regulatory reporting of serious adverse drug reactions (SARs) that are reported in clinical studies.

**BNT162b2**

Based on post-authorization experience with BNT162b2, anaphylactic reaction has been identified as a SAR that is considered expected by the sponsor for regulatory reporting purposes, all other SARs are considered unexpected and thus qualify for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting.

**BNT162a1, BNT162b1, BNT162b3, BNT162c2, and BNT162b2 (B.1.351)**

For BNT162a1, BNT162b1, BNT162b3, BNT162c2, BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), BNT162b2 (B.1.1.7 + B.1.617.2), and BNT162b2 (B.1.351) also referred to as BNT162b2s01 and BNT162b2SA, no SARs are considered `expected´ at this time.

All SARs will therefore be considered as unexpected and thus qualify for SUSAR reporting.

## 7.9 Overdose

Participants who received 58 µg of BNT162b2 in clinical studies did not report an increase in reactogenicity or AEs.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

No cases of overdose have occurred in the ongoing clinical studies with the BNT162a1, BNT162b1, BNT162b3, BNT162c2, BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), BNT162b2 (B.1.1.7 + B.1.617.2), and BNT162b2 (B.1.351).

## 7.10 Drug abuse and dependence

There is currently no data about drug abuse and dependence with BNT162 (including BNT162b2) vaccine candidates. However, BNT162 vaccines are not expected to cause drug abuse or dependence.

## 7.11 Evolving clinical safety information

### *7.11.1 Exposure*

For a summary of human exposure to BNT162b2 following marketing approval or emergency use, see Section 6.2.

### *7.11.2 Specific adverse events of note*

For a discussion on adverse events of clinical interest in Study C4591001/BNT162-02, refer to Section 6.1.2.4.2.

### *7.11.3 Known drug class effects and other human experience*

VAED for vaccines against related coronaviruses (SARS-CoV-1 and MERS) has been reported only in animal models (Lambert et al. 2020; Haynes et al. 2020). To date, no enhanced disease has been observed in SARS-CoV-2 animal models with any SARS-CoV-2 vaccine platform, including RNA-based vaccines. Such effects have not been documented so far for SARS-CoV-2. Current data cannot fully exclude that BNT162 vaccines may cause enhanced disease in vaccinated participants. An effective vaccine against COVID-19 that produces high neutralizing titers and a Th1 predominant $CD4^+$ T-cell response and strong $CD8^+$ T-cell response, is expected to mitigate the risk of VAED/VAERD (Lambert et al. 2020; Graham 2020); that immune profile is elicited by BNT162b2 in clinical and preclinical studies of BNT162b2 (Sahin et al. 2020b; Vogel et al. 2021). The ongoing and planned clinical studies will include monitoring of possible COVID-19-related symptoms in study participants and monitoring for VAED will take place through ongoing pharmacovigilance activities post-authorization/approval.

## 7.12 Overall conclusions

**BNT162a1, BNT162b1, BNT162b3, BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), and BNT162b2 (B.1.351)**

The AEs observed after administration of BNT162a1, BNT162b1, BNT162c2, BNT162b3, BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), BNT162b2 (B.1.1.7 + B.1.617.2), and BNT162b2 (B.1.351) in the ongoing clinical studies were mostly reflective of mild to moderate local and systemic reactogenicity events. The AEs reported appear similar to anticipated reactogenicity events for vaccines administered IM. Reactogenicity was mostly mild to moderate and short-lived after dosing, and the AE profile did not suggest any serious safety concerns.

**BNT162b2**

The totality of the safety data from clinical studies and post-authorization use supports a favorable benefit-risk profile for the use of BNT162b2 in individuals 5 yrs of age and older and supports the continued development of BNT162b2.

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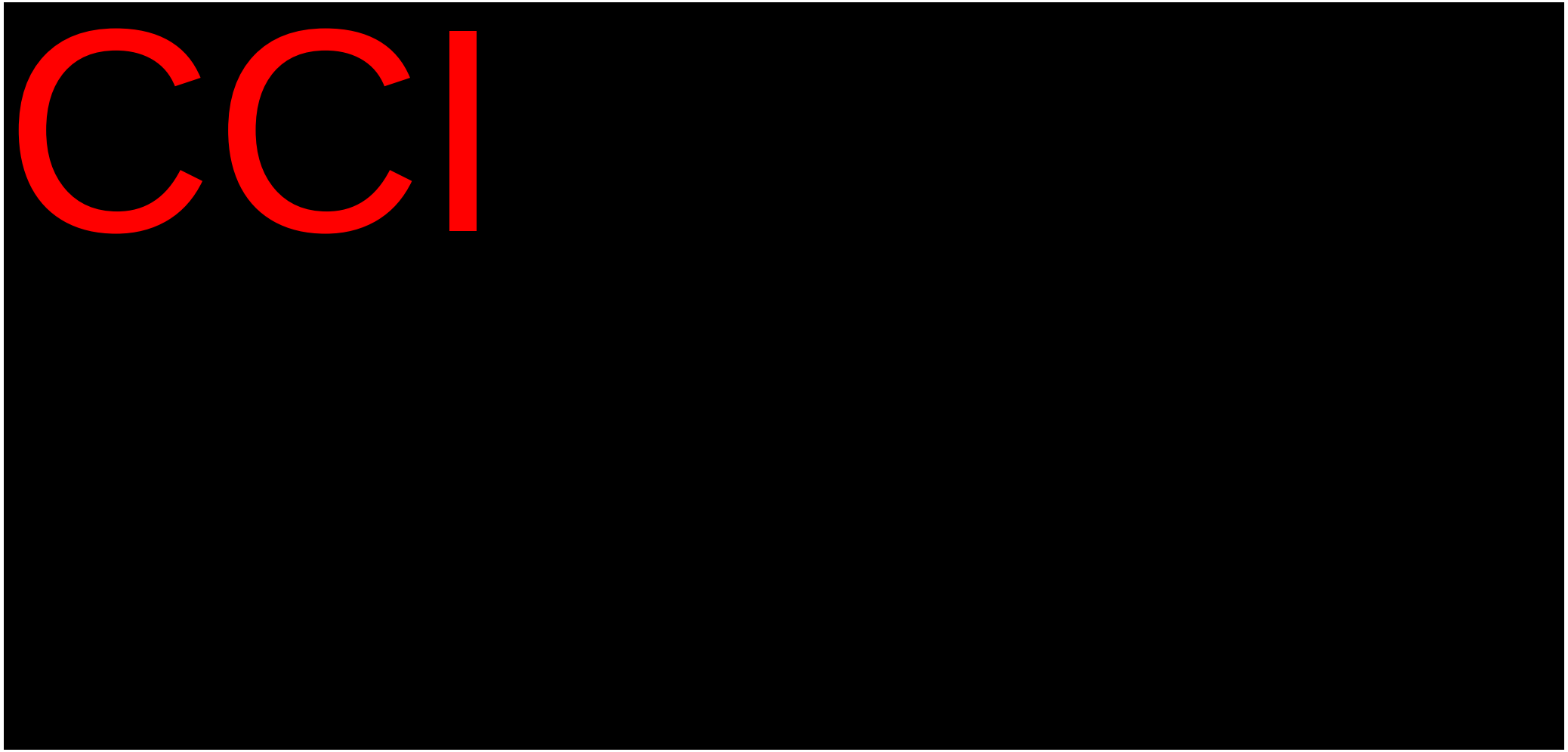
# 9 APPENDICES



| Study number | Study type | Species / Test system | Product code, (RNA type, sequence variant) | | Dose [µg] | Results | Cross reference |
|---|---|---|---|---|---|---|---|
| **Supportive studies (non-clinical candidates)** | | | | | | | |
| R-20-0074 | *In vitro* antigen expression and localization | HEK293T cells | BNT162a2<br>BNT162b2<br>BNT162c1<br>BNT162c2 | (uRNA, V8)<br>(modRNA, V8)<br>(saRNA, V5)<br>(saRNA, V8) | 1, 2.5 | All tested items expressed the encoded S protein derived antigen. | Section 5.1.1.1 |
| R-20-0073 | *In vivo* immunogenicity | Mice BALB/c | - | (modRNA encoding influenza virus hemagglutinin) | 1 | The viral antigen delivered by the LNP-formulated modRNA platform induced a strong antibody immune response and antigen-specific T-cell activity. | n.a. |
| R-20-0052 | *In vivo* immunogenicity | Mice BALB/c | BNT162a2 | (uRNA, V8) | 1, 5, 10 | Immunogenicity was shown in all tested doses. | n.a. |
| R-20-0041 | *In vivo* immunogenicity | Mice BALB/c | BNT162c1 | (saRNA, V5) | 0.2, 1, 5 | Immunogenicity was shown in all tested doses. | n.a. |
| R-20-0054 | *In vivo* immunogenicity | Mice BALB/c | BNT162b2 | (modRNA, V8) | 0.2, 1, 5 | Immunogenicity was shown in all tested doses. | n.a. |
| Study 38,166 | *In vivo* immunogenicity | Wistar Han rats | BNT162b2<br>BNT162c1 | (modRNA, V8)<br>(saRNA, V5) | 100<br>30 | Immunogenicity was shown in all tested doses. | Section 5.1.1.2.2 |
| VAC-2020-NIRC-COVID-1681 | *In vivo* immunogenicity | NHP rhesus macaques (*Maccaca mulatta)* | BNT162b2 | (modRNA V8) | 30, 100 | Immunogenicity was shown in all tested doses. | Section 5.1.1.3.1 |

All study types are based on the analysis of S-specific immune responses elicited in BALB/c mice. The study for BNT162b3 is ongoing.
NHP = non-human primate.

**Table 31: Overview of all clinical studies with BNT162 vaccines (as of 01 OCT 2021)**

| Study number (NCT)<br>Country(ies) | Study title | Study status |
|---|---|---|
| BNT162-01<br>(NCT04380701)<br>Germany | 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 and immunocompromised adults | Ongoing |
| C4591001/BNT162-02<br>(NCT04368728)<br>US, Argentina, Brazil, Turkey, Germany, South Africa | A Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals | Ongoing |
| BNT162-03<br>(NCT04523571)<br>China | A multi-site, Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of a prophylactic SARS-CoV-2 RNA vaccine (BNT162b3) against COVID-19 using different dosing regimens in healthy adults | Ongoing |
| BNT162-04<br>(NCT04537949)<br>Germany | A multi-site, Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of a prophylactic SARS-CoV-2 RNA vaccine (BNT162b3) against COVID-19 using different dosing regimens in healthy adults | Ongoing |
| BNT162-05 / C4591005<br>(NCT04588480)<br>Japan | A Phase 1/2, placebo-controlled, randomized, and observer-blind study to evaluate the safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy Japanese adults | Ongoing |
| BNT162-06<br>(NCT04649021)<br>China | A Phase 2, randomized, placebo-controlled, observer-blinded study investigating the safety and immunogenicity of BNT162b1.<br>(Participants are randomized: 3 active vaccine to 1 placebo) | Ongoing |
| BNT162-07 / C4591007<br>(NCT04816643)<br>US, Spain, Poland, Finland | A Phase 1, open-label, dose-finding study to evaluate safety, tolerability, and immunogenicity and Phase 2/3 placebo-controlled observer-blinded safety, tolerability, and immunogenicity study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy children and young adults | Ongoing |
| BNT162-09 / C4591017<br>(NCT04713553)<br>US | A Phase 3, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of multiple production lots and dose levels of the vaccine candidate BNT162b2 against COVID-19 in healthy participants 12 through 50 yrs of age and the safety, tolerability, and immunogenicity of BNT162b2 RNA-based COVID-19 vaccine candidates as a booster dose in healthy participants 18 through 50 yrs of age | Ongoing |

| Study number (NCT)<br>Country(ies) | Study title | Study status |
|---|---|---|
| BNT162-10 / C4591015<br>(NCT04754594)<br>US, Brazil, South Africa, Spain, UK | A Phase 2/3, placebo-controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 yrs of age and older | Ongoing |
| BNT162-11 / C4591020<br>(NCT04816669)<br>US | A Phase 3, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of multiple formulations of the vaccine candidate BNT162b2 against COVID-19 in healthy adults 18 through 55 yrs of age | Ongoing |
| BNT162-14<br>(NCT04949490)<br>Germany | A Phase II, open-label, rollover trial to evaluate the safety and immunogenicity of one or two boosting doses of Comirnaty or one dose of BNT162b2s01 in BNT162-01 trial subjects, or two boosting doses of Comirnaty in BNT162-04 trial subjects | Ongoing |
| BNT162-17<br>(NCT05004181)<br>US and Germany | A Phase II trial to evaluate the safety and immunogenicity of a SARS-CoV-2 multivalent RNA vaccine in healthy subjects | Ongoing |
| C4591024<br>(NCT04895982)<br>US, Brazil, Germany, Mexico | A Phase 2b open-label study to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants ≥2 years of age | Ongoing |
| C4591031<br>(NCT04955626)<br>US, Brazil, South Africa | A Phase 3 master protocol to evaluate additional dose(s) of BNT162b2 in healthy individuals previously vaccinated with BNT162b2 | Ongoing |

Source: Pfizer and BioNTech data on file.

# 10 SUMMARY OF CHANGES TO THE LAST IB VERSION

This tabulation summarizes the key changes introduced when preparing this IB version. This summary does not include editorial or formatting changes.

| IB Section updated | Summary of the updates |
|---|---|
| 2 Summary | There were substantial changes.<br>This section was updated to reflect changes in Section 6. |
| 3 Introduction | No substantial changes. This section was shortened and updated to introduce new variants of the SARS-CoV-2 virus and the BNT162b2-based variant vaccine candidates. |
| 4 Physical, chemical, and pharmaceutical properties and formulation | No substantial changes. |
| 5 Non-clinical studies | There were substantial changes. The presented non-clinical pharmacology data was shortened, given the available clinical data and the development focus on BNT162b2. |
| 6 Effects in humans | There were substantial changes. This section was updated to reflect the data reported for BNT162-01 CSR (which included additional $CD4^+/CD8^+$ T-cell response data documenting the persistence of the immune response after dosing with BNT162b1 and BNT162b2), data reported in the BNT162-03 and BNT162-04 studies, data reported for C4591001/BNT162-02 (which included results following booster dosing [Dose 3]), and data reported for pediatric study C4591007/ BNT162-07 (which included Phase 1 data in children 6 months to < 12 yrs and Phase 2/3 data in 5 to <12 yrs). |
| 7 Summary of data and guidance for the investigator | There were substantial changes. This section was updated to reflect changes in Section 6 and in the BNT162b2 US Emergency Use Authorization and the EU conditional marketing authorization labeling (which included updates regarding booster dosing and use in children 5 to 12 yrs of age). |
| 8 References | No substantial changes. This section was updated to reflect changes in other sections. |
| 9 Appendices | No substantial changes. This section was updated to reflect changes in Section 6. Table 30 was added to provide an overview of all clinical studies with BNT162b2. |