DEVELOPMENT SAFETY UPDATE REPORT No. 1
for
COVID-19 Vaccine (BNT162, PF-07302048)

PERIOD COVERED BY THIS REPORT:
22 APRIL 2020 to 21 APRIL 2021

DATE OF THIS REPORT: 10 June 2021

Pfizer on behalf of BioNTech SE

Please note that this report may contain unblinded clinical trial information.

DATE OF THIS REPORT: 10 June 2021

SIGNATURE: ____ (b) (6) _____**Date**: 10 June 2021

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EXECUTIVE SUMMARY

This is the first Development Safety Update Report (DSUR) for Pfizer-BioNTech COVID-19 messenger ribonucleic acid (mRNA) vaccine (BNT162/PF-07302048) (hereafter referred to as COVID-19 vaccine), covering the reporting period 22 April 2020 through 21 April 2021.

COVID-19 vaccine is highly purified single-stranded, 5'-capped mRNA produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The RNA is formulated in lipid nanoparticles (LNPs), which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the S antigen, which may contribute to protection against COVID-19.

COVID-19 vaccine (BNT162b2) is a white to off-white frozen product (pH: 6.9 - 7.9), provided as concentrate for dispersion for injection (sterile concentrate) as a multidose vial (MDV) to be diluted before use. The MDV contains 6 doses (0.3 mL) after dilution. Each dose contains 30 µg of BNT162b2. The dosing schedule under investigation is 2 doses given approximately 21 days apart.

Pfizer is responsible for the preparation of the DSUR according to the pharmacovigilance agreement (PVA) in place. BioNTech SE is the sponsor for the all the clinical trials (CTs) included in this report.

Data from BioNTech' license partner (LP) Shanghai Fosun Pharmaceutical Inc., that conducts the clinical studies in China on BioNTech SE's behalf, are included in this report to fulfill China Center for Drug Evaluation (CDE) DSUR requirements.[1]

Data from respective LPs are presented individually in this report.

During this reporting period, there were 10 ongoing[2] sponsor-initiated clinical trials involving COVID-19 vaccine: C4591001, C4591005, C4591007, C4591015, C4591017, C4591020 ('C459' implies conducted by Pfizer), BNT162-01, BNT162-04 (conducted by BioNTech), BNT162-03, and -BNT162-06 (conducted by Fosun).

There were no completed clinical trials with final clinical study reports (CSRs) available.

Moreover, there were 2 ongoing non-interventional post-authorization studies (PASS): C4591008 (voluntary) and C4591012 (committed).

[1] Management Regulation of DSUR (for trial implementation) applicable for DSURs with DLP post-July 2020.

[2] Includes ongoing studies as well as studies in which patient enrollment and follow-up have been completed, but the analysis and CSR are in-progress.

Cumulatively, it is estimated that 49,315 subjects have participated in COVID-19 vaccine C459 clinical trials (CTs) worldwide. Additionally, 1691 subjects have participated in BNT CTs, of which 1103 in the Chinese BNT CTs conducted by Fosun.

As of the Data Lock Point (DLP) of this DSUR, COVID-19 vaccine has received temporary authorization for emergency use in 31 countries and conditional marketing authorization approval in 42 countries globally. In the UK, conditional marketing authorization approval was granted after the DLP, on 22 April 2021, while the authorization for emergency use still remained active for an overlapping time frame.

Cumulatively, it is estimated that 354,705,000 COVID-19 vaccine doses were supplied worldwide since its first supply to the countries. Additionally, an estimate of (b) (4) doses were distributed in Hong Kong (HK) and Macau through Fosun.

The reference safety information (RSI) for this DSUR is the BNT162/PF-07302048 Investigator's Brochure (IB), v. 3.0 dated 17 April 2020, which was updated 3 times during the reporting interval, on 03 Jul 2020 (v. 4.0), 12 Aug 2020 (v. 5.0), and 29 Jan 2021 (v. 6.0). RSI Sections 7. *Summary of data and guidance for the investigators* and Section 7.8.2 *Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions* were used post version 4.0 (previously named Section 6.2 *Reference safety information* in IB versions 3.0 and 4.0). Updates were made to include emerging data from the ongoing clinical trials including additional safety data.

There were no significant actions taken due to safety reasons by Health Authorities or the MAH(s).

Based on pharmacovigilance monitoring activities, since first authorization, hypersensitivity reactions (other than Anaphylaxis), Diarrhoea, Pain in extremity (arm), Vomiting, Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats[3] are identified risks (not important for the purpose of risk management planning) and were included/are being included in the product labeling. Vaccine stress-related responses (including Dizziness, Paraesthesia and Tachycardia among others) were included in the RSI as reactions to the vaccination process.

The following reactogenicity events are identified risks in the clinical trials not considered important: Injection site pain, Injection site swelling and Injection site redness, Fever, Chills, Fatigue, Headache, Muscle pain, and Joint pain.

As per the EU-RMP (version 1.0, dated December 2020) in effect at the beginning of the reporting period, 'Anaphylaxis' is an important identified risk for COVID-19 vaccine, while 'Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD) is an important potential risk. The EU-RMP was updated to v. 1.1 during the reporting interval and received CHMP approval on 15 April 2021. A further

[3] Please note that Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats were identified as risks post the DLP, on 27 April 2021.

EU-RMP update (v 2.0, 29 Apr 2021) to include individuals aged 12-15 years was approved post the data-lock point, on 31 May 2021. There were no updates to the safety concerns made.

Based on the available safety and efficacy data for COVID-19 vaccine, the benefit-risk profile of the vaccine remains favorable.

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LIST OF ABBREVIATIONS

Abbreviation	Term
20vPnC	20-valent pneumococcal conjugate vaccine
AE	Adverse event
ALC-0159	2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
ALC-0315	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
AML	Acute myeloblastic leukemia
BNT	BioNTech
CBER	Center for Biologics Evaluation and Research
CDE	(China) Center for Drug Evaluation
CHMP	Committee for Medicinal Products for Human Use
CO_2	Carbon dioxide
Cont'd	Continued
COVID-19	coronavirus disease 2019
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLP	Data Lock Point
DNA	Deoxyribonucleic acid
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
DSUR	Development Safety Update Report
EMA	European Medicine Agency
EUA	Emergency use authorization
EU RMP	European Union risk management plan
F	Female
FDA	(US) Food and Drug Administration
FSFV	First subject first visit
GMT	Geometric mean concentration
IB	Investigator's brochure
ICD	Informed consent document
ICH	International Council on Harmonization
IG	immunoglobulin
IgG	immunoglobulin G
IND	Investigational new drug
IVPB	Intravenous piggyback
LNP	Lipid-nanoparticle
LP	License partner
LSLV	Last subject last visit
M	male
MAH	Marketing Authorization holder
MDV	Multi-dose vial
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger RNA
NR	Not resolved
OPA	opsonophagocytic activity
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike protein
PASS	Post authorization safety study
PI	Product information
PT	(MedDRA) Preferred Term
PVA	Pharmacovigilance agreement
R	resolved
RBD	receptor-binding domain
RG	resolving
RNA	ribonucleic acid

Abbreviation	Term
RSI	Reference safety information
S	spike (protein)
SAE	Serious adverse event
SAR	Serious adverse reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDV	Single dose vial
SIRVA	Shoulder injury related to vaccine administration
SOC	(MedDRA) System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
UK	United Kingdom
US	United States
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
VE	Vaccine efficacy
VHA	Veterans' Health Administration

1. INTRODUCTION

This is the first Development Safety Update Report (DSUR) for COVID-19 vaccine (BNT162/PF-07302048), covering the reporting period 22 April 2020 through 21 April 2021. The report follows the general format proposed by ICH Guideline E2F Note for guidance on development safety update report (EMA/CHMP/ICH/309348/2008 [September 2010]). In accordance with this guidance, the reporting period for this DSUR is aligned with the first authorization to conduct a clinical trial in any country worldwide, using the development international birth date. This DSUR is also being prepared in support of US FDA BB-IND #19736 to comply with 21 CFR 312.33.

Pfizer is responsible for the preparation of the DSUR according to the PVA in place between Pfizer and BioNTech. BioNTech SE is the sponsor for all CTs included in this report.

Data from BioNTech's LP, Shanghai Fosun Pharmaceutical Inc., that conducts the clinical studies in China, are included in this report to fulfill China CDE DSUR requirements.[4]

Data from respective LPs are presented individually in this report.

COVID-19 vaccine is a highly purified single-stranded, 5'-capped mRNA produced using a cell-free *in vitro* transcription from the corresponding DNA template, encoding the viral S protein of SARS-CoV-2. The RNA is formulated in LNPs, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the S antigen, which may contribute to protection against COVID-19.

COVID-19 vaccine (BNT162b2) is a white to off-white frozen product (pH: 6.9 - 7.9), provided as concentrate for dispersion for injection (sterile concentrate) in an MDV to be diluted before use. The MDV contains 6 doses (0.3 mL) after dilution. Each dose contains 30 µg of COVID-19 vaccine. The vaccine also contains (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159), 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose and water for injections as excipients. The dosing schedule under investigation is 2 doses given approximately 21 days apart.

The clinical development of COVID-19 vaccine started with the investigation of four BNT162 vaccine candidates (BNT162a1, BNT162b1, BNT162b2, BNT162c2). A fifth vaccine candidate (BNT162b3) was later added to the program.

BNT162b2 was selected for further development and has been authorized for emergency use or been given conditional marketing authorization in numerous countries worldwide for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older. Conditional marketing authorization was granted for

[4] Management Regulation of DSUR (for trial implementation) applicable for DSURs with DLP post-July 2020.

administration to adolescents 12 to 15 years of age after the data-lock point of this report, on 31 May 2021. Further clinical investigation of BNT162b2 is ongoing to expand the studied populations.

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

2. WORLDWIDE MARKETING APPROVAL STATUS

COVID-19 vaccine (BNT162b2) received first temporary authorization for emergency supply under regulation 174 in the UK on 01 December 2020 and is currently authorized for emergency use in 31 countries.

COVID-19 vaccine received first regulatory conditional marketing authorization approval in Switzerland on 19 December 2020 and is currently conditionally approved in 42 countries.

Of note, in the UK, the conditional marketing authorization approval was granted in addition to the authorization for emergency supply under regulation 174 post the DLP, on 22 April 2022.

There were no authorization withdrawals for safety reasons during the reporting interval.

Details of its current marketing authorization status, including information on cumulative countries' approvals, approval dates, and local trade names, are presented in Appendix 8.

3. ACTIONS TAKEN IN THE REPORTING PERIOD FOR SAFETY REASONS

During the reporting period, no significant actions have been taken with respect to COVID-19 vaccine for safety reasons, either by a Health Authority or by the MAH.

There have been no regulatory authority requests that have placed a limitation on the clinical development of COVID-19 vaccine.

4. CHANGES TO REFERENCE SAFETY INFORMATION

The RSI for this DSUR is the BNT162/PF-07302048 IB active at the beginning of the reporting interval (v. 3.0 dated 17 April 2020), which is located in Appendix 1. The IB was updated 3 times, on 03 Jul 2020 (v. 4.0), 12 Aug 2020 (v. 5.0), and 29 Jan 2021 (v. 6.0). The updated IBs can be found in Appendix 1.2, 1.3, and 1.4. (See also Section 7.1)

Updates were made to include data emerging from clinical trials, including additional safety data.

5. INVENTORY OF CLINICAL TRIALS ONGOING AND COMPLETED DURING THE REPORTING PERIOD

During the reporting period, there were no completed clinical trials involving COVID-19 vaccine that have final CSRs (Appendix 3.1 is N/A for this report.)

There were 10 ongoing[5] sponsor-initiated interventional clinical trials: C4591001, C4591005, C4591007, C4591015, C4591017, C4591020, BNT162--01, BNT162-03, BNT162-04, and BNT162-06.

Details of Pfizer-conducted studies are summarized in Table 1 below. Of note, Study C4591001/BNT162-02 had an interim study report that is available upon request.

Table 1. Inventory of COVID-19 Vaccine Clinical Trials During the DSUR Reporting Period (Conducted by Pfizer)

Protocol No./ Study Alias [EudraCT No. (if available)]/ Phase No.	Title	Status	Country(ies)/ Reference Document
Study vaccine: BNT162b1, BNT162b2			
C4591001/ BNT162-02 [2020-002641-42]/ Phase 1,2,3	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[a]	Argentina, Brazil, Germany, South Africa, Turkey, US/IB
Study vaccine: BNT162b2			
C4591005/ Phase 1/2	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[a]	Japan/IB
C4591007 [2020-005442-42] Phase 1/2/3	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 <12 Years of Age	Ongoing[a]	US/IB
C4591015/[b] [2020-005444-35] Phase 2/3	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 Years of Age and Older	Ongoing[a]	US/IB
C4591017/ Phase 3	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 Years of Age	Ongoing[a]	US/IB
C4591020 Phase 3	A Phase 3, Randomized, Observer-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Lyophilized Formulation of the Vaccine Candidate BNT162b2 Against COVID-19 in Healthy Adults 18 Through 55 Years of Age	Ongoing[a]	US/IB

[5] "Ongoing studies" include ongoing studies as well as studies in which patient enrollment and follow-up have been completed, but the analysis and CSR are in-progress.

Table 1. Inventory of COVID-19 Vaccine Clinical Trials During the DSUR Reporting Period (Conducted by Pfizer)

Protocol No./ Study Alias [EudraCT No. (if available)]/ Phase No.	Title	Status	Country(ies)/ Reference Document

Abbreviations: DSUR = development safety update report; IB = investigator brochure; PASS = post authorization safety Study; RNA = ribonucleic acid.
a. "Ongoing studies" include ongoing studies as well as studies in which participant enrollment and follow-up have been completed, but the analysis and CSR are in-progress.
b. Post authorization safety study

Details of BioNTech/Fosun CTs are summarized in Table 2 below. Of note, BNT162-01[6] and BNT162-03[7] had interim study reports that are available upon request.

Table 2. Inventory of COVID-19 Vaccine Clinical Trials During the DSUR Reporting Period (Conducted by BioNTech/Fosun)

Protocol No./ Study Alias [EudraCT No. (if available)]/ Phase No.	Title	Status	Country(ies)/ Reference Document
Study vaccine: BNT162a1, BNT162b1, BNT162b2, and BNT162c2			
BNT162-01 [2020-001038-36] Phase 1/2	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-2019 Using Different Dosing Regimens in Healthy and Immunocompromised Adults	Ongoing[a,b]	Germany/IB
Study vaccine: BNT162b1			
BNT162-03[c] Phase 1	Safety and Immunogenicity of SARS-CoV-2 mRNA Vaccine (BNT162b1) in Chinese Healthy Subjects: A Phase I, Randomized, Placebo-controlled, Observer-blind Study	Ongoing[a]	China/ IB
Study vaccine: BNT162b2			
BNT162-06[c] Phase 2	Safety and Immunogenicity of SARS-CoV-2 mRNA Vaccine (BNT162b2) in Chinese Healthy Population: A Phase II, Randomized, Placebo-controlled, Observer-blind Study	Ongoing[a]	China/IB
Study vaccine: BNT162b3			
BNT162-04 [2020-003267-26]/ Phase 1/2	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)	Ongoing[a]	Germany/ IB

[6] Three interim reports were issued for Study BNT162-01: v. 1 (23 Sep 2020); v. 2 (28 Nov 2020); v. 3 (22 Mar 2021).

[7] An interim report for Study BNT162-03 was issued on 08 Feb 2021.

Table 2. Inventory of COVID-19 Vaccine Clinical Trials During the DSUR Reporting Period (Conducted by BioNTech/Fosun)

Protocol No./ Study Alias [EudraCT No. (if available)]/ Phase No.	Title	Status	Country(ies)/ Reference Document
	Against COVID-19 Using Different Dosing Regimens in Healthy Adults		

a. "Ongoing studies" include ongoing studies as well as studies in which participants enrollment and follow-up have been completed, but the analysis and CSR are in-progress.
b. This trial has two parts. Part A and Part B. Due to changes in the overall clinical development plan, Part B will no longer be conducted. The objectives originally described for Part B have been implemented in the ongoing development via a pivotal Phase 1/2/3 trial BNT162-02/C4591001.
c. This study is conducted by Shanghai Fosun Pharmaceutical Development, Inc.

Appendix 3.2 presents a tabular inventory of trials conducted by Pfizer 'C459' that were ongoing[5] or completed without a finalized CSR during the reporting period Appendix 3.3 includes the total number of subjects per treatment arm from the start of these clinical trials. Appendix 3.2.1 presents a tabular inventory of BioNTech / Fosun ongoing[5] trials.

6. ESTIMATED CUMULATIVE EXPOSURE

6.1. Cumulative Subject Exposure in the Development Programme

Cumulatively, it is estimated that 49,315 subjects have participated in the COVID-19 vaccine 'C459' CTs: 195 subjects received BNT162b1; 41,368 subjects received BNT162b2 (of which, 20,291 subjects received BNT162b2 post-unblinding and had received Placebo before, and 758 subjects received a blinded boost with either BNT162b2 or BNT162b2s01 and had received BNT162b2 before); 329 received BNT162b2s01,[8] 6370 subjects received blinded-therapy; and 1053 subjects received placebo.

Additionally, 1691 subjects have participated in BioNTech/Fosun CTs, of which 1103 participated to the Chinese studies conducted by Fosun.

Subject demographics data (e.g. age, gender, race) for 'C459' CTs is presented by treatment group in Appendix 4. Cumulative CT exposures with demographic data from BioNTech/Fosun CTs is presented in Appendices 4.2 and 4.3.

6.2. Patient Exposure from Marketing Experience

It is not possible to determine with certainty the number of individuals who received COVID-19 vaccine during the period of this review. Estimated worldwide shipped doses may serve as a reasonable indicator of subject exposure, considering that approximately 80% of the shipped doses were administered.

[8] BNT162b2s01 is also referred to as BNT162b2SA.

With these caveats in mind, the estimated cumulative worldwide shipped doses for COVID-19 vaccine from first emergency use supply through 21 April 2021 is approximately 354,705,000 doses.

Additionally, an estimate of (b) (4) doses were distributed in Hong Kong and Macau through Fosun.[9]

7. DATA IN LINE LISTINGS AND SUMMARY TABULATIONS

7.1. Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 has been used to code adverse events in line listings and summary tables. During the reporting period, the IBs versions 3.0 to 6.0, Section 7.8.2 *Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions* (available from version 5.0)[10], were used to determine event expectedness at the time of individual case processing, for expedited reporting purposes of SUSARs. The RSI is presented in Section 4, *Changes to Reference Safety Information*.

7.2. Line Listings of Serious Adverse Reactions During the Reporting Period

Appendix 5 and Appendix 5.1 provide line-listings of serious adverse events (SAEs) reported in clinical trial cases that contain at least one suspected serious adverse reaction (SAR) received by the sponsor from 22 April 2020 through 21 April 2021. These appendices are organized according to SOC corresponding to the primary AE reported in each case.

During this DSUR reporting period, 11 cases[11] contained 12 SARs considered possibly related to the study vaccines [BNT162/Placebo], [BNT162b1; Placebo], BNT162b2, and/or the clinical trial procedure. All reported SARs were single occurrences [PTs: Acute myeloid leukaemia, Anaphylactoid reaction, Cystitis, Hyperthyroidism, Lymphadenopathy, Myocardial infarction, Neuritis, Paraesthesia, Psoriatic arthropathy, Shoulder injury related to vaccine administration, Thyroid mass, Ventricular arrhythmia (1 each)]. Of these 11 cases, 1 SAR was considered related to blinded therapy. None of these SARs were expected, as per BNT162/PF-07302048 IBs (versions 3.0 to 6.0) RSI.

Of the 11 cases noted above, 9 cases contained 10 suspected SUSARs, which were considered related to the study vaccines [BNT162b2; Placebo], [BNT162b2; Placebo], or BTN162b2 given as a single agent by either the Investigator or sponsor. Of these, 1 SUSAR was also considered possibly related to a clinical trial procedure (vaccine administration) by either the Investigator or the sponsor. The SUSARs encoded to the following MedDRA PTs:

[9] Note that the COVID-19 vaccine is distributed/marketed through Shanghai Fosun Pharmaceutical in these territories.

[10] This was named Section 6.2 *Reference Safety Information* in prior IB versions 3.0 (17 April 2020) and 4.0 (03 July 2020).

[11] Please note that events reported in 1 case [Hyperthyroidism, Thyroid mass (SARs/SUSARs), Hepatic failure, Neutropenia, Urinary tract infection, Pulmonary mass (SAEs)] do not display in the DSUR appendices as this was received 11 days post the awareness day (15-Apr-2021; received on 26-Apr-2021).

Acute myeloid leukaemia, Anaphylactoid reaction, Cystitis, Hyperthyroidism, Lymphadenopathy, Myocardial infarction, Paraesthesia, Shoulder injury related to vaccine administration [SIRVA], Thyroid mass, Ventricular arrhythmia (1 each).

7.3. Cumulative Summary Tabulations of Serious Adverse Events

Appendices 6 and 6.1 provide cumulative summary tabulations of SAEs reported in clinical trial cases received by the sponsor.[11] This appendix is organized according to SOC.

8. SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING PERIOD

8.1. Completed Clinical Trials

As noted above (Section 5), no clinical trials were completed during this reporting period.

8.2. Ongoing Clinical Trials

During the reporting period, there were 10 ongoing[5] sponsor-initiated clinical trials: C4591001, C4591005, C4591007, C4591015, C4591017, C4591020, BNT162-01, BNT162-04, BNT162-03, and BNT162-06. Clinically important emerging efficacy and/or safety findings were identified for Study C4591001/BNT162-02 and C4591005 and are summarized below.

- Study C4591001/BNT162-02

Title: 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
Countries: Argentina, Brazil, Germany, South Africa, Turkey, US

Study C4591001/BNT162-02 is an ongoing, randomized, placebo-controlled, observer-blind, dose-finding Phase 1/2/3 registration study evaluating the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals. 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 to accrue sufficient COVID-19 cases to conduct an efficacy assessment. The protocol was initiated in adults 18 years of age and older and subsequently amended to include adolescents as young as 12 years of age. The study has enrolled approximately 46,000 participants, including 2,260 young adolescents 12 to 15 years of age. Data from the Phase 1 part of the study was 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, BNT162b2, and is intended to support licensure globally.

The available clinical evidence for BNT162b2 includes a tolerable safety profile and high VE against COVID-19 in individuals ≥12 years of age.

The potential risks are based on the observed safety profile to date, which shows mostly mild to moderate reactogenicity, an acceptable incidence of severe or serious events, and no clinically concerning safety observations. The vaccine appears to be safe and well tolerated

across the safety population and within demographic subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status. The preponderance of severe cases of COVID-19, as defined by the FDA Guidance for Industry (June 2020),[12] in the placebo group relative to the BNT162b2 group (9 of 10) suggests no evidence of vaccine-associated enhanced disease.

Vaccine efficacy was ≥95% for participants without prior evidence of SARS-CoV-2 infection and >94% for those irrespective of prior infections. Observed VE was >93% when data were stratified by age, sex, race/ethnicity, and country with the exception of the "all others" race group (89.3% VE) and Brazil (87.7% VE).

Severe cases evaluated for efficacy were confined predominantly to the placebo group; only 1 severe case was reported in the BNT162b2 group in the final analysis. The efficacy data suggest high efficacy against COVID-19 in a broad population of individuals.

- Study C4591005

Title: 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
Country: Japan

Study C4591005 is a Phase 1/2, randomized, placebo-controlled, and observer-blind study in healthy Japanese adults. The study will evaluate the safety, tolerability, and immunogenicity of the SARS-CoV-2 mRNA vaccine candidate (BNT162b2) against COVID-19 administered as two 30-µg doses, 21 days apart, in Japanese adults 20 to 85 years of age.

Clinical laboratory tests were performed for the first 24 participants (12 participants 20 to 64 years of age and 12 participants 65 to 85 years of age) (clinical laboratory subset). Local reactions (redness, swelling, and pain at the injection site), systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain), and use of antipyretic medication were collected by all participants in an e-diary from Day 1 through Day 7 after each administration of study intervention. AEs were collected from the time the participant provided informed consent through 1 month after Dose 2. SAEs will be collected from the signing of the ICD to approximately 12 months after Dose 2.

In this study, 160 Japanese participants (including 130 participants 20 to 64 years of age [younger age group] and 30 participants 65 to 85 years of age [older age group]) were randomized in an approximate 3:1 ratio of BNT162b2 to placebo. Interim data show BNT162b2 was well tolerated, with local reactions and systemic events mostly mild or moderate in severity, and no immediate AEs within 30 minutes reported. An acceptable safety profile was observed in both younger and older Japanese adults with no SAEs reported

[12] Development and Licensure of Vaccines to Prevent COVID-19 Guidance for Industry June 2020.

through 1 month after Dose 2. Immune responses elicited by BNT162b2 were robust 1 month after Dose 2, consistent with data from the global program. These encouraging results led to the marketing authorization of BNT162b2 in Japan. This study has since been converted to a postmarketing study.

Based upon the available clinical data reviewed during the reporting period, no clinically significant safety and/or efficacy information has emerged from BioNTech/Fosun's ongoing clinical trials (Study BNTN162-01, BNT162-03, BNT162-04, and BNT162-06).

During the reporting period, 11 cases from ongoing studies [C4591001 (9), BNT162-01 (1), or BNT162-03] reported SARs (ie, adverse event that were considered to be related to the study vaccines [BNT162b2; Placebo], [BNT162b1; Placebo], BNT162b2, and/or the clinical trial procedure by the Investigator and/or the sponsor); one case ((b) (6) ; Anaphylactoid reaction) was determined to be relevant to the safety concerns listed in Section 18.1; none represented a signal. The overall 11 cases are presented by Protocol in Table 3 (SUSARs denoted in bold).

Table 3. Serious Adverse Reactions Reported During the DSUR Period (22 Apr 2020 to 21 Apr 2021)

AER #/ Country/Age (years)/ Gender	PT (SUSARs denoted in bold)/ Outcome	Comment
Study C4591001		
(b) (6) /US[a] 30F	**Shoulder injury related to vaccine administration** [SIRVA] [R]	The subject had a history of allergies and received 2 doses of the study vaccine, on 17 Aug 2020 and on 09 Sep 2020. SIRVA occurred on the same day of the second dose administration. The event improved upon physical therapy and the subject completely recovered on 08 Feb 2021. The investigator considered there was a reasonable possibility that the event was related to the clinical procedure (vaccine administration) and the study vaccine (BNT162b2; Placebo). The Company agrees with the Investigator assessment.
(b) (6) /US[a] 48F	**Lymphadenopathy [R]**	The subject had a history of seasonal allergies, sinus headache, benign paroxysmal vertigo, osteoarthritis and eczema; she also had uterine fibroids/ menorrhagia from 2003 to 2005. She received a single dose of vaccine, on 04 Sep 2020; the second dose, due on 25 Sep 2020, was not administered. The subject experienced right axillary lymphadenopathy on 16 Sep 2021 and was treated with ketorolac. Biopsy completed on 05 Oct 2020 showed no markers for lymphoma or other cancer. She completely recovered on 20 Nov 2020. The Investigator considered the event as possibly related to the study vaccine (BNT162b2; Placebo). The company did not concur with the Investigator's assessment; the vaccine was administered on the left deltoid muscle whereas lymphadenopathy occurred in the right axilla.
(b) (6) /US[a] 71F	**Ventricular arrhythmia [R]**	The subject had a relevant cardiac history of complete atrioventricular block, for which a cardiac pacemaker was inserted, sinoatrial node dysfunction, paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia.

Table 3. Serious Adverse Reactions Reported During the DSUR Period (22 Apr 2020 to 21 Apr 2021)

AER #/ Country/Age (years)/ Gender	PT (SUSARs denoted in bold)/ Outcome	Comment
		She received 2 doses of the vaccine, on 21 Sep 2020 and on 14 Oct 2020. Since the day of the second dose, she experienced episodes of ventricular tachycardia on each of the following 5 days associated with fatigue and malaise. The patient underwent electrophysiology study (no cardioverter-defibrillator placement). The subject recovered on 21 Oct 2020. The investigator considered there was a reasonable possibility that the event 'paroxysmal ventricular arrhythmias' was related to the blinded vaccine (BNT162b2; Placebo), based on the temporal relationship. The company considered the subject's underlying condition a more plausible cause.
(b) (6) /US[a] 53F	**Paraesthesia [RG]**	The subject had a history of chronic migraines, neck pain, vitamin D deficiency, and Vitamin B12 deficiency. She received 2 doses of the vaccine, on 14 Aug 2020 and on 04 Sep 2020. On 20 Oct 2020, the subject started experiencing right leg paraesthesia, closer to 5 weeks after vaccination #2. The Investigator considered the event possibly related to the study vaccine ((BNT162b2; Placebo) based on a temporal relationship and no alternative causes; the company considered the subject's underlying known neurological conditions a more plausible cause.
(b) (6) /US 52F	Neuritis [R]	The subject had a history of deviated septum. She received 2 doses of the vaccine, on 24 Jun 2020 and on 15 Jul 2020. On 29 Jul 2020, the subject experienced neuritis, which had been occurring intermittently since a blood draw done in the right antecubital fossa on visit 6. She recovered on 17 Mar 2021. The investigator considered there was a reasonable possibility that the event neuritis was related to clinical trial procedure (unrelated to blinded study vaccine and concomitant medication). The company concurred with the Investigator's assessment.
(b) (6) /US 26M	Psoriatic arthropathy [NR]	The subject had a history of seasonal allergy and migraines. He received 2 doses of the vaccine, on 30 Jul 2020 and on 20 Aug 2020. More than one month following the second dose of the blinded study vaccine, he developed psoriatic arthritis, which did not recover at the time of the report. The investigator considered there was a reasonable possibility that the event psoriatic arthritis was related to the blinded study vaccine and to the clinical trial procedure. The company considered the event an incidental medical condition and did not consider it related.
(b) (6) /Turkey 41M	**Myocardial infarction [R]**	The subject, with no prior medical history reported, received 2 doses of the study vaccine, on 04 Nov 2020 and 25 Nov 2020. On 03 Feb 2021, the subject experienced a probable heart attack. The investigator considered that there was a reasonable possibility that the event was related to blinded study vaccine (BNT162B2/Placebo) as the subject described himself as healthy, having no cardiac disease, no cardiac complaint, no coronary obstruction before

Table 3. Serious Adverse Reactions Reported During the DSUR Period (22 Apr 2020 to 21 Apr 2021)

AER #/ Country/Age (years)/ Gender	PT (SUSARs denoted in bold)/ Outcome	Comment
		vaccination, and no family history of heart disease. The company did not concur with the Investigator assessment based on the finding of slow flow and plaque in the left descending coronary artery, on the pathophysiology of the event and the temporal relationship (2 months 8 days latency).
Study C4591001 – Open label		
(b) (6) /US 17F	**Anaphylactoid reaction [R]**	The subject was in the open-label phase of the study when the event occurred; she had a history of multiple allergies (food and medication) with anaphylaxis. She received 2 prior doses of placebo, on 20 Nov 2020 and 15 Dec 2020 and received the first dose of BNT162b2 on 25 Jan 2021. Two days later, she experienced left-arm hives, shortness of breath and a diagnosis of anaphylactoid reaction. The subject self-administered her epi-pen to treat symptoms, which resolved. The second dose of BNT162b2 was not administered within study conduct. She received a second dose 40 days after the first one through her primary care without AEs. The Investigator considered the event to be possibly related to the first BNT162b2 dose. The company concurred with the Investigator assessment.
(b) (6) /US 63M	**Acute myeloid leukaemia [NR]**	The subject was in the open-label phase of the study when the event occurred; he received 2 doses of Placebo, on 29 Aug 2020 and 19 Sep 2020 and was administered first and second doses of BNT162b2 on 11 Jan 2021 and 01 Feb 2021, respectively. The subject was diagnosed with acute myeloblastic leukemia (AML) on 11 Mar 2021. He had multiple medical histories including diabetes mellitus type 2, hypercholesterolemia, obesity, hypertension, sleep apnea, knees' osteoarthritis, gastroesophageal reflux disease. Additionally, medical conditions reported post BNT162b2 vaccination included: coronary artery disease, productive cough, hypokalemia, potentially decompensated early angina, pneumonia, elevated troponin level, non-ST elevation myocardial infarction (AER (b) (6) , with coronary spasm (AER (b) (6)), coronary blood stasis (AER (b) (6)) and worsening of elevated troponin level reported concomitantly to the AML diagnosis. The subject was admitted to the hospital for induction chemotherapy on protocol on 01 Apr 2021, with planned treatment dates through 25 Aug 2021 with azacytidine 190mg intravenous piggyback (IVPB), venetoclax 100mg oral 1x/day and ivosidenib. Concomitant medications included rivaroxaban, isosorbide, atorvastatin, metoprolol, ipratropium bromide, ipratropium bromide/albuterol, valacyclovir, sitagliptin, metformin, insulin lispro, caspofungin, ceftazidime, linezolid, levocetirizine. Additional medications include paracetamol,

Table 3. Serious Adverse Reactions Reported During the DSUR Period (22 Apr 2020 to 21 Apr 2021)

AER #/ Country/Age (years)/ Gender	PT (SUSARs denoted in bold)/ Outcome	Comment
		hydroxyurea, allopurinol. The outcome of the event was not recovered. The investigator considered there was a reasonable possibility that AML was related to BNT162b2, while unrelated to blinded study vaccine, concomitant drugs, or clinical trial procedure. The investigator had considered the timeframe of the event as it occurred within 2 months of the subject's vaccination and the lack of alternative explanation. The company did not concur with the investigator's assessment based on the absence of a plausible pathophysiological mechanism by which the vaccine would be expected to cause the event.
Study BNT162-01 (Open label)		
(b) (6) /Germany 24F	**Cystitis** [R]	The subject received 2 doses of BNT162b2, on 09 Dec 2020 and 29 Dec 2020, respectively. Two days post the second dose, she experienced abdominal pain and a diagnosis of cystitis (CTCAE grade 3) was made at the hospital. The subject was treated with paracetamol 500mg, Fosfomycin 3g (single doses), and IV metamizole 2g/day for 2 days. She was discharged from the hospital on 03 Jan 2021. Abdominal pain (NS) recurred on 05 Jan 2021 and recovered upon treatment with oral cefozidime (200mg thrice daily for 6 days). Symptoms were reported as resolved as of 07 Jan 2021. The Investigator did not consider the event to be related to BNT162b2; however, the MAH did not exclude a causal relationship based on the temporal relationship.
BNT162-03		
(b) (6) /China[11] 51F	**Hyperthyroidism [RG], Thyroid mass [NR]**[b]	The subject received 2 doses of the study vaccine [BNT162b1; placebo] on 28 Jul 2020 and on 18 Aug 2020, respectively. On 19 Jan 2021, abnormal thyroid function was detected. The patient was hospitalized on 26 Mar 2021. Diagnosis on discharge, on 01 Apr 2021, was hyperthyroidism; hepatic insufficiency; neutropenia; fatty liver; thyroid nodule; solitary pulmonary nodule; urinary tract infection. The Investigator considered that the events of Hyperthyroidism and Thyroid nodule were possibly related to the study vaccine. The MAH considered the events as unrelated (the reported SUSARs 'thyroid nodule', 'hyperthyroidism', and SAE mild fatty liver were subject's pre-existing conditions)

Clinical Outcomes. NR = Not resolved; R = resolved; RG = resolving

a. Polack FP, Thomas SJ, Kitchin N et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. NEJM 2020; 383:2603-15. DOI: 10.1056/NEJMoa2034577.

b. The following unrelated events were also reported for this subject: Hepatic failure, Neutropenia, Urinary tract infection, Pulmonary mass.

As noted in Table 3 (bolded SARs), there were 9 cases reporting event(s) considered SUSARs for study vaccines [BNT162b2; Placebo], [BNT162b1; Placebo], or BNT162b2.

During the reporting period, there were no cases with a fatal outcome that were considered possibly related to the COVID-19 vaccine.

8.3. Long-term Follow-up

There is no information with regards to long-term follow-up of clinical trial participants for this reporting period.

8.4. Other Therapeutic Use of Investigational Drug

There is no relevant information pertaining to other therapeutic uses of COVID-19 for this reporting period.

8.5. New Safety Data Related to Combination Therapies

COVID-19 vaccine is not used in fixed or multi-drug combination with other compounds.

9. SAFETY FINDINGS FROM NON-INTERVENTIONAL STUDIES

During this reporting period, there were 3 ongoing non-interventional studies (C4591006, C4591008, and C4591012), which are presented in Table 4 below.

Table 4. Non-Interventional Studies Ongoing During the Reporting Period

Study No.	Study Title and Country
C4591006	**Study Title:** General Investigation of COMIRNATY Intramuscular Injection (Follow-up study for Subjects [Healthcare Professionals] Who are Vaccinated at an Early post-Approval Stage) **Country:** Japan **Study objective:** The healthcare professionals who are vaccinated with this product early after the marketing approval of this product (participants in the Investigation of Health Status of Recipients Vaccinated First conducted by the Science Research Group of the Ministry of Health, Labour and Welfare) will be followed for 11 months from the day following 28 days after the final vaccination of this product (end date of observation period in Investigation of Health Status of Recipients Vaccinated First) to 12 months after the final vaccination of this product, information on serious adverse events and COVID-19 observed during the follow-up period will be collected, and the long-term safety of this product will be assessed (to be conducted as 11-month follow-up investigation after completion of Investigation of Health Status of Recipients Vaccinated First).
C4591008[a] PASS	**Study Title**: HERO Together: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 vaccine in US healthcare workers. **Country**: United States **Primary study objectives**: • Estimate the real-world incidence of safety events of interest and other clinically significant events among US healthcare workers vaccinated with the Pfizer-BioNTech COVID-19 vaccine following Emergency Use Authorization.

Table 4. Non-Interventional Studies Ongoing During the Reporting Period

Study No.	Study Title and Country
	Secondary objectives: • Evaluate whether the vaccine recipients experience increased risk of safety events of interest and other clinically significant events post vaccination. • Estimate the incidence rates of safety events of interest and other clinically significant events among sub cohorts of interest such as individuals who are pregnant, individuals who are immunocompromised, and stratified by age.
C4591012[b] PASS	**Study Title**: Post-Emergency Use Authorization Active Safety Surveillance Study among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine **Country**: United States **Primary study objectives:** • To assess whether individuals in the VHA system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine. • To assess whether sub-cohorts of interest (i.e., immunocompromised, elderly, individuals with specific comorbidities, individuals receiving only one dose of the Pfizer-BioNTech COVID-19 vaccine, and individuals with prior SARS-CoV-2 infection) in the VHA system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine. **Secondary study objective**: • To characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among individuals within the VHA, including estimating the proportion of individuals receiving vaccine, 2-dose vaccine completion rate, and distribution of time gaps between the first and second dose, demographics and health histories of recipients, overall and among the sub-cohorts of interest.

a. Voluntary PASS.
b. Committed PASS (Category 3 Study in the EU).

During this reporting period, there was no new safety information reported regarding these ongoing non-interventional studies.

There were no NISs completed during this reporting period.

10. OTHER CLINICAL TRIAL/STUDY SAFETY INFORMATION

During this reporting period, there was no new safety information reported from other clinical trials.

11. SAFETY FINDINGS FROM MARKETING EXPERIENCE

As stated in Section 2, as of the DLP of this report, COVID-19 vaccine has been authorized for emergency use or been given conditional marketing authorization in overall 73 countries worldwide, with more than 355 million doses distributed. Most commonly reported AEs in the post-authorization review (which includes global reporting) reflect the same profile observed in the blinded placebo-controlled follow-up period of the pivotal clinical study, primarily reflecting short-lived and resolving reactogenicity events. AEs of clinical interest continue to be evaluated in the post-authorization setting.

Based on pharmacovigilance monitoring activities, since first authorization, anaphylaxis has been recognized as an important identified risk. Hypersensitivity reactions (other than Anaphylaxis), Diarrhoea, Pain in extremity (arm) and Vomiting were also assessed as identified risks (not important for the purpose of risk management planning) and added as adverse reactions to the labeling. Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats were evaluated to be identified risks (not important for the purpose of risk management planning) and they will be added to the RSI. Vaccine stress-related responses (including Dizziness, Paraesthesia and Tachycardia among other) were included in the RSI as reactions to the vaccination process.

Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD) is an important potential risk for COVID-19 vaccine.

Based on safety and efficacy data available to date for BNT162b2, the benefit-risk profile of COVID-19 vaccine remains favorable.

12. NON-CLINICAL DATA

During the reporting period, no new non-clinical safety findings were identified.

13. LITERATURE

Non-Clinical (Published)

A search of the Medline and Embase databases did not identify non-clinical studies that presented important new safety findings for COVID-19 vaccine.

Clinical (Published)

A search of the Medline and Embase databases identified 4 clinical trials that presented important new safety/efficacy findings for Covid-19 vaccine when administered in at risk patients (ie, patients on hemodialysis) or special population, including elderly and pregnant/lactating women. The abstracts are presented in Table 5 below. Full publications are available upon request.

Table 5. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

No.	Citation/Abstract
At Risk Patients	
1.	Grupper A, Sharon N, Finn T, et al. Humoral Response to the Pfizer BNT162b2 Vaccine in Patients Undergoing Maintenance Hemodialysis. Clin J Am Soc Nephrol. 2021. doi: 10.2215/CJN.03500321.

Table 5. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

No.	Citation/Abstract
	Background and objectives: Coronavirus disease 2019 (COVID-19) is associated with higher morbidity and mortality in patients on maintenance hemodialysis. Patients on dialysis tend to have a reduced immune response to infection or vaccination. We aimed to assess, for the first time to the best of our knowledge, the humoral response following vaccination with the BNT162b2 vaccine in patients on maintenance hemodialysis and the factors associated with it. **Design, setting, participants, & measurements:** The study included 56 patients on maintenance hemodialysis (dialysis group) and a control group composed of 95 health care workers. All participants had received two doses of the BNT162b2 (Pfizer-BioNTech) vaccine. The serology testing was done using Quant II IgG anti-Spike severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) assay by Abbott a median of 30 days after receipt of the second dose of the vaccine. **Results:** All subjects in the control group developed an antibody response compared with 96% (54 of 56) positive responders in the dialysis group. The IgG levels in the dialysis group (median, 2900; interquartile range, 1128–5651) were significantly lower than in the control group (median, 7401; interquartile range, 3687–15,471). A Mann–Whitney U test indicated that this difference was statistically significant (U=1238; P<0.001). There was a significant inverse correlation of age and IgG levels in both groups. The odds of being in the lower quartile were significantly higher for older individuals (odds ratio, 1.11 per year of age; 95% confidence interval, 1.08 to 1.20; P=0.004) and for the dialysis group compared with the control group (odds ratio, 2.7; 95% confidence interval, 1.13 to 7.51; P=0.05). Within the dialysis group, older age and lower lymphocyte count were associated with antibody response in the lower quartile (odds ratio, 1.22 per 1-year older; 95% confidence interval, 1.13 to 1.68; P=0.03 and odds ratio, 0.83 per 10-e3/µl-higher lymphocyte count; 95% confidence interval, 0.58 to 0.97; P=0.05). **Conclusions**: Although most patients on maintenance hemodialysis developed a substantial humoral response following the BNT162b2 vaccine, it was significantly lower than controls. Age was an important factor in the humoral response, regardless of chronic medical conditions
	Special Patient Population(s)
2.	Abu Jabal K, Ben-Amram H, Beiruti K, et al. Impact of age, ethnicity, sex and prior infection status on immunogenicity following a single dose of the BNT162b2 mRNA COVID-19 vaccine: Real-world evidence from healthcare workers, Israel, December 2020 to January 2021. Euro Surveill. 2021; 26(6):2100096. doi: 10.2807/1560-7917.ES.2021.26.6.2100096 The BNT162b2 mRNA COVID-19 vaccine showed high efficacy in clinical trials but observational data from populations not included in trials are needed. We describe immunogenicity 21 days post-dose 1 among 514 Israeli healthcare workers by age, ethnicity, sex and prior COVID-19 infection. Immunogenicity was similar by ethnicity and sex but decreased with age. Those with prior infection had antibody titres one magnitude order higher than naïve individuals regardless of the presence of detectable IgG antibodies pre-vaccination
3.	Rottenstreich A, Zarbiv G, Oiknine-Djian E, et al. Efficient maternofetal transplacental transfer of anti-SARS-CoV-2 spike antibodies after antenatal SARS-CoV-2 BNT162b2 mRNA vaccination. Clin Infect Dis. 2021: ciab266. doi: 10.1093/cid/ciab266. (Accepted manuscript). Maternal and cord blood sera were collected from 20 parturients who received the BNT162b2 vaccine. All women and infants were positive for anti S- and anti-RBD-specific IgG. Cord blood antibody concentrations were correlated to maternal levels and to time since vaccination. Antenatal SARS-CoV-2 vaccination may provide maternal and neonatal protection.
4.	Kelly JC, Carter EB, Raghuraman N, et al. Anti-SARS-CoV-2 antibodies induced in breast milk after Pfizer-BioNTech/BNT162b2 vaccination: SARS-CoV-2 antibodies in breast milk after vaccination. Am J Obstet Gynecol. 2021: S0002-9378(21)00211-8. doi: 10.1016/j.ajog.2021.03.031.

Table 5. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

No.	Citation/Abstract
	Objective: In December 2020, 2 lipid nanoparticle-formulated, nucleoside-modified messenger RNA–based vaccines received emergency use authorization by the US Food and Drug Administration, after their trials demonstrated 94% to 95% efficacy in preventing coronavirus disease 2019 (COVID-19). Although no lactating people were included in the vaccine trials, national organizations support vaccination of this population, suggesting potential infant protection by passive transfer of maternal antibodies. The authors sought to characterize breast milk levels of anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies in lactating people undergoing COVID-19 vaccination. **Study Design:** Participants were prospectively recruited during phase IA rollout of the COVID-19 vaccine at a tertiary care center, after institutional review board approval. Inclusion criteria included lactation and planned vaccination with the Pfizer-BioNTech BNT162b2 vaccine. After obtaining informed consent, participants provided frozen breast milk samples at the following time points of vaccination: before, within the first 24 hours, and the following week. Samples were assessed for SARS-CoV-2 RNA by quantitative real-time polymerase chain reaction and antispike immunoglobulin (Ig) G and IgA by an enzyme-linked immunosorbent assay. **Results:** A total of 5 subjects and 29 human milk samples were included in the analysis. All prevaccine milk samples tested negative for SARS-CoV-2 RNA, as defined by the cycle threshold value of >40 for the N1 target. Antispike IgG and IgA levels were significantly elevated relative to the prevaccine baseline at all time points. Antispike protein IgG remained sustained at a significant elevation beginning at 20 days after the first dose compared with the prevaccine baseline (P=.0061), through the final milk sample (day 30–39 P=.0095, >40 days P=.0040. Levels of antispike protein IgA were significantly elevated from baseline, starting 2 weeks after the first dose (P=.0286) through to the final sample (day 20–29 P=.0121, day 30–39 P=.0095, >40 days P=.0040); however, individual level data suggest a possible gradual decline in antispike IgA in human milk over time after the second dose.

Unpublished manuscripts/abstracts/scientific meeting findings

During the reporting period, no new safety findings were identified.

14. OTHER DSURS

During the reporting period, the sponsor, Pfizer, and Fosun did not submit another DSUR for COVID-19 vaccine

15. LACK OF EFFICACY

During the reporting period, no relevant lack of efficacy information was identified that could constitute a significant risk to clinical trial subjects.

16. REGION SPECIFIC INFORMATION

Appendices R16.1 and R16.1.1[11] provide cumulative summary tabulations of SARs received by the sponsor and identifies unexpected adverse reaction terms, including SUSARs. This appendix is organized according to SOC.

Appendix R16.1.2 provides a line-listing of cases reporting SUSARs during the reporting period. Please note that due to a technical issue, the SUSAR case(s) received from BNT162-01 (open label) and BNT162-03[11] CTs are not shown in this Appendix.

Appendix R16.2 provides a line-listing of subjects who died during reporting period regardless of relatedness (all from Study C4591001). During the reporting period, no subject deaths were reported from Studies BNT162-01, -03, -04, and -06.

Appendices R16.3, R16.3.1, and R16.3.2 provide line-listings of subjects who dropped out of clinical trials (Pfizer's, BioNTech, and Fosun CTs), respectively, during the reporting period due to an associated AE.

During the reporting period, there were no significant phase 1 protocol modifications made that were not previously reported to the IND in a protocol amendment (Appendix R16.4 is N/A).

Appendix R16.5.1 and Appendix R16.5.2 describe significant manufacturing changes that occurred during the current reporting period in the US and China, respectively.

Appendix R16.6.1 provides a description of the general investigational plan for the upcoming year with respect to a US IND, whereas Appendix R16.6.2 provides a description of the general investigational plan specific to China; of note, with the exception of the currently ongoing Studies (BNT162-03 and BNT162-06) described, there are no planned investigations for the upcoming year specific to China.

17. LATE-BREAKING INFORMATION

After the data lock point of this DSUR, the EU-RMP v. 2.0 dated 29 April 2021 has been approved expanding the conditional marketing authorization to include administration in adolescents 12 to 15 years old.

18. OVERALL SAFETY ASSESSMENT

18.1. Evaluation of the Risks

Not all potential or identified risks for the vaccine are considered to meet the level of importance necessitating inclusion in the list of safety concerns for the purpose of risk management planning.

The following reactogenicity events are identified risks not considered as Important: Injection site pain, Injection site swelling and Injection site redness, Fever, Chills, Fatigue, Headache, Muscle pain, and Joint pain.

Very rare potential risks for any medicinal treatment, including vaccines, which are well known to healthcare professionals are not included in the list of safety concerns.

The reactogenicity profile of COVID-19 vaccine is discussed below with respect to observed differences in solicited reactogenicity systemic events between Dose 1 and Dose 2. The observed differences do not impact the safety profile of the vaccine and are not proposed to

be included in the list of safety concerns, rather they are discussed for completeness in the presentation of the safety profile.

Based on the recency of approval of the conditional authorization in adolescents, 12 to 15 years of age, reactogenicity data is presented separately with respect to that of individuals ≥16 years included in the initial marketing authorization application.

Safety Population – Adults 16-55 Years of Age

The safety population age group of adults (16-55 years of age) included 13,069 participants in the BNT162b2 group and 13,095 participants in the placebo group.

Reactogenicity – Adults 16-55 Years of Age

Reactogenicity (local reactions and systemic events) was assessed via e-diary in a subset of participants in up to 7 days after each dose.

- **Local Reactions**

Among adults 16-55 years of age in the BNT162b2 group, pain at the injection site was the most frequently reported local reaction, with similar frequency after Dose 1 compared with Dose 2 of BNT162b2.

In the BNT162b2 group, frequencies of redness (5.4% vs 5.6%) and swelling (6.3% vs 6.8%) were similar after Dose 1 and 2. In the placebo group, redness and swelling were reported infrequently (≤1.1%) after Doses 1 and 2. Pain at injection site was reported with a higher frequency in the BNT162b2 group after Dose 1 and Dose 2 than in the placebo group (Dose 1: 83.7% vs 14.2%; Dose 2: 78.3% vs 11.6%).

Overall, 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. After either dose, most local reactions were mild or moderate in severity. Severe local reactions were reported infrequently (≤2.5%) in the BNT162b2 group after either dose. No Grade 4 local reactions were reported.

Local reactions for the adult age group after either dose had a median onset day on Day 1 (Day 1 was the day of vaccination) and resolved with a median duration of 1-2 days.

- **Systemic Events**

Systemic events in the adult group (16-55 years of age) were generally increased in frequency and severity with number of doses, with the exceptions of vomiting and diarrhea, which were reported unfrequently and at similar incidences after each dose.

Systemic events in decreasing order of frequency by dose (Dose 1 vs Dose 2), were:

- Fatigue: BNT162b2 (49.4% vs 61.5%) compared to placebo (33.0% vs 22.9%);
- headache: BNT162b2 (43.5% vs 54.0%) compared to placebo (33.5% vs 24.3%);

- muscle pain: BNT162b2 (22.9% vs 39.3%) compared to placebo (11.3% vs 8.8%);
- chills: BNT162b2 (16.5% vs 37.8%) compared to placebo (6.8% vs 4.2%);
- joint pain: BNT162b2 (11.8% vs 23.8%) compared to placebo (5.8% vs 5.5%);
- fever: BNT162b2 (4.1% vs 16.4%) compared to placebo (0.9% vs 0.4%);
- vomiting: reported infrequently and similar after either dose;
- diarrhea: reported infrequently and similar after each dose.

Systemic events were generally reported less frequently in the placebo group than in the BNT162b2 group, with some exceptions. Vomiting and diarrhea (after Dose 1 and Dose 2) were reported at similar frequencies in the placebo group and the BNT162b2 group.

In the BNT162b2, use of antipyretic/pain medication was 27.8% vs 45.2% after Dose 1 and Dose 2, respectively. Use of antipyretic/pain medication was less frequent in the placebo group after Dose 1 and Dose 2 (13.7% and 11.9%) than in the BNT162b2 group.

After the first and second dose, the majority of systemic events were mild or moderate in severity. Severe fever (>38.9 °C to 40.0 °C) was reported in the BNT162b2 group after Dose 1 for 0.3% and after Dose 2 for 1.5% of participants, and in the placebo group after Dose 1 for 0.1% and after Dose 2 for 0.1% of participants. Grade 4 fever (>40 °C) was reported for 1 participant in the BNT162b2 group and no participants in the placebo group.

Systemic events for the adult (16-55 years of age) group after either dose had a median onset day of Day 2 (Day 1 was the day of vaccination) and resolved with a median duration of 1-2 days. No clinically meaningful differences in systemic events were observed by age and/or baseline SARS-CoV-2 status subgroups.

Safety Population – Adolescents 12-15 Years of Age

The safety populations, including subsets and exclusions, for adolescents (12-15 years of age) and young adults (16-25 years of age) were similar in the corresponding BNT162b2 and placebo groups. Safety analysis results are presented for adolescent and young adult safety population (including the reactogenicity subset) up to 1 month after Dose 2 and for all available data up to the 13 March 2021.

Reactogenicity – Adolescents 12-15 Years of Age

Reactogenicity (local reactions and systemic events) was assessed via e-diary in all adolescents and a subset of young adult participants up to 7 days after each dose.

- **Local Reactions**

In the BNT162b2 group, pain at the injection site was most frequently reported in adolescents and young adults, and frequency was similar after Dose 1 and after Dose 2 of BNT162b2 in adolescents (86.2% vs 78.9%) and in young adults (83.4% vs 77.5%). In the placebo group, pain at the injection site after Doses 1 and 2 was similar in adolescents (23.3% and 17.9%, respectively) and young adults (15.9% and 12.1%, respectively).

In the BNT162b2 group, frequencies of redness and swelling were similar between adolescents and young adults after Doses 1 and 2 (Figure 3). Frequencies of redness were generally low and unchanged from after Dose 1 compared with Dose 2 of BNT162b2 in adolescents (5.8% vs 5.0%) and in young adults (6.4% vs 5.7%). Frequencies of swelling were similarly low and slightly reduced after Dose 1 compared with Dose 2 of BNT162b2 in adolescents (6.9% vs 4.9%) and in young adults (8.3% vs 6.8%). In the placebo group, redness and swelling were infrequent in the adolescent (≤1.1%) and young adult (≤1.1%) groups after Doses 1 and 2.

After the first and second dose and in both age groups, most local reactions were mild or moderate in severity. Severe local reactions were reported infrequently and at lower incidence in adolescents (≤1.5%) compared with young adults (≤3.4%) across the BNT162b2 and placebo groups after any dose. No Grade 4 local reactions were reported in either age group.

Across age groups, median onset for all local reactions after either dose of BNT162b2 was Day 1 to Day 3 (Day 1 was the day of vaccination) and resolved with a median duration of 1-3 days.

- **Systemic events**

Systemic events were generally similar in frequency and severity in adolescents compared with young adults, with frequencies and severity increasing with number of doses for most events, with the exception of vomiting and diarrhea, which were reported infrequently and at similar incidences after each dose, and muscle and joint pain which was reported at higher frequencies in the young adults. Systemic events in the adolescent group compared with the young adult group, in decreasing order of frequency by dose (Dose 1 vs Dose 2), were:

- Fatigue: adolescents (60.1% vs 66.2%) compared to young adults (59.9% vs 65.6%).
- Headache: adolescents (55.3% vs 64.5%) compared to young adults (53.9% vs 60.9%)
- Chills: adolescents (27.6% vs 41.5%) compared to young adults (25.0% vs 40.0%)
- Muscle pain: adolescents (24.1% vs 32.4%) compared to young adults (26.9% vs 40.8%)
- Joint pain: adolescents (9.7% vs 15.8%) compared to young adults (13.2% vs 21.9%)
- Fever: adolescents (10.1% vs 19.6%) compared to young adults (7.3% vs 17.2%)
- Vomiting: reported infrequently in both age groups and similar after either dose.
- Diarrhea: reported infrequently in both groups and similar after each dose.

Systemic events were generally reported less frequently in placebo versus BNT162b2 groups.

Following both Dose 1 and Dose 2, use of antipyretic/pain medication was similar in adolescents (36.6% and 50.8%) and in young adults (31.5% and 45.7%), 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 adolescent and young adult placebo groups (ranging from 8.8% to 11.9%).

After the first and second dose and in both age groups, most systemic events were mild or moderate in severity. Severe systemic events were reported infrequently and at lower incidence in adolescents (≤3.5%) compared with young adults (≤6.0%) across BNT162b2 and placebo groups after any dose. One adolescent in the BNT162b2 group had Grade 4 pyrexia (40.4 °C) on Day 2 after Dose 1, with temperature returning to normal by Day 4; it was also reported as an AE leading to withdrawal.

Across age groups, median onset for all systemic events after either dose of BNT162b2 was Day 1 to Day 4 (Day 1 was the day of vaccination). Systemic events resolved post each dose with a median duration of 1 day, except fatigue and chills which resolved within a median of 1-2 days.

In summary, increases in some systemic reactogenicity events (fever, chills, headache, fatigue, muscle pain and joint pain) were observed in the week following Dose 2 when compared with the week following Dose 1. The differences are small enough that they are unlikely to discourage vaccinees from completing the full 2-dose regimen for vaccination neither do they impact the benefit risk profile of the vaccine overall. Overall, the reactogenicity events have only temporary clinical impact on patients in relation to the potential severity of the disease prevented.

18.1.1. Important Identified Risks

Anaphylaxis has been recognized as an important identified risk during the reporting period and was included in the initial EU RMP (v. 1.0, December 2020). Anaphylaxis is a serious adverse reaction that, although very rare, can be life-threatening.

18.1.2. Important Potential Risks

Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD) is an important potential risk for COVID-19 vaccine.

Although not observed or identified in clinical studies with COVID-19 vaccines, there is a theoretical risk, mostly based on non-clinical betacoronavirus data, of VAED occurring either before the full vaccine regimen is administered or in vaccinees who have waning immunity over time. If VAED were to be identified as a true risk, depending on its incidence and severity, it may negatively impact the overall vaccine benefit risk assessment for certain individuals.

Of note, the EU-RMP was updated to v. 1.1 during the reporting interval and received CHMP approval on 15 April 2021. A subsequent EU-RMP update (v. 2.0 dated 29 April 2021) expanding the conditional authorization to adolescents 12 to 15 years old has been approved post the DLP, on 31 May 2021. There were no updates to the safety concerns made.

18.2. Benefit-Risk Considerations

COVID-19 is a serious and potentially fatal or life-threatening human infection. COVID-19 vaccine is being developed for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus. The available clinical evidence for BNT162b2 effectiveness includes induction of strong immune responses and overwhelmingly high vaccine efficacy with a satisfactory

profile, suggesting that the vaccine confers safe and effective protection against COVID-19 in individuals ≥12 years of age.

The potential risks are based on the observed clinical study safety profile to date, which shows mostly mild reactogenicity, low incidence of severe or serious events, and no new clinically concerning safety observations or safety concerns. The vaccine has been shown to be safe and well-tolerated across age groups and irrespective of prior infection with SARS-CoV-2. Confinement of severe COVID-19 cases mostly to placebo recipients versus BNT162b2 recipients (all reported in adult age groups to date) suggests no evidence of VAED or VAERD.

Post-authorization safety reviews including spontaneous safety reporting from all countries/regions in which BNT162b2 is authorized or conditionally approved, of which a summary report is submitted to regulatory authorities on a monthly basis, have suggested no new important risks except for anaphylaxis which has been included as an identified risk in the EU-RMP.

Efficacy data suggest highly effective protection against COVID-19 in a broad population of individuals across demographic characteristics including age and prior SARS-CoV-2 infection, with 95 to 100% VE observed in adults and adolescents 12-15 years of age respectively. Immunobridging for adolescents 12-15 years of age, who had noninferior neutralizing GMTs compared to young adults 16-25 years of age, supports evidence of vaccine effectiveness in the adolescent age group.

Overall, the potential risks and benefits, as assessed by the safety profile and the efficacy and immunogenicity of BNT162b2, are balanced in favor of the potential benefits to prevent COVID-19 in immunized adults and adolescents 12-15 years of age. Important risks of BNT162b2 are described in the EU RMP and will continue to be assessed and minimized as described in the EU RMP. The public health impacts that include individual and community health, education, and socio-economic outcomes also weigh in favor of immunizing individuals 12 years of age and older with BNT162b2.

Anaphylaxis is an important identified risk and VAED/VAERD are important potential risks. Based on the available safety and efficacy data for COVID-19 vaccine, the benefit risk profile of the medicinal product remains favorable.

19. SUMMARY OF IMPORTANT RISKS

This section summarizes the important identified and potential risks that have been recognized during the conduct of the COVID-19 vaccine clinical development program. A summary of the important risks associated with COVID-19 vaccine is presented in Table 6.

Table 6. Summary of Important Risks from the COVID-19 Vaccine Development Program

Risk	Nonclinical Data	Clinical Data	Measures in Place and Actions to be Taken[a]
Identified Risks			
Anaphylaxis	No data	There was one report of Anaphylactoid reaction that occurred during the open label phase of Study C4591001. Please refer to Section 8.2, Table 3 for case details.	Pharmacovigilance activities to address the safety concerns include: - Study C4591001[b] (Ongoing). The objective of the study is to evaluate the safety, tolerability, immunogenicity, and efficacy of COVID-19 mRNA vaccine. An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19, in particular for severe COVID-19, may suggest the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2. - C4591010 (Planned) will evaluate occurrence of safety events in real-world use of COVID-19 mRNA vaccine. - Study C4591011 (Planned)[c] will evaluate occurrence of safety events of interest, including severe or atypical COVID-19 in a cohort of people within the Department of Defense Healthcare System. - C4591012[c] will evaluate the occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine. - ACCESS/VAC4EU (*Planned*) will evaluate occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.
Potential Risks			
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	No data	No data	Additional pharmacovigilance activities: - C4591001[b] - C4591011[c] - C4591012[c] - ACCESS/VAC4EU (See above for details)

a. Source EU-RMP v. 1.0 dated December 2020 (and EU RMP v. 2.0 dated April 2021 to reflect current study status).
b. Category 2 study in the EU.
c. Category 3 Study in the EU

20. CONCLUSION

Anaphylaxis is an important identified risk identified during the reporting period and VAED including VAERD are important potential risks. These important risks will continue to be closely monitored as COVID-19 vaccine development program progresses.

During the reporting period, there were 10 ongoing clinical trial(s): C4591001, C4591005, C4591007, C4591015, C4591017, C4591020, BNT162-01, BNT162-03, BNT162-04, and BNT162-06. Studies C4591001, C4591007, C4591015, C4591017, C4591020, and BNT162-06 were still blinded at the DLP; however, no additional clinically important information has emerged from these ongoing clinical trials.

The sponsor will continue to monitor all clinical trial safety information received from worldwide sources and will revise the protocols, consent forms, and/or product documents if an evaluation of surveillance data yields significant new information.

Based on the available safety and efficacy data for COVID-19 vaccine, the benefit risk profile of the medicinal product remains favorable. Further development of COVID-19 vaccine is justified by the anticipated benefits expected for patients who may be exposed to SARS CoV-2 infection.

INVESTIGATOR'S BROCHURE

CorVAC / BNT162

Version: 3.0 **Date:** 17 APR 2020

Sponsor: BioNTech RNA Pharmaceuticals GmbH
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55131 Mainz,
Germany

Reference safety information for the investigational medicinal products (IMPs) is provided in Section 6.2.

Document History

Use	Date	Version number
First 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

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
ALAT	Alanine-aminotransferase
ASAT	Aspartate-aminotransferase
aPTT	Activated partial thromboplastin time
BNT162a	BNT162 RNA-LNP vaccine utilizing uridine 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.)
COVID-19	Coronavirus Disease 2019
d	Day(s)
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ELISA	Enzyme-Linked Immunosorbent Assay
ER	Endoplasmic reticulum
GGT	Gamma(γ)-glutamyl transpeptidase
GLP	Good Laboratory Practice
h	Hour(s)
HA	Hemagglutinin
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
IFN	Interferon
IgG	Immunoglobulin G
IL	Interleukin
IM	Intramuscular(ly)
IMP	Investigational Medicinal Product
IV	Intravenous(ly)
LNP	Lipid nanoparticle
mRNA	messenger RNA
modRNA	Nucleoside modified messenger RNA
pVNT	pseudovirus-based neutralization assay
RBD	Receptor Binding Domain
RNA	Ribonucleic acid
RNA-LPX	RNA complexed with liposomes
saRNA	Self-amplifying messenger RNA
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	The virus leading to COVID-2019

Abbreviation	Explanation
Th1	Type 1 T helper cells
TNF	Tumor necrosis factor
uRNA	Non-modified uridine messenger RNA
pVNT	pseudovirus-based neutralization assay
VSV	Vesicular Stomatitis Virus
WHO	World Health Organization
wk(s)	Week(s)

NOTES FOR THE READER

The BioNTech group is a holding comprising several subsidiaries including BioNTech RNA Pharmaceuticals GmbH.

1 SUMMARY

There is an urgent need for the development of a new prophylactic vaccine given the threat posed by the increasing number of globally distributed outbreaks of Severe Acute Respiratory Syndrome (SARS) -CoV-2 infection and thus its associated disease Coronavirus Disease 2019 (COVID-19).

The development of a ribonucleic acid (RNA)-based vaccine encoding a viral antigen that is translated by the vaccinated organism to protein to induce a protective immune response provides significant advantages over more conventional vaccine approaches.

At BioNTech, there are three different RNA platforms under development, namely non-modified uridine containing mRNA (uRNA), nucleoside modified mRNA (modRNA), and self-amplifying mRNA (saRNA).

Taken together, all three RNA platforms have been tested in more than a dozen non-clinical good laboratory practice (GLP) safety studies and clinical safety data are available for uRNA and modRNA. These data have been obtained primarily with RNAs formulated with liposomes and lipid nanoparticles which are related, but not identical, to those that will be used in the planned clinical trials.

The non-clinical toxicity data generated by BioNTech suggest a favorable safety profile for uRNA, modRNA, and saRNA formulated with different nanoparticles for various administration routes including for intravenous (IV) injection. The favorable safety profile after IV dosing is notable because IV injection results in a higher systemic exposure than the intramuscular (IM) injection planned in the clinical trials. Overall, the findings were mild and mostly related to the mode-of-action and the RNA-intrinsic stimulation of innate immune sensors. No unsuspected target organs of toxicity were identified. The non-clinical safety profile of uRNA and modRNA in rodents was predictive for clinical safety.

The non-clinical safety and toxicity of the BNT162 family of lipid nanoparticle (LNP) enveloped uRNA, modRNA, and saRNA vaccine platforms encoding SARS-CoV-2 antigens are currently being analyzed in a GLP-compliant repeat-dose toxicity study.

There are currently no data available on the effects of any of the BNT162 vaccine candidates in humans.

The potential safety and immunogenicity of four BNT162 vaccine candidates (BNT162a1, BNT162b1, BNT162b2, and BNT162c2) against SARS-CoV-2 will be investigated clinically, as part of a program to develop a prophylactic vaccine to prevent infection with SARS-CoV-2 and thus its associated disease COVID-19.

The data cut-off date for this document is April 15th, 2020.

2 INTRODUCTION

2.1 Background

SARS-CoV-2 infections and the disease this virus causes, COVID-19 are increasing every day and is spreading globally. The World Health Organization (WHO) classified the COVID-19 outbreak as pandemic on March 11th, 2020. The WHO Situation Update Report dated April 15th, 2020 noted 1,914,916 confirmed cases with 123,010 deaths globally (WHO Situation Update Report 85).

There are currently no approved vaccines or antiviral drugs to prevent or treat infection with SARS-CoV-2 or its associated disease COVID-2019 (Habibzadeh and Stoneman 2020).

2.2 BioNTech's diversified expertise in RNA therapeutics

BioNTech has longstanding and diversified expertise in utilizing messenger RNA (mRNA) to deliver genetic information to cells, where it is used to express proteins for the therapeutic effect. BioNTech has been working in the RNA field for more than a decade and is developing a portfolio of RNA therapies that utilize four different mRNA formats and three different formulations to derive five distinct platforms, each optimized for delivering a particular therapeutic mode-of-action.

These mode-of-actions include using mRNA as a vaccine to induce antibody and T-cell immune responses. Three of these platforms are currently in human testing in oncology indications, primarily as repeatedly IV administered therapeutic cancer vaccines, where over 613 patients have been dosed to date (for further details, see Section 2.5). This clinical experience includes a large number of patients who have had long term exposure, i.e., who have received more than 8 IV administrations.

RNA is a highly versatile multi-purpose molecule. What makes it attractive as vaccine platform is that it enables timely and effective response to emerging threats. RNA 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 is considered safe. Vaccination with RNA in general generates robust immune responses as RNA not only delivers the vaccine antigen, but also has intrinsic adjuvanticity.

The production of RNA requires only a single development and manufacturing platform, irrespective of the encoded pathogen antigens. Thus, RNA has the potential of rapid, cost-efficient, high-volume manufacturing and flexible stockpiling (long term storage of low-volume libraries of frozen plasmid and unformulated RNA, which can be rapidly formulated and distributed). BioNTech has expertise in production-process development for various RNA chemistries and formulations.

2.3 Introduction to BioNTech RNA-based vaccines

A LNP-formulated RNA-based vaccine would provide one of the most flexible, scalable, and fastest approaches to provide protection against a new, fast spreading, virus infections (Rauch et al. 2018; Sahin et al. 2014).

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

RNA vaccines are molecularly defined, highly purified immunogens. 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 an 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 used three different RNA platforms for the development of BNT162 vaccine candidates: RNA which contains the standard nucleoside uridine (uRNA;), nucleoside-modified RNA (modRNA), in which uridine is replaced by the nucleoside pseudo-uridine;, and self-amplifying RNA (saRNA), which also contains uridine nucleosides (Figure 1).

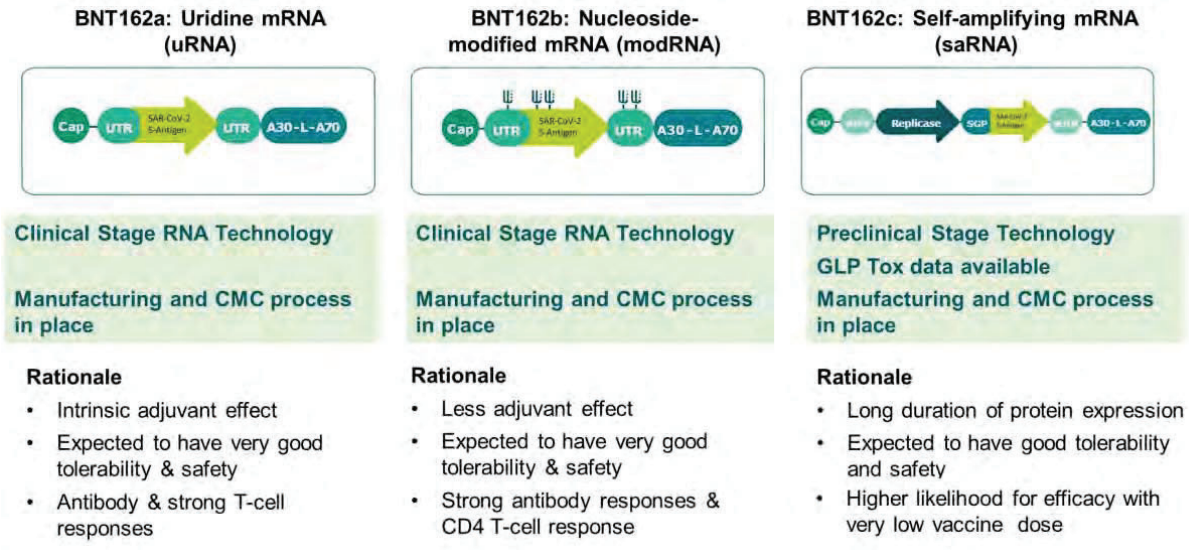


Figure 1: Overview of the three RNA platforms

The RNA vaccine molecules are capped, contain open reading frames (ORFs,) flanked by the untranslated regions (UTR), and have a polyA-tail at the 3' end. The ORF of the uRNA and modRNA vectors encode the vaccine antigen. The saRNA has two ORFs. The first ORF encodes an alphavirus-derived RNA-dependent RNA polymerase (replicase), which upon translation mediates self-amplification of the RNA. The second ORF encodes the vaccine antigen.

The utility of each of these RNA platforms for the development of infectious disease vaccines is supported by various non-clinical studies that demonstrated the efficient

induction of potent neutralizing antibody and T-cell responses against a variety of viral pathogens including influenza, Ebola, human immunodeficiency virus (HIV), and Zika virus (Vogel et al. 2018; Moyo et al. 2018; Pardi et al. 2017).

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 2). 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.

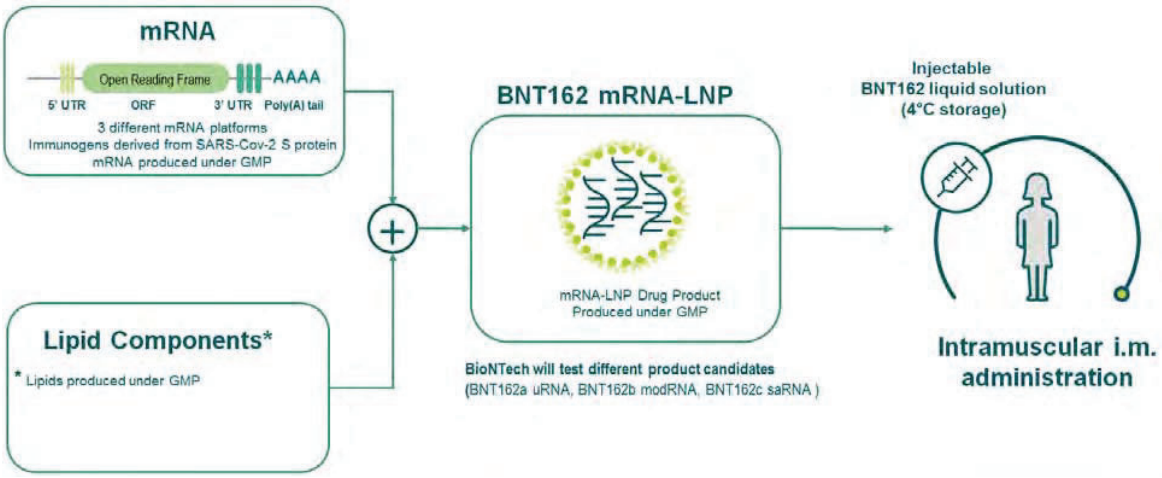


Figure 2: RNA-LNP-based BNT162 vaccines

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 IM injection.

The three RNA platforms used in the BNT162 vaccine candidates have complementary strengths (Figure 1): 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 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.

All vaccine candidates may be administered using prime/boost or prime-only administration regimens (Figure 3).

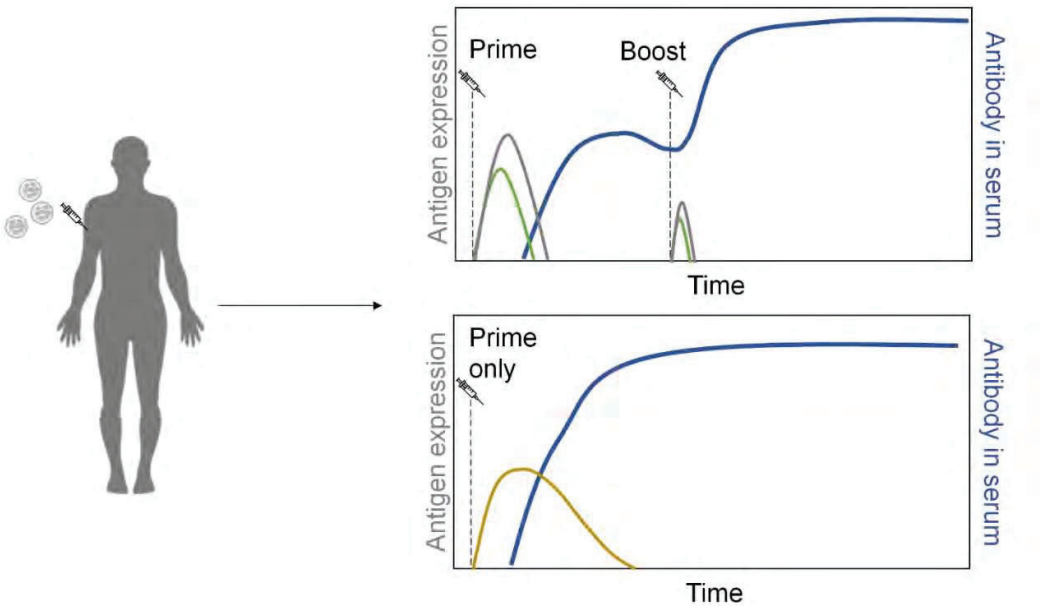


Figure 3: Rationale for the administration schema of BNT162 vaccines

Coronavirus spike 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 spike glycoprotein (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 4 and Figure 5). The 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 receptor-binding domain (RBD) recognizes the host receptor and binds to the target host cell. SARS-CoV and SARS-CoV-2 have similar structural properties and bind to the same host cell receptor, angiotensin converting enzyme 2 (ACE-2) (Zhou et al. 2020). The S protein is not only pivotal for host cell recognition and entry, but also for the induction of virus neutralizing antibodies by the host immune system (Zakhartchouk et al. 2007; Yong et al. 2019).

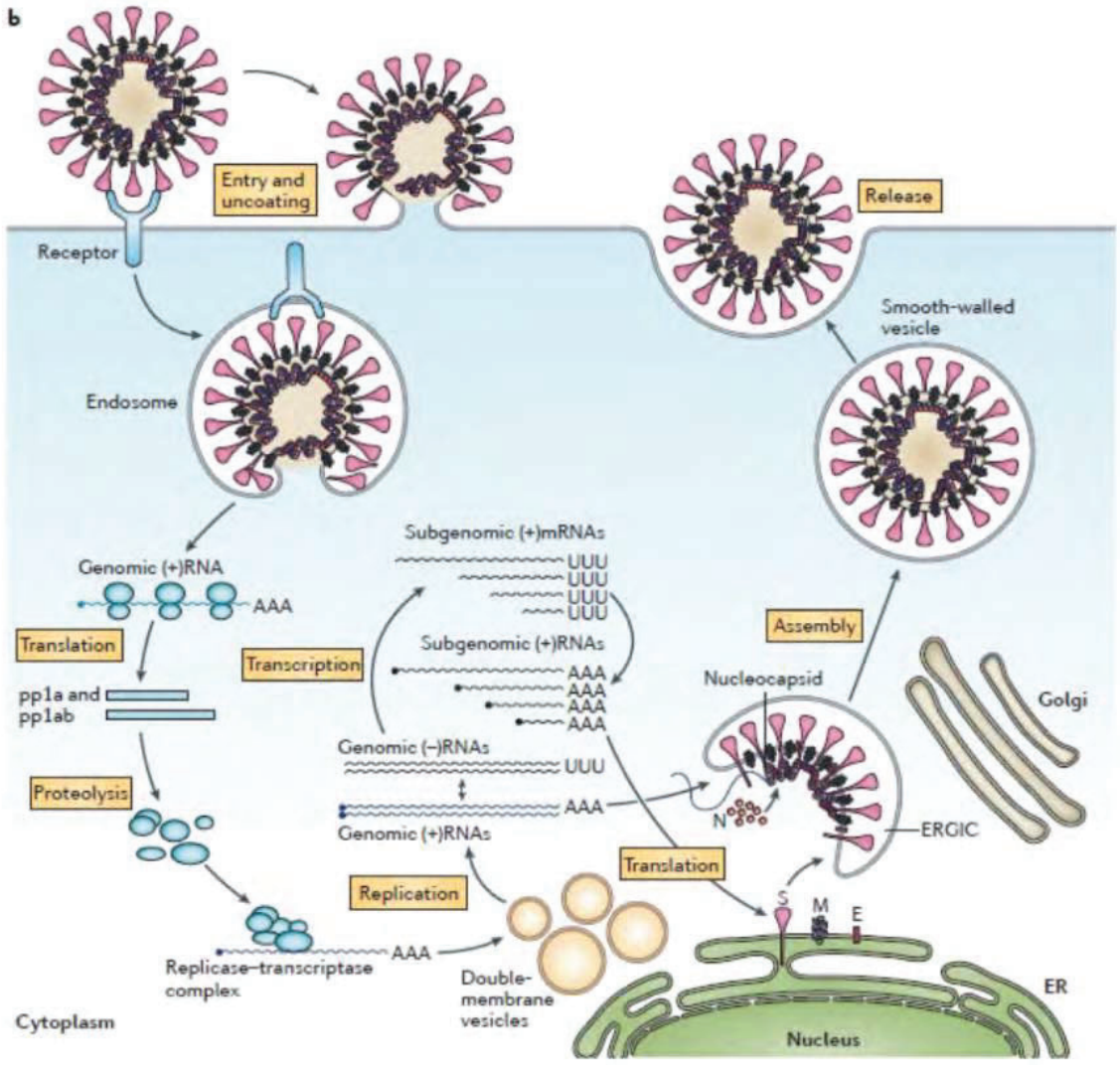


Figure 4: Schematic life circle of a Coronavirus

(Source: de Wit et al. 2016)

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).

Targeting the S protein, as well as its S1 cleavage fragment or the RBD alone, with vaccines is sufficient to induce neutralizing immune responses (Al-Amri et al. 2017). The RBD forms membrane distal "heads" on the S protein that are connected to the 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, a P2 mutant, "heads up," stabilized, pre-fusion conformation variant of S protein can induce a stronger neutralizing antibody response than the native S protein (Pallesen et al. 2017; Wrapp et al. 2020).

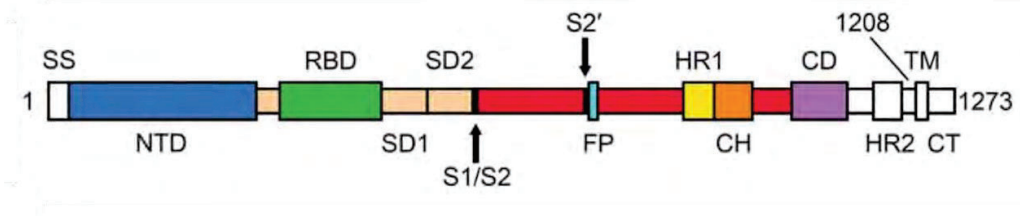


Figure 5: Schematic overview of the organization of the SARS-CoV-2 S glycoprotein

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); source: modified from Wrapp et al. 2020.

The BNT162 vaccine candidates selected for clinical testing feature the following vaccine antigens (Figure 1).

- A secreted, trimerized variant of the RBD of the SARS CoV-2 S-protein (called V5) (Kirchdoerfer et al. 2018).
- Membrane-anchored full-length S protein with two point mutations within the central helix domain (called V8 or V9). Mutation of the two amino acids to proline, (KV286-287PP) locks the S protein in an antigenically optimal prefusion conformation (Wrapp et al. 2020; Pallesen et al. 2017).

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 (Figure 6).

The LNPs are composed of four different lipids in a defined ratio. During mixing of the RNA and the dissolved lipids, the lipids form the nanoparticles encapsulating the RNA. After injection, the LNPs are taken up by the cells, and the RNA is released into the cytosol. In the cytosol, the RNA is translated to the encoded viral antigen.

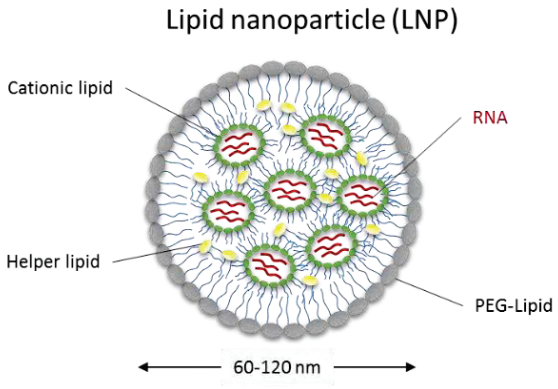


Figure 6: Schematic overview of a LNP

The antigen may be incorporated into the cellular membrane or secreted into the extracellular environment and induce an adaptive immune response. In addition, as S protein is the antigen that recognizes and drives infection of the host cells, it is a key target of virus neutralizing antibodies. Furthermore, as RNA-expressed S protein is fragmented intracellularly, the resulting peptides can be presented at the cell surface, triggering a specific T cell-mediated immune response with activity against the virus.

2.4 Clinical development

Four different BNT162 vaccine candidates based on three RNA platforms (uRNA, modRNA, and saRNA) will be tested clinically. For the BNT162 vaccines, the nomenclature is as follows:

- BNT162a1: uRNA-LNP, viral S protein of the SARS-CoV-2 (partial sequence, RBD of S1S2 protein).
- BNT162b1: modRNA-LNP, secreted variant of the RBD of the SARS-CoV-2 S protein.
- BNT162b2: modRNA-LNP, S protein (S1S2 protein) of the SARS-CoV-2 (S1S2 full-length protein, sequence variant).
- BNT162c2: saRNA-LNP, S protein (S1S2 protein) of the SARS-CoV-2 (S1S2 full-length protein, sequence variant).

There are currently no data available on the effects of any of the BNT162 vaccine candidates in humans.

The safety and immunogenicity of four BNT162 vaccine candidates (BNT162a1, BNT162b1, BNT162b2, BNT162c2) will be investigated clinically, as part of a program to develop a prophylactic vaccine to prevent infection with SARS-CoV-2 and thus its associated disease COVID-19. The clinical program will start with the immunization of healthy adults, both men and women, aged between 18 and 55 years. If the immunization is found to be well tolerated, immunization will also be investigated in the older healthy

adults, and the likely target population (e.g., at risk populations such as elderly and/or immunocompromised populations).

Since the BNT162 vaccine candidates utilize the same LNP formulation, the observed safety profiles will be considered representative for all candidate vaccines in combination with the respective platform. Likewise, since some of BNT162 vaccine candidates lead to expression of the same encoded viral antigen, the observed safety profiles will be considered representative for all candidate vaccines utilizing the same encoded viral antigen.

2.5 Supportive clinical background information

Whereas the combination of each of the three RNA formats (uRNA, modRNA, saRNA) with the specific LNP composition used in the BNT162 vaccine candidates has not been tested in humans before, BioNTech has collected clinical experience on two of the RNA formats used in BNT162 vaccines, namely uRNA and modRNA. Both RNA formats are being used in BioNTech`s immune oncology programs as summarized in Table 1.

Table 1: BioNTech clinical platform experience with uRNA and modRNA as off April 2020

Liposomally formulated RNAs were formulated with similar but not identical lipid composition as those used in BNT162 vaccines. *3 patients dosed at 200 µg, one patient dosed 400 µg

RNA Clinical experience	N
uRNA, liposomally formulated, intravenous injection, dose range: 7.2 to 100 µg* (encoding various shared tumor antigens and individual cancer mutations)	
• Trial NCT02410733 (Phase I) in melanoma patients (Lipo-MERIT)	108
• Trial NCT02316457 (Phase I) in triple negative breast cancer patients (TNBC-MERIT)	42
• Trial NCT03418480 (Phase I) in HPV16+ head-neck cancer patients (HARE-40)	19
• Trial 2018-004321-86 (Phase I) in prostate cancer patients (PRO-MERIT)	3
• Trial NCT04163094 (Phase I) in ovarian cancer patients (OLIVIA)	3
• Trial NCT03289962 (Phase I) in patients with solid cancers	203
• Trial NCT03815058 (RCT Phase II) in patients with solid cancers	18
uRNA, non-liposomally formulated, injection into lymph nodes, dose range: 50 to 1000 µg (encoding various shared tumor antigens and individual cancer mutations)	
• Trial NCT01684241 in melanoma patients (MERIT)	32
• Trial NCT02035956 in melanoma patients (IVAC)	13
uRNA, non-liposomally formulated, product for DTH intradermal injection, dose range: 7.2 to 400 µg (encoding various shared tumor antigens)	
• Trial NCT02410733 (Phase I) in melanoma patients (Lipo-MERIT)	118
• Trial NCT01684241 in melanoma patients (MERIT)	32
modRNA, non-liposomally formulated, intratumor injection, 8 µg to 4000 µg (encoding various cytokines)	
• Trial NCT03871348 in patients with solid cancers	22

DTH = Delayed-type hypersensitivity reaction testing; IV = intravenous; IT = intratumoral; N = number of patients.

uRNA in conjunction with a formulation, which is similar but not identical with the specific LNP composition used in BNT162a1, has been investigated by BioNTech in various oncology clinical trials with more than 613 patients dosed repeatedly.

modRNA (non-liposomally formulated) has been administered to 22 patients in an ongoing oncology clinical trial.

The sum of the data collected across these trials is supportive for the risk assessment of BNT162 vaccines.

The key observations in the clinical trials listed above were:

- uRNA (liposomally formulated) injected intravenously had a favorable safety profile. In these trials, systemic exposure at doses up to 400 µg of uRNA complexed with liposomes injected IV was tolerated. In line with the transient, pulsatile secretion of a distinct range of cytokines at supra-physiological but not pathological plasma levels observed in these patients. The adverse event (AE) profile was dominated by mild to moderate flu-like symptoms, e.g., pyrexia and chills. These immune modulation-related AEs started within 2-6 h after IV injection, were manageable with anti-pyretics, were self-limiting and resolved within 24 h.
- uRNA (non-lipid formulated) administered intradermally or injected into inguinal lymph nodes was tolerated with only occasional and mild local injection site reactions. Systemic reactions after local application were not observed.
- modRNA (non-lipid formulated) administered into tumor lesions of cancer patients was tolerated with occasional mild injection site reactions. Systemic reactions after local application were not observed.

Based on the aggregate clinical data of lipid formulated uRNA and modRNA components that are used in the BNT162 vaccines, a favorable safety profile of BNT162 products is expected with mild, localized and transient effects. The listed risks related to BNT162 vaccine are expected to be manageable using routine symptom driven standard of care by the investigators.

In addition to BioNTech`s own data, data from clinical studies conducted by other parties, supports a favorable risk profile of lipid-formulated and non-lipid-formulated RNAs administered via various routes. Exemplary reported clinical trials are the following ones:

- **ModRNAs formulated with related but not identical lipid compositions administered intramuscularly** were used in two Phase I clinical trials NCT03076385 and NCT03345043 performed by Moderna (Cambridge, MA, USA) to evaluate safety and immunogenicity against potentially pandemic avian influenza viruses in healthy adults (Feldman et al. 2019). Doses ranging from 25 to 400 µg IM (one order of magnitude higher than planned for BNT162 vaccines) (prime/boost, 3 wks apart) were safely administered.

  Overall, injection site pain after either dose was the most common solicited local AE. The most common solicited systemic AEs after either IM dose were myalgia, fatigue, arthralgia and headache, all mostly of grade 1 to 2 in severity, of short duration, and resolved without intervention.

For both trials, there were no AEs related to potentially immune-mediated medical conditions or cases of new onset of chronic illness.

- **Non-lipid formulated uRNA administered intramuscularly** was used in a Phase I clinical trial NCT02241135 by CureVac (Tübingen, Germany) for testing safety and immunogenicity of a rabies virus glycoprotein vaccine (Alberer et al. 2017). In this trial, 101 healthy adults received dose levels ranging from 80 to 640 µg RNA according to a 3-dose prime/boost schema. The vaccine was safe with a reasonable tolerability profile.

Moreover, several clinical trials with saRNA-based vaccines (NCT04062669, rabies vaccine), (NCT03632941, cancer vaccine), and with liposomally formulated modRNA vaccines (NCT04144348, parainfluenza vaccine), (NCT03829384, chikungunya vaccine) are in the recruiting stage.

3 PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

The following section gives general information about the physical, chemical and pharmaceutical properties of the BNT162 family of prophylactic RNA-based vaccine candidates encoding viral antigens that are translated by the vaccinated organism to protein to induce a protective immune response. The RNA components of the RNA-LNP drug products of the three different RNA platforms for clinical investigation are the non-modified uridine containing mRNA (uRNA), nucleoside modified mRNA (modRNA), and self-amplifying mRNA (saRNA), each encoding full-length or parts of the viral S protein of the SARS-CoV-2.

3.1 Description of the drug substance

3.1.1 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 viral S protein of SARS-CoV-2.

Non-modified uridine mRNA (uRNA)

The active principle of the non-modified messenger RNA (uRNA) drug substance is a single-stranded, 5′-capped mRNA that is translated upon entering the cell. In addition to the sequence encoding the SARS-CoV-2 antigen (i.e., open reading frame), 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).

Nucleoside modified mRNA (modRNA)

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

Self-amplifying mRNA (saRNA)

The active principle of the self-amplifying mRNA (saRNA) drug substance is a single-stranded 5'-capped RNA, which self-amplifies upon 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., open reading frame) and the common structural elements in the uRNA and modRNA, the saRNA vector contains an additional open reading frame, which encodes the Venezuelan equine encephalitis (VEE) virus RNA-dependent RNA polymerase replicase and a subgenomic promotor plus conserved sequence elements supporting replication and translation, but no other VEE virus coding sequences.

The physicochemical properties of the RNA drug substances are listed in Table 2.

Table 2: General properties of uRNA, modRNA and saRNA drug substances

Parameter	Value/Description	
	uRNA/modRNA	saRNA
Appearance	Clear, colorless liquid	
Theoretical length	~1200 to 4500 nucleotides*	~10,000 to 13,000 nucleotides*
Concentration	1.70 ± 0.17 mg/mL	
Extinction coefficient at 260 nm	25 L/g × cm	
pH	7.0 ± 1.0	

* Depending on the finally selected antigen.

3.2 Description of the drug product

The drug product is a preservative-free, sterile dispersion of RNA formulated in lipid nanoparticles (LNP) in aqueous cryoprotectant buffer for IM administration. The RNA drug substance is the only active ingredient in the drug product. The product is stored frozen at -80 to -60°C. The drug product is filled at 0.5 ± 0.13 mg/mL in glass vials and closed with stoppers and flip off crimping caps.

The composition of RNA drug products for use in the planned clinical trials and the function of the respective components are given in Table 3. The LNP composition is the same for all four BNT162 vaccine candidates.

Table 3: Composition of drug products

Component	Quality standard	Function
Drug substance	In-house	Active
ALC-0315 [1]	In-house	Functional lipid
ALC-0159 [2]	In-house	Functional lipid
DSPC [3]	In-house	Structural lipid
Cholesterol	Ph. Eur.	Structural lipid
Sucrose	NF/Ph. Eur.	Cryoprotectant
NaCl	USP/Ph. Eur.	Buffer
KCl	USP/Ph. Eur.	Buffer
Na_2HPO_4	USP/Ph. Eur.	Buffer
KH_2PO_4	NF/Ph. Eur.	Buffer
Water for injection	Ph. Eur.	Solvent/Vehicle

[1] ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
[2] ALC-0159 = 2-[(polyethylene glycol)-2000]-*N,N*-ditetradecylacetamide
[3] DSPC = 1,2-distearoyl-*sn*-glycero-3-phosphocholine
q.s. = quantum satis (as much as may suffice)

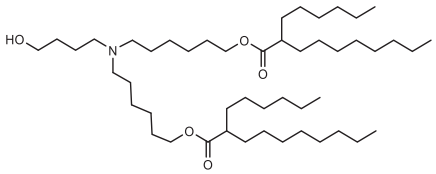
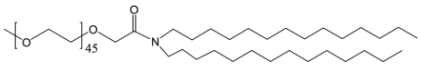
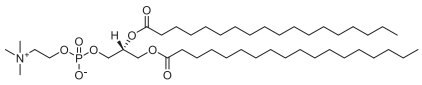
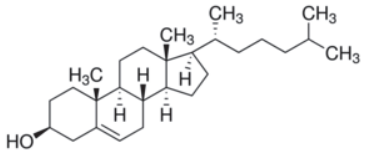
3.2.1 Description of the excipients

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

The drug product contains the two functional lipids ALC-0315 and ALC-01592 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 4.

Table 4: 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 (not applicable)	766	$C_{48}H_{95}NO_5$	Liquid (oil) -20ºC	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) 
ALC-0159 (1849616-42-7)	~2400-2600	$C_{30}H_{60}NO(C_2H_4O)_nCH_3$ n=45-50	Solid -20ºC	2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide 
DSPC (816-94-4)	790	$C_{44}H_{88}NO_8P$	Solid -20ºC	1,2-Distearoyl-*sn*-glycero-3-phosphocholine 
Cholesterol (57-88-5)	387	$C_{27}H_{46}O$	Solid -20ºC	

CAS = Chemical Abstracts Service; DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine.

3.3 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.

3.4 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., uRNA (product code BNT162a1), modRNA (product code BNT162b1 + BNT162b2), saRNA (product code BNT162c2).
IMP administration route:	Solution for IM injection.
Dosage frequency:	The BNT162 vaccines will be administered either using single dose or prime/boost regimens.

3.5 Storage and handling of the IMP

The drug product is a supplied as sterile dispersion of RNA formulated in LNP in an aqueous cryoprotectant buffer for IM administration. Prior to injection, the RNA-LNP products are diluted with isotonic NaCl solution (0.9%) to the intended concentration according to the Pharmacy Manual and administered to the trial subject.

Due to the pandemic urgency, details on reconstitutions and application scheme at the hospital site are currently under development. In-use as well as drug product stability studies have been started, details are provided in the Investigational Medicinal Product Dossier (IMPD) and/or relevant Investigational New Drug (IND) sections.

4 NON-CLINICAL STUDIES

RNA vaccines have shown great potential in generating immune responses in animal models and confer protection against various viruses such as Zika, HIV, and Influenza (Vogel et al. 2018; Moyo et al. 2018; Pardi et al. 2017). Unpublished immunogenicity data from RNA based vaccines against other viruses such as Ebola, Marburg, and Lassa virus indicate that the range of applications for anti-viral RNA vaccines is broad (data on file).

In the planned clinical trials, four BNT162 vaccine candidates based on three RNA platforms will be evaluated (for details, see Section 2.3), i.e., BNT162a1, BNT162b1, BNT162b2, and BNT162c2.

The primary pharmacology of the BNT162 vaccines was evaluated in a range of non-clinical pharmacology studies *in vitro* and *in vivo*. Expression of RNA-encoded antigens, the secreted, trimerized receptor binding domain (RBD) variant ("V5") and the P2 mutant, "heads up," prefusion stabilized full-length spike (S) protein (P2 S, "V8/V9"), was studied *in vitro*. The two versions V8 and V9 encode for the same antigen with the identical amino acid sequence, but differ in the nucleotide coding sequence.

In immunogenicity studies of the BNT162 vaccine candidates, antigen binding immunoglobulin G (IgG) responses are detected by an enzyme-linked immunosorbent assay (ELISA).

Functional antibody responses to the vaccine candidates are detected by a pseudovirus-based neutralization assay (pVNT). The pVNT uses a vesicular stomatitis virus (VSV) vector that expresses a fluorescent marker and lacks the VSV G glycoprotein. The pseudotype virus instead bears the SARS-CoV-2 S protein, which mediates cell entry. Therefore, the pseudovirus can be inactivated by neutralizing antibodies that bind SARS-CoV-2 S.

In vivo studies were performed to benchmark different vaccine antigens (all derived from SARS-CoV-2 S) and to provide proof-of-concept, i.e., to demonstrate that BNT162 vaccines can induce an anti-SARS-CoV-2 immune response and are safe, supporting clinical investigation in humans.

Table 5 summarizes the nomenclature used for the BNT162 vaccine candidates to facilitate the review of the provided non-clinical information.

In some of the experiments described below test items are LNP-formulations of one of the three RNA-platforms in conjunction with:

- a non-SARS-CoV-2 derived viral gene such as Influenza HA (e.g. 4.1.1.2.1)
- one of the two SARS-CoV-2 derived vaccine antigens, but not the one used for the respective clinical candidate (e.g. 4.1.1.2.2, 4.1.1.2.3, 4.1.1.2.4)

The data obtained in those experiments are considered representative for the safety profile of the respective LNP-RNA platform and its capability to induce immune responses and as independent of the encoded antigen and are therefore presented as supportive data.

Table 5: Nomenclature of the pre-clinically evaluated vaccines

Product Code	RNA platform	Antigen	Translated Protein	Variant code
BNT162a1	uRNA	V5	Secreted RBD variant with a C-terminal trimerization domain	RBL063.3
BNT162a2	uRNA	V8	Membrane anchored, mutated full-length S protein	RBL063.1
BNT162b1	modRNA	V5	Secreted RBD variant with a C-terminal trimerization domain	RBP020.3
BNT162b2	modRNA	V8	Membrane anchored, mutated full-length S protein	RBP020.1
BNT162b2	modRNA	V9	Membrane anchored, mutated full-length S protein	RBP020.2
BNT162c1	saRNA	V5	Secreted RBD variant harboring a C-terminal trimerization domain	RBS004.3
BNT162c2	saRNA	V9	Membrane anchored, full-length S protein mutated	RBS004.2

4.1 Non-clinical pharmacology

4.1.1 Primary Pharmacodynamics

Table 6 summarizes the studies on primary pharmacodynamics.

Table 6: Studies on primary pharmacodynamic effects

All study types are based on the analysis of S-specific immune responses elicited in BALB/c mice. Some of these studies are ongoing.

Study number	Study Type	Species / Test System	Test Item	Dose [µg]	Results	Cross reference
BNT162 vaccine studies						
R-20-0074	*In vitro* antigen expression and localization	HEK293T cells	BNT162a1 (RBL063.3) BNT162b1 (RBP020.3) BNT162b2 (RBP020.1) BNT162c1 (RBS004.3)	2.5	All tested items expressed the encoded S protein derived antigen.	Section 4.1.1.1
R-20-0040	*In vivo* immunogenicity	Mice BALB/c	BNT162a1 (RBL063.3)	1, 5, 10	Immunogenicity was shown in all tested doses.	Section 4.1.1.3.1
R-20-0042	*In vivo* immunogenicity	Mice BALB/c	BNT162b1 (RBP020.3)	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 4.1.1.3.2
R-20-0085	*In vivo* immunogenicity	Mice BALB/c	BNT162b2 (RBP020.2)	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 4.1.1.3.3
R-20-0053	*In vivo* immunogenicity	Mice BALB/c	BNT162c2 (RBS004.2)	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 4.1.1.2.3
Supportive studies						
R-20-0073	In vivo immunogenicity	Mice BALB/c	modRNA encoding a non-SARS-CoV-2 viral antigen	1	The viral antigen delivered by the LNP-formulated modRNA platform induced a strong ant body immune response and antigen-specific T cell activity.	Section 4.1.1.2
R-20-0052	*In vivo* immunogenicity	Mice BALB/c	RBL063.1	1, 5, 10	Immunogenicity was shown in all tested doses.	Section 4.1.1.2.2
R-20-0041	*In vivo* immunogenicity	Mice BALB/c	RBS004.3	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 4.1.1.2.3
R-20-0054	*In vivo* immunogenicity	Mice BALB/c	BNT162b2 (RBP020.1)	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 4.1.1.2.4
R-20-0053	*In vivo* immunogenicity	Mice BALB/c	RBS004.2	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 4.1.1.3.4
R-20-0072	*In vivo* distribution	Mice BALB/c	modRNA encoding luciferase	2	The surrogate of the BNT162b platform was expressed in mice with distribution in the muscle (injection site) and liver.	Section 4.2.3

n/a = not applicable.

4.1.1.1 *In vitro* expression of BNT162 vaccine RNA-components

To analyze whether RBD variant 5 (V5) and the mutated full length S protein (V8/V9) are robustly translated from the respective RNA drug substances, *in vitro* assays were performed and antigen expression assessed by western blot (Figure 7), or immune-fluorescence analysis (Figure 8).

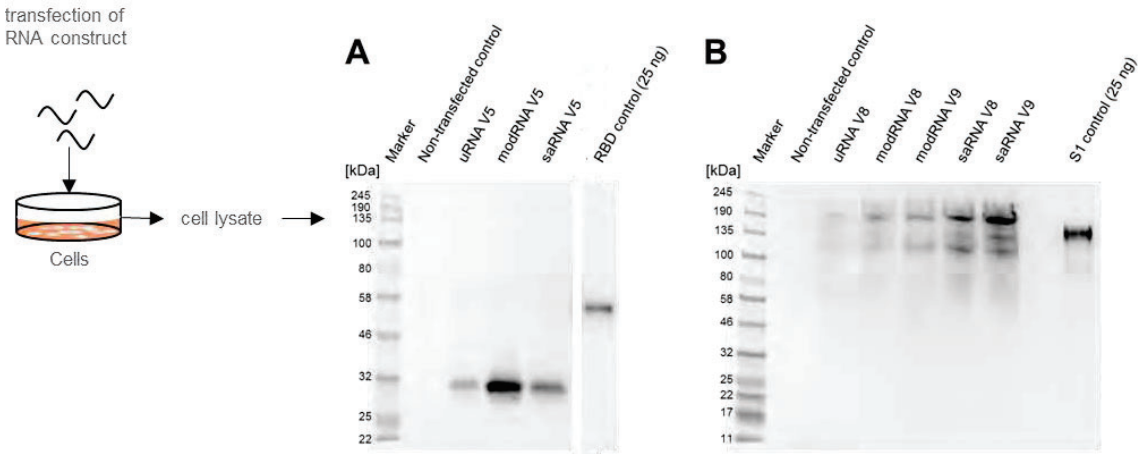


Figure 7: Western Blot analysis for detection of antigen expression

HEK 293T cells were transfected using RiboJuice™ mRNA transfection reagent (Merck Millipore) with 1 µg of the RNA substances (A) uRNA encoding V5, modRNA encoding V5 and saRNA encoding V5. (B) For the construct testing encoding V8/V9 version, uRNA, modRNA and saRNA was tested, and 18 h after transfection, cell lysates were transferred to a sodium dodecyl sulfate (SDS)–polyacrylamide gel electrophoresis (PAGE) system followed by western blot analysis using a polyclonal SARS Coronavirus Spike S1 Subunit Protein Antibody. All samples showed specific antigen expression and specific bands were detected for the V5-encoding constructs at 30 kDa, while the V8 encoded protein runs at an expected size of 140 kDa. Recombinant proteins (RBD [50 ng] control, expected size: 52 kDa / S1 control [25 ng], expected size 102 kDa) were used as assay controls. Note that V5 constructs were separated with a 10% polyacrylamide gel. A recombinant SARS-COV-2 RBD protein (51.5 kDa) was used as a positive control. For V8 and V9 constructs, separation was performed with a 4–15% polyacrylamide gel. A recombinant SARS-CoV-2 S1 Subunit protein (101.7 kDa) was used as a positive control.

RNA constructs encoding the V5 have a predicted size of 29.46 kDa, and for V8 and V9 constructs the size prediction is 141.14 kDa. Western blot analysis confirmed the expression and size of all tested RNAs in cell lysates of HEK293T cells indicating correct expression in a eukaryotic system.

Co-localization of the RBD antigen construct and the full length S protein constructs with an endoplasmic reticulum (ER) marker was shown by immunofluorescence experiments in HEK293T cells expressing BNT162b1 (modRNA encoding V5) and BNT162c2 (saRNA encoding V9), respectively. These results suggest that both, RBD and full length S protein are processed within the ER for surface expression or secretion, which is a prerequisite for increased bioavailability and improved induction of immune response.

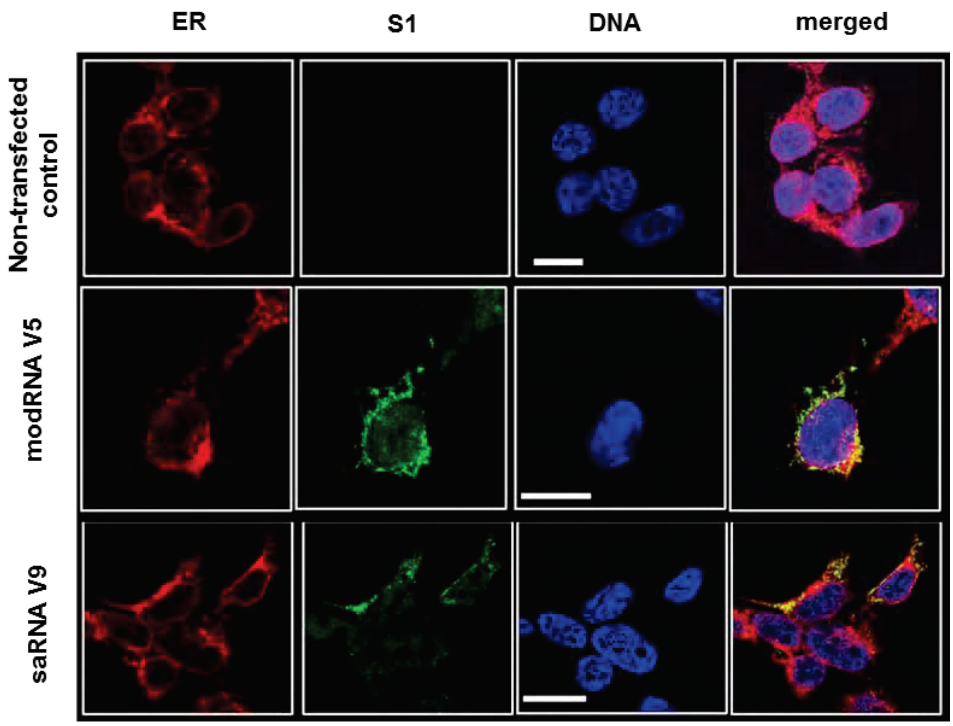


Figure 8: Immunofluorescence staining of cells transfected with modRNA encoding the RBD or saRNA encoding the P2 S-V9

HEK293T cells were transfected with 2.5 µg of modRNA encoding the RBD (V5) or saRNA encoding the membrane anchored, mutated full-length S protein (V9) using RiboJuice™ RNA transfection reagent (Merck Millipore). After 18 h in culture, cells were fixed and stained for the endoplasmic reticulum (ER); Concanavalin A, Alexa Fluor™ 594 conjugate, red), the S1 protein subdomain using a polyclonal that antibody also recognizing the receptor binding domain (RBD), domain (anti-S1 antibody and for Alexa Fluor® 488, green) and deoxyribonucleic acid (DNA) to define the nucleus (Hoechst, blue). The merged colored picture show that the RBD expressed by modRNA V5 and the P2 S expressed by saRNA V9 each co-localize with the ER marker localization (scale: 10 µm). A control using non-transfected cells is shown at the top.

4.1.1.2 *In vivo data* - Supportive immunogenicity studies

The mRNA formats (uRNA, modRNA, saRNA) used for development of BNT162 vaccines have been previously evaluated in studies with other viral antigens as immunogens (Vogel et al. 2018; Pardi et al. 2017; Pardi et al. 2018).

Vaccines based on these mRNA platforms were shown to induce strong antibody responses and prime and expand multifunctional $CD4^+$ and $CD8^+$ T cells. The properties of antigen specific immune responses induced by vaccination with these mRNA formats were studied in several species (see Table 7). Vaccination with nucleoside modified (modRNA) is characterized by the strong expansion of Th1 skewed antigen-specific T follicular helper (Tfh) cells. These cells stimulate and expand germinal center B cells, which results in particularly strong, long-lived, high-affinity antibody responses. The uRNA and saRNA formats are TLR7/8 agonists and exhibit a higher immune stimulatory activity, which

results in type-I interferon release and a strongly Th1 biased $CD4^+$ T cell response as well as strong expansion of cytotoxic T cells (Sahin et al. 2014). Due to self-amplification and prolonged translation, saRNA is able to induce strong $CD4^+$ and $CD8^+$ T cell responses by a prime only administration schedule (Vogel et al. 2018).

Table 7: Characteristics of adaptive immune response for the mRNA formats

	uRNA	modRNA	saRNA
	Source: Pardi et al. 2017, 2018, 2019; Vogel et al. 2018, Kranz et al. 2016	Source: Vogel et al. 2018, Kranz et al. 2016, Pardi et al. 2017, 2018, 2019	Source: Vogel et al. 2018, Moyo et al. 2018
$CD4^+$ T cell response	• Induction of multifunctional strongly Th1+, skewed immune response with induction of IFN-γ^+, TNF-α^+, IL-2^+ $CD4^+$ T cells. • Strong expansion of follicular helper Tfh cells with an IFN-γ+, TfH cells (mouse, human NHP).	• Strong induction of multi-functional Th1 skewed immune response with induction of +, IFN-γ^+, TNF-α^+, IL-2^+ $CD4^+$ T cells. • Strong expansion of follicular helper Tfh cells with an IFN-γ+, TfH cells (mouse, human NHP).	• Expansion of a strongly Th1 skewed immune response with, multifunctional Th1+, IFN-γ+, TNF-α+, IL-2+ CD4+ T cells (mouse).
$CD8^+$ T cell response	• Expansion of multifunctional CD8 cytotoxic, effector and long lived memory T cells with an IFN-γ+, TNF-α+, CD107+ phenotype (mouse), human).	• Expansion of multifunctional cytotoxic, effector and long lived memory CD8 T cells with an IFN-γ+, TNF-α+, CD107+ phenotype (mouse, human)).	• Strong expansion of long-lived effector and central memory CD8+ T cells with an IFN-γ+, TNF-α+, CD107+ phenotype (mouse).
Antibody response	• High-titer, high-affinity, long lived neutralizing antibody responses after prime only/boost (mouse, rats, NHP) • ADCC activity (rabbits). • Mouse IgG1 ~ IgG2a).	• High-titer, high-affinity, long lived neutralizing antibody responses after prime/boost only (mouse, rats), NHP). • ADCC activity (rabbits) • Mouse IgG1 ~ IgG2a.	• High-titer, neutralizing antibody responses after prime only (mouse, rats, pig, NHP). • Mouse IgG2a >>IgG1.

ADCC = Antibody-dependent cellular cytotoxicity; IgG = Immunoglobulin G; IL interleukin; IFN = Interferon; NHP = Non-human primate; Tfh = T follicular helper; TNF = Tumor necrosis factor.

4.1.1.2.1 Immunogenicity using influenza hemagglutinin as a model antigen

In murine influenza virus challenge models, all three mRNA formats (uRNA, modRNA, saRNA) have been shown to confer strong prophylactic vaccine activity.

One study used a modRNA-LNP vaccine that encodes influenza HA. Mice were injected IM with 1 µg on days 0 and 28 with the HA-encoding, formulated RNA. On days 14, 28 and 49, blood samples were drawn and were then tested for antibody and cellular responses to flu HA. The analysis showed a high serum antibody response, demonstrated by very high levels of antigen-specific IgG in serum and high influenza virus neutralization titers (Figure 9). Moreover, strong Th1 $CD4^+$ and $CD8^+$ T cell responses (Figure 10) were induced by the modRNA vaccine.

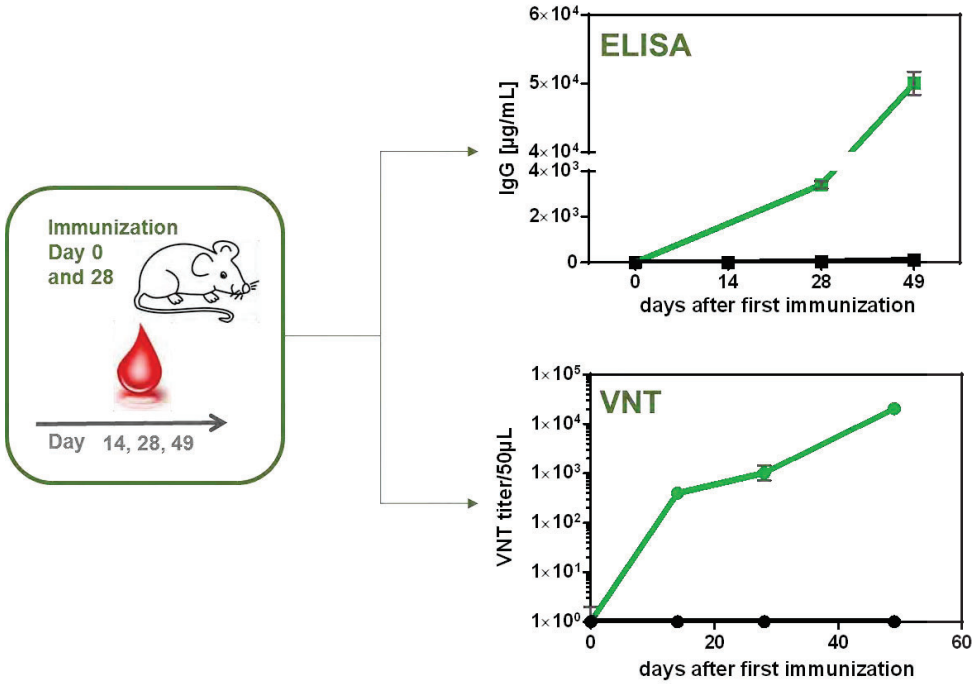


Figure 9: Antibody response elicited by influenza HA using LNP-formulated modRNA

BALB/c mice were immunized twice IM with 1 µg of the vaccine candidate. HA-specific IgG was measured by ELISA. The functionality of the antibodies was measured by influenza virus neutralization.

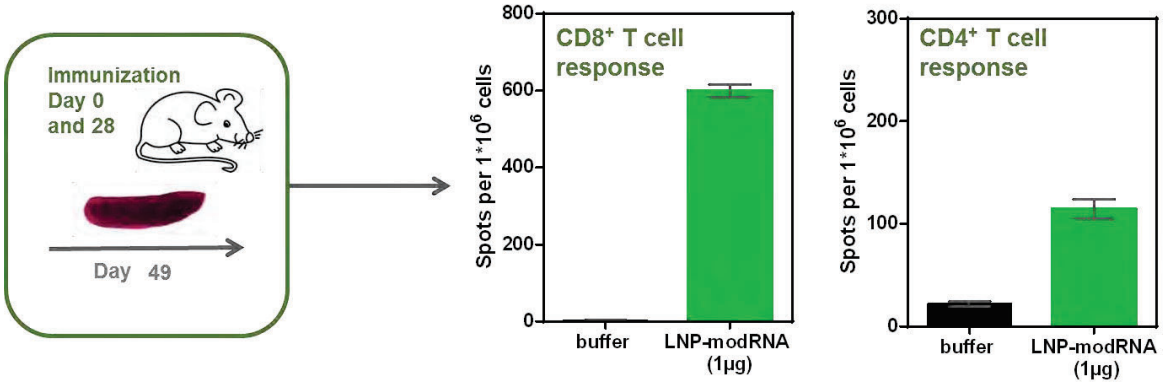


Figure 10: T cell response against influenza HA using the LNP-formulated modRNA platform

BALB/c mice were immunized IM with 1 µg of the vaccine candidate, twice. The T cell response was analyzed using antigen specific peptides to stimulate T cells recovered from the spleen. Interferon (IFN)γ release was measured after peptide stimulation using an ELISpot assay.

Treatment with the LNP-formulated modRNA induced a strong immune response across the observation period of 49 d after one immunization, and a second immunization strongly boosted the anti-HA IgG antibody generation (Figure 9).

Similar to the antibody response, the LNP-formulated modRNA encoding for HA induced a high T-cell response (Figure 10).

Various other immunogenicity studies in mice have documented the induction of neutralizing antibodies and antigen-specific Th1 type T cell responses with uRNA and saRNA vaccines encoding influenza HA (Vogel et al. 2018).

4.1.1.2.2 Immunogenicity study of the LNP-formulated uRNA encoding P2 S-V8 (RBL063.1/BNT162a2)

The potency of the LNP-formulated uRNA coding for P2 S-V8 (RBL063.1) was tested in mice. Of note, in the clinical trial uRNA encoding the RBD alone (BNT162a1) but not P2 S-V8 is used.

Animals were immunized, weekly bled and at day 28 sacrificed for the final bleeding time point and IFNγ-release T cell analysis via ELISpot. The ELISA data show an early, dose-dependent IgG response recognizing S1 and the RBD (The potency of the LNP-formulated uRNA coding for P2 S-V8 (BNT162a2; RBL063.1) was tested in mice (for details, see the figure legend for Figure 11). The final analysis is pending.

BALB/c mice were immunized IM once as outlined in Table 8. At day 28, animals were sacrificed for the final bleeding time point and IFNγ-release T cell analysis via ELISpot. The final analysis is pending.

The ELISA data show an early, dose-dependent IgG response recognizing SARS-CoV-2 S1 Subunit protein (S1) and the RBD (Figure 11). Sera obtained 14, 21 and 28 d after immunization show dose-dependent SARS-CoV-2 pseudovirus neutralization (Figure 12). The study is ongoing.

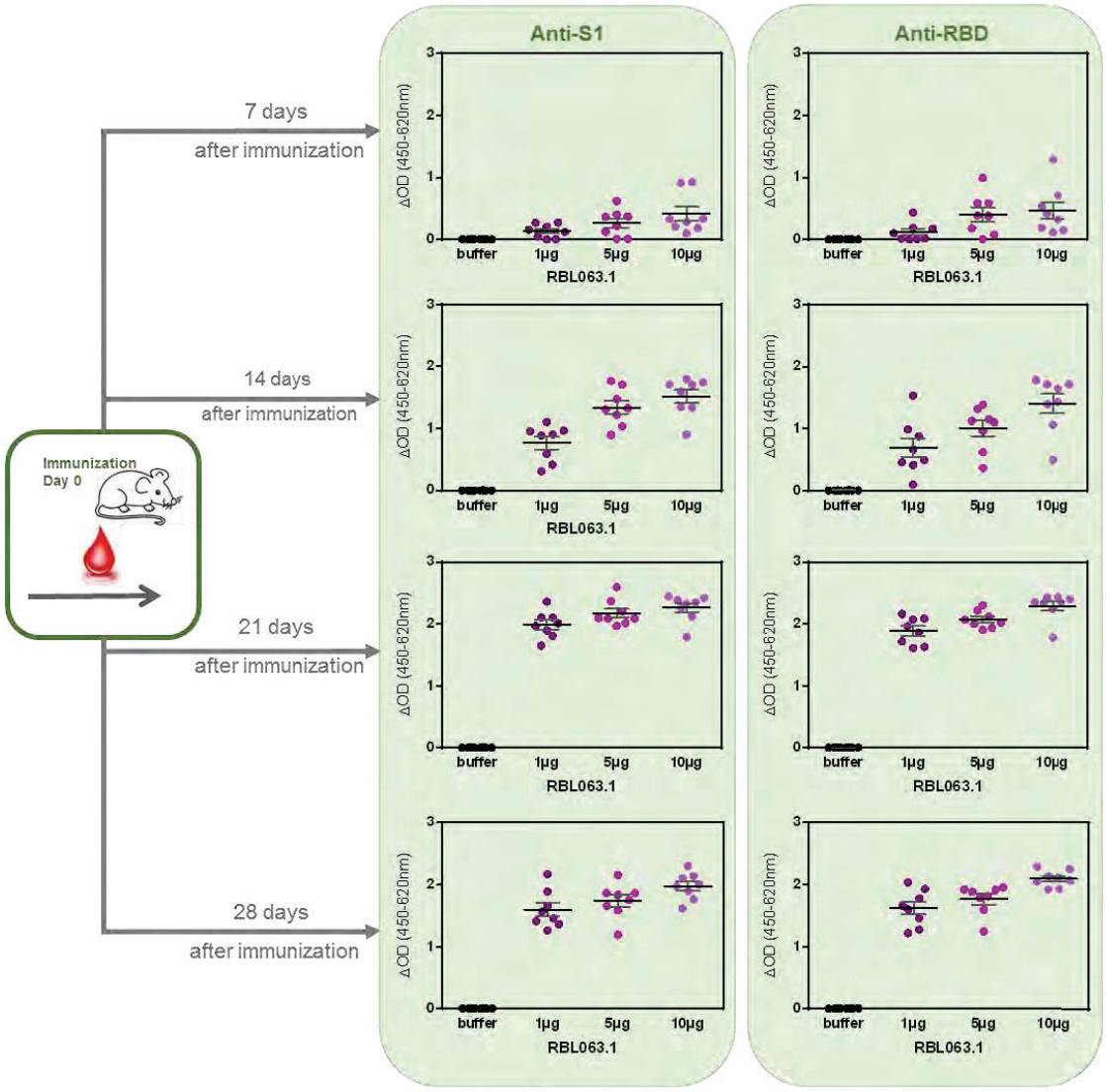


Figure 11: Anti-S IgG response 7, 14, 21 and 28 d after immunization with RBL063.1

BALB/c mice were immunized IM once with 1, 5 or 10 µg of LNP-formulated RBL063.1. On 7, 14, 21 and 28 d after immunization, animals were bled, and the serum samples were analyzed for anti-S1 (left) and anti-RBD (right) antigen-specific IgG by ELISA. For day 7 (1:100), day 14 (1:100), day 21 (1:300) and d28 (1:900) results from different serum dilutions are depicted on the graphs. One point in the graph stands for one mouse. Every mouse serum was measured in duplicate. Group size n=8. Mean ± SEM are depicted by the horizontal lines with whiskers for each group.

Antibody concentrations in the serum samples were calculated for the individual sampling days and the kinetics of IgGs against S1 and RBD proteins is shown in Figure 12. Antibody concentrations against S1 (Figure 12A) and RBD (Figure 12B) increased in a dose-dependent manner over time.

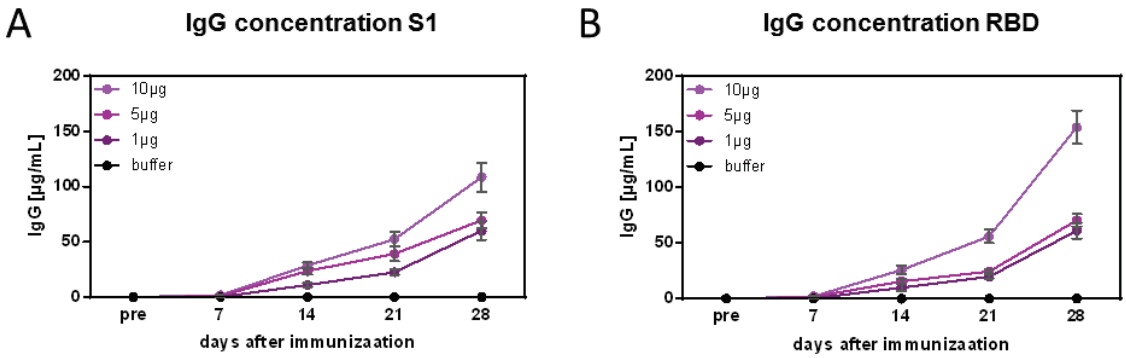


Figure 12: Kinetics of the antibody concentration against the viral antigen

For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean antibody concentrations are shown (±SEM).

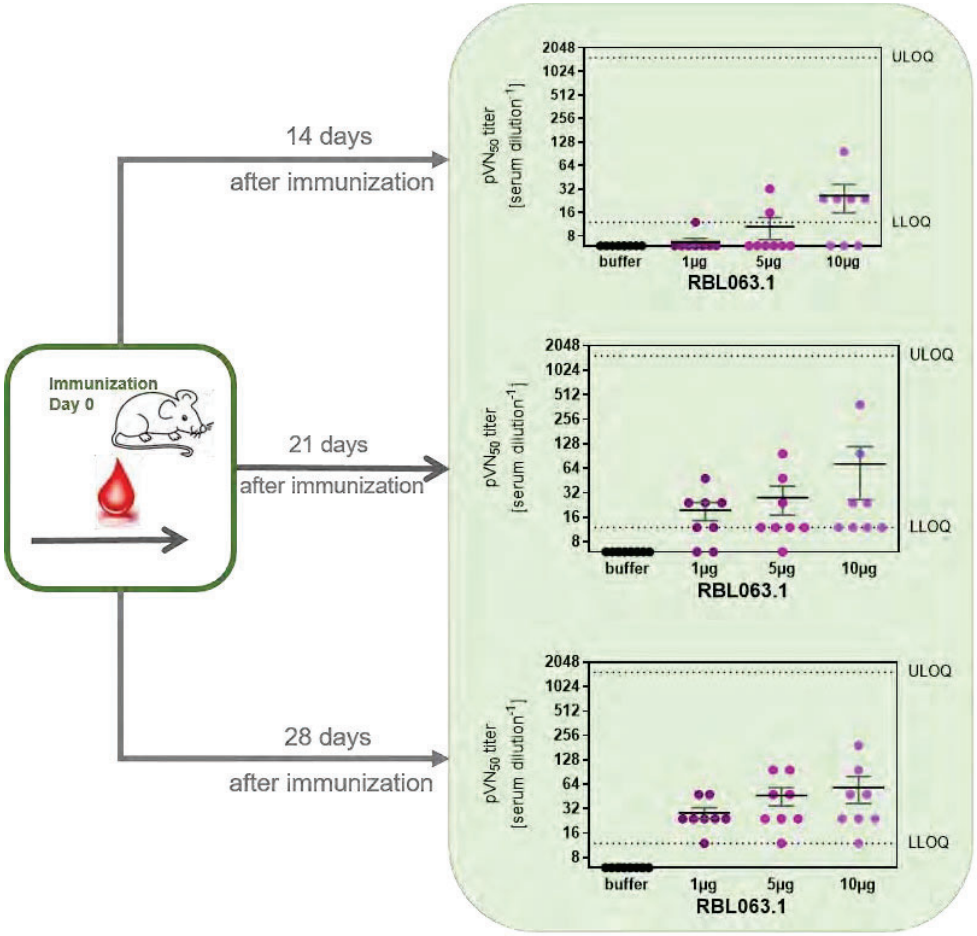


Figure 13: Neutralization of SARS CoV-2 pseudovirus 14, 21 and 28 d after immunization with RBL063.1

BALB/c mice were immunized IM once with 1, 5 or 10 µg of LNP-formulated RBL063.1. On 14, 21 and 28 d after immunization, animals were bled, and the sera were tested for SARS CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

4.1.1.2.3 Immunogenicity study of the LNP-formulated saRNA encoding the receptor binding domain (RBS004.3)

To dissect the potency of the LNP-formulated saRNA, BALB/c mice were immunized IM with RBL004.3-encoding for the viral RBD once as outlined in Table 8 and the antibody immune response will be analyzed.

This study is ongoing. At this time point, ELISA data 7, 14 and 21 d after the immunization are available that show an early, dose-dependent immune activation against the

S1 protein and the receptor binding domain (Figure 14). Furthermore, pVNT elicits neutralizing antibodies already 14 d after immunization (Figure 15).

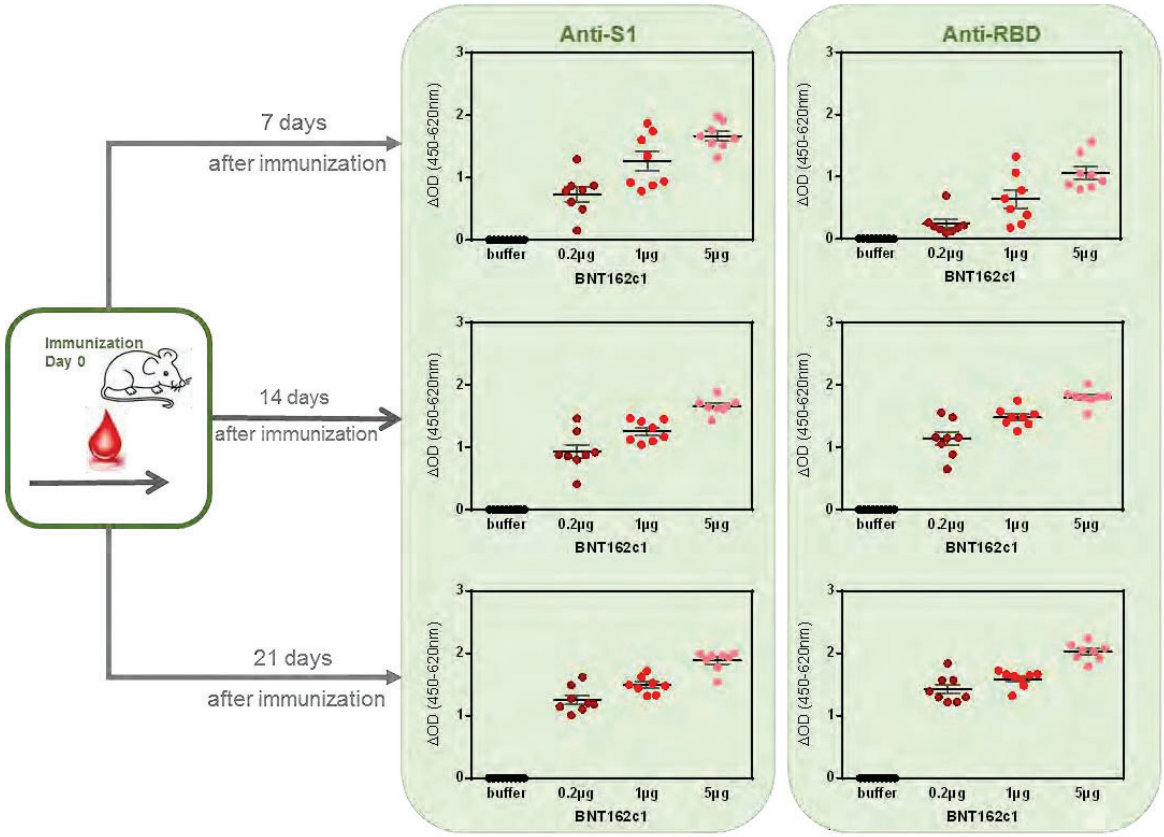


Figure 14: Anti-S protein IgG response 7, 14 and 21 d after immunization with RBS004.3

BALB/c mice were immunized IM once with 0.2, 1 or 5µg of LNP-formulated RBS004.3. 7, 14 and 21 d after immunization, animals were bled and the serum samples were analyzed for total amount of anti-S1 (left) and anti-RBD (right) antigen specific immunoglobulin G (IgG) measured via ELISA. For day 7 (1:100), day 14 (1:300) and days 21 (1:900) different serum dilution were included in the graph. One point in the graph stands for one mouse, every mouse sample was measured in duplicates (group size n=8; mean ± SEM is included for the groups).

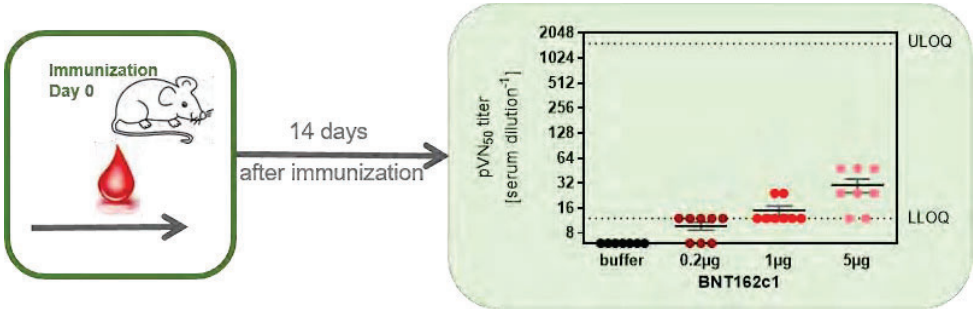


Figure 15: Neutralization of SARS CoV-2 pseudovirus 14 d after immunization with RBS004.3

BALB/c mice were immunized IM once with 0.2, 1 or 5 µg of LNP-formulated RBS004.3. On 14 d after immunization, animals were bled and the sera were tested for SARS CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

4.1.1.2.4 Immunogenicity study of the LNP-formulated modRNA encoding the viral S protein-V8 (RBP020.1)

To dissect the potency of the LNP-formulated modRNA a version coding for the viral S protein-V8 (RBP020.1) was investigated. For this purpose, a dose titration study in BALB/c mice was initiated where the immune response will be analyzed focusing on the antibody immune response.

This study is ongoing. At this time point, ELISA data 7 and 14 d after the first immunization are available that show an early, dose-dependent immune activation against the S1 protein and the RBD (Figure 16).

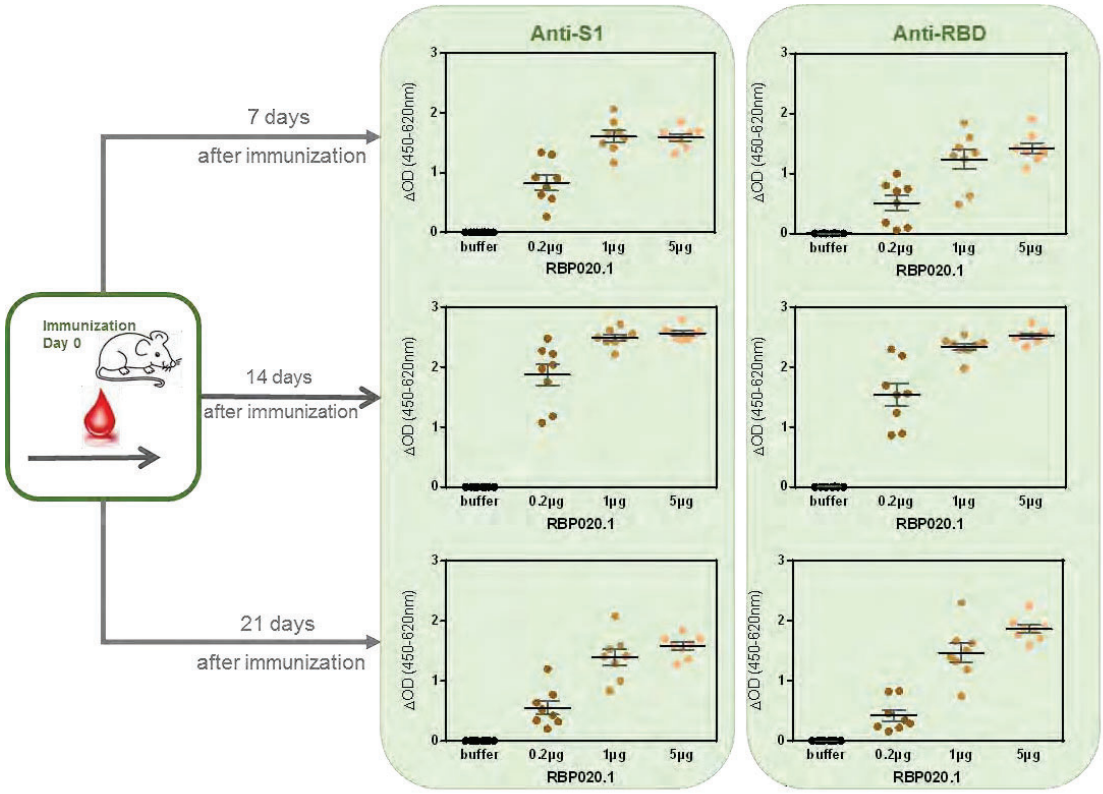


Figure 16: Anti-S protein IgG response 7, 14 and 21 d after immunization with RBP020.1

BALB/c mice were immunized IM once with 0.2, 1 or 5 µg of LNP-formulated modRNA RBP020.1. 7, 14 and 21 d after immunization, animals were bled and the serum samples were analyzed for total amount of anti-S1 (left) and anti-RBD (right) antigen specific immunoglobulin G (IgG) measured via ELISA. For day 7 (1:100), day 14 (1:300) and day 21 (1:1100) different serum dilution were included in the graph. One point in the graph stands for one mouse, every mouse sample was measured in duplicates (group size n=8; mean ± SEM is included for the groups).

Currently SARS-CoV-2 pVNT data are available for day 14 after immunization, which showed dose-dependent pseudovirus neutralization activity of the serum samples (Figure 17). The study is ongoing.

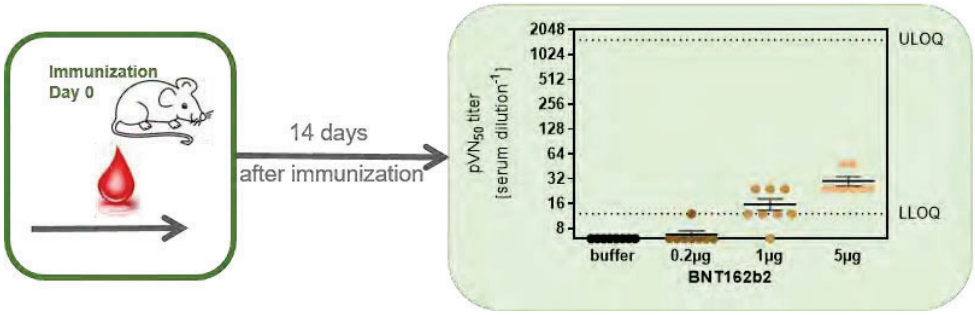


Figure 17: Neutralization of SARS CoV-2 pseudovirus 14 d after immunization with RBP020.1

BALB/c mice were immunized IM once with 0.2, 1 or 5 µg of LNP-formulated modRNA RBP020.1. On 14 d after immunization, animals were bled and the sera were tested for SARS CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

4.1.1.3 *In vivo* immunogenicity studies for BNT162 vaccine candidates

The immunogenicity studies and their analysis are currently ongoing for all BNT162 vaccines including BNT162a1, BNT162b1, BNT162b2, and BNT162c2. Antibody response data analyzing total IgG but also pseudovirus neutralizing antibody titers from different post-vaccination time points are available for all candidates and show immunogenicity for both S protein antigens, namely the RBD V5 (i.e., BNT162a1, BNT162b1) and the P2 S V9 (i.e., BNT162a1, BNT162b1). Data available at the point of time of completing this IB is reported below and updates will be provided as they become available.

Table 8: Study design

Group no	No of animals	Vaccine dose	Immunization day	Dose volume [µL] / route	Blood collection day	End of in-life phase
1	8	buffer	0	20 / IM	7, 14, 21	28
2	8	Low	0	20 / IM	7, 14, 21	28
3	8	Medium	0	20 / IM	7, 14, 21	28
4	8	High	0	20 / IM	7, 14, 21	28

4.1.1.3.1 Immunogenicity study of the BNT162a1 (RBL063.3)

To assess the potency of the LNP-formulated uRNA vaccine candidate BNT162a1, which encodes the RBD V5, BALB/c mice were immunized IM once as outlined in Table 8. ELISA data from sera obtained 7, 14, 21 and 28 d after the immunization show an early, dose-dependent IgG response recognizing S1 and the RBD (Figure 18. Corresponding showed only minimal to absent pseudovirus neutralization activity of the serum samples across all time-points analyzed (Figure 20). However, this might be due to the single

administration of BNT162a1 in mice, since in rats pVNT data showed pronounced pseudovirus neutralization after three weekly immunization rounds (Section 4.1.1.3.5). The mouse study will be repeated with a smaller group.

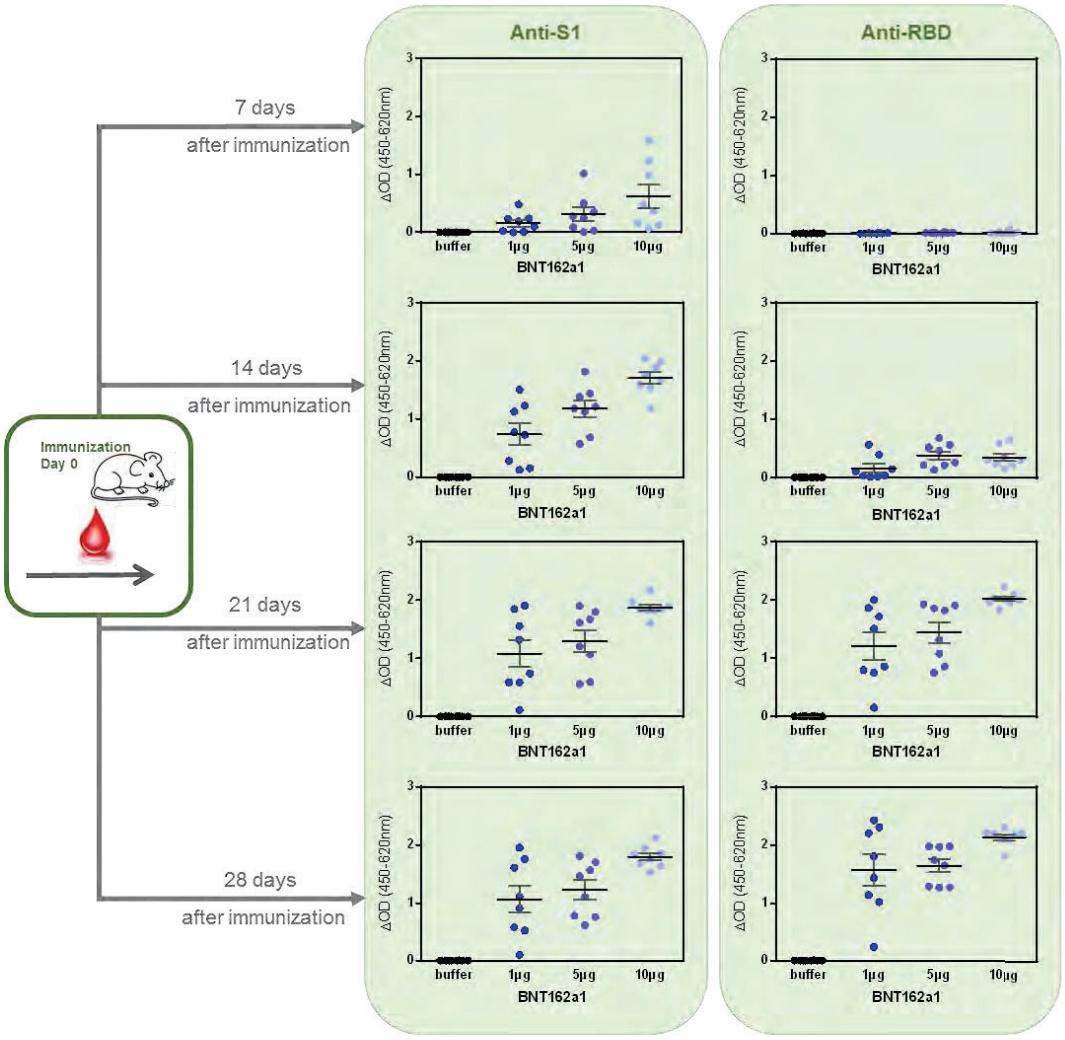


Figure 18: Anti-S protein IgG response 7, 14, 21 and 28 d after immunization with BNT162a1

BALB/c mice were immunized IM once with 1, 5 or 10 µg of LNP-formulated RBL063.3. On 7, 14, 21 and 28 d after immunization, animals were bled, and the sera were analyzed for anti-S1 (left) and anti-RBD (right) antigen-specific IgG by ELISA. On 7, 14, 21 and 28 d after immunization, animals were bled, and the sera were analyzed for anti-S1 (left) and anti-RBD (right) antigen-specific IgG by ELISA. For all time points, values for a serum dilution of 1:100 were included on the graphs. For all time points, values for a serum dilution of 1:100 were included on the graphs. One point in the graph stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is depicted as a horizontal line with whiskers for each groups.

Antibody concentrations in the serum samples were calculated for the individual sampling days and the kinetics of IgGs against S1 and RBD proteins is shown in Figure 19.

Antibody concentrations against S1 (Figure 19A) and RBD (Figure 19B) increased in a dose-dependent manner over time.

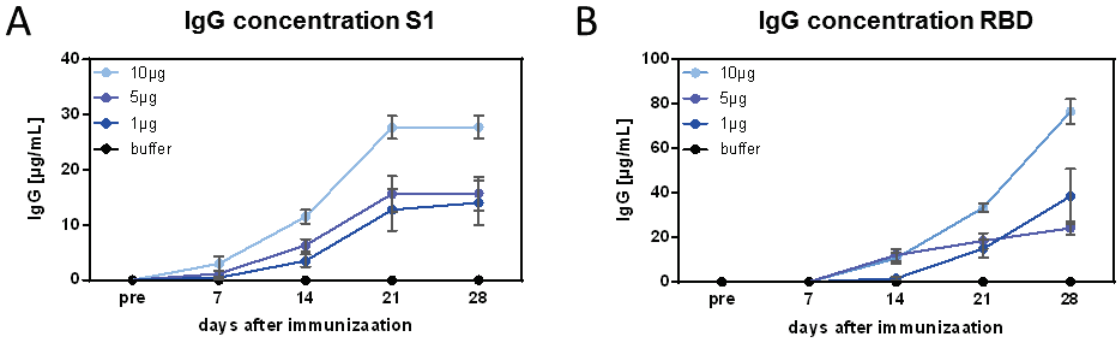


Figure 19: Kinetics of the antibody concentration against the viral antigen

For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean antibody concentrations are shown (±SEM). Note that for the S1 and the RBD, 1mg/mL protein were coated onto a 96well plate. BNT162b2 encodes for the receptor binding domain only. As the RBD has a smaller size than the S1, more antibody binding sites are available within 1 mg/mL of RBD compared to S1 which could explain the higher antibody concentration calculated against RBD.

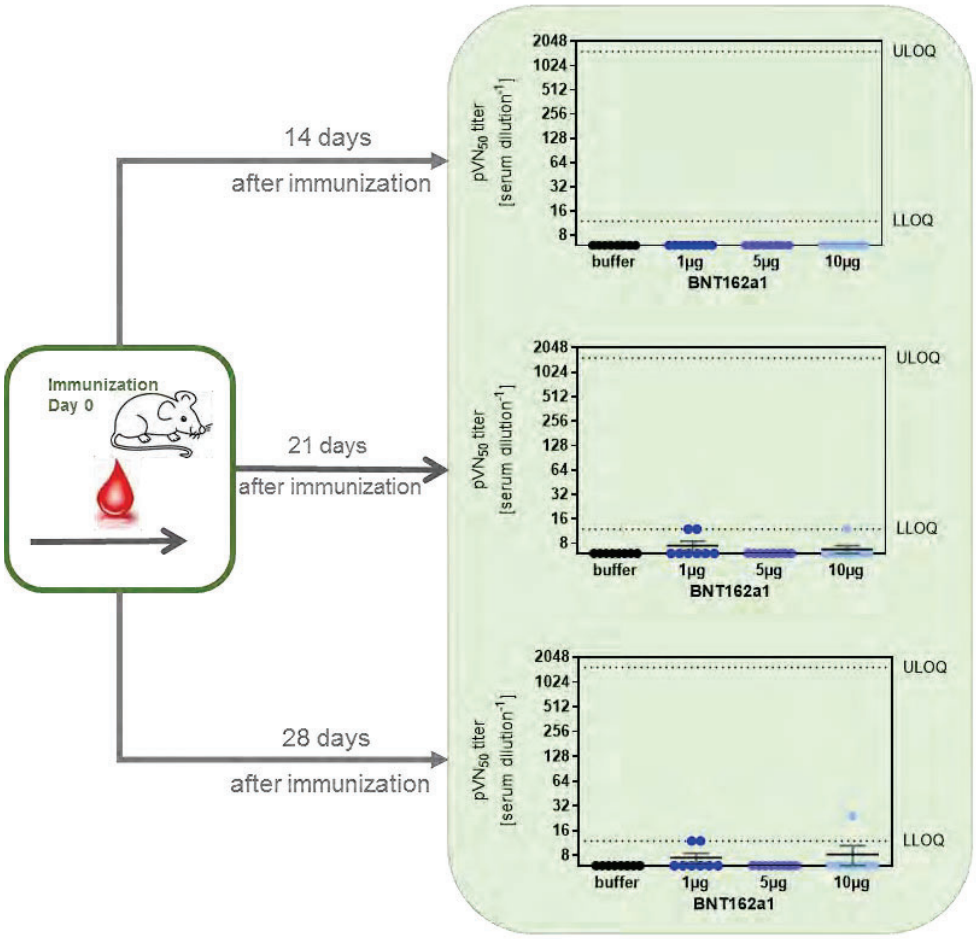


Figure 20: Neutralization of SARS CoV-2 pseudovirus 14, 21 and 28 d after immunization with BNT162a1

BALB/c mice were immunized IM once with 1, 5 or 10 µg of BNT162a1. On 14, 21 and 28 d after immunization, animals were bled, and the sera were tested for SARS CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

4.1.1.3.2 Immunogenicity study of the BNT162b1 (RBP020.3)

To assess the potency of the LNP-formulated modRNA vaccine candidate BNT162b1, which encodes RBD V5, BALB/c mice were immunized IM once as outlined in Table 8. To assess the potency of the LNP-formulated modRNA vaccine candidate BNT162b1, which encodes RBD, BALB/c mice were immunized IM once as outlined in Table 8. ELISA data from sera obtained 7, 14 and 21 d after immunization show an early, dose-dependent IgG response recognizing S1 and the RBD.

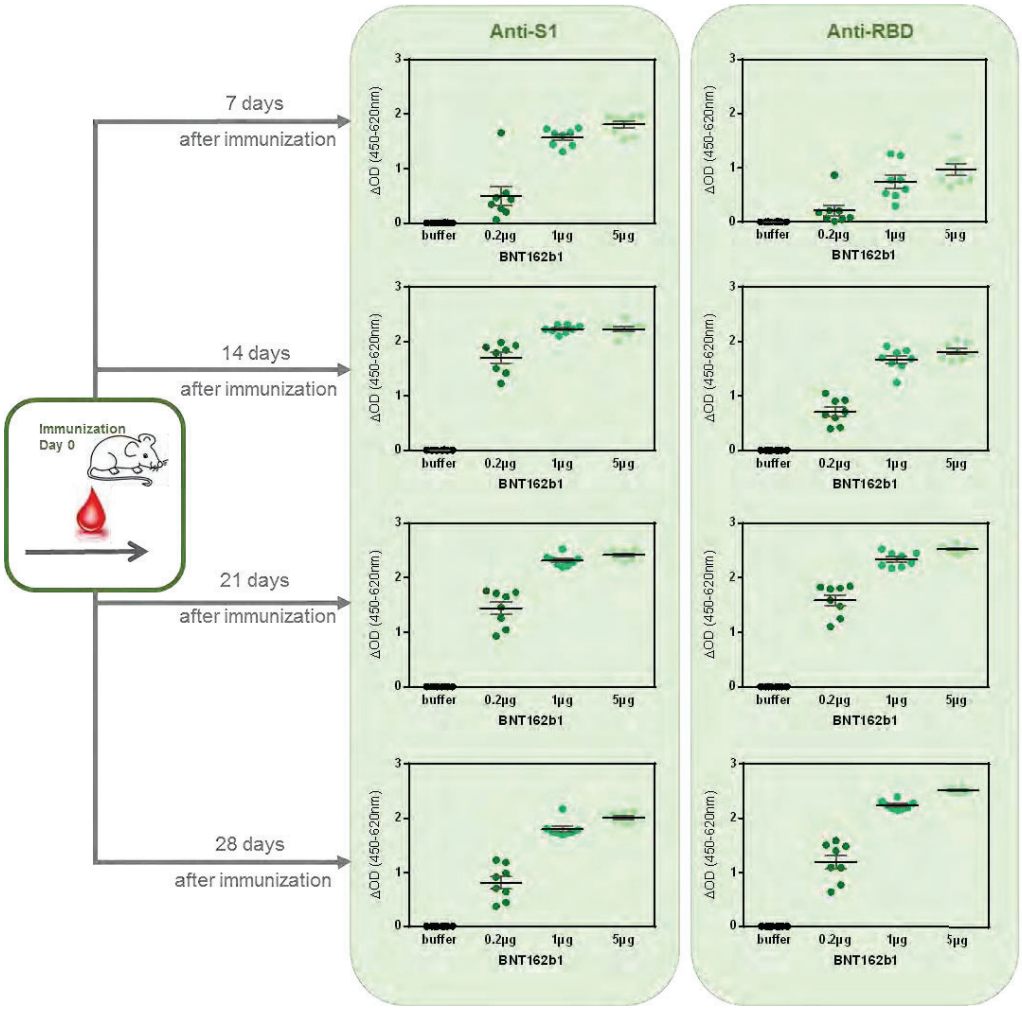


Figure 21: Anti-S IgG response 7, 14, 21 and 28 d after immunization with BNT162b1

BALB/c mice were immunized IM once with 0.2, 1 or 5 µg of LNP-formulated modRNA vaccine candidate encoding the RBD (BNT162b1). On 7, 14, 21 and 28 d after immunization, animals were bled, and the sera were analyzed for anti-S1 (left) and anti-RBD (right) antigen-specific IgG by ELISA. For day 7 (1:100), day 14 (1:300), day 21 (1:900) and day 28 (1:2700), data from different serum dilutions were included on the graphs. One point on the graphs stands for one mouse. Every serum sample was measured in duplicate. Group size n=8. Mean ± SEM is depicted by a horizontal line with whiskers for each group.

Antibody concentrations in the serum samples were calculated for the individual sampling days and the kinetics of IgGs against S1 and RBD proteins is shown in Figure 22. Antibody concentrations against S1 (Figure 22A) and RBD (Figure 22B) increased in a dose-dependent manner over time.

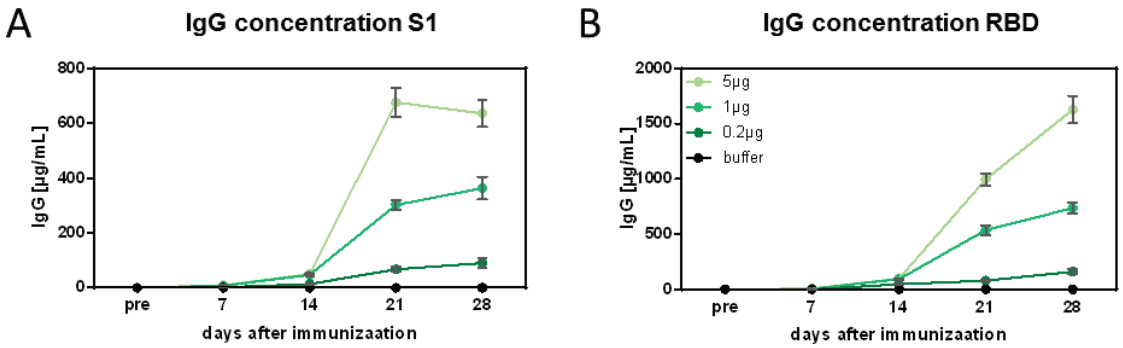


Figure 22: Kinetics of the antibody concentration against the viral antigen

For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean antibody concentrations are shown (±SEM). Note that for the S1 and the RBD, 1mg/mL protein were coated onto a 96well plate. BNT162b2 encodes for the receptor binding domain only. As the RBD has a smaller size than the S1, more antibody binding sites are available within 1 mg/mL of RBD compared to S1 which could explain the higher antibody concentration calculated against RBD.

Sera obtained 14, 21, and 28 d after immunization show high SARS-CoV-2 pseudovirus neutralization, especially sera from mice immunized with 1 or 5 µg BNT162b1 and correlating with the strong increase of IgG antibody titers (Figure 23).

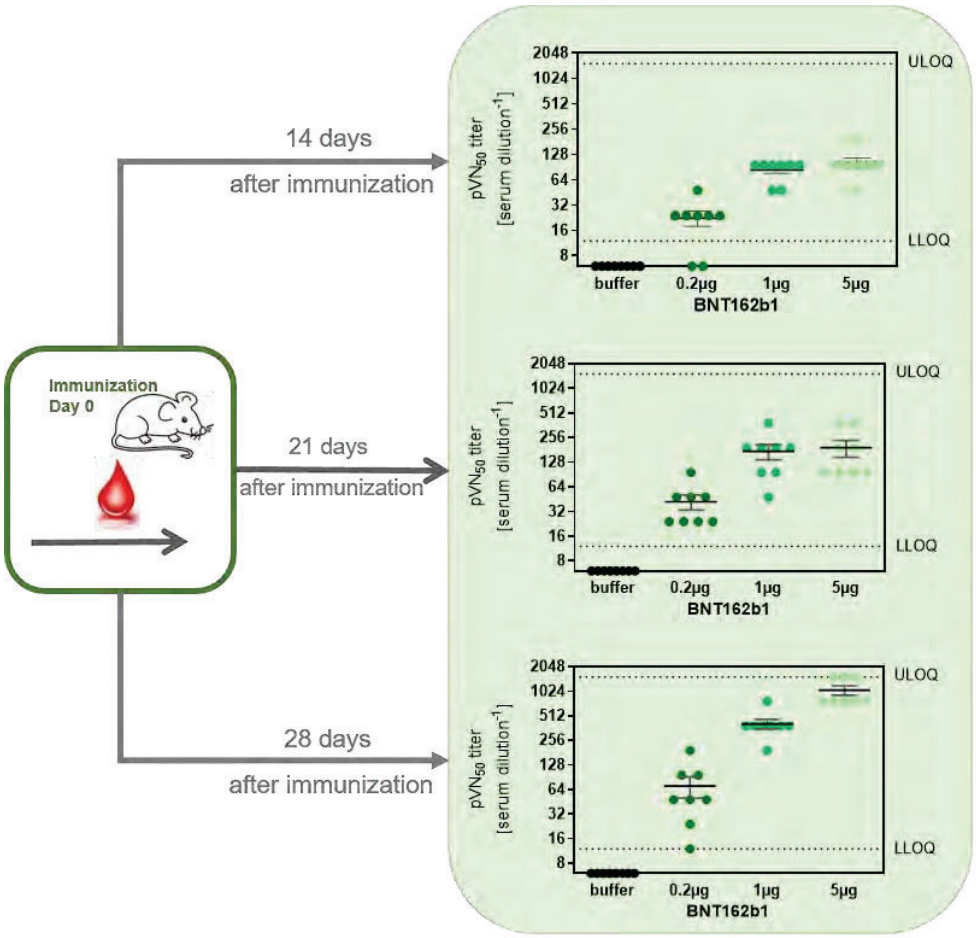


Figure 23: Neutralization of SARS CoV-2 pseudovirus 14, 21 and 28 d after immunization with BNT162b1

BALB/c mice were immunized IM once with 0.2, 1 or 5 µg of BNT162b1. On 14, 21 and 28 d after immunization, animals were bled, and the sera were tested for SARS CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

4.1.1.3.3 Immunogenicity study of BNT162b2 (RBP020.2)

To dissect the potency of BNT162b2, the immunogenicity vaccine candidate was investigated. For this purpose, a dose titration study in BALB/c mice was initiated in which the immune response will be analyzed focusing on the antibody immune response.

This study is ongoing. At this time point, ELISA data 7 and 14 21 d after the first immunization are available that show an early, dose-dependent immune activation against the S1 protein and the receptor binding domain (Figure 24).

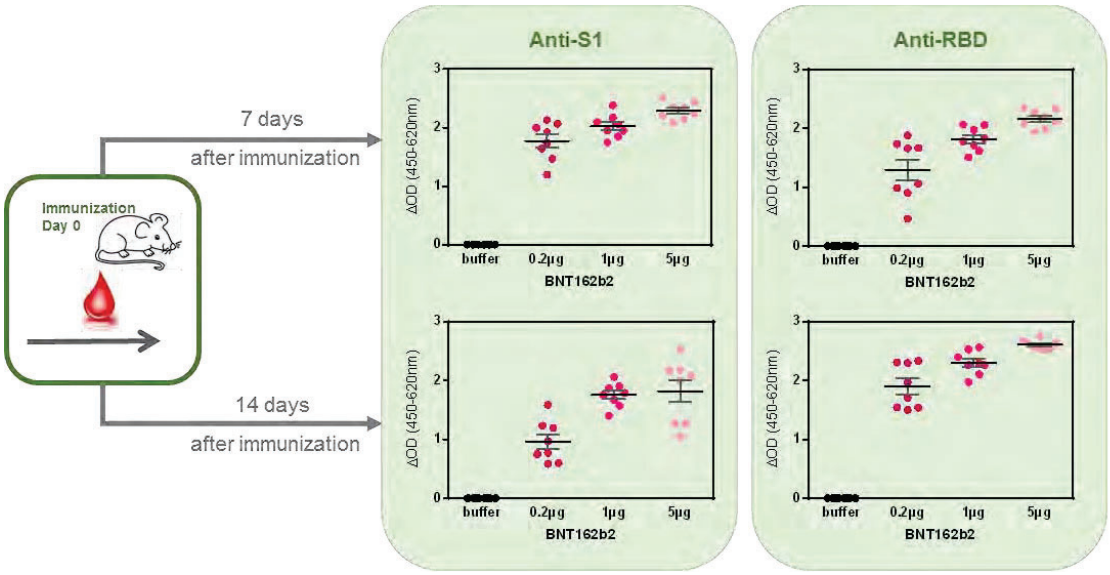


Figure 24: Anti-S IgG response 7 and 14 d after immunization with BNT162b2

BALB/c mice were immunized IM once with 0.2, 1 or 5 µg of LNP-formulated modRNA vaccine candidate encoding the P2 S-V9 (BNT162b2). On 7 and 14 d after immunization, animals were bled, and the sera were analyzed for anti-S1 (left) and anti-RBD (right) antigen-specific IgG by ELISA. For day 7 (1:300) and day 14 (1:900), data from different serum dilutions were included on the graphs. One point on the graphs stands for one mouse. Every serum sample was measured in duplicate. Group size n=8. Mean ± SEM is depicted by a horizontal line with whiskers for each group.

4.1.1.3.4 Immunogenicity study of BNT162c2 (RBS004.2)

To dissect the potency of the saRNA vaccine candidate encoding the P2 S-V9 (BNT162c2), BALB/c mice were immunized IM once as outlined in Table 8. The mice will be bled and immunogenicity of the RNA vaccine will be investigated by focusing on the antibody immune response. The sera are being tested for antigen binding and SARS CoV-2 pseudovirus neutralization. Next to an ELISA analysis, the sera are being tested for antigen binding and SARS CoV-2 pseudovirus neutralization. This study is ongoing.

At this time point, ELISA data 7 and 14 d after the immunization are available that show an early, dose-dependent immune activation against the S1 protein and the receptor binding domain (Figure 25). Furthermore, pVNT elicits neutralizing antibodies already 14 d after immunization in all animals including all serum samples from mice immunized with 0.2 µg of BNT162c2 only (Figure 26).

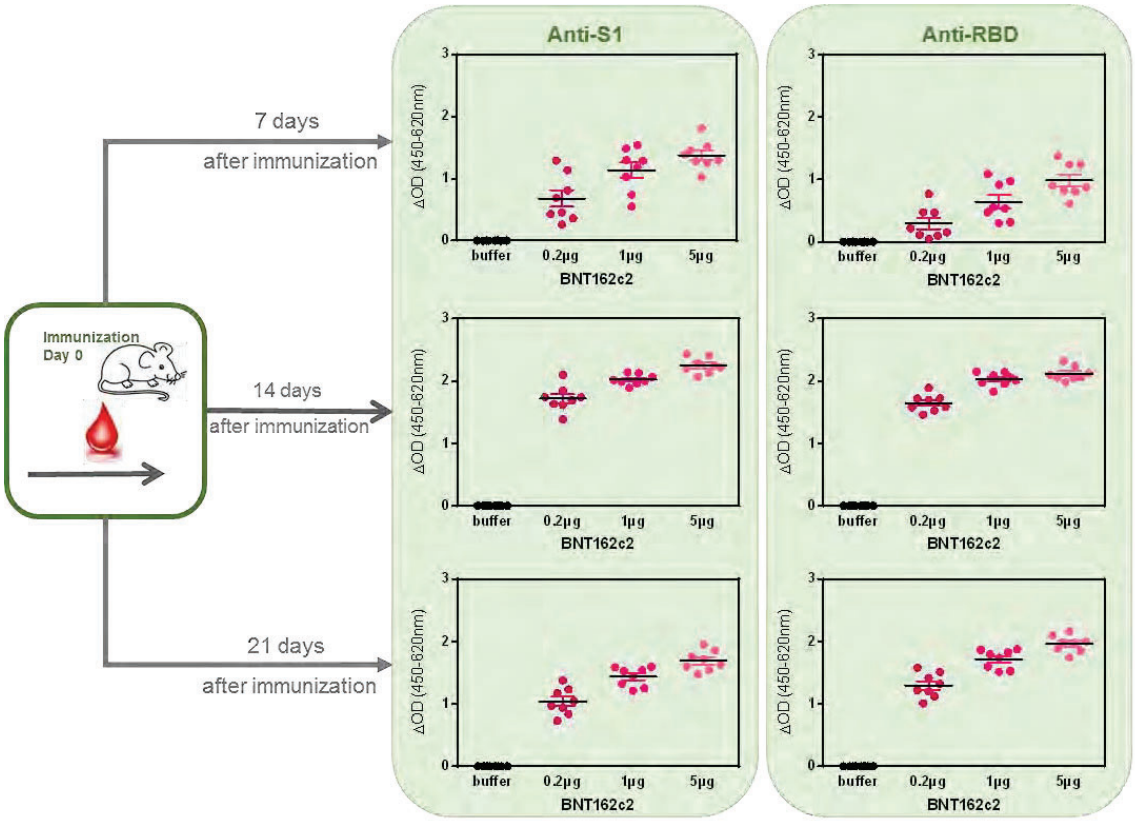


Figure 25: Anti-S protein IgG response 7, 14 and 121 d after immunization with BNT162c2

BALB/c mice were immunized IM once with 0.2, 1 or 5 µg of LNP-formulated saRNA vaccine candidate encoding the P2 S-V9 (BNT162c2). 7, 14 and 21 d after immunization, animals were bled and the serum samples were analyzed for total amount of anti-S1 (left) and anti-RBD (right) antigen specific immunoglobulin G (IgG) measured via ELISA. For day 7 (1:100), day 14 (1:300) and day 21 (1:900) different serum dilutions were included in the graph. One point in the graph stands for one mouse, every mouse sample was measured in duplicates (group size n=8; mean ± SEM is included for the groups).

SARS-CoV-2 pVNT data are available for days 14 and 21 after immunization, which showed potent dose-dependent pseudovirus neutralization activity of the serum samples (Figure 26).

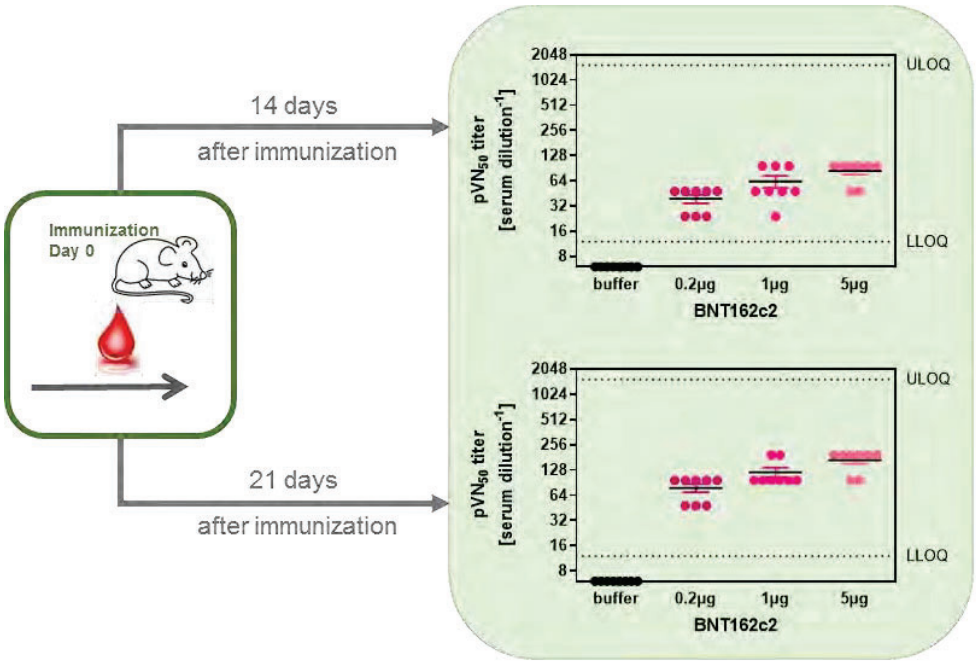


Figure 26: Neutralization of SARS CoV-2 pseudovirus 14, and 21 d after immunization with BNT162c2

BALB/c mice were immunized IM once with 0.2, 1 or 5 µg of BNt162c2. On 14, and 21 d after immunization, animals were bled, and the sera were tested for SARS CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

4.1.1.3.5 Immunogenicity of BNT162 vaccine candidates in rats after repeated dosing

In the GLP compliant repeat-dose toxicity study in rats (section 4.3.2, Study No. 38166), the immunogenicity of the administered RNA vaccines BNT162a1, BNT162b1, BNT162b2, and BNT162c1 was investigated. Serum samples were collected from repeatedly dosed main study animals at day 10 (BNT162c1) or at day 17 after first immunization (BNT162a1, BNT162b1, and BNT162b2) and the elicited antibody immune response analyzed by S1 domain (Figure 27) and RBD sub-domain (Figure 28) specific ELISA, as well as SARS-CoV2-S pseudovirus neutralization assay (Figure 29).

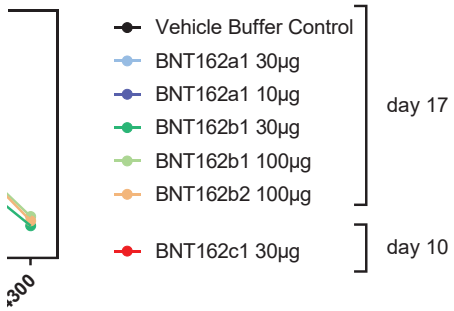


Figure 27: ELISA screening analysis to detect antibody responses directed against the recombinant SARS-CoV-2 spike protein S1 domain

Wistar Han rats were immunized IM with three weekly injections of 10 or 30 µg BNT162a1, 30 or 100 µg BNT162b1, 100 µg BNT162b2, or two weekly injections of 30 µg BNT162c1. On day 10 (BNT162c1) or day 17 (all other cohorts) animals were bled and the sera were tested for total amount of anti-S1 antigen specific immunoglobulin G (IgG) measured via ELISA. Different serum dilutions were tested ranging from 1:100 to 1:24300. One point in the graph stands for the ΔOD group mean value at a particular given serum dilution (group size n=20).

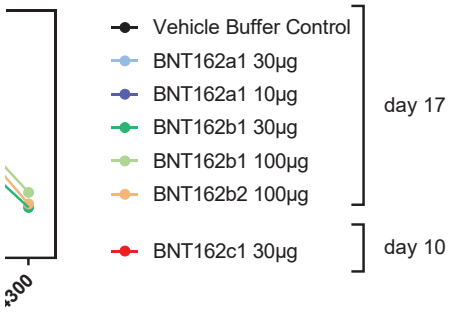


Figure 28: ELISA screening analysis to detect antibody responses directed against the recombinant SARS-CoV-2 spike protein RBD domain

Wistar Han rats were immunized IM with three weekly injections of 10 or 30 µg BNT162a1, 30 or 100 µg BNT162b1, 100 µg BNT162b2, or two weekly injections of 30 µg BNT162c1. On day 10 (BNT162c1) or day 17 (all other cohorts) animals were bled and the sera were tested for total amount of anti-RBD antigen specific immunoglobulin G (IgG) measured via ELISA. Different serum dilutions were tested ranging from 1:100 to 1:24300. One point in the graph stands for the ΔOD group mean value at a particular given serum dilution (group size n=20).

Treatment of rats with each of the BNT162 vaccine candidates resulted in the formation of antibodies of the IgG isotype against the S1 domain as well as the RBD sub-domain of the SARS-CoV2 spike protein (Figure 27 and Figure 28). The analysis showed a weak antibody immune response for BNT162c1 treated animals at day 10, a moderate antibody

immune response for BNT162a1 treated animals at day 17, and a strong antibody immune response for both modRNA based vaccines, BNT162b1 and BNT162b2, at day 17, irrespective of the vaccine antigen used.

Antibody concentrations in the serum samples were calculated for the individual samples and the IgG concentration against S1 and RBD proteins is given in Table 9. Antibody concentrations against S1 and RBD increased in a dose-dependent manner over time only for the modRNA based vaccine BNT162b1. In rats, the lower concentration of BNT162a1 induced a slightly higher IgG concentration against the two antigens in comparison to the 30µg of BNT162a1.

Table 9: IgG antibody concentration against the viral antigen in Wistar Han rats

For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against the S1 protein and RBD. Group mean antibody concentrations are shown (±SEM) that were graphed in Figure 27 and Figure 28. For the individual titer

IgG total [µg/mL]	17 d after first immunization					10 d after first immunization
	BNT162a1 30 µg	BNT162a1 10 µg	BNT162b1 100 µg	BNT162b1 30 µg	BNT162b2 100 µg	BNT162c1 30 µg
Against S1	83.0 ± 13.6	149.8 ± 24.6	1844.2 ± 243.4	1502.9 ± 269.9	1755.9 ± 164.1	19.3 ± 3.7
Against RBD	192.6 ± 35.2	208.3 ± 28.9	2632.6 ± 270.9	2017.0 ± 257.1	2331.4 ± 185.1	56.3 ± 12.0

Sera of all immunized animals show SARS-CoV-2 pseudovirus neutralization to a varying extent (Figure 29). In-line with ELISA data, a weak neutralizing activity is induced by BNT162c1 treatment at day 10, a moderate neutralizing activity is induced by BNT162a1 treatment at day 17, and a high viral-neutralization activity is induced by BNT162b1 and BNT162b2 treatment at day 17 after first immunization.

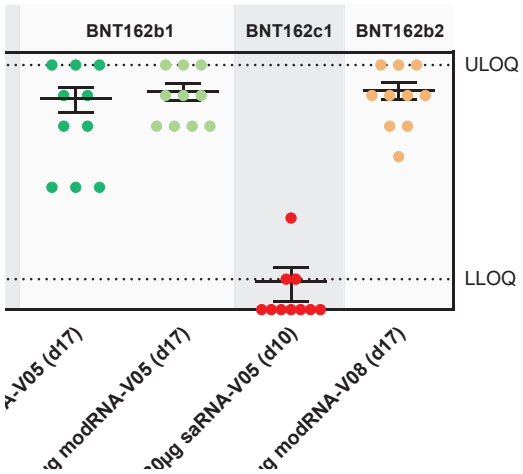


Figure 29: Antibody titer resulting in 50% pseudovirus neutralization activity (pVN_{50})

Wistar Han rats were immunized IM with three weekly injections of 10 or 30 µg BNT162a1, 30 or 100 µg BNT162b1, 100 µg BNT162b2, or two weekly injections of 30 µg BNT162c1. On day 10 (BNT162c1) or day 17 (all other cohorts) animals were bled and the sera were tested for SARS CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one rat. Every rat sample was measured in duplicate. Group size n=5 male and n=5 female rats. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

4.1.2 Secondary pharmacodynamics

No secondary pharmacodynamics studies were conducted for the BNT162 vaccine candidates.

4.1.3 Safety pharmacology

No safety pharmacology studies were conducted as they are not considered necessary according to the WHO guideline (WHO Technical Report Series, No. 927, "Annex 1: WHO guidelines on nonclinical evaluation of vaccines", 2005).

4.1.4 Non-clinical pharmacology - Conclusions

All non-clinical pharmacology studies and their analysis are still ongoing.

The currently available data demonstrate that vaccines based on all three RNA platforms (uRNA, modRNA, and saRNA) in conjunction with both the RBD with a trimerization domain ("V5") and the mutated full-length S protein ("V8"/"V9") including the clinical vaccine candidates, BNT162a1, BNT162b1, BNT162b2, and BNT162c2 are capable of inducing robust immune responses in mice and rat.

In mice, the antibody response was detected at a very early time point by IgG analysis on 7 d post-immunization. The induction of an antibody response by a very low immunization

dose of 0.2 µg with the modRNA platform (BNT162b1, BNT162b2) and the saRNA platform (BNT162c2) indicate high vaccine potency. Also immune responses by SARS-CoV-2 pseudovirus neutralization are detectable 14 d post-immunization in the mice immunized with intermediate doses. Similar results indicating immunogenicity were obtained in an accessory study to the GLP-compliant repeat-dose toxicology study in rats (Study No. 38166).

As both antigen variants (RBD and full length S protein) are immunogenic, including the induction of virus-neutralizing antibodies, and all RNA platforms have already shown immunogenicity for other viral antigens, these preliminary data support the clinical testing of each of these vaccine candidates.

A comparison of the three RNA platforms with regard to their immunogenicity in mice and rats may not be predictive for their relative immunogenicity in humans due to species-specific differences in innate immunity mechanisms; therefore, this differentiation will require clinical investigation in humans.

4.2 Non-clinical pharmacokinetics and metabolism

No pharmacokinetic studies were conducted for the BNT162 vaccine candidates as they are considered not necessary according to the WHO guideline (WHO Technical Report Series, No. 927, "Annex 1: WHO guidelines on nonclinical evaluation of vaccines", 2005).

4.2.1 Methods of analysis

Not applicable.

4.2.2 Absorption

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

4.2.3 Distribution

No biodistribution studies were performed with the BNT162 vaccine candidates.

The biodistribution of luciferase as a surrogate marker protein for the antigens encoded in the BNT162 vaccine candidates was assessed using an RNA encoding luciferase formulated like the BNT162 vaccines.

Based on extensive prior experience with RNA therapeutics, we routinely test new drug candidates for their ability to deliver RNA *in vivo* using luciferase-encoding RNA as reporter. Luciferase expression can be detected *in vivo* after injection of luciferin by measuring the luminescence *in vivo*. Using this methodology, we demonstrated that the modRNA, as representative for all three RNA platforms, induces a high and long luciferase expression (Figure 30).

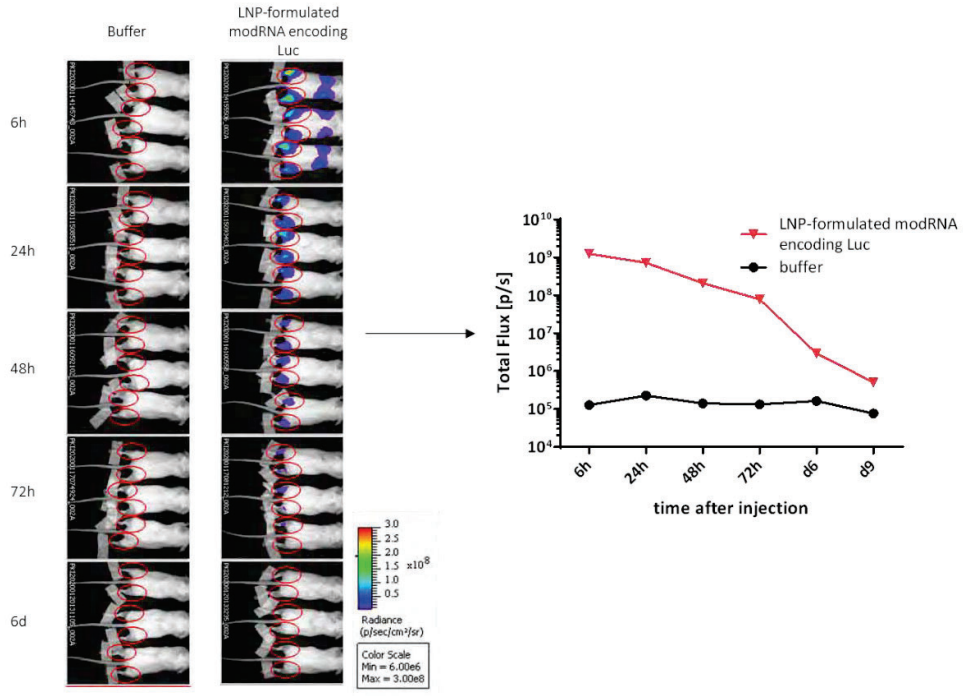


Figure 30: Bioluminescence imaging (BLI) measurement using the LNP-candidate formulated modRNA encoding luciferase

BALB/c mice were injected IM with1 µg of LNP-formulated modRNA encoding luciferase in each hind leg. At time points after injection, the luciferase expression *in vivo* was measured by luciferin application. After 9 d, luciferase expression dropped to background levels.

Based on our previous experience, we anticipate that the biodistribution of the antigen encoded by the RNA components of the BNT162 vaccine candidates will be dependent on the LNP distribution. Therefore, the modRNA results shown below are considered to be representative for all three BNT162 RNA platforms.

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.

4.2.4 Metabolism and excretion

RNA, including pseudouridine modified RNA and saRNA, 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.

Proteins encoded by the RNA in the BNT162 vaccine candidates are proteolytically degraded, just like other endogenous proteins. Therefore, no RNA or protein metabolism or excretion studies will be 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 pharmacokinetic profile of the two novel lipids (ALC-0315 and ALC-0159) will be characterized at a later stage of non-clinical development.

For the above-noted reasons, no metabolism or excretion studies were conducted.

4.2.5 Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies were performed.

4.2.6 Non-clinical pharmacokinetics and metabolism - Conclusions

Pharmacokinetic studies were conducted using a luciferase reporter RNA, and protein expression after IM injection was demonstrated *in vivo*. The luciferase biodistribution profile resembles that of similar RNA products developed by BioNTech, some of which have been safely tested at higher doses non-clinically and clinically using IV administration. Although liver parameters will be carefully monitored during the clinical development of the BNT162 vaccines, prior clinical experience with similar RNA products developed by BioNTech indicates that the distribution to the liver does not pose a safety risk.

4.3 Toxicology

To enable the rapid development of a prophylactic vaccine during a public health emergency, as is the case for the current SARS-CoV-2 outbreak, the WHO has published recommendations on the content of a minimum non-clinical safety package to support initiation of clinical testing (see "WHO Technical Report Series, No. 1011", "Annex 2: Guidelines on the quality, safety and efficacy of Ebola vaccines, 2018", WHO, Technical Report Series, No. 1011, 2018). According to WHO recommendation, interim data from a GLP repeat-dose toxicity study may support clinical testing of a vaccine in an outbreak situation.

For the BioNTech RNA platforms encoding different proteins, existing non-clinical and clinical safety data suggest a favorable safety profile.

4.3.1 Non-clinical data from prior toxicology studies

In prior studies, the company has generated non-clinical toxicology data for multiple related RNA-based therapeutics. Various non-clinical studies testing uRNA, modRNA and saRNA formats with different formulations have been conducted (an overview is given in Table 10). In these studies, different routes of administration, including IM, IN (intranodal), IT (intratumoral), and IV, were used. So far, data from non-clinical toxicity studies suggest a favorable safety profile for IV administered uRNA (as used for BNT162a1) and modRNA (as used for BNT162b1 and BNT162b2), as well as IM injected saRNA (as used for BNT162c1), formulated with different nanoparticles. Overall, the findings for different lipid-formulated RNA formats in the toxicity studies were mild, and mostly related to the RNA-intrinsic immunostimulatory capacity. All changes attributed to immune stimulation were fully reversibly for all RNA formats. Most notably, the non-clinical safety profile of uRNA (as used for BNT162a1) and modRNA (as used for BNT162b) was predictive of clinical safety when encoding cancer–related antigens or cytokines.

Table 10: BioNTech non-clinical platform experience

RNA	Relevant non-clinical safety studies
uRNA	**GLP-toxicity studies in mouse**: • 4 studies testing uRNA formulated in Ringer solution (IN) • 3 studies testing uRNA formulated in liposome containing lipoplexes (RNA-LPX, IV) **Non-GLP-Study in cynomolgus:** • 2 studies testing uRNA formulated in liposome containing lipoplexes (RNA-LPX, IV) Route: IV, intranodal Dose: up to 60 µg/mouse, up to approx. 80 µg/kg in cynomolgus monkeys **Overall safety conclusion:** IV injection of multiple liposome formulated vaccine antigens was very well tolerated in mice with doses at least 100-fold over the target dose in the clinical trials. Moderate and transient lymphopenia, considered to be triggered by in toll-like receptor (TLR)-mediated cytokine induction – an intended pharmacological effect. Most findings are the result of adaptive changes to the immune system which were reversible and are thus considered consistent with test article pharmacology.
modRNA	**GLP toxicity studies in mouse:** • 2 studies testing modRNA formulated in LNPs (IV) • 2 studies testing modRNA formulated in Ringer solution (IT and IV) **Non-GLP safety studies in cynomolgus:** • 4 studies testing modRNA formulated in LNPs (IV) Route: IV, IT (intratumoral), (other routes in R&D studies) Dose: up to 200 µg/mouse, up to 1.6 mg/kg in cynomolgus monkeys **Overall safety conclusions:** No test-item related findings were noted for Ringer-solution formulated modRNA after IV and IT administration. IV administration of high doses of LNP formulated modRNA was generally well tolerated. Slight to moderate effects on hematology, clinical parameters (liver enzymes) and on lymphoid organs (spleen, liver) were noted, but were ameliorated after a 2-3 wk recovery period. In studies in cynomolgus monkeys almost no test-item related findings were noted on safety parameters. Slight, but reversible effects on hematology were detected, that were attributed to the mode of action of the encoded proteins.
saRNA	**GLP toxicity studies in rabbit:** 1 study testing polyplex formulated saRNA Route: intramuscular Dose: up to 30 µg/rabbit **Overall safety conclusions:** No test-item related findings were noted for polyplex formulated saRNA.

IN = intranodal; IT = intratumoral; IV = intravenous.

Prior immunotoxicology experience

Unmodified and modified RNAs encoding antigens or functional proteins were evaluated in a number of repeat-dose toxicology studies after intravenous or intratumoral administration. Immunotoxicological inspections were implemented in these studies, including all three RNA platforms. Relevant parameters were measured, for example:

clinical signs/systemic tolerance, body weight, macroscopic and histopathological assessment of lymphatic organs, bone marrow smears, absolute and relative differential blood count, albumin/immunoglobulin ratio, and coagulation parameters.

The RNAs were formulated with either salt buffers or liposomal formulations. In general, changes observed in these studies were mild and mostly related to inflammatory responses, e.g., transient cytokine increase, hematological changes and effects on lymphoid organs.

Findings in these toxicity studies were mainly related to the mode of action of the encoded protein or dependent on the immune stimulatory capacity of RNA itself. Doses of up to 60 µg/animal uRNA or 200 µg/animal modRNA were tested without any sign of unpredictable overstimulation of the immune system in mice.

So far, clinical data suggest that the non-clinical immunotoxicity profile was predictive for the clinical setting, although the rodent model is less sensitive for some immunotoxicological parameters such as cytokines.

Conclusions from prior toxicology experience

Various non-clinical studies testing uRNA, modRNA, and saRNA components with different formulations have been conducted. So far, data from the non-clinical toxicity studies suggest a favorable safety profile of IV administered uRNA and modRNA, as well as intramuscularly injected saRNA formulated with different nanoparticles.

For uRNA and modRNA encoding various antigens and proteins, the non-clinical safety profile was predictive for the clinical safety profile seen when BioNTech tested total doses of up to 400 µg uRNA and 1 mg modRNA in different clinical trials. These results support the consistent safety profiles across each platform. The highest absolute doses of uRNA (such as in BNT162a1) and modRNA (such as in BNT162b) that will be used in the planned clinical trials will be at least 10-fold lower than the highest doses of uRNA and modRNA administered clinically so far.

Based on BioNTech's non-clinical and clinical experience with the RNA components and, given that the same LNP formulation in the BNT162 vaccine candidates is already being evaluated clinically with another RNA-containing infectious disease vaccine candidate, BNT162 vaccine candidates are anticipated to have a favorable safety - benefit balance.

4.3.2 Repeat-dose toxicology to support the clinical evaluation of BNT162 vaccine candidates

Toxicology of BNT162 vaccine candidates was studied in a GLP compliant repeat-dose study.

The study design is based on guideline recommendations ("WHO Technical Report Series, No. 927", "Annex 1: WHO guidelines on nonclinical evaluation of vaccines, 2005". The study design is summarized in Table 11.

Table 11: Design of the GLP compliant repeat-dose toxicity study (Study No. 38166)

Test Items	• BNT162a1 (uRNA-LNP, RBD of the SARS-CoV-2 S protein) • BNT162b1 (modRNA-LNP, RBD of the SARS-CoV-2 S protein) • BNT162b2 (modRNA-LNP, mutated full-length S protein of the SARS-CoV-2 S protein ("V8" variant")) • BNT162c1 (saRNA-LNP, RBD of the SARS-CoV-2 S protein)	
Species(age)	Wistar Han rat (10-14 wks)	
Administrations	Three (BNT162a1, BNT162b1 and BNT162b2) or two (BNT162c1) administrations on day 1, 8 and (if applicable) 15 followed by a 3-week recovery period	
Route	Intramuscular into the *M. biceps femoris*	
Dose groups	**Test Item**	**Dose level**
1	Control = Buffer	/
2	**BNT162a1** (uRNA RBD)	30 µg
3		10 µg
4	**BNT162b1** (modRNA RBD)	30 µg
5		100 µg
6	**BNT162c1** (saRNA RBD)	30 µg
7	**BNT162b2** (modRNA mutated full-length S protein)	100 µg
Satellite group (SA1)	SA1: for cytokine response analysis	3/sex/group
Group size	Group 1-7	10 (+ 5 recovery)/sex/group

A relevant animal model for toxicity assessment of vaccines is one that develops an immune response similar to the expected human response after vaccination, while also allowing administration of the absolute clinical dose (WHO Technical Report Series, No. 927, "Annex 1: WHO guidelines on non-clinical evaluation of vaccines", 2005). Since the rat develops an immune responses similar to the expected human response after RNA vaccination and is a commonly used species in vaccine toxicology studies, it was chosen as the animal model for toxicity assessment of the BNT162 vaccines.

The repeat-dose study investigated to what extent any observed side effect is related to:

- the RNA platform (uRNA, modRNA, and saRNA),
- the LNP formulation in combination with the respective platform,
- the vaccine dose, and/or
- the encoded antigen.

Examples for each of the three RNA platforms (uRNA, modRNA and saRNA) used in the BNT162 vaccine candidates were investigated utilizing the same LNP formulation and therefore the observed safety profiles are considered representative for all candidate vaccines based on these RNA platforms.

Different vaccine doses, covering the highest anticipated clinical doses, were tested for the modRNA and uRNA platforms. For modRNA, the doses tested were 30 µg and 100 µg. For uRNA, the doses 10 µg and 30 µg were tested. For the saRNA, a 30 µg dose was tested. All three RNA platforms were evaluated for at least one encoded antigen (RBD and, for modRNA, p2 S protein as well).

For the vaccine candidates that use the 21-day prime/boost dosing regimens, the dosing prime/boost interval was deliberately shortened to 7 d to exaggerate vaccine exposure.

The primary study endpoint is safety evaluation of the three different RNA platforms (uRNA, modRNA and saRNA) encapsulated in the same LNP after IM administration. An additional endpoint is the safety evaluation of the immunogens encoded by the respective vaccines.

The parameters assessed in the repeat-dose toxicity study are summarized in Table 12.

Based on previous non-clinical and clinical experience with the different RNA platforms, a transient pro-inflammatory cytokine response is anticipated due to the immune stimulus. This might lead to local reactions (such as swelling/edema or redness) and body temperature increase. Therefore, special attention was paid to the duration and extent of cytokine release of the following cytokines: IFN-γ, TNF-α, IL-1-β, IL-6, IL-10. At the end of in-life and after recovery, full histopathological analysis will be performed according to guidance (EMA Guideline on Repeated Dose Toxicity; WHO Guidelines on Nonclinical Evaluation of Vaccines).

The repeat-dose study is still ongoing, preliminary results are summarized in Table 12. These results are preliminary and may be subject to change.

Table 12: Parameters assessed in the repeat-dose toxicity study

Parameter	Time of assessment	Observation
Mortality	At least twice daily	Until 21 d post 1st immunization no mortality was observed in any group
Clinical signs	At least twice daily	Until 21 d post 1st immunization no systemic intolerance was observed in any group
Body weight *(also see Section 4.3.2.2)*	Twice weekly (prior and one day post each administration)	A slight reduction of bodyweight was seen 24 h after the administrations in animals of all treatment groups (up to ~10%) compared to pre-dose values. No such reduction was noted for the control group 1. Body weight gain between the administrations was comparable to the control group.
Food consumption *(also see Section 4.3.2.2)*	Weekly	A slight reduction in food consumption was seen in animals receiving 30 µg BNT162a1, 10 µg BNT162a1, 100 µg BNT162b1, 100 µg BNT162b2 and 30 µg BNT162c1 of in comparison with control group 1 during test week 1, which improved during the following test week.

Parameter	Time of assessment	Observation
Local tolerance (*also see Section 4.3.6*)	+4 h and 24 h post each administration	Group 1 showed no local reaction. All animals of the treatment groups developed mainly slight to moderate edema at the injection site 24 h after 1st dose. In most of the animals these injection site reactions only occurred after the second dose, where moderate to severe erythema was seen in many rats in receiving 30 µg BNT162a1, 100 µ BNT162b1, 100 µg BNT162b2 and 30 µg BNT162c1 at 144 hr after the 2nd dose. For rats given a third dose, all findings resolved prior to the third administration
Body temperature (*also see Section 4.3.7*)	+4 h and 24 h post each administration, weekly during recovery	A slight increase of body temperature was noted 24 h post administration compared to 4 h values (approx. 0.9 °C) in all animals including controls. It was more pronounced in the treatment groups. For single animals, temperature reached 40 °C, but was reduced again 24 h later.
Cytokines	Prior to and 6 h post each dosing and at the end of in-life	Levels of IFN-γ, TNF-α, IL-1-β, IL-6, IL-10 were comparable in buffer and vaccine administered animals.
Hematology *(also see Section 4.3.2.3)*	3 d post first administration and at the end of in-life/recovery	Most hematological parameters remained unchanged 3 d after the first and 2 d after the last dose. A dose dependent decrease was noted for reticulocytes 3 d after 1st dose in all treatment groups, which was less pronounced after the last dose. Hemoglobin or erythrocyte values were unaffected. The absolute number of platelets is slightly reduced at the end of the main study. White blood cells (neutrophils and monocytes) were increased in all vaccinated groups, large unclassified cells in all but BNT162c1 vaccinated animals at the end of the in-life phase.
Clinical chemistry incl. acute phase proteins *(also see Section 4.3.2.4)*	3 d post first administration and at the end of in-life/recovery	Clinical chemistry parameters were not affected, except for a slight increase in γ-glutamyl-transpeptidase for all treatment groups 3 d after 1st dose and 2 d after the last dose. Acute phase proteins alpha1-acid glycoprotein, alpha2 macroglobulin and fibrinogen were increased in all treatment groups 3 d after the 1st dose or at the end of in-life, respectively.
Coagulation	At the end of in-life/recovery	Slight prolongation of activated partial thromboplastin time (aPTT) in almost all vaccine treated groups, considered to be dependent on acute phase response.
Ophthalmology/ Auditory	At the end of in-life/recovery	No findings in any group.
Urine composition	At the end of in-life/recovery	No changes in pH were observed, the relative urine volume was decreased in all vaccinated animals.
Organ weight	At the end of in-life/recovery	In the majority of organs, no difference in relative and absolute weight was observed. Spleen weight was increased in females and males of all vaccinated animals when compared with buffer treated animals.
Macroscopic pathology	At the end of in-life/recovery	A thickened injection site was the most common observation in all vaccine treated animals (20/20 for 30 µg BNT162a1, 15/20 in for 10 µg BNT162a1, 13/20 for 30 µg BNT162b1, 6/20 for 100 µg BNT162b1, 20/20 in 30 µg BNT162c1 and 18/20 for BNT162b2). Some animals also displayed enlarged iliac lymph nodes and/or enlarged spleens.
Histopathology	At the end of in-life/recovery	Not yet available

Parameter	Time of assessment	Observation
Dose exposure serology *(also see Section 4.1.1.3.5)*	At the end of in-life/recovery	Treatment with all BNT162 vaccine candidates resulted in the formation of neutralizing antibodies protecting against pseudovirus infection. No neutralization was observed in buffer control treated animals.

4.3.2.1 Mortality and clinical signs

In the repeat-dose toxicity study, no mortality was observed throughout the course of the main study or in the recovery phase until data-cut-off date. All scheduled administrations for main and recovery animals have been performed. No clinical signs were noted until data-cut-off after the 1st immunization in any group.

4.3.2.2 Body weight and food consumption

In the repeat-dose toxicity study, the body weight was decreased 24 h after the administrations in all treatment groups compared to pre-dose levels (up to approx. 13%). No reduction was noted for the control Group 1. Body weight gain between the administrations was comparable to the control group (Figure 31).

A slight reduction in food consumption was seen in animals of Groups 2, 3, 5, 6 and 7, in comparison with control Group 1 during test week 1, which improved during the following test week.

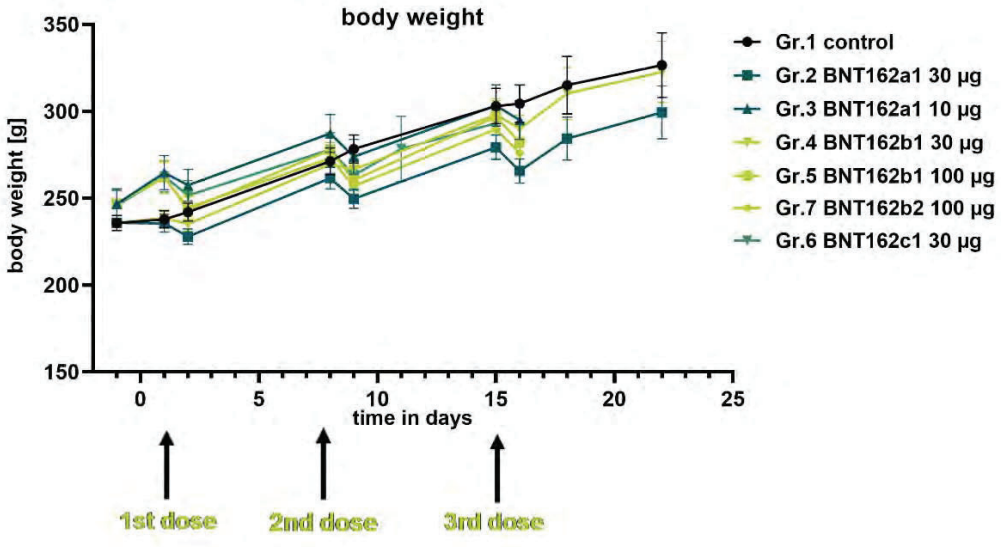


Figure 31: Development of body weight in the repeat-dose toxicity study

Wistar Han rats (n=15 male and female) were injected IM with buffer control [black], 10 or 30 µg/animal BNT162a1 (uRNA RBD) [dark green], 30 or 100 µg/animal BNT162b1 (modRNA RBD) [light green], 100 µg/animal BNT162b2 (modRNA mutS) [light green] or 30 µg BNT162c1 (saRNA RBD) [turquoise] at the indicated time points. Body weight was

measured twice weekly. Arithmetic mean (±SEM) body weight observed in the GLP toxicity study (Study No. 38166) of all groups is depicted.

4.3.2.3 Hematology

In the repeat-dose toxicity study most hematological parameters remained unchanged 3 d after the first dose and 2 d after the last dose.

A dose-dependent decrease was noted for reticulocytes 3 d after 1st dose in all treatment groups, which was less pronounced 2 d after the last dose for all groups treated with 30 µg/animal (Figure 32). The reticulocyte decrease was not accompanied by a reduction of erythrocyte counts or hemoglobin content (Figure 33).

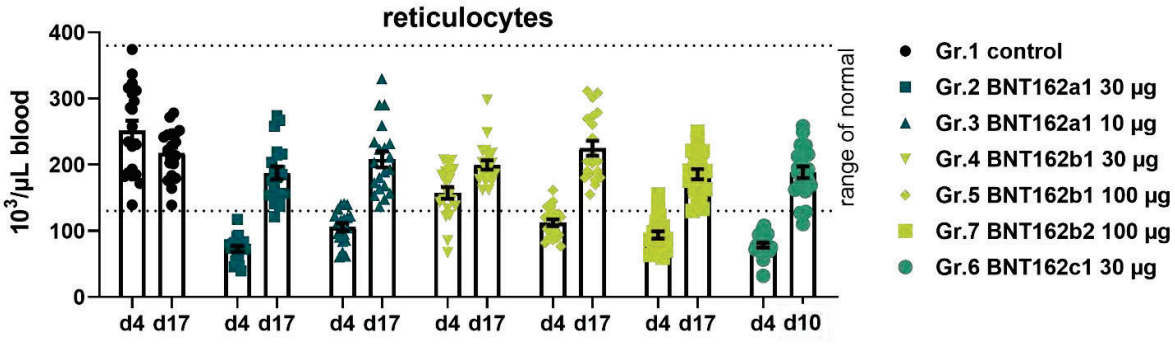


Figure 32: Reticulocytes are decreased by BNT162 after the 1st dose but recover by end of in-life in the repeated-dose toxicity study

Wistar Han rats (n=10 male and female) were in injected IM with buffer control [black], 10 or 30 µg/animal BNT162a1 (uRNA RBD) [dark green], 30 or 100 µg/animal BNT162b1 (modRNA RBD) [light green], 100 µg/animal BNT162b2 (modRNA mutS) [light green] or 30 µg BNT162c1 (saRNA RBD) [turquoise] at days 1, 8 and 15. Hematology parameters were assessed 3 d after the 1st dose and 2 d after the last dose. Arithmetic mean values of absolute reticulocyte counts (±SEM) observed in the GLP toxicity study (Study No. 38166) are shown. Range of standard laboratory values is given as dashed lines.

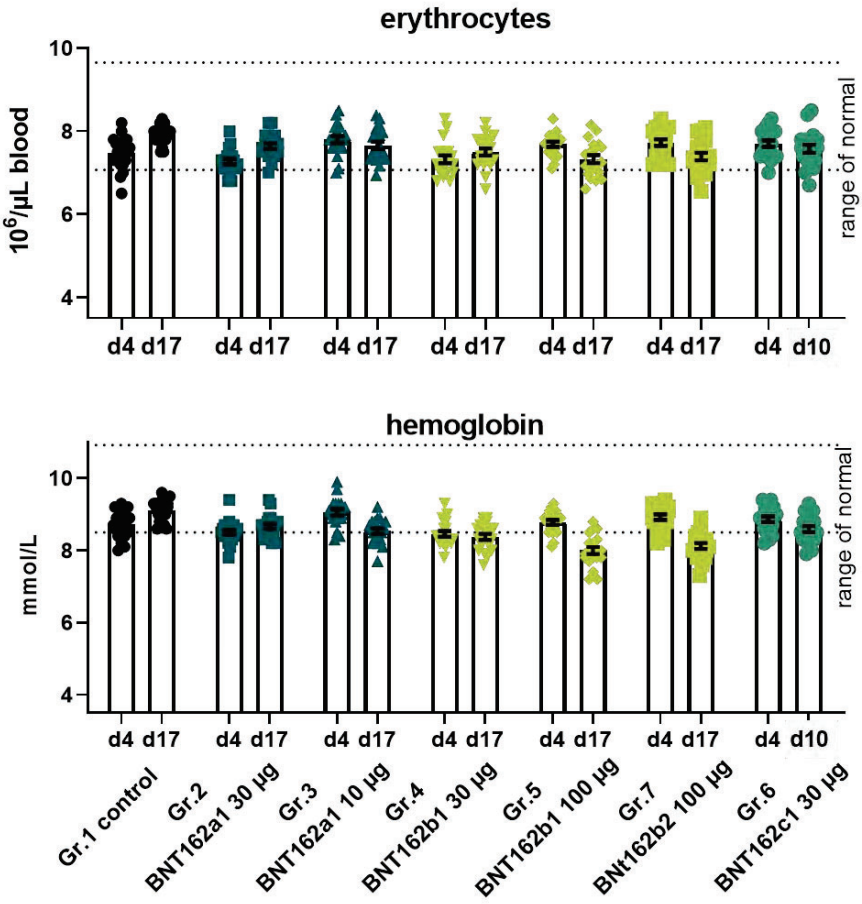


Figure 33: Erythrocytes and hemoglobin content is not influenced after BNT162 treatment in the repeated-dose toxicity study

Wistar Han rats (n=10 male and female) were in injected IM with buffer control [black], 10 or 30 µg/animal BNT162a1 (uRNA RBD) [dark green], 30 or 100 µg/animal BNT162b1 (modRNA RBD) [light green], 100 µg/animal BNT162b2 (modRNA mutS) [light green] or 30 µg BNT162c1 (saRNA RBD) [turquoise] at days 1, 8 and 15. Hematology parameters were assessed 3 d after the 1st dose and 2 d after the last dose. Range of standard laboratory values is given as dashed lines. Arithmetic mean values of absolute reticulocyte counts (±SEM) are shown. GLP toxicity study (Study No. 38166).

White blood cells (neutrophils and monocytes) were increased in number in all vaccinated groups and the number of large unclassified cells was elevated in all but buffer and BNT162c1 treated animals (Figure 34).

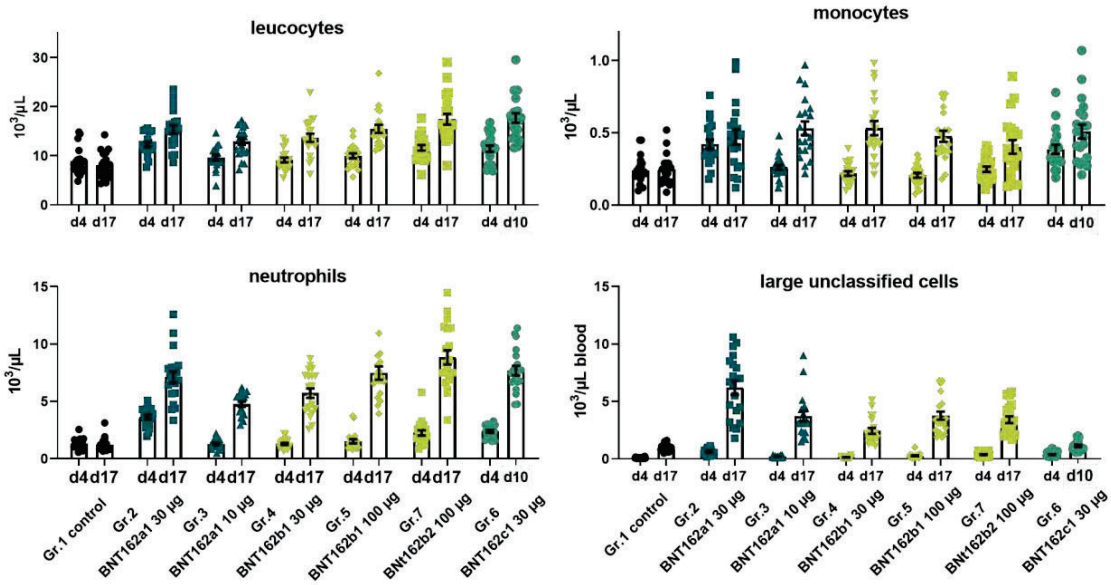


Figure 34: Numbers of leukocytes and large unclassified cells are increased at the end of in-life

Wistar Han rats (n=10 male and female) were in injected IM with buffer control [black], 10 or 30 µg/animal BNT162a1 (uRNA RBD) [dark green], 30 or 100 µg/animal BNT162b1 (modRNA RBD) [light green], 100 µg/animal BNT162b2 (modRNA mutS) [light green] or 30 µg BNT162c1 (saRNA RBD) [turquoise] at days 1, 8 and 15. Hematology parameters were assessed 3 d after the 1st dose and 2 d after the last dose. Arithmetic mean values of absolute reticulocyte counts (±SEM) are shown. GLP toxicity study (Study No. 38166).

Lastly, at the end of in-life, 2 d post last immunization a slight decrease in platelet counts was observed (Figure 35).

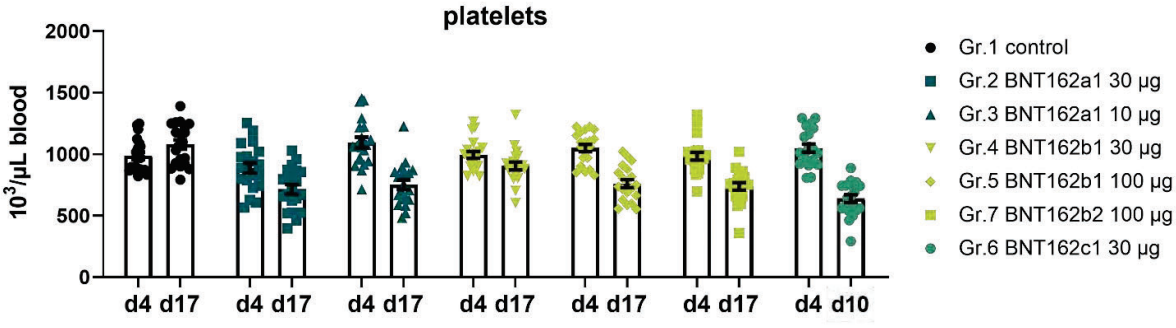


Figure 35: Numbers of platelets are slightly decreased at the end of in-life

Wistar Han rats (n=10 male and female) were in injected IM with buffer control [black], 10 or 30 µg/animal BNT162a1 (uRNA RBD) [dark green], 30 or 100 µg/animal BNT162b1 (modRNA RBD) [light green], 100 µg/animal BNT162b2 (modRNA mutS) [light green] or 30 µg BNT162c1 (saRNA RBD) [turquoise] at days 1, 8 and 15. Hematology parameters were assessed 3 d after the 1st dose and 2 d after the last dose. Arithmetic mean values of absolute reticulocyte counts (±SEM) are shown. GLP toxicity study (Study No. 38166).

4.3.2.4 Clinical chemistry and acute phase proteins

In the repeat-dose toxicity study almost all clinical chemistry parameters were unchanged.

Only a slight, most probably dose-dependent increase in γ-glutamyl transpeptidase (GGT) was noted for all treatment groups 3 d after 1st dose and 2 d after the last dose (Figure 36). Of note, this finding was not accompanied by the elevation of other liver parameters as alanine-aminotransferase (ALAT) and aspartate-aminotransferase (ASAT) (Figure 37).

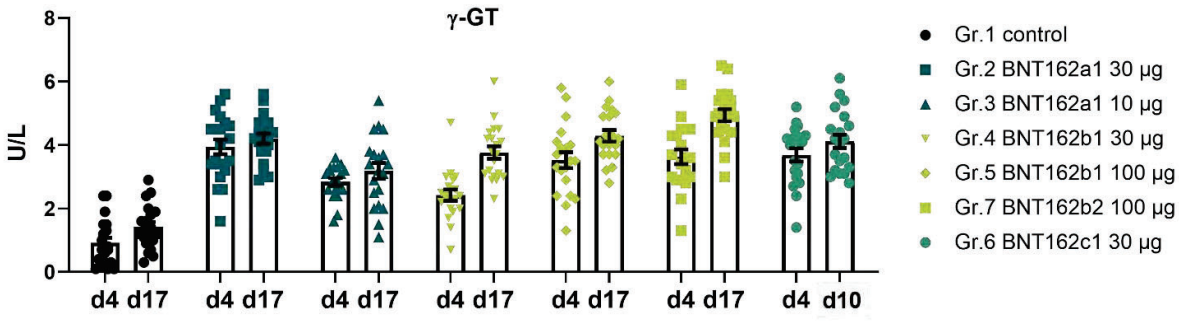


Figure 36: Slight elevation of GGT in the repeated-dose toxicity study

Wistar Han rats (n=10 male and female) were in injected IM with buffer control[black], 10 or 30 µg/animal BNT162a1 (uRNA RBD) [dark green], 30 or 100 µg/animal BNT162b1 (modRNA RBD) [light green], 100 µg/animal BNT162b2 (modRNA mutS) [light green] or 30 µg BNT162c1 (saRNA RBD) [turquoise] at days 1, 8 and 15. Clinical chemistry parameters were assessed 3 d after the 1st dose and 2 d after the last dose. Arithmetic mean values of GGT values (±SEM) observed in the GLP toxicity study (Study No. 38166) are shown in U/L.

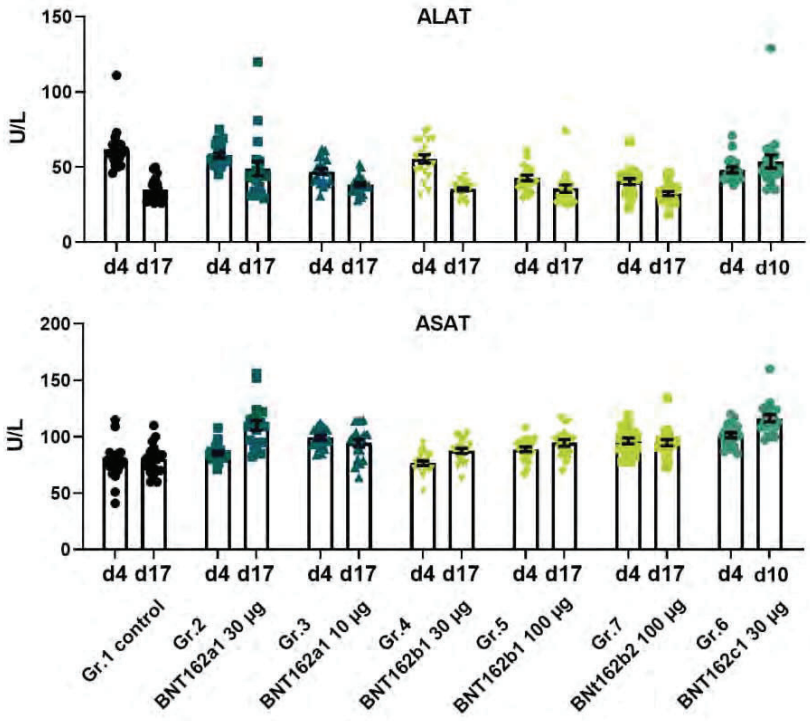


Figure 37: No elevation of liver-specific enzymes ALAT and ASAT in the repeated-dose toxicity study

Wistar Han rats (n=10 male and female) were in injected IM with buffer control [black], 10 or 30 µg/animal BNT162a1 (uRNA RBD) [dark green], 30 or 100 µg/animal BNT162b1 (modRNA RBD) [light green], 100 µg/animal BNT162b2 (modRNA mutS) [light green] or 30 µg BNT162c1 (saRNA RBD) [turquoise] at days 1, 8 and 15. Clinical chemistry parameters were assessed 3 d after the 1st dose and 2 d after the last dose. Arithmetic mean values of absolute ALAT and ASAT values (±SEM) observed in the GLP toxicity study (Study No. 38166) are shown in U/L.

Acute phase proteins alpha1-acid glycoprotein, alpha2 macroglobulin and fibrinogen were measured to assess vaccine-induced inflammatory reactions. The markers were increased in the treatment groups 3 d after the 1st dose or at the end of the in-life phase, respectively (Figure 38).

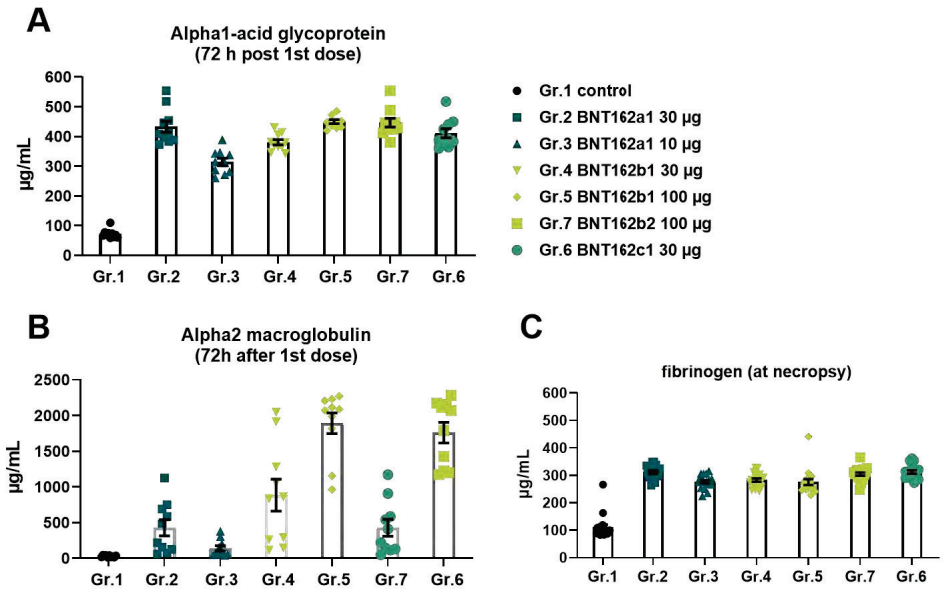


Figure 38: Acute phase proteins and fibrinogen are increased for treatment groups in the repeated-dose toxicity study

Wistar Han rats (n=10 male and female) were in injected IM with buffer control [black], 10 or 30 µg/animal BNT162a1 (uRNA RBD) [dark green], 30 or 100 µg/animal BNT162b1 (modRNA RBD) [light green], 100 µg/animal BNT162b2 (modRNA mutS) [light green] or 30 µg BNT162c1 (saRNA RBD) [turquoise] at days 1, 8 and 15. A, B Acute phase proteins, alpha1 acid glycoprotein and alpha2 macroglobulin, were assessed 3 d after the 1st dose (n=5 males and females). C F brinogen was measured in the GLP toxicity study (Study No. 38166). at necropsy 2 d after the last dose (n=10 males and females). Arithmetic mean values of the proteins (±SEM) are shown in µg/mL.

4.3.2.5 Coagulation

Coagulation parameters prothrombin time (PT), aPTT and fibrinogen were measured at the end of in-life phase. Fibrinogen was elevated in all vaccine treated groups around 3-fold compared to control (Figure 38). This induction is most probably due to the vaccine-induced inflammatory reaction.

aPTT was slightly elevated in Groups 2, 3, 5, 6 and 7 compared to the control group. The slight increase is considered to be secondary to the acute phase response.

4.3.2.6 Ophthalmological and auditory assessments

Examinations of the eye are performed on all animals before first dosing and at the end of the main study and, for all recovery animals, at the end of the recovery period.

The pupillary reflex, adnexa oculi (i.e., lids, lacrimal apparatus), conjunctiva, cornea, anterior chamber, lens, vitreous body, fundus (retina, optic disc) are examined and scored. In addition, auditory acuity is checked with a simple noise test.

Prior to and at the end of dosing period ophthalmological and auditory assessments resulted in detection of no changes.

4.3.2.7 Urine composition

At the end of in-life, urine was collected over a period of 24 h from main study animals. No changes in pH were observed, but the relative urine volume was decreased and specific gravity slightly increased in all vaccinated animals.

4.3.2.8 Macroscopic pathology

Main study animals were dissected following a randomization scheme 2 d after the last administration.

The most common observation in all treatment groups was a thickened injection site and/or induration at the injected muscle (see Table 13 for all findings). This finding is test-item related and is caused by the local inflammation process. Furthermore, enlarged spleen and iliac lymph nodes were noted in a number of animals in the test-item treated groups. The effects on the lymphoid organs are most probably effects of the induction of an inflammatory response by the vaccine.

Single female animals from Groups 2, 3, 4 and 7 were reported to have a dilated uterus filled with clear liquid. This change is considered to be a normal variation associated with reproductive cycling. All other findings are considered random as they only appeared, if at all, in single animals.

Special attention will be payed to the histopathology data of the mentioned organs, that is not yet available to interpret the findings further.

Table 13: Summary of macroscopic findings – main study

Group	Findings in male and female animals
1	• Emphysematous lung (1/20 animals) • Reddened thymus (1/20 animals)
2	• Thickened / hardened injection site and/or muscle (20/20 animals) • Enlarged spleen (6/20 animals) • Enlarged iliac lymph nodes (2/20 animals) • Dilated uterus (1/10 animals) • Enlarged adrenal gland (1/20 animals) • Prostate reduced in size (1/10 animals) • Seminal vesicle reduced in size (1/10 animals)
3	• Thickened / hardened injection site and/or muscle (15/20 animals) • Enlarged spleen (7/20 animals) • Enlarged iliac lymph nodes (7/20 animals) • Dilated uterus (3/10 animals) • Enlarged adrenal gland (1/20 animals)

4	• Thickened / hardened injection site and/or muscle (13/20 animals) • Enlarged spleen (2/20 animals) • Enlarged iliac lymph nodes (10/20 animals) • Dilated uterus (1/10 animals)
5	• Thickened / hardened injection site and/or muscle (14/20 animals) • Enlarged spleen (12/20 animals) • Enlarged iliac lymph nodes (15/20 animals) • Enlarged adrenal gland (2/20 animals)
6	• Thickened / hardened injection site and/or muscle (20/20 animals) • Enlarged spleen (6/20 animals) • Enlarged iliac lymph nodes (3/20 animals)
7	• Thickened / hardened injection site and/or muscle (15/20 animals) • Enlarged spleen (9/20 animals) • Enlarged iliac lymph nodes (11/20 animals) • Dilated uterus (1/10 animals)

4.3.2.9 Organ weight

In the majority of weighed organs no difference in relative and absolute organ weight between vaccinated and buffer treated animals were observed. Congruent with the macroscopic observations (Section 4.3.2.7), the average spleen weight was increased in male and female animals vaccinated with the BNT162 vaccine candidates.

4.3.3 Genotoxicity

The components of all BNT162 vaccine excipients, lipids and RNA, are not suspected to have genotoxic potential. No impurity or component of the delivery system warrants genotoxicity testing. In accordance with the WHO guideline (WHO Technical Report Series, No. 927, "Annex 1: WHO guidelines on nonclinical evaluation of vaccines", 2005), no genotoxicity studies were performed.

4.3.4 Carcinogenicity

RNA itself, and the lipids used in the BNT162 vaccines have no carcinogenic or tumorigenic potential. Furthermore, according to ICH S1A (ICH S1A Guideline: "Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals", November 1995), no carcinogenicity studies are required for therapeutics that are not continuously administered.

4.3.5 Reproductive and developmental toxicity

Macroscopic and microscopic evaluation of male and female reproductive tissues were included in all previous GLP toxicity studies of all three RNA platforms and are included in the ongoing GLP repeat-dose toxicity study testing BNT162a1, BNT162b1, BNT162b2, and BNT162c1 (Section 4.3.2). Previous GLP toxicity studies showed no changes in reproductive organs. Since effects on reproduction cannot be excluded at this stage, women of childbearing potential and men of reproductive potential are required to use

effective contraception during the planned clinical trials. Also sperm donation by male trial subjects will be prohibited during the planned clinical trials.

4.3.6 Local tolerance

Special attention was paid to the local tolerance of vaccines BNT162a1, BNT162b1, BNT162b2, and BNT162c1 at the injection site, in the repeated-dose toxicity study (Section 4.3.2).The injection sites were assessed for erythema/eschar/edema formation and induration/hardening following palpation. Any reactions such as formation of erythema, edema or induration of injection site observed were scored with a grading similar to DRAIZE (Appraisal of the Safety of Chemicals in Food, Drugs and Cosmetics, Association of Food and Drug Officials of the United States, Austin, Texas, 1959). Occurrence of edema was scored as described in Table 14.

Table 14: Grading of edema formation

Edema formation	Value
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approx. 1 mm)	3
Severe erythema (raised more than 1 mm and extending beyond area of exposure)	4

Until data cut-off date for this document data from up to 7 d post third administration are available for all groups (15 d after the second administration for Group 6 BNT162c1). Until then, no induration of the injection site was observed in any group. For Group 2 (30 µg BNT162a1) pain and eschar formation at the injection site was apparent for some animals 24 h after the 2nd dose, but resolved 24 h later.

Reversible erythema formation of grade 1 was noted from 48 to 96 h post first immunization in some animals of Group 2 (30 µg BNT162a1) and only in some animals of the other treatment groups. After the second immunization, Grade 1 - 2 erythema were noted in some animals from 24 h to 48 h (Groups 2, 30 µg BNT162a1, and 4, 30 µg BNT162b1). For a few animals (Groups 3, 10 µg BNT162a1, and 5, 100 µg BNT162b1) at 96 h and at 144 h in (Groups 3, 5, 6, 30 µg BNT162 c1, and 7,100 µg BNT162b2) grade 4 erythema was observed. These observations resolved within the following 24 h.

The most common local reaction observed was edema as indicated in Figure 39.

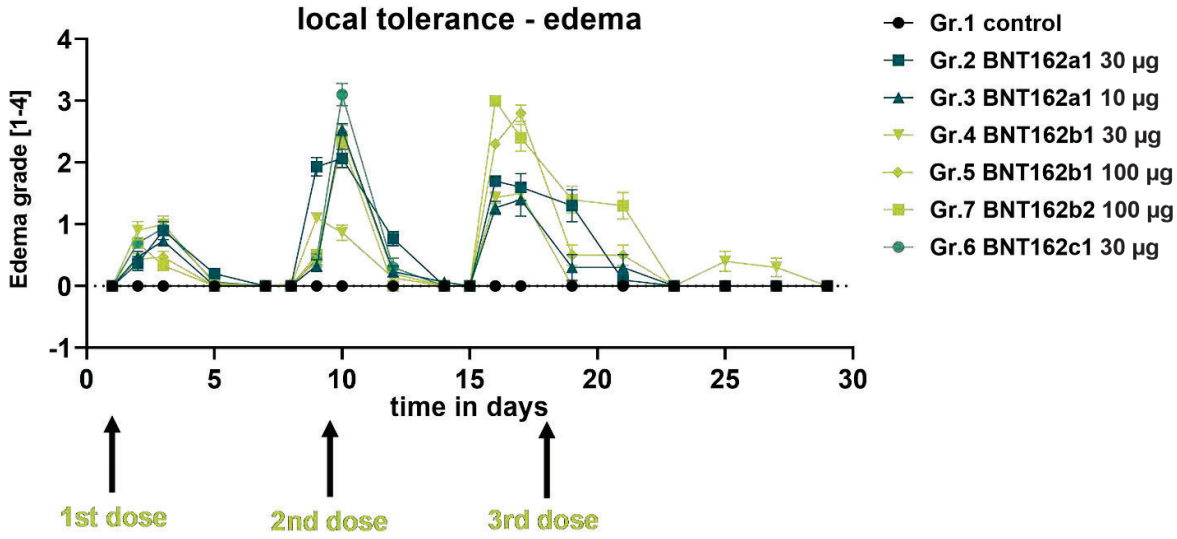


Figure 39: Local reactions were slight after first immunization but more pronounced after boost with a reduced immunization interval

Wistar Han rats (n=15 male and female) were in injected IM with buffer control [black], 10 or 30 µg/animal BNT162a1 (uRNA RBD) [dark green], 30 or 100 µg/animal BNT162b1 (modRNA RBD) [light green], 100 µg/animal BNT162b2 (modRNA mutS) [light green] or 30 µg BNT162c1 (saRNA RBD) [turquoise] at days 1, 8 and 15. Edema formation was scored daily after first and second dose using a grading system from 0 – 4 (not present – severe). Arithmetic mean values of edema grade (±SEM) observed in the GLP toxicity study (Study No. 38166) are shown.

After the first immunization, slight edema (grade 1 to 2) were noted in some animals across treatment groups 24 h post administration. The reaction resolved within the following 24 to 48 h. After the second immunization, with a short immunization interval just one week later into the same injection site, the reaction was more pronounced (grade 1 to 3) and present in more, though not in all animals. An overview over the time points and frequencies of certain grades of edema noted throughout the study is given in Table 15.

Table 15: Frequency of highest edema score noted post first and second vaccine dose in GLP repeated-dose toxicity study

Group	Time Points	Frequency of highest edema score/total number of animals				
		0	1	2	3	4
Gr. 1 Control = Buffer	all	30/30	0/30	0/30	0/30	0/30
Gr. 2 30 µg BNT162a1 (uRNA RBD variant)	Post 1. dose	6/30	15/30	9/30	0/30	0/30
	Post 2. dose	1/30	2/30	13/30	14/30	0/30
Gr. 3 10 µg BNT162a1 (uRNA RBD variant)	Post 1. dose	8/30	22/30	0/30	0/30	0/30
	Post 2. dose	0/30	0/30	14/30	16/30	0/30
Gr. 4 30 µg BNT162b1 (modRNA RBD variant)	Post 1. dose	6/30	11/30	13/30	0/30	0/30
	Post 2. dose	1/30	22/30	7/30	0/30	0/30
Gr. 5 100 µg BNT162b1 (modRNA RBD variant)	Post 1. dose	9/30	21/30	0/30	0/30	0/30
	Post 2. dose	0/30	1/30	13/30	16/30	0/30
Gr. 6 30 µg BNT162c1 (saRNA RBD)	Post 1. dose	3/30	23/30	4/30	0/30	0/30
	Post 2. dose*	12/30	6/30	1/30	9/30	2/30
Gr. 7 100 µg BNT162b2 (modRNA mutated full-length S protein)	Post 1. dose	4/30	26/30	0/30	0/30	0/30
	Post 2. dose	0/30	3/30	14/30	13/30	0/30

*Only recovery animals were scored past 24 h post 2. dose

Almost all animals show local reactions after the first immunization with the undiluted vaccine, but only edema of low extent (grade 1-2). Of note, no grade 3 or 4 local reactions occurred after the first immunization. The occurrence of higher grade local reactions after boost immunizations is 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.

In the clinical trial in humans the same dose will be administered into a larger muscle with a diluted drug product. Also the dose-to-body-weight ratio will be more favorable and the dosing interval of 21 d between prime and boost immunizations will be longer. These may also contribute to a milder local tolerance profile of BNT162 vaccines in humans as compared to the one observed in this animal study.

4.3.7 Immunotoxicology

Immunotoxicity of BNT162a1, BNT162b1, BNT162b2, and BNT162c1, is assessed in the GLP compliant repeated-dose toxicity study in rats (Section 4.3.2). The parameters measured in the study include: clinical signs/systemic tolerance, body weight, macroscopic and histopathological assessment of lymphatic organs, bone marrow smears, absolute and relative differential blood count, albumin/immunoglobulin ratio, coagulation parameters, and changes in body temperature.

As of the data cut-off date for this document, data from up to 21 d after the first administration were available for all groups apart from cytokines where only data for Groups 1, 2 and 4 were evaluated.

No systemic intolerance or mortality was observed. Almost no changes were observed in the absolute and differential blood count, as described in Section 4.3.2.3. Body weight was decreased 24 h after the administrations in all treatment groups compared to pre-dose (up to approx. 13%), but body weight gain between the administrations was comparable to the control group (Section 4.3.2.2).

An increase of body temperature was noted at 24 h post each administration compared to values 4 h post administration in all groups. This increase was generally higher in immunized rats than in buffer treated animals. Of note, the physiological body temperature of rats is approx. 1°C higher than of humans and body temperatures observed 24 h post injection in rats did not exceed 40.2°C. In general, only individual animals displayed temperatures beyond 40°C, and then only after the second or third immunization. The temperature increase, displayed in Figure 40, was fully reversible within 48-72 h post immunization.

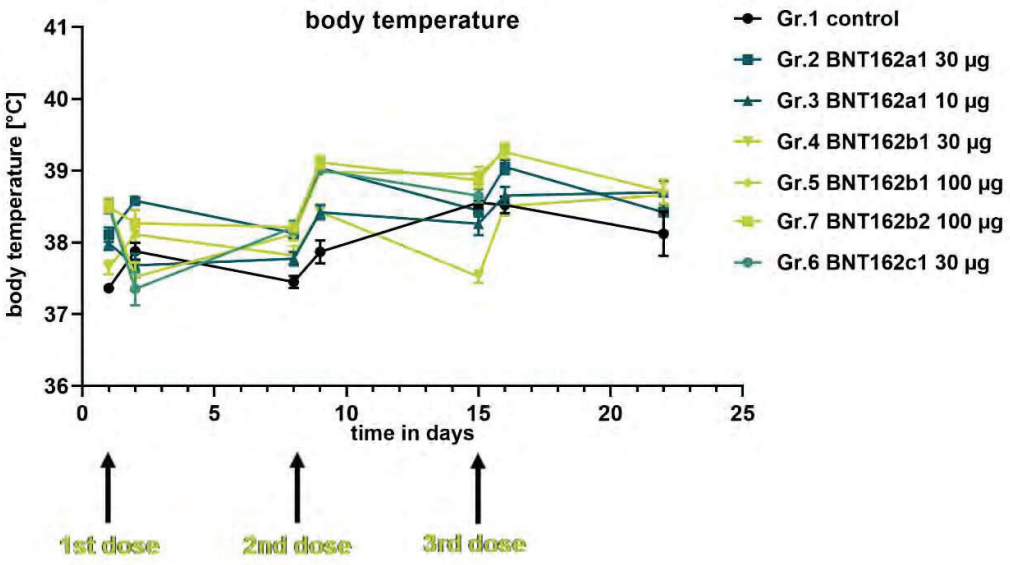


Figure 40: Course of body temperature during repeated-dose toxicity study

Wistar Han rats (n=15 male and female) were injected IM with buffer control [black], 10 or 30 µg/animal BNT162a1 (uRNA RBD) [dark green], 30 or 100 µg/animal BNT162b1 (modRNA RBD) [light green], 100 µg/animal BNT162b2 (modRNA mutS) [light green] or 30 µg BNT162c1 (saRNA RBD) [turquoise] at days 1, 8 and 15. Body temperature was measured 4 h and 24 h after each dosing. Arithmetic mean values of body temperature (±SEM) observed in the GLP toxicity study (Study No. 38166) are shown.

All cytokines assessed displayed high background levels/variability and were similarly elevated in control and vaccinated animals (see Figure 41).

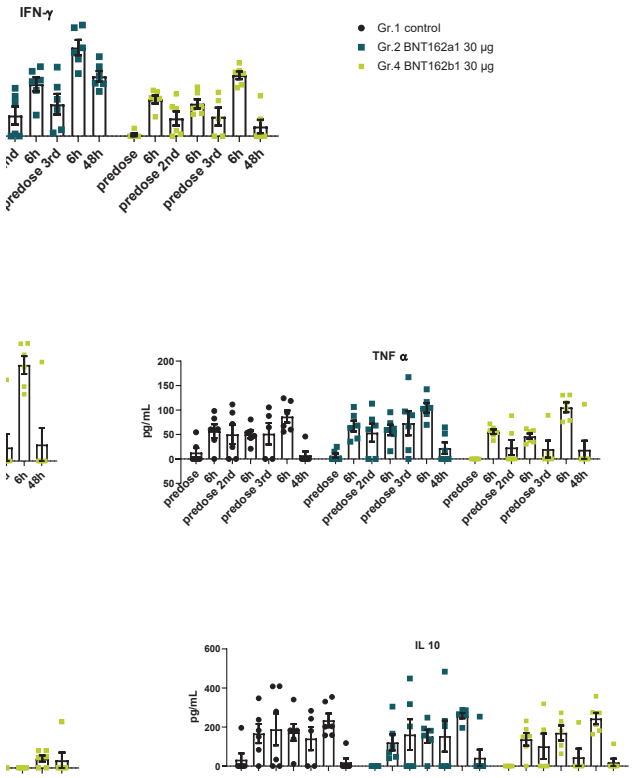


Figure 41: Elevation in cytokine levels is similar in buffer and vaccine treated groups

Wistar Han rats (n=15 male and female) were injected IM with buffer control [black], 10 or 30 µg/animal BNT162a1 (uRNA RBD) [dark green], 30 or 100 µg/animal BNT162b1 (modRNA RBD) [light green], 100 µg/animal BNT162b2 (modRNA mutS) [light green] or 30 µg BNT162c1 (saRNA RBD) [turquoise] at days 1, 8 and 15. Levels of IFNγ, IL-1β, TNF-α, IL-6 and IL-10 were measured prior to and 6 h post each dose. Arithmetic mean values of body temperature (±SEM) observed in the GLP toxicity study (Study No. 38166) are shown.

4.3.8 Toxicology - Conclusions

The presented preliminary results support the benign safety profile previously observed with other BioNTech RNA platforms. Through the entire main study and, until data cut-off date, through the recovery phase of the repeat-dose toxicity study, there were no clinical signs or mortalities observed.

As expected, the BNT162 vaccines induce a pro-inflammatory response, which manifests in a reduction in body weight (up to approximately 13%) 24 h post immunization without affecting body weight gain overall. The temporary weight loss is probably caused by

shortly reduced food and water consumption after administration, which also leads to less urine production immediately after immunization.

The observed increases in typical inflammatory blood parameters such as fibrinogen and acute phase proteins support this hypothesis. The transient and reversible elevation of GGT activity in serum in the absence of elevation of liver specific inflammation markers, such as ALAT or ASAT is considered a general inflammation marker (Singh et al. 1986).

Few hematological changes were observed: an increase in large unclassified cell and leukocyte (monocyte and neutrophil) counts, as well as a transient, dose-dependent reduction in reticulocytes after first immunization. The reduction in reticulocytes was reversed under continued immunizations and did not affect erythrocyte or hemoglobin levels and is considered to be species-specific. These changes have been observed in rats treated with the licensed LNP-small interfering RNA (siRNA) pharmaceutical Onpattro™ (FDA assessment report of Onpattro™ 2018), but have not been observed in patients treated with this compound. After the last immunization, a slight reduction in platelet numbers was observed. This effect is most likely attributable to inflammation specific platelet consumption and though it mediates a slight prolongation of aPTT in Groups 2, 3, 5, 6 and 7 of 2-3 seconds, it is not considered a safety concern but rather a pharmacodynamics attribute (Davidson 2013; Middleton et al. 2016).

As an 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, local reactions were anticipated. The only local reactions observed after the first immunization were very slight to slight (grade 1 – 2) edema. Of note, no grade 3 or 4 local reactions occurred after the first immunization. The occurrence of higher grade local reactions after boost immunizations is considered to be attributable to the undiluted status of the vaccines and to the - in relation to body weight of the rat - high vaccine dose (approximately up to 0.5 mg/kg), in addition to the short interval of 7 d between immunizations. It is not anticipated to occur in the clinical trial, in which boost immunizations of a maximum dose of 0.002 mg/kg (e.g., for the highest dose of 100 µg in a participant weighing 50 kg) will be administered 21 d apart.

Macroscopic observations of indurated injection sites and – in some animals – enlarged spleens and/or draining lymph nodes (as described in Section 4.3.2.8) together with a tendency of increased spleen weights in vaccinated animals (Section 4.3.2.9), support the hypothesis that the vaccine candidates generate a pro-inflammatory environment. In rats, the potent immune response observed can already be detected 17 d post first immunization (Section 4.1.1.3.5).

Taking together the previous non-clinical and clinical experience with the preliminary results of the BNT162 vaccine toxicity study, a benign clinical safety profile is anticipated.

5 EFFECTS IN HUMANS

There are currently no data available on the effects of the BNT162 vaccine candidates in humans.

The BNT162 vaccine candidates have neither been approved for use nor been marketed in any country.

6 SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

For a summary of the relevant non-clinical and clinical information, see Section 1.

All non-clinical pharmacology studies and their analysis are still ongoing. The currently available data demonstrate that vaccines based on all three RNA platforms (uRNA, modRNA, and saRNA) in conjunction with both the RBD with a trimerization domain ("V5") and the mutated full-length S protein ("V8"/"V9") including the clinical vaccine candidates, BNT162a1, BNT162b1, BNT162b2, and BNT162c2 are capable of inducing robust immune responses in mice and rat.

In mice, the antibody response was detected at a very early time point, by IgG analysis on 7 d post-immunization. The induction of an antibody response by a very low immunization dose of 0.2 µg with the modRNA platform (BNT162b1, BNT162b2) and the saRNA platform (BNT162c2) indicate high vaccine potency. Also immune responses by SARS-CoV-2 pseudovirus neutralization are detectable 14 d post-immunization in the mice immunized with intermediate doses. Similar results indicating immunogenicity were obtained in an accessory study to the GLP-compliant repeat-dose toxicology study in rats (Study No. 38166).

As both antigen variants (RBD and full length S protein) are immunogenic, including the induction of virus-neutralizing antibodies, and all RNA platforms have already shown immunogenicity for other viral antigens, these preliminary data support the clinical testing of each of these vaccine candidates.

A comparison of the three RNA platforms with regard to their immunogenicity in mice and rats may not be predictive for their relative immunogenicity in humans due to species-specific differences in innate immunity mechanisms; therefore, this differentiation will require clinical investigation in humans.

Pharmacokinetic studies were conducted using a luciferase reporter RNA, and protein expression after IM injection was demonstrated *in vivo*. The luciferase biodistribution profile resembles that of similar RNA products developed by BioNTech, some of which have been safely tested at higher doses non-clinically and clinically using IV administration. Prior clinical experience with similar RNA products developed by BioNTech indicates that the distribution to the liver does not pose a safety risk.

The presented preliminary results support the benign safety profile previously observed with other BioNTech RNA platforms. Through the entire main study and, until data cut-off date, through the recovery phase of the repeat-dose toxicity study, there were no clinical signs or mortalities observed.

As expected, the BNT162 vaccines induce a pro-inflammatory response, which manifests in a reduction in body weight (up to approximately 13%) 24 h post immunization without affecting body weight gain overall. The temporary weight loss is probably caused by shortly reduced food and water consumption after administration, which also leads to less urine production immediately after immunization.

The observed increases in typical inflammatory blood parameters such as fibrinogen and acute phase proteins support this hypothesis. The transient and reversible elevation of

GGT activity in serum in the absence of elevation of liver specific inflammation markers, such as ALAT or ASAT is considered a general inflammation marker (Singh et al. 1986).

Few hematological changes were observed: an increase in large unclassified cell and leukocyte (monocyte and neutrophil) counts, as well as a transient, dose-dependent reduction in reticulocytes after first immunization. The reduction in reticulocytes was reversed under continued immunizations and did not affect erythrocyte or hemoglobin levels and is considered to be species-specific. These changes have been observed in rats treated with the licensed LNP-small interfering RNA (siRNA) pharmaceutical Onpattro™ (FDA assessment report of Onpattro™ 2018), but have not been observed in patients treated with this compound. After the last immunization, a slight reduction in platelet numbers was observed. This effect is most likely attributable to inflammation specific platelet consumption and though it mediates a slight prolongation of aPTT in Groups 2, 3, 5, 6 and 7 of 2-3 seconds, it is not considered a safety concern but rather a pharmacodynamics attribute (Davidson 2013; Middleton et al. 2016).

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Macroscopic observations of indurated injection sites and – in some animals – enlarged spleens and/or draining lymph nodes (as described in Section 4.3.2.8) together with a tendency of increased spleen weights in vaccinated animals (Section 4.3.2.9), support the hypothesis that the vaccine candidates generate a pro-inflammatory environment. In rats, the potent immune response observed can already be detected 17 d post first immunization (Section 4.1.1.3.5).

Taking together the previous non-clinical and clinical experience with the preliminary results of the BNT162 vaccine toxicity study, a benign clinical safety profile is anticipated.

There are currently no data available on the effects of the BNT162 vaccine candidates in humans. However, as presented in Section 2.5 in more detail, BioNTech has clinical experience with two of the RNA formats used in BNT162 vaccines, namely uRNA and modRNA and in addition to BioNTech`s own data, clinical trials with the three RNA formats in similar liposomal formulations are conducted by other parties.

Based on all available non-clinical data with BNT162 vaccine candidates and on data from non-clinical studies and clinical trials with the same or related RNA components or antigens, the expected adverse reactions after vaccination are expected to be manageable using routine symptom driven standard of care as determined by the investigators.

6.1 Guidance for the investigator

6.1.1 Posology and method of administration

The BNT162 vaccines are intended for IM administration in the upper arm (musculus deltoideus) using single dose and prime/boost regimens.

6.1.2 Restrictions

Currently there are no data available from BioNTech clinical trials on the use of BNT162 vaccines, therefore standard precautionary restrictions for vaccinations and blood draws should be implemented.

6.1.3 Information relevant to special populations

Currently there are no data available from BioNTech clinical trials on the use of BNT162 vaccines in special populations including the elderly, renally/hepatically impaired people, and/or pregnant or breastfeeding women.

6.1.4 Special warnings and precautions for use

In the absence of clinical experience with BNT162 immunization, the following warnings will apply:

- Strenuous physical activity will not be allowed on visit days.
- Subjects will be warned not to drive vehicles or to operate dangerous machinery for up to 24 h after the last immunization or blood draw, whichever is later.

6.2 Reference safety information

As there is no human exposure data for any of the BNT162 vaccines, no adverse drug reactions are known at this time for regulatory reporting hence no Serious Adverse Reactions (SARs) are considered ´expected´. All serious and adverse reactions will therefore be considered as unexpected.

A tabular summary of reference safety information, i.e., listing any identified expected SARs by standard organ class, preferred term, and frequency, will be added here in future versions of this document.

6.3 Risks

6.3.1 General risks

The risks linked to the trial-specific procedures are as follows:

- The volume of blood drawn will kept to a minimum and will remain less than that drawn when donating blood will be drawn per subject over the complete trial.
- All trial-specific procedures will be performed by qualified trial site personnel.

The risks linked to vaccinations in general are as follows:

- Due to the IM route of administration, there is the risk of localized injection site reactions, e.g., erythema, pruritus, pain, tenderness, swelling, sweating.
- Due to their immune-modulatory effect, vaccines may cause systemic flu-like reactions such as temporary headache, fatigue, loss of appetite, myalgia, arthralgia, fever. Rarely, with certain prophylactic vaccines (e.g., as seen for vaccines using attenuated viruses) severe allergic reaction or a neurological side effects, such as a seizure, were seen. Although these rare side effects are a concern, the risk of a vaccine causing serious harm or death is considered to be extremely small, in particular for BNT162 vaccines, which are molecularly defined, highly purified and based on RNA, which naturally occurs and is metabolized in the human organism.

6.3.2 Potential risks

The combination of each of the three RNA formats with the specific LNP composition used in the BNT162 vaccines has not been tested in humans. However, as presented in Section 2.5 in more detail, BioNTech has clinical experience with two of the RNA formats used in BNT162 vaccines, namely uRNA and modRNA and in addition to BioNTech`s own data, clinical trials with the three RNA formats in similar liposomal formulations are conducted by other parties.

BioNTech`s immune oncology programs using uRNA and modRNA in clinical trials are summarized in Table 1. More than 613 patients have been dosed repeatedly with uRNA in a similar but not identical liposomal formulation as well as non-liposomally formulated uRNA in BioNTech`s oncology clinical trials. Furthermore, 22 patients have been dosed with BioNTech's modRNA (non-liposomally formulated) in an ongoing clinical trial.

Based on the sum of such data the potential risks linked to the trial treatments are expected to be mostly related to the mode-of-action and the RNA-intrinsic stimulation of innate immune sensors initiated at the site of local application.

As such, mostly injection site reactions of transient nature may be a potential risk. Another potential risk may be systemic reactions. The listed risks can be managed using routine symptom driven standard of care.

Prior clinical experience with similar RNA products developed by BioNTech indicates that the RNA distribution to the liver does not pose a safety risk, nonetheless, liver parameters will be carefully monitored in the planned clinical trials.

Vaccine-related enhanced disease has been reported in the literature from non-clinical studies investigating different vaccine formulations tested to prevent various coronavirus-induced diseases. Such effects have not been documented so far for SARS-CoV-2. No data are currently available to exclude that BNT162 may cause enhanced disease in vaccinated subjects. The planned clinical trials will include monitoring of possible COVID-19-related symptoms in trial subjects.

6.3.3 Identified risks

Currently, there are no data available from the use of the BNT162 vaccines in humans. Therefore, no risks have been identified.

6.3.4 Risk evaluation summary

The sponsor considers all of the listed risks to be manageable using routine symptom driven standard of care and justified given:

- the urgent need for the development of new prophylactic vaccines,
- the threat posed by the increasing number of globally distributed outbreaks of SARS-CoV-2 infection,
- the potential of the BioNTech platform of RNA-based vaccines:
    - to rapidly deliver high numbers of vaccine doses rapidly in a single production campaign, and
    - to be both well tolerated and effective.

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INVESTIGATOR'S BROCHURE

BNT162/C4591001

Version: 4.0 **Date:** 03 JUL 2020

Sponsor: BioNTech RNA Pharmaceuticals GmbH
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55131 Mainz,
Germany

Reference safety information for the investigational medicinal products (IMPs) is provided in Section 6.2.

Document History

Use	Date	Version number
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With updated non-clinical content.	17 APR 2020	3.0
With updated non-clinical and clinical content.	03 JUL 2020	4.0

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
ALAT	Alanine-aminotransferase
ALKP	Alkaline phosphatase
ASAT	Aspartate-aminotransferase
BNT162a	BNT162 RNA-LNP vaccine utilizing uridine 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.)
COVID-19	Coronavirus Disease 2019
d	Day(s)
ELISA	Enzyme-Linked Immunosorbent Assay
GGT	Gamma (γ)-glutamyl transpeptidase
GLP	Good Laboratory Practice
h	Hour(s)
HA	Hemagglutinin
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IL	Interleukin
IM	Intramuscular(ly)
IMP	Investigational Medicinal Product
IV	Intravenous(ly)
LNP	Lipid nanoparticle
modRNA	Nucleoside modified messenger RNA
mRNA	Messenger RNA
NCT	ClinicalTrials.gov identifier
NHP	Non-human primates
pVNT	Pseudovirus-based neutralization assay
RBC	Red blood cell
RBD	Receptor Binding Domain
RNA	Ribonucleic acid
S protein	SARS-CoV-2 spike-protein
saRNA	Self-amplifying messenger RNA
SARS-CoV-2	The virus leading to COVID-2019
Th1	Type 1 T helper cells
uRNA	Non-modified uridine messenger RNA
WHO	World Health Organization

NOTES FOR THE READER

The BioNTech group is a holding comprising several subsidiaries including BioNTech RNA Pharmaceuticals GmbH.

1 SUMMARY

There is an urgent need for the development of a new prophylactic vaccine given the threat posed by the increasing number of globally distributed outbreaks of Severe Acute Respiratory Syndrome (SARS) -CoV-2 infection and thus its associated disease Coronavirus Disease 2019 (COVID-19).

The development of a ribonucleic acid (RNA)-based vaccine encoding a viral antigen that is translated by the vaccinated organism to protein to induce a protective immune response provides significant advantages over more conventional vaccine approaches.

At BioNTech, 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 non-clinical safety and toxicity of the BNT162 family of lipid nanoparticle (LNP) enveloped uRNA, modRNA, and saRNA vaccine platforms encoding SARS-CoV-2 antigens was tested in a GLP-compliant repeat-dose toxicity study. In this study in Wistar Han rats, administration of the vaccine candidates BNT162a1, BNT162b1, BNT162b2, or BNT162c1 using intramuscular (IM) injections weekly for 2 (BNT162c1) or 3 administrations was tolerated without evidence of systemic toxicity. Non-adverse inflammatory changes at the injection sites and the draining lymph nodes, increased hematopoiesis in the bone marrow and spleen, and clinical pathology changes consistent with an immune response or inflammation in the injection sites were observed. The findings in this study are consistent with those typically associated with the IM administration of antigens and/or LNPs.

BNT162 vaccine candidates based on the uRNA, modRNA, and saRNA formats are currently under investigation in two clinical trials with healthy subjects (men and women) aged between 18 and 85 years. Two further clinical trials are planned.

As of June 22nd 2020, a total of 248 subjects (men and women) were vaccinated with BNT162 candidate vaccines in the ongoing clinical trials BNT162-01 and BNT162-02/C4591001: BNT162a1 (75 single-dose [SD] and 42 prime/boost [P/B]), BNT162b1 (105 [SD] and 46 [P/B]), BNT162b2 (44 [SD] and 0 [P/B]), and BNT162c2 (24 [SD]).

In the ongoing trials, the pattern of tolerability is, as anticipated, broadly typical of vaccines administered intramuscularly, consistent with the mode of action of the BNT162 vaccines and the available non-clinical/clinical data, with most subjects reporting flu-like symptoms and injection site reactions. Based on reports in subject diaries, the local tolerability of BNT162b1 in elderly subjects aged 65 to 85 years was comparable to that recorded for younger subjects aged 18 to 55 years. Based on reports in subject diaries, the pattern of systemic reactogenicity appears similar between the two age groups, possibly with a lower overall incidence in the elderly subjects in comparison to the younger adults at equal doses. Reactogenicity seems slightly more pronounced following the boost (second) dose 21 days after the initial prime dosing. All unsolicited adverse events (AEs) resolved spontaneously or with simple medical management. Most of the unsolicited AEs were mild or moderate in severity. No serious adverse events (SAEs) were reported within the post-vaccination observation period. No subjects were withdrawn due to related AEs. Preliminary data in elderly subjects show a comparable to lower reactogenicity based on

the observed local reactions and system events in similar doses. This observation may indicate a lower innate immune activation capability of elderly.

Preliminary data in younger subjects (aged 18 to 55 years) treated in the ongoing BNT162 trials, backed by non-human primate (rhesus macaque) immunogenicity data, have shown that BNT162b1 is immunogenic in the tested dose range. Immunogenicity in humans aged >55 years is not yet known.

BNT162b3 encodes a membrane-anchored variant of the receptor binding domain (RBD) of the SARS-CoV-2 spike-protein (S protein). The candidate is highly homologous to BNT162b1 and BNT162b2 with regard to the RNA chemistry (modRNA containing pseudo-methyl uridine). As RNA-chemistry defines the innate immune activation pattern and thus potential reactogenicity, tolerability data obtained with the BNT162b1 and BNT162b2 vaccine variants is indicative for tolerability of BNT162b3. BNT162b1 and BNT162b3 encode the same antigen, the difference being that the antigen is presented in a different way to the immune system. BNT162b3 vaccine has shown superior early immunogenicity in mice as well as in non-human primates (NHP), and thus may show the superior vaccine performance compared with BNT162b1.

2 INTRODUCTION

2.1 Background

SARS-CoV-2 infections and the disease this virus causes, COVID-19 are increasing every day and is spreading globally. The World Health Organization (WHO) classified the COVID-19 outbreak as pandemic on March 11th, 2020. The WHO Situation Update Report dated June 30th, 2020 noted 9,843,073 confirmed cases with 495,760 deaths globally (WHO Situation Update Report 160).

There are currently no approved vaccines or antiviral drugs to prevent or treat infection with SARS-CoV-2 or its associated disease COVID-2019 (Habibzadeh and Stoneman 2020).

2.2 BioNTech's RNA therapeutics

BioNTech has longstanding and diversified expertise in utilizing messenger RNA (mRNA) to deliver genetic information to cells, where it is used to express proteins for the therapeutic effect. BioNTech has been working in the RNA field for more than a decade and is developing a portfolio of RNA therapies that utilize four different mRNA formats and three different formulations to derive five distinct platforms, each optimized for delivering a particular therapeutic mode-of-action.

These mode-of-actions include using mRNA as a vaccine to induce antibody and T-cell immune responses. Three of these platforms are currently in human testing in oncology indications, primarily as repeatedly IV administered therapeutic cancer vaccines, where over 613 patients have been dosed to date (data on file). This clinical experience includes a large number of patients who have had long term exposure, i.e., who have received more than 8 IV administrations.

RNA is a highly versatile multi-purpose molecule. What makes it attractive as vaccine platform is that it enables timely and effective response to emerging threats. RNA 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 is considered safe. Vaccination with RNA in general generates robust immune responses as RNA not only delivers the vaccine antigen, but also has intrinsic adjuvanticity.

The production of RNA requires only a single development and manufacturing platform, irrespective of the encoded pathogen antigens. Thus, RNA has the potential of rapid, cost-efficient, high-volume manufacturing and flexible stockpiling (long term storage of low-volume libraries of frozen plasmid and unformulated RNA, which can be rapidly formulated and distributed). BioNTech has expertise in production-process development for various RNA chemistries and formulations.

2.3 Introduction to BioNTech RNA-based vaccines

A LNP-formulated RNA-based vaccine would provide one of the most flexible, scalable, and fastest approaches to provide protection against new, fast spreading, virus infections (Rauch et al. 2018; Sahin et al. 2014).

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

RNA vaccines are molecularly defined, highly purified immunogens. 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 an 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: RNA which contains the standard nucleoside uridine (uRNA;), nucleoside-modified RNA (modRNA), in which uridine is replaced by the nucleoside pseudo-uridine;, and self-amplifying RNA (saRNA), which also contains uridine nucleosides (Figure 1).

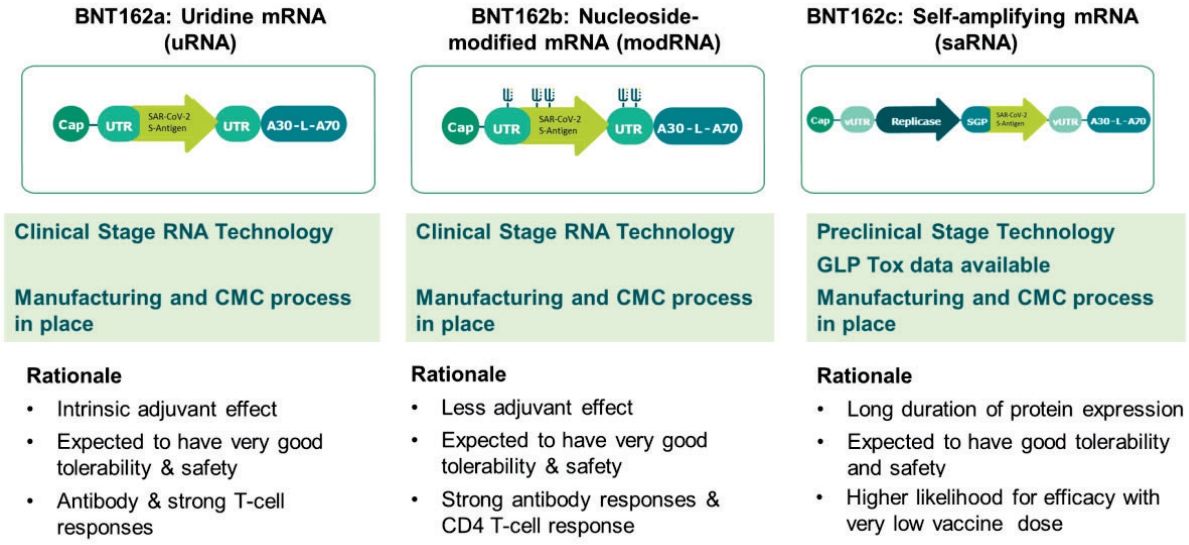


Figure 1: Overview of the three RNA platforms

The RNA vaccine molecules are capped, contain ORFs flanked by the UTR, and have a polyA-tail at the 3' end. The ORF of the uRNA and modRNA vectors encode the vaccine antigen. The saRNA has two ORFs. The first ORF encodes an alphavirus-derived RNA-dependent RNA polymerase (replicase), which upon translation mediates self-amplification of the RNA. The second ORF encodes the vaccine antigen.

Abbreviations: A30-L-A70 = poly(A) tail interrupted by a linker; CMC = chemistry, manufacturing and controls; SGP= subgenomic promotor; ORF = open reading frame; UTR = untranslated region; vUTR = viral untranslated region.

The utility of each of these RNA platforms for the development of infectious disease vaccines is supported by various non-clinical studies that demonstrated the efficient induction of potent neutralizing antibody and T-cell responses against a variety of viral pathogens including influenza, Ebola, human immunodeficiency virus (HIV), and Zika virus (Vogel et al. 2018; Moyo et al. 2018; Pardi et al. 2017).

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 2). 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.

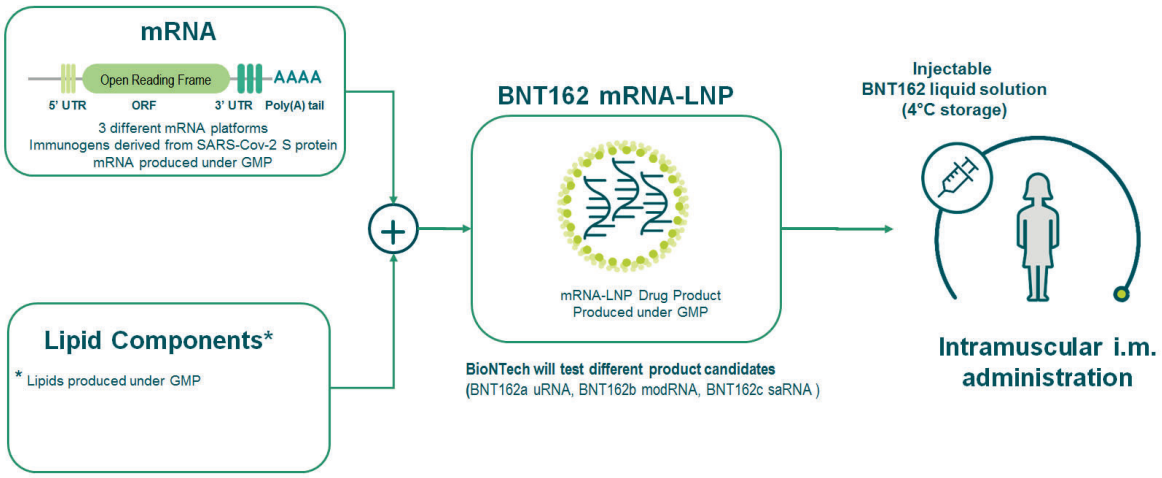


Figure 2: RNA-LNP-based BNT162 vaccines

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 IM injection. Abbreviations: GMP = good manufacturing practice; i.m. = intramuscular; mRNA = messenger RNA; ORF = open reading frame; RNA-LNP = RNA complexed with liposomes; UTR = untranslated region.

The three RNA platforms used in the BNT162 vaccine candidates have complementary strengths (Figure 1): 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 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.

All vaccine candidates may be administered using prime/boost or prime-only administration regimens (Figure 3).

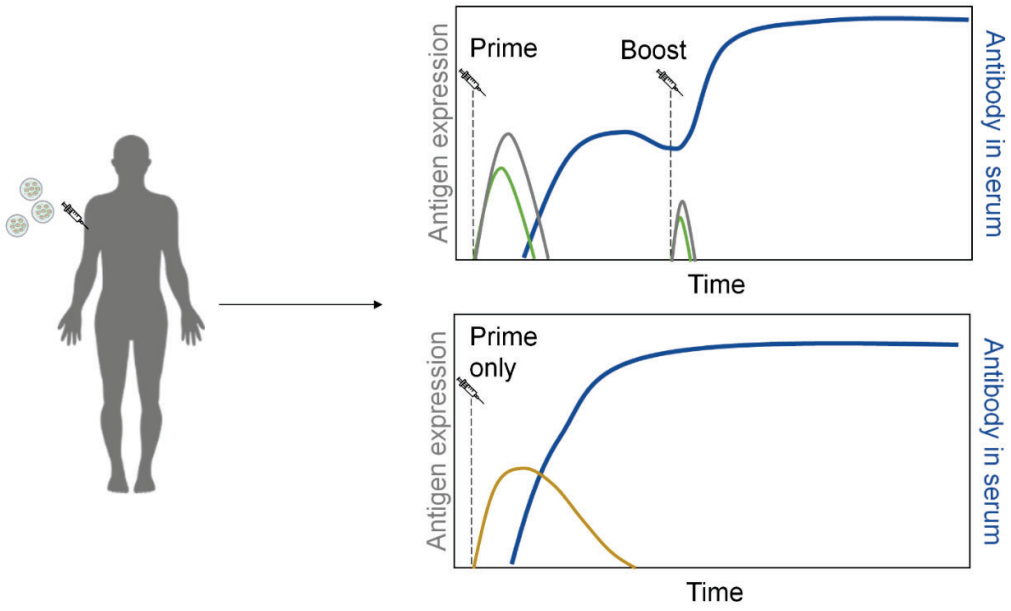


Figure 3: Rationale for the administration schema of BNT162 vaccines

Two different dosing regimens are proposed for the different BNT162 vaccines. While vaccines based on the BNT162a and BNT162b platforms have the highest antigen expression shortly after immunization, a second immunization may be necessary to induce a higher antibody generation (see the upper graph). For vaccines based on the BNT162c platform, due to the self-amplification properties of the saRNA, the antigen expression peaks later and is more prolonged, therefore enabling one immunization to induce a high antibody generation (see the lower graph).

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 spike glycoprotein (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 4 and Figure 5). The 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 receptor-binding domain (RBD) recognizes the host receptor and binds to the target host cell. SARS-CoV and SARS-CoV-2 have similar structural properties and bind to the same host cell receptor, angiotensin converting enzyme 2 (ACE-2) (Zhou et al. 2020). The S protein is not only pivotal for host cell recognition and entry, but also for the induction of virus neutralizing antibodies by the host immune system (Zakhartchouk et al. 2007; Yong et al. 2019).

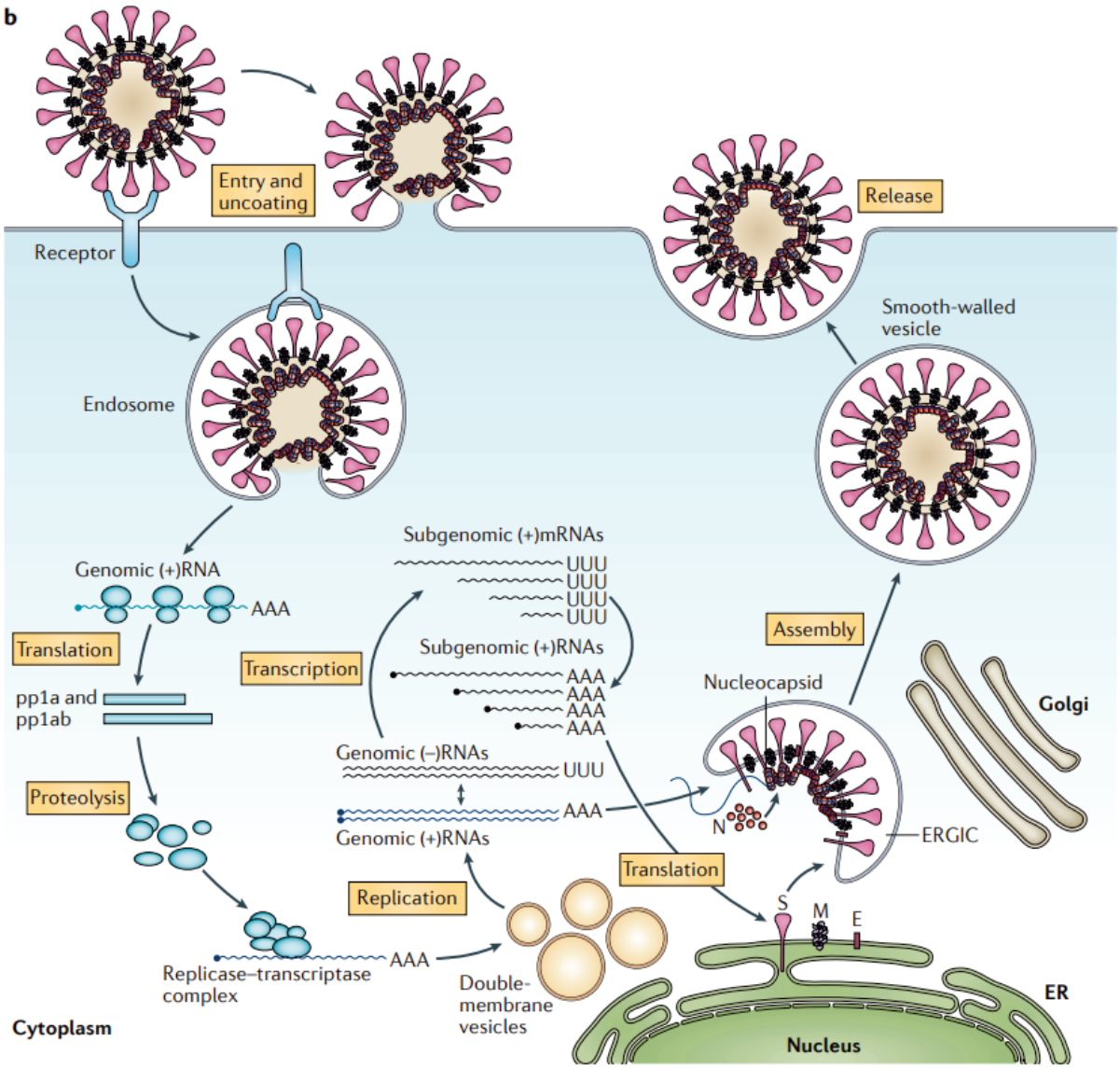


Figure 4: Schematic lifecycle of a Coronavirus

(Source: de Wit et al. 2016)

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).

Targeting the S protein, as well as its S1 cleavage fragment or the RBD alone, with vaccines is sufficient to induce neutralizing immune responses (Al-Amri et al. 2017). The RBD forms membrane distal "heads" on the S protein that are connected to the 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).

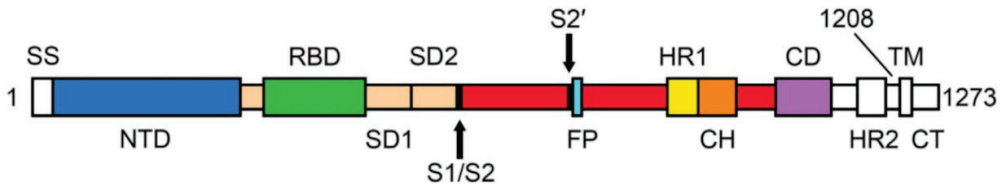


Figure 5: Schematic overview of the organization of the SARS-CoV-2 S glycoprotein

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); source: modified from Wrapp et al. 2020. NTD = N-terminal Domain.

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 (Figure 6).

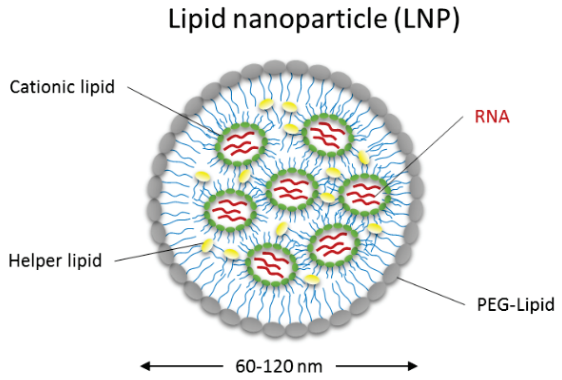


Figure 6: Schematic overview of a LNP

The LNPs are composed of four different lipids in a defined ratio. During mixing of the RNA and the dissolved lipids, the lipids form the nanoparticles encapsulating the RNA. After

injection, the LNPs are taken up by the cells, and the RNA is released into the cytosol. In the cytosol, the RNA is translated to the encoded viral antigen.

The antigen may be incorporated into the cellular membrane or secreted into the extracellular environment and induce an adaptive immune response. In addition, as S protein is the antigen that recognizes and drives infection of the host cells, it is a key target of virus neutralizing antibodies. Furthermore, as RNA-expressed S protein is fragmented intracellularly, the resulting peptides can be presented at the cell surface, triggering a specific T cell-mediated immune response with activity against the virus.

2.4 Clinical development

BNT162 vaccine candidates based on the uRNA, modRNA, and saRNA formats are currently under investigation in two clinical trials with healthy subjects (men and women) aged between 18 and 85 years. Two further clinical trials are planned.

For an overview of the different BNT162 vaccine candidates under clinical investigation, see Table 1.

Table 1: Characteristics of the different BNT162 vaccine candidates subjected to clinical investigation

RNA platform	BNT162 vaccine candidate (Product code)	Encoded antigen	Evaluation in clinical trial
uRNA	BNT162a1	SARS-CoV-2 RBD, a secreted variant	BNT162-01 (GER)
modRNA	BNT162b1	SARS-CoV-2 RBD, a secreted variant	BNT162-01 (GER) and C4591001 (USA) BNT162-03 (CHN) - in planning
	BNT162b2	Full length SARS-CoV-2 spike protein bearing mutations preserving neutralization-sensitive sites	BNT162-01 (GER) and C4591001 (USA)
	BNT162b3	SARS-CoV-2 RBD, a membrane-bound variant	BNT162-04 (GER) – in planning
saRNA	BNT162c2	Full length SARS-CoV-2 S protein bearing mutations preserving neutralization-sensitive sites	BNT162-01 (GER)

CHN = China; GER = Germany; modRNA = modified RNA; RBD = receptor binding domain; saRNA = self-amplifying RNA; uRNA = uridine RNA; USA = United States (of America).

The safety and immunogenicity of five BNT162 vaccine candidates (BNT162a1, BNT162b1, BNT162b2, BNT162b3, BNT162c2) will be investigated clinically, as part of a program to develop a prophylactic vaccine to prevent infection with SARS-CoV-2 and thus its associated disease COVID-19.

The clinical program started with the immunization of healthy adults, both men and women, aged between 18 and 55 years, and has since then been expanded to include older healthy adults aged between 56 and 85 years. If the immunization is found to be well

tolerated, immunization will also be investigated in the likely target population (e.g., at risk populations such as immunocompromised populations).

Since the BNT162 vaccine candidates utilize the same LNP formulation, the observed safety profiles will be considered representative for all candidate vaccines in combination with the respective platform. Likewise, since some of BNT162 vaccine candidates lead to expression of the same encoded viral antigen, the observed safety profiles will be considered representative for all candidate vaccines utilizing the same encoded viral antigen.

3 PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

The following section gives general information about the physical, chemical and pharmaceutical properties of the BNT162 family of prophylactic RNA-based vaccine candidates encoding viral antigens that are translated by the vaccinated organism to protein to induce a protective immune response. The RNA components of the RNA-LNP drug products of the three different RNA platforms for clinical investigation are the non-modified uridine containing mRNA (uRNA), nucleoside modified mRNA (modRNA), and self-amplifying mRNA (saRNA), each encoding 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 1.

3.1 Description of the drug substance

3.1.1 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 viral S protein of SARS-CoV-2.

Non-modified uridine mRNA (uRNA)

The active principle of the non-modified messenger RNA (uRNA) drug substance is a single-stranded, 5′-capped mRNA that is translated upon entering the cell. In addition to the sequence encoding the SARS-CoV-2 antigen (i.e., open reading frame), 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).

Nucleoside modified mRNA (modRNA)

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

Self-amplifying mRNA (saRNA)

The active principle of the self-amplifying mRNA (saRNA) drug substance is a single-stranded 5'-capped RNA, which self-amplifies upon 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., open reading frame) and the common structural elements in the uRNA and modRNA, the saRNA vector contains an additional open reading frame, which encodes the Venezuelan equine encephalitis (VEE) virus RNA-dependent RNA polymerase replicase and a subgenomic promotor plus conserved sequence elements supporting replication and translation, but no other VEE virus coding sequences.

The physicochemical properties of the RNA drug substances are listed in Table 2.

Table 2: General properties of uRNA, modRNA and saRNA drug substances

Parameter	Value/Description	
	uRNA/modRNA	saRNA
Appearance	Clear, colorless liquid	
Theoretical length	~1200 to 4500 nucleotides*	~10,000 to 13,000 nucleotides*
Concentration	1.70 ± 0.17 mg/mL; 2.25 ± 0.25 mg/mL**	
Extinction coefficient at 260 nm	25 L/g × cm	
pH	7.0 ± 1.0	

* Depending on the finally selected antigen.
** Depending on batch size.

3.2 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 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 composition of RNA drug products for use in the planned clinical trials and the function of the respective components are given in Table 3. The LNP composition is the same for all five BNT162 vaccine candidates.

Table 3: Composition of drug products

Component	Quality standard	Function
Drug substance	In-house	Active
ALC-0315 [1]	In-house	Functional lipid
ALC-0159 [2]	In-house	Functional lipid
DSPC [3]	In-house	Structural lipid
Cholesterol	Ph. Eur.	Structural lipid
Sucrose	NF/Ph. Eur.	Cryoprotectant
NaCl	USP/Ph. Eur.	Buffer
KCl	USP/Ph. Eur.	Buffer
Na_2HPO_4	USP/Ph. Eur.	Buffer
KH_2PO_4	NF/Ph. Eur.	Buffer
Water for injection	Ph. Eur.	Solvent/Vehicle

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

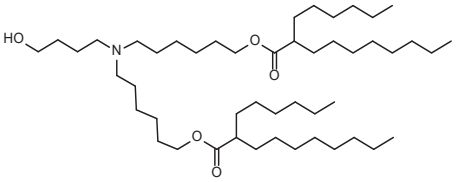
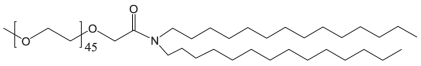
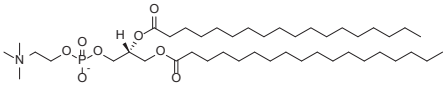
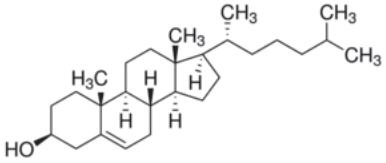
3.2.1 Description of the excipients

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

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 4.

Table 4: 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 (not applicable)	766	$C_{48}H_{95}NO_5$	Liquid (oil) -20ºC	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) 
ALC-0159 (1849616-42-7)	~2400-2600	$C_{30}H_{60}NO(C_2H_4O)_nOC_{34}H_{68}NO$ n=45-50	Solid -20ºC	2-[(polyethylene glycol)-2000]-N,N-ditetradecyclacetamide 
DSPC (816-94-4)	790	$C_{44}H_{88}NO_8P$	Solid -20ºC	1,2-Distearoyl-*sn*-glycero-3-phosphocholine 
Cholesterol (57-88-5)	387	$C_{27}H_{46}O$	Solid -20ºC	

CAS = Chemical Abstracts Service; DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine.

3.3 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.

3.4 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., uRNA (product code: BNT162a1), modRNA (product codes: BNT162b1, BNT162b2, BNT162b3), saRNA (product code: BNT162c2).

IMP administration route:	Solution for IM injection.
Dosage frequency:	The BNT162 vaccines will be administered either using single dose or prime/boost regimens.

3.5 Storage and handling of the IMP

Drug product of BNT162 will be provided as a frozen concentrate for solution for injection at a concentration of 0.50 mg/mL. For preparation of solution for injection, the drug product will be thawed and diluted with isotonic sodium chloride solution (0.9% NaCl, saline) by a one-step dilution process. The concentration of the final solution for injection varies depending on the respective dose level to be administered.

Administration has to be performed within 6 h after begin of preparation due to the risk of microbial contamination and considering the multiple-dose approach of the preparation process. In this period of 6 h, two conditions are allowed: room temperature for preparation, handling and transfer as well as 2 to 8°C for storage.

Detailed instruction for storage and handling are given in Pharmacy Manual.

4 NON-CLINICAL STUDIES

RNA vaccines have shown great potential in generating immune responses in animal models and confer protection against various viruses such as Zika, human immunodeficiency virus (HIV), and Influenza virus (Vogel et al. 2018; Moyo et al. 2018; Pardi et al. 2017). Unpublished immunogenicity data from RNA based vaccines against other viruses such as Ebola, Marburg, and Lassa virus indicate that the range of applications for anti-viral RNA vaccines is broad (data on file).

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. For this purpose, mice were immunized once with the vaccine candidate and different immunological read-outs were performed during the individual studies. In serology analysis, antigen binding immunoglobulin G (IgG) responses were detected by an enzyme-linked immunosorbent assay (ELISA) as well as functional antibody responses to the vaccine candidates by a pseudovirus-based neutralization assay (pVNT). Cellular analysis included the T-cell specific response against the antigen. Candidate specific data reports are available.

Furthermore, supportive data are provided. The safety and immunogenic supportive data from the described studies are considered to be representative of the respective LNP-RNA platform and independent of the encoded antigen. Supportive test items are LNP-formulations of one of the three RNA-platforms in conjunction with:

- a non-SARS-CoV-2-derived viral gene such as Influenza HA (e.g., Sections 4.1.1.2.1)
- one of the two SARS-CoV-2-derived vaccine antigens, but not the one used for the respective clinical candidate (e.g., Sections 4.1.1.2.2, 4.1.1.2.3, 4.1.1.2.4)

Table 5 summarizes the nomenclature used for the BNT162 vaccine candidates to facilitate the review of the provided non-clinical information.

Table 5: Characteristics of the different BNT162 vaccine candidates subjected to non-clinical investigation

RNA platform	Product code	Encoded antigen	Sequence variant **	Evaluation in non-clinical studies
uRNA	BNT162a1	SARS-CoV-2 RBD, a secreted variant	V5	Toxicology study 38166 Immunological studies R-20-0040 and R-20-0140
	BNT162a2	Full length SARS-CoV-2 spike protein bearing mutations preserving neutralization-sensitive sites	V8	Immunological study R-20-0052
modRNA	BNT162b1	SARS-CoV-2 RBD, a secreted variant	V5	Toxicology study 38166, Immunological studies R-20-0042 and R-20-0084, VAC-2020-NIRC-COVID-1681*
	BNT162b2	Full length SARS-CoV-2 spike protein bearing mutations preserving neutralization-sensitive sites[#]	V8 [#]	Toxicology study 38166, Immunological studies R-20-0054, VAC-2020-NIRC-COVID-1681*
			V9 [#]	Immunological study R-20-0085
	BNT162b3	SARS-CoV-2 RBD, a membrane-bound variant	V5TM	Immunological study R-20-0145*
saRNA	BNT162c1	SARS-CoV-2 RBD, a secreted variant	V5	Toxicology study 38166, Immunological study R-20-0041*
	BNT162c2	Full length SARS-CoV-2 spike protein bearing mutations preserving neutralization-sensitive sites	V9	Immunological study R-20-0053

* Final report pending.

** Sequence variant refers to the nucleotide sequence of the RNA component encoding the antigen.

[#] Note that the two variants of the BNT162b2 vaccine. The RNA component of the two variants have different nucleotide sequences, but both encode the same antigen, i.e., the full length SARS-CoV-2 sp ke protein bearing mutations preserving neutralization-sensitive sites.

4.1 Non-clinical pharmacology

4.1.1 Primary Pharmacodynamics

Table 6 summarizes the studies on primary pharmacodynamics.

Table 6: Studies on primary pharmacodynamic effects

Study number	Study Type	Species / Test System	Product code		Dose [µg]	Results	Cross reference
BNT162 vaccine studies (clinical candidates)							
R-20-0074	*In vitro* antigen expression and localization	HEK293T cells	BNT162a1 BNT162b1 BNT162b2 BNT162c2	uRNA V5 modRNA V5 modRNA V9 saRNA V9	1, 2, 5	All tested items expressed the encoded S protein derived antigen.	Section 4.1.1.1
R-20-0040 and R-20-0140	*In vivo* immunogenicity	Mice BALB/c	BNT162a1	uRNA V5	1, 5, 10	Immunogenicity was shown in all tested doses.	Section 4.1.1.3.1
R-20-0042 and R-20-0084	*In vivo* immunogenicity	Mice BALB/c	BNT162b1	modRNA V5	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 4.1.1.3.2
VAC-2020-NIRC-COVID-1681*	*In vivo* immunogenicity	Non-human primate (NHP) Maccaca mulatta	BNT162b1	modRNA V5	30, 100	Immunogenicity was shown in all tested doses.	Section 4.1.1.3.6
R-20-0085	*In vivo* immunogenicity	Mice BALB/c	BNT162b2	modRNA V9	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 4.1.1.3.3
R-20-0145*	*In vivo* immunogenicity	Mice BALB/c	BNT162b3	modRNA V5TM	0.2, 1	Immunogenicity was shown in all tested doses.	Section 4.1.1.3.4
COVID-Rh-2020-01	*In vivo* immunogenicity	Non-human primate (NHP) Maccaca mulatta	BNT162b3	modRNA V5TM	30	Immunogenicity was shown.	Section 4.1.1.3.6
R-20-0053	*In vivo* immunogenicity	Mice BALB/c	BNT162c2	saRNA V9	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 4.1.1.3.5

Study number	Study Type	Species / Test System	Product code		Dose [µg]	Results	Cross reference
Supportive studies (non-clinical candidates)							
R-20-0074	*In vitro* antigen expression and localization	HEK293T cells	BNT162a2 BNT162b2 BNT162c1 BNT162c2	uRNA V8 modRNA V8 saRNA V5 saRNA V8	1, 2.5	All tested items expressed the encoded S protein derived antigen.	Section 4.1.1.1
R-20-0073	In vivo immunogenicity	Mice BALB/c	-	modRNA encoding a non-SARS-CoV-2 antigen (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.	Section 4.1.1.2.1
R-20-0052	*In vivo* immunogenicity	Mice BALB/c	BNT162a2	uRNA V8	1, 5, 10	Immunogenicity was shown in all tested doses.	Section 4.1.1.2.2
R-20-0041*	*In vivo* immunogenicity	Mice BALB/c	BNT162c1	saRNA V5	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 4.1.1.2.3
R-20-0054	*In vivo* immunogenicity	Mice BALB/c	BNT162b2	modRNA V8	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 4.1.1.2.4
VAC-2020-NIRC-COVID-1681*	*In vivo* immunogenicity	NHP Maccaca mulatta	BNT162b2	modRNA V8	30, 100	Immunogenicity was shown in all tested doses.	Section 4.1.1.3.6
R-20-0072	*In vivo* distribution	Mice BALB/c	-	modRNA encoding luciferase	2	The surrogate of the BNT162b platform was expressed in mice with distribution in the muscle (injection site) and liver.	Section 4.2.3

All study types are based on the analysis of S-specific immune responses elicited in BALB/c mice. The study for BNT162b3 is ongoing.

* Final report pending.

4.1.1.1 *In vitro* expression of BNT162 RNA

To analyze whether the two SARS-CoV2 derived vaccine antigens V5 and V8/V9 are robustly translated from the respective RNA drug substances, *in vitro* assays were performed and antigen expression was assessed using Western blots (Figure 7), or immune-fluorescence analysis (Figure 8). All RNA-components expressed the desired immunogens (see also data report R-20-0074).

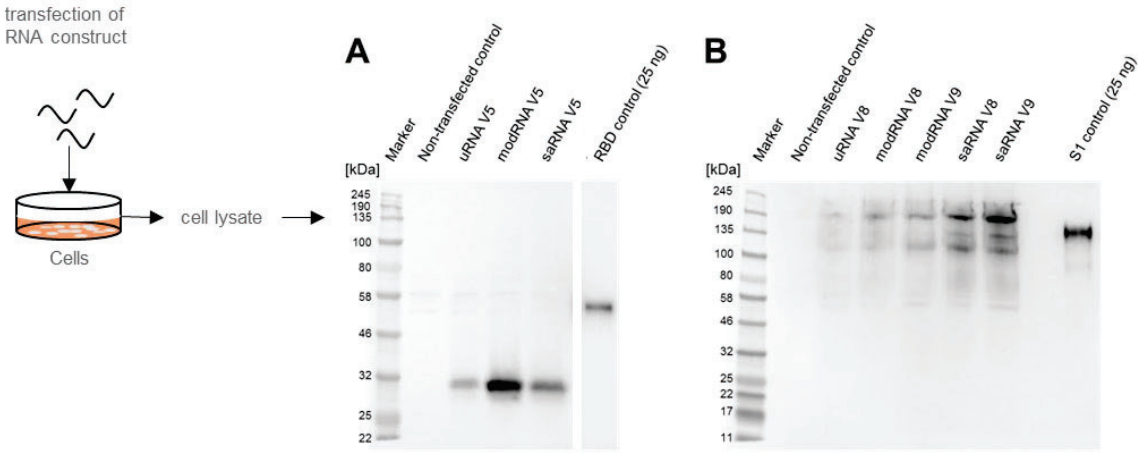


Figure 7: Detection of antigen expression using Western blot analysis

HEK 293T cells were transfected with 1 µg of the RNA substances (A) BNT162a1 (uRNA encoding V5), BNT162b1 (modRNA encoding V5) and BNT162c1 (saRNA encoding the V5). For the V8/V9 constructs (membrane-anchored full-length S protein with two point mutations within the central helix domain which lock the S protein in an antigenically optimal prefusion conformation), (B) BNT162a2 (uRNA encoding V8), BNT162b2 (modRNA encoding V8/V9) and BNT162c2 (saRNA encoding V8/V9) were tested. After 18 h of transfection, cell lysates were transferred to for Western blot and detected proteins are visualized. All samples showed antigen expression and specific bands were detected for the V5-encoding constructs at 30 kDa, while the V8/V9 encoded protein runs at an expected size of 140 kDa. Recombinant proteins (RBD [25 ng], expected size: 52 kDa / S1 [25 ng], expected size 102 kDa) were used as assay controls.

Co-localization of the immunogens with an endoplasmic reticulum marker was shown by immunofluorescence experiments in HEK293T cells expressing BNT162b1 (modRNA encoding V5) and BNT162c2 (saRNA encoding V9), respectively. These results suggest that both the secreted, trimerized variant of the RBD of the SARS-CoV-2 S protein and the membrane-anchored full-length S protein with two point mutations are processed within the endoplasmic reticulum for secretion or surface expression, which is a prerequisite for increased bioavailability and improved induction of immune response.

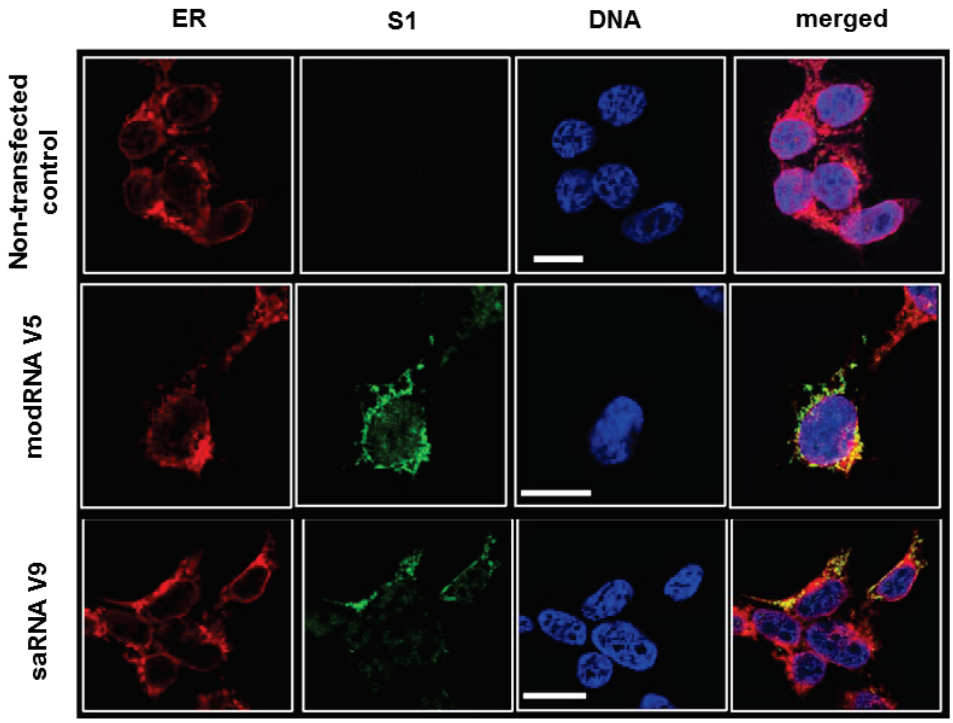


Figure 8: Immunofluorescence staining of cells transfected with modRNA encoding V5 or saRNA encoding V9

HEK293T cells were transfected with 2.5 µg of modRNA encoding the secreted, trimerized RBD (V5) or saRNA encoding the membrane anchored, mutated full-length S protein (V9). After 18, cells were fixed and stained for the endoplasmic reticulum (endoplasmic reticulum, red), the S1 protein subdomain (RBD, green) and for deoxyribonucleic acid (DNA; blue). The merged colored picture shows that both, V5 and V9 co-localize with the endoplasmic reticulum marker localization (scale: 10 µm). A control using non-transfected cells is shown at the top.

As there is information suggesting that membrane-bound antigens are particularly potent in activating B-cells (Batista and Harwood 2009; Bergtold et al. 2005), an additional vaccine candidate was designed and included in the development pipeline. The new RNA-LNP vaccine candidate, BNT162b3, uses a modRNA encoding a membrane-anchored, trimerized variant of the RBD of the SARS-CoV-2 S protein (V5TM).

To analyze whether the antigen V5TM is expressed by the respective mRNA and transported to the cell surface, *in vitro* assays were performed and antigen expression was assessed by flow cytometry or immune-fluorescence analysis (Figure 9). BNT162b3 was detected on the cell surface while BNT162b1 was only detected intracellularly demonstrating a correct and functional design of the constructs.

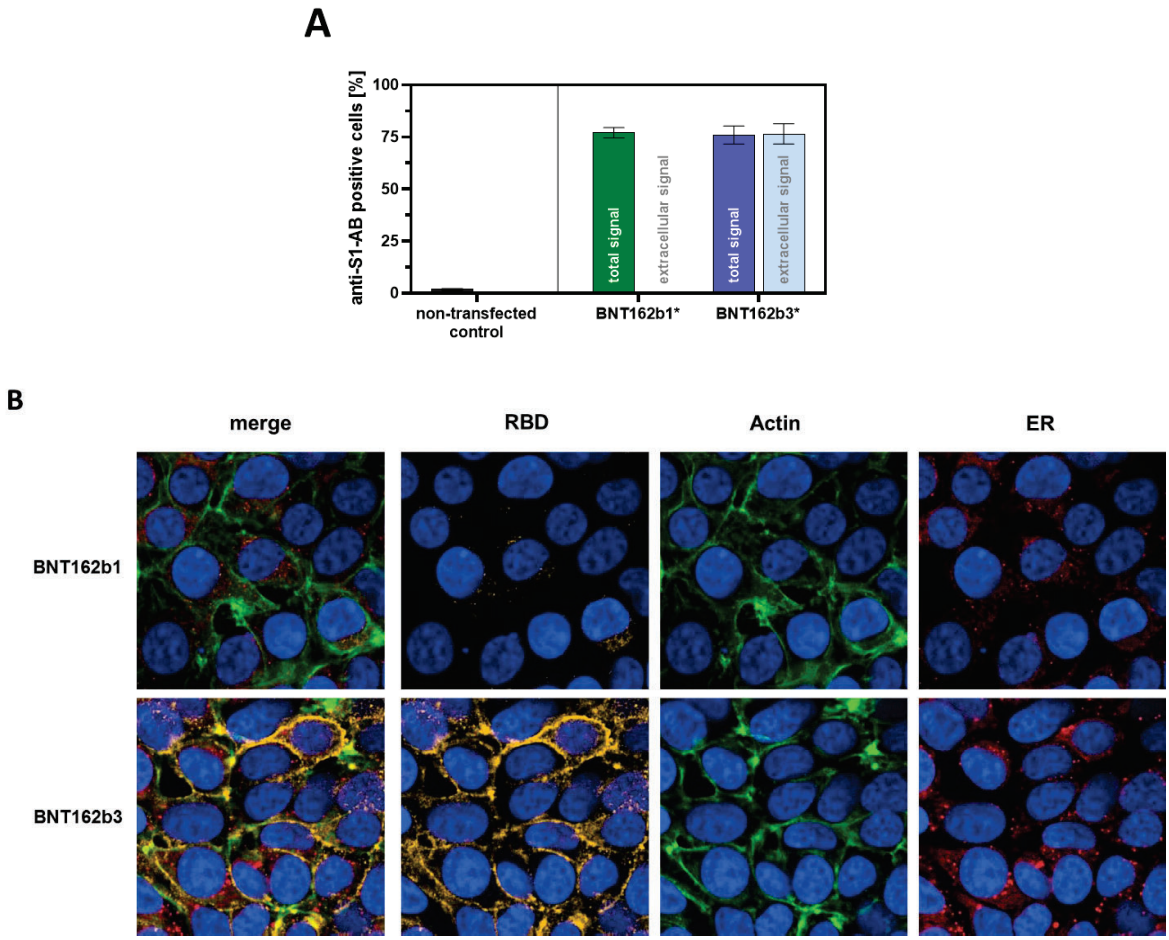


Figure 9: Flow cytometry and immune-fluorescence analysis of BNT162b1 and BNT162b3

A) HEK293T cells were transfected with 1 µg BNT162b1 or BNT162b3. After 18 h, SARS-CoV-2 S1 protein was detected via flow cytometry analysis either as total signal or extracellular only.

* Note that for flow cytometric analysis, only the non-formulated modRNA drug substance (with transfection reagent) was used.

B) Immune-fluorescence analysis of HEK293T cells one day after transfection with BNT162b1 or BNT162b3. Receptor binding domain (RBD) expression is indicated in orange, actin in green and the endoplasmic reticulum (ER) in red; nuclei were stained with DAPI (blue). The diffuse signal after BNT162b1 transfection shows an intracellular distr bution of the antigen localized in the ER, while the BNT162b3 transfection shows in addition a strong membrane localization.

4.1.1.2 *In vivo data* - Supportive immunogenicity studies in mice

The mRNA platforms (uRNA, modRNA, saRNA) used for development of the BNT162 vaccines have been previously evaluated in studies with other viral antigens as immunogens (Moyo et al. 2018; Vogel et al. 2018; Pardi et al. 2017; Pardi et al. 2018).

Vaccines based on these RNA platforms were shown to induce strong antibody responses and expand multifunctional $CD4^+$ and $CD8^+$ T cells. The properties of antigen-specific immune responses induced by vaccination with these RNA platforms were studied in several species (see Table 7). Vaccination with modRNA is characterized by the strong

expansion of Th1-skewed antigen-specific T follicular helper (Tfh) cells. These cells stimulate and expand germinal center B cells, which results in particularly strong, long-lived, high-affinity antibody responses. The uRNA and saRNA platforms are TLR7/8 agonists and exhibit a higher immune stimulatory activity, which results in type-I interferon release and a strongly Th1 biased $CD4^+$ T cell response as well as strong expansion of cytotoxic T cells (Sahin et al. 2014). Due to self-amplification and prolonged translation, saRNA is able to induce strong $CD4^+$ and $CD8^+$ T cell responses by a prime only administration schedule (Vogel et al. 2018).

Table 7: Platform-specific characteristics of adaptive immune response patterns

	uRNA	modRNA	saRNA
	Source: Pardi et al. 2017, 2018, 2019; Vogel et al. 2018, Kranz et al. 2016	Source: Vogel et al. 2018, Kranz et al. 2016, Pardi et al. 2017, 2018, 2019	Source: Vogel et al. 2018, Moyo et al. 2018
$CD4^+$ T cell response	• Induction of multifunctional strongly Th1+, skewed immune response with induction of IFN-γ+, TNF-α+, IL-2+ CD4+ T cells. • Strong expansion of follicular helper Tfh cells with an IFN-γ+, Tfh cells (mouse, human NHP).	• Strong induction of multi-functional Th1 skewed immune response with induction of +, IFN-γ+, TNF-α+, IL-2+ CD4+ T cells. • Strong expansion of follicular helper Tfh cells with an IFN-γ+, Tfh cells (mouse, human NHP).	• Expansion of a strongly Th1 skewed immune response with, multifunctional Th1+, IFN-γ+, TNF-α+, IL-2+ CD4+ T cells (mouse).
$CD8^+$ T cell response	• Expansion of multifunctional CD8 cytotoxic, effector and long lived memory T cells with an IFN-γ+, TNF-α+, CD107+ phenotype (mouse), human).	• Expansion of multifunctional cytotoxic, effector and long lived memory CD8 T cells with an IFN-γ+, TNF-α+, CD107+ phenotype (mouse, human)).	• Strong expansion of long-lived effector and central memory CD8+ T cells with an IFN-γ+, TNF-α+, CD107+ phenotype (mouse).
Antibody response	• High-titer, high-affinity, long lived neutralizing antibody responses after prime only/boost (mouse, rats, NHP). • ADCC activity (rabbits). • Mouse IgG1 ~ IgG2a).	• High-titer, high-affinity, long lived neutralizing antibody responses after prime/boost only (mouse, rats), NHP). • ADCC activity (rabbits). • Mouse IgG1 ~ IgG2a.	• High-titer, neutralizing antibody responses after prime only (mouse, rats, pig, NHP). • Mouse IgG2a >>IgG1.

ADCC = Antibody-dependent cellular cytotoxicity; IgG = Immunoglobulin G; IL interleukin; IFN = Interferon; NHP = Non-human primate; Tfh = T follicular helper; TNF = Tumor necrosis factor.

4.1.1.2.1 Immunogenicity using influenza hemagglutinin as a model antigen

In murine influenza virus challenge models, all three mRNA platforms (uRNA, modRNA, saRNA) have been shown to confer strong prophylactic vaccine activity.

One study (data report R-20-0073) used a modRNA-LNP vaccine that encodes influenza HA. Mice were injected IM with 1 µg on days 0 and 28 with the HA-encoding, formulated modRNA. On days 14, 28, and 49, blood samples were drawn and tested for antibody and cellular responses to the Influenza virus HA antigen. The analysis showed a high serum antibody response, demonstrated by very high levels of antigen-specific IgG in serum and high influenza virus neutralization titers (Figure 10). Moreover, strong Th1 $CD4^+$ and $CD8^+$ T cell responses (Figure 11) were induced by the modRNA vaccine.

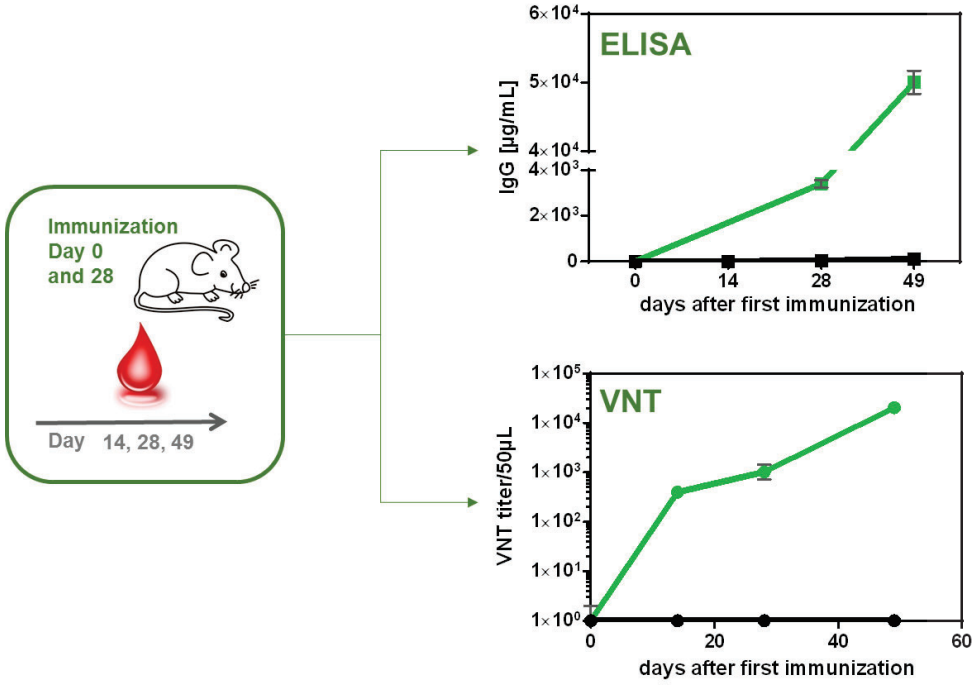


Figure 10: Antibody response elicited by influenza HA using LNP-formulated modRNA

BALB/c mice were immunized twice IM with 1 µg of the vaccine candidate. HA-specific IgG was measured by ELISA. The functionality of the antibodies was measured by influenza virus neutralization.

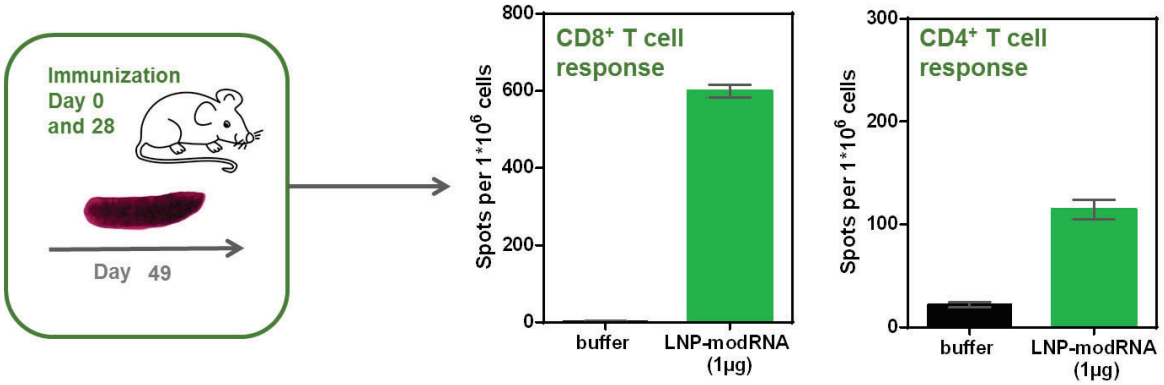


Figure 11: T cell response against influenza HA using the LNP-formulated modRNA platform

BALB/c mice were immunized IM with 1 µg of the vaccine candidate, twice. The T cell response was analyzed using antigen specific peptides to stimulate T cells recovered from the spleen. Interferon IFN-γ release was measured after peptide stimulation using an ELISpot assay.

Treatment with the LNP-formulated modRNA induced a strong immune response across the observation period of 49 d after one immunization, and a second immunization strongly boosted the anti-HA IgG antibody generation (Figure 10).

Similar to the antibody response, the LNP-formulated modRNA encoding for HA induced a high T-cell response (Figure 11).

Various other immunogenicity studies in mice have documented the induction of neutralizing antibodies and antigen-specific Th1 type T cell responses with uRNA and saRNA vaccines encoding influenza virus HA (Vogel et al. 2018).

4.1.1.2.2 Immunogenicity study: BNT162a2 (uRNA encoding antigen V8)

The potency of the LNP-formulated uRNA encoding BNT162a2 was tested in mice. The detailed results are provided in the data report R-20-0052.

BALB/c mice were immunized IM once as outlined in Table 8. Four groups of eight female BALB/c mice were immunized on day 0 with doses of 1 µg, 5 µg or 10 µg per animal of the uRNA encapsulated in LNPs, or with the buffer alone (control group), by intramuscular injection. Blood was collected on days 7, 14, 21, and 28 after immunization to analyze the antibody immune response by ELISA and pVNT.

Total IgG ELISA showed that the construct is immunogenic and induced a dose-dependent generation of antibodies against the S protein S1 antigen and the RBD (Figure 12). First detection of IgG antibodies was possible from day 7 after immunization with an increase of total antibody amount until day 28. Fourteen days after immunization, first animals developed functional neutralizing antibodies. In pVNT analysis all animals displayed neutralizing antibodies on day 28 (Figure 13).

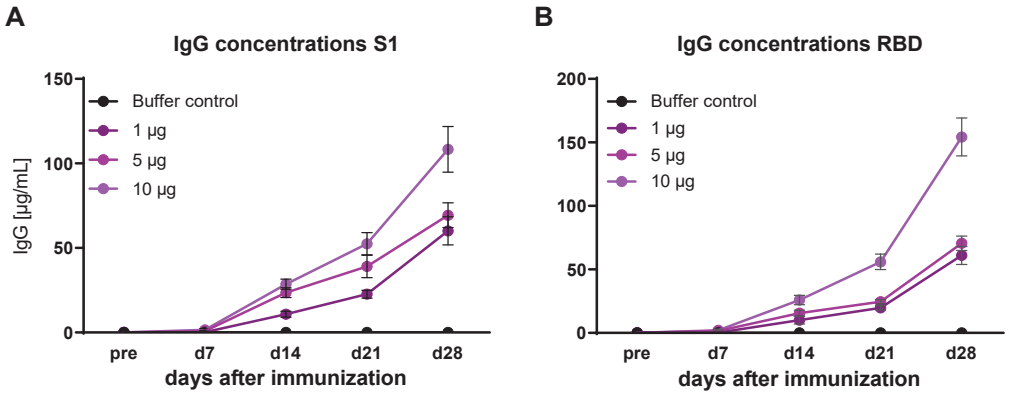


Figure 12: Anti-S IgG response 7, 14, 21, and 28 d after immunization with BNT162a2

BALB/c mice were immunized IM once with 1, 5 or 10 µg of uRNA encoding V8 or buffer. On 7, 14, 21, and 28 days after immunization, animals were bled and the serum samples were analyzed. For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean ant body concentrations are shown (±SEM). Group size n=8.

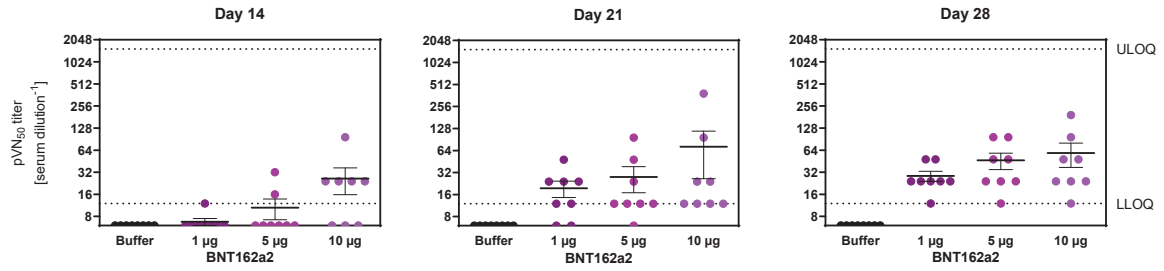


Figure 13: Neutralization of SARS-CoV-2 pseudovirus 14, 21, and 28 d after immunization with BNT162a2

Serum samples were collected on days 14, 21 and 28 after immunizations and titers of virus-neutralizing antibodies were determined by pVNT. Individual VNT titers are shown by dots; group mean values are indicated by horizontal bars (±SEM, standard error of the mean). ULOQ: Upper limit of quantification, LLOQ: Lower limit of quantification. * $p \leq 0.05$.

In summary, the V8 antigen encoded by the uRNA was immunogenic and the antibody titer on day 28 were as follows:

	BNT162a2 1 µg	BNT162a2 5 µg	BNT162a2 10 µg
Anti S1 protein total IgG [µg/mL]	60.1 ± 8.3	69.4 ± 41.6	108.3 ± 13.5
Anti RBD protein total IgG [µg/mL]	61.1 ± 7.1	70.6 ± 5.6	154.3 ± 14.9
pVN50 titer [reciprocal dilution]	28.5 ± 4.2	46.5 ± 10.9	58.5 ± 19.8

4.1.1.2.3 Immunogenicity study: BNT162c1 (saRNA encoding antigen V5)

To understand the potency of the LNP-formulated BNT162c1, BALB/c mice were immunized IM with saRNA encoding for V5 once as outlined in Table 8 and the antibody immune response was analyzed.

Total IgG ELISA showed that the construct is immunogenic and induced a dose-dependent generation of antibodies against the S1 antigen and the RBD within the S1 (Figure 14). Profiling the IgG subtypes, a ratio with a higher level of IgG2a in comparison to IgG1 was detected. In pVNT analysis all animals displayed a dose-dependent formation of neutralizing antibodies (Figure 15).

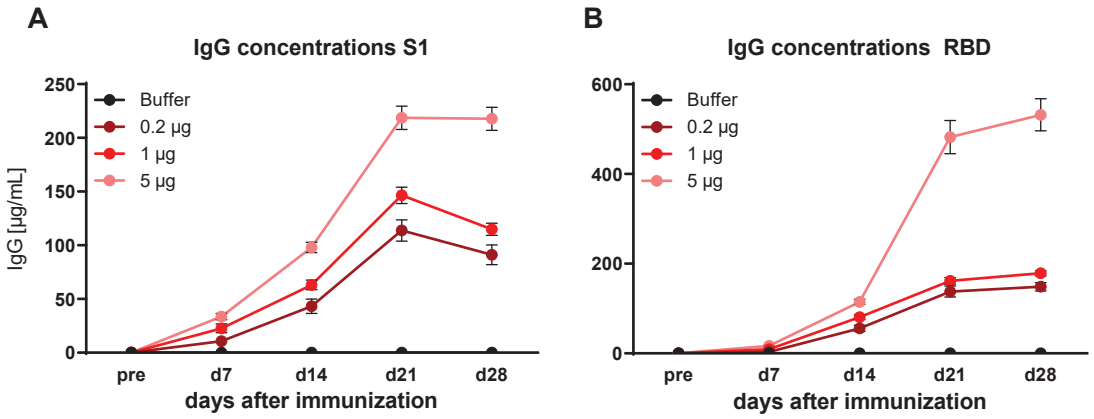


Figure 14: Anti-S IgG response 7, 14, 21, and 28 d after immunization with BNT162c1

BALB/c mice were immunized IM once with 0.2, 1 and 5 µg of saRNA encoding V5 or buffer. On 7, 14, 21, and 28 d after immunization, animals were bled and the serum samples were analyzed. For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean ant body concentrations are shown (±SEM). Group size n=8.

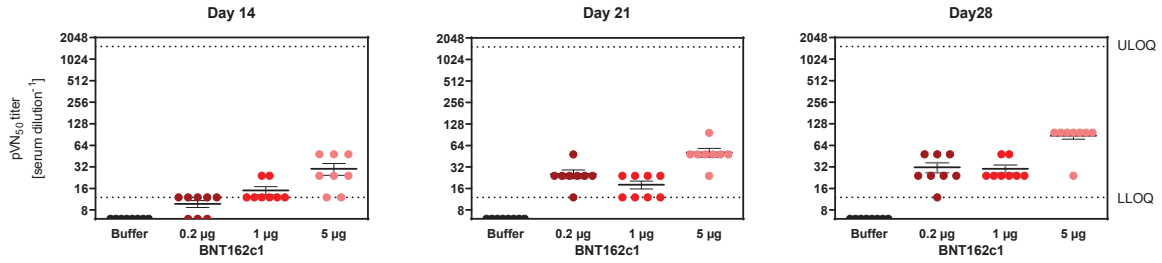


Figure 15: Neutralization of SARS-CoV-2 pseudovirus 14, 21, and 28 d after immunization with BNT162c1

Serum samples were collected on days 14, 21, and 28 after immunizations and titers of virus-neutralizing antibodies were determined by pseudovirus-based neutralization test (pVNT). Individual VNT titers are shown by dots; group mean values are indicated by horizontal bars (±SEM, standard error of the mean). ULOQ: Upper limit of quantification, LLOQ: Lower limit of quantification.

The summary of antibody titer on day 28 is as follows:

	BNT162c1 0.2 µg	BNT162c1 1 µg	BNT162c1 5 µg
Anti S1 protein total IgG [µg/mL]	91.2 ± 9.1	114.9 ± 5.7	217.7 ± 10.8
Anti RBD protein total IgG [µg/mL]	148.5 ± 9.2	178.7 ± 5.8	531.9 ± 35.1
pVN50 titer [reciprocal dilution]	31.5 ± 4.7	30 ± 3.7	87.0 ± 8.4

4.1.1.2.4 Immunogenicity study: BNT162b2 (modRNA encoding V8)

The potency of the LNP-formulated BNT162b2 (V8) was tested in mice (data report R-20-0054).

Four groups of 8 female BALB/c mice were immunized on day 0 with doses of 0.2 µg, 1 µg or 5 µg per animal of the modRNA encapsulated in LNPs, or with the buffer alone (control group), by IM injection. Blood was collected on days 7, 14, 21, and 28 after immunization to analyze the antibody immune response by ELISA and pVNT.

ELISA analysis showed a strong generation of antibodies (Figure 16). First detection of IgG antibodies was possible 7 days after immunization for all groups with an increase of total antibody amount until day 28. pVNT analysis also showed the formation of functional antibodies with a strong response in animals immunized with 5 µg BNT162b2 (Figure 17).

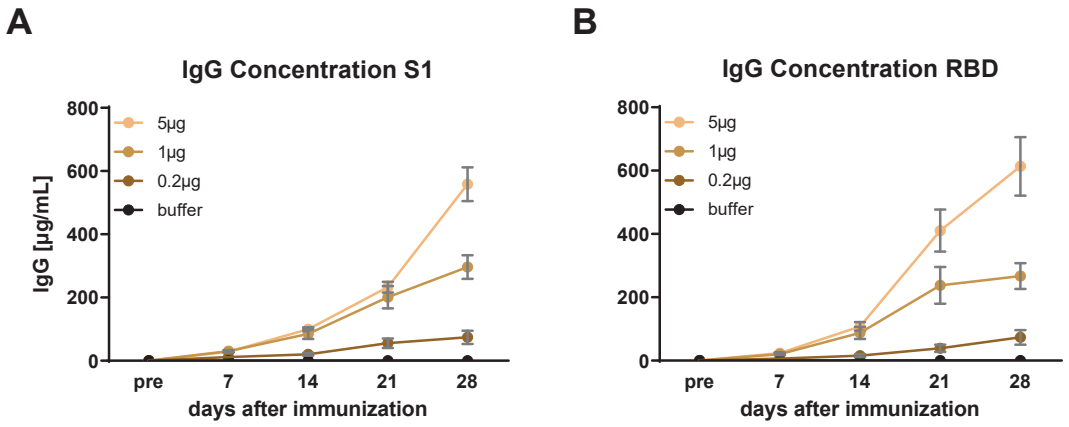


Figure 16: Anti-S IgG response 7, 14, 21, and 28 d after immunization with BNT162b2

BALB/c mice were immunized IM once with 0.2, 1 and 5 µg of modRNA encoding V8 or buffer. On 7, 14, 21, and 28 days after immunization, animals were bled and the serum samples were analyzed. For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean ant body concentrations are shown (±SEM). Group size n=8.

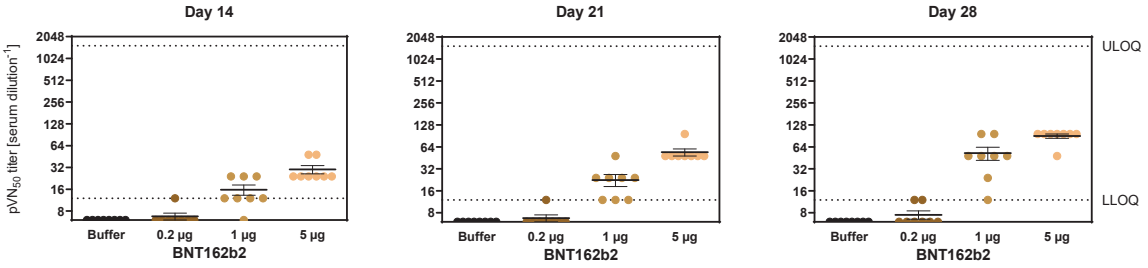


Figure 17: Neutralization of SARS-CoV-2 pseudovirus 14, 21, and 28 d after immunization with BNT162b2

Serum samples were collected on days 14, 21, and 28 after immunizations and titers of virus-neutralizing antibodies were determined by pseudovirus-based neutralization test (pVNT). Individual VNT titers are shown by dots; group mean values are indicated by horizontal bars (±SEM, standard error of the mean). ULOQ: Upper limit of quantification, LLOQ: Lower limit of quantification.

The summary of antibody titers on day 28 is as follows:

	BNT162b2 (V8) 0.2 µg	BNT162b2 (V8) 1 µg	BNT162b2 (V8) 5 µg
Anti S1 protein total IgG [µg/mL]	74.0 ± 21.3	296.2 ± 37.2	558.4 ± 53.
Anti RBD protein total IgG [µg/mL]	73.4 ± 23.1	266.9 ± 40.6	410.5 ± 66.3
pVN50 titer [reciprocal dilution]	7.5 ± 0.9	52.5 ± 10.6	90.0 ± 5.6

4.1.1.3 *In vivo* immunogenicity studies for BNT162 vaccine clinical candidates in mice

Non-clinical immunogenicity studies were performed for the BNT162 vaccines including BNT162a1, BNT162b1, BNT162b2 (V9), BNT162b3 and BNT162c2.

To benchmark the different vaccine candidates, mice were immunized once and different immunological read-outs were performed similar to the study designs reported in the supportive study section and outlined in Table 8.

Table 8: Study design

Group no	No of animals	Vaccine dose	Immunization day	Dose volume [µL] / route	Blood collection day	End of in-life phase
1	8	buffer	0	20 / IM	7, 14, 21	28
2	8	Low	0	20 / IM	7, 14, 21	28
3	8	Medium	0	20 / IM	7, 14, 21	28
4	8	High	0	20 / IM	7, 14, 21	28

4.1.1.3.1 Immunogenicity study of the BNT162a1 (uRNA encoding V5)

The immunogenicity of the LNP-formulated uRNA encoding RBD V5 (vaccine candidate BNT162a1) was tested in mice (data report R-20-0140).

Four groups of four female BALB/c mice were immunized on day 0 with doses of 0 (buffer), 1 µg, 5 µg or 10 µg per animal of the uRNA encapsulated in LNPs, or with the buffer alone (control group), by intramuscular injection. Blood was collected on days 7, 14, 21 and 28 after immunization to analyze the total IgG antibody immune response by ELISA; a pVNT was performed for day 14 to 28.

The vaccine candidate was immunogenic in mice, but with a low performance. Total IgG ELISA showed that the construct induced a weak generation of antibodies against the RBD and the S1 antigen (Figure 18). Profiling the IgG subtypes, a balanced ratio between IgG2a and IgG1 was detected. In pVNT analysis, only one mouse (dosed with 10 µg BNT162a1) showed antibodies with neutralizing functionality (Figure 19).

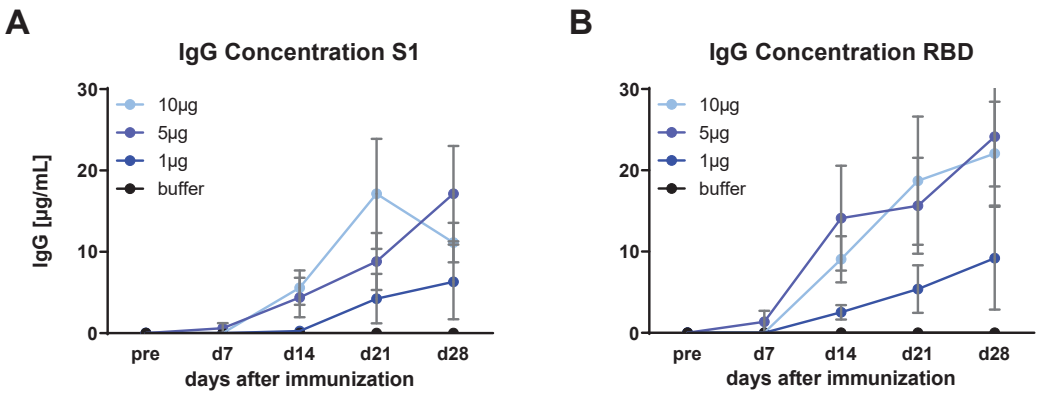


Figure 18: Anti-S IgG response 7, 14, 21, and 28 d after immunization with BNT162a1

BALB/c mice were immunized IM once with 1, 5 and 10 µg BNT162a1 or buffer. On 7, 14, 21, and 28 days after immunization, animals were bled and the serum samples were analyzed. For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean ant body concentrations are shown (±SEM). Group size n=8.

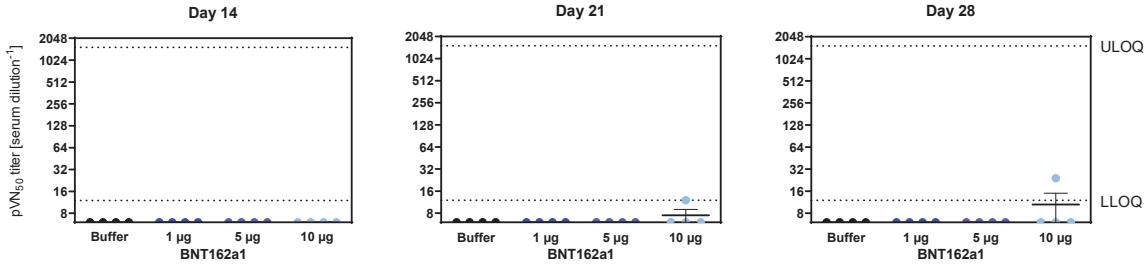


Figure 19: Neutralization of SARS-CoV-2 pseudovirus 14, 21, and 28 d after immunization with BNT162a1

BALB/c mice were immunized IM once with 1, 5 or 10 µg of BNT162a1. On 14, 21, and 28 d after immunization, animals were bled, and the sera were tested for SARS-CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

The summary of antibody titers on day 28 is as follows:

	BNT162a1 1 µg	BNT162a1 5 µg	BNT162a1 10 µg
Anti S1 protein total IgG [µg/mL]	14.0 ± 4.1	15.6 ± 3.0	27.8 ± 2.1
Anti RBD protein total IgG [µg/mL]	38.4 ± 12.3	24.2 ± 2.9	76.6 ± 5.5
pVN50 titer [reciprocal dilution]	6.0 ± 0.0	7.5 ± 0.9	7.5 ± 0.9

In summary, the vaccine candidate was immunogenic, however showed only weak responses in mice. The repetition of the study confirmed the overall results previously obtained in study R-20-0040.

4.1.1.3.2 Immunogenicity study of the BNT162b1 (modRNA encoding V5)

The immunogenicity of BNT162b1 was tested in mice (data report R-20-0042).

Four groups of eight female BALB/c mice were immunized on day 0 with doses of 0 (buffer), 0.2 µg, 1 µg or 5 µg per animal of BNT162b1 or with the buffer alone (control group) as outlined in Table 8. Blood was collected on days 7, 14, 21 and 28 after immunization to analyze the antibody immune response by ELISA and pVNT.

Profiling the IgG subtypes, a ratio with higher levels of IgG2a in comparison with IgG1 was detected, suggestive of a Th1-skewed antibody response (Figure 20). We have observed similar trends for the other BNT162 vaccine candidates (data not shown).

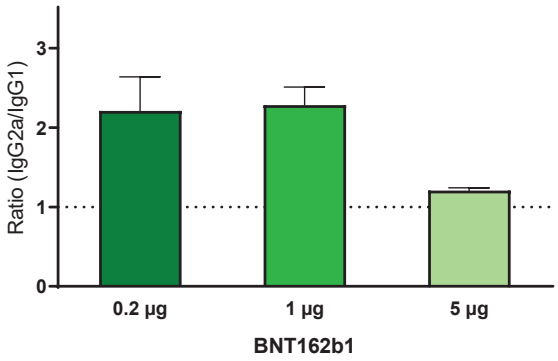


Figure 20: IgG2a/IgG1 subtype ratio on day 28

The ΔOD for every single sample was used to calculate the ratio of IgG2a and IgG1. For this purpose, the ΔOD value of IgG2a was divided by the ΔOD values of IgG1 per mouse. Group mean values (+SEM) are shown. The value of "1" in the graph would give the equal signal between the two subtypes while ratio > 1 mirror a higher IgG2a subtype detection.

Total IgG ELISA showed that the construct is highly immunogenic and induced a dose-dependent generation of antibodies against the S1 antigen and the RBD (Figure 21).

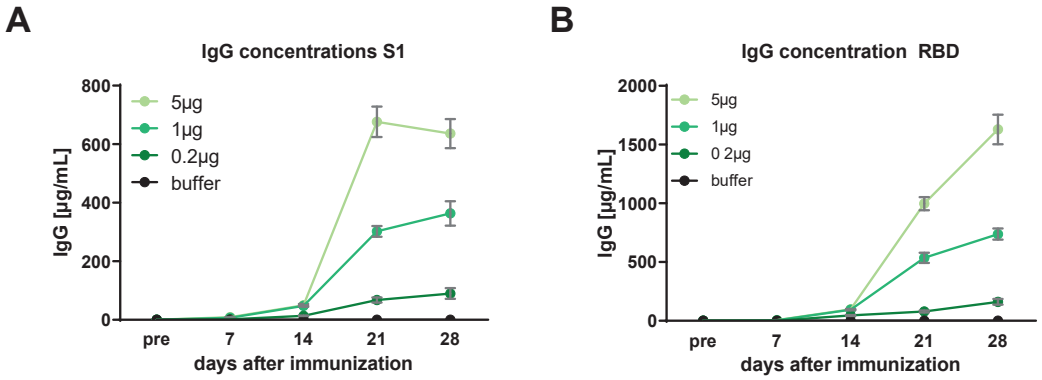


Figure 21: Anti-S IgG response 7, 14, 21, and 28 d after immunization with BNT162b1

BALB/c mice were immunized IM once with 0.2, 1 and 5 µg BNT162b1 or buffer. On 7, 14, 21, and 28 days after immunization, animals were bled and the serum samples were analyzed. For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean ant body concentrations are shown (±SEM). Group size n=8.

In pVNT analysis, all animals displayed a dose-dependent increase in neutralizing titers (Figure 22).

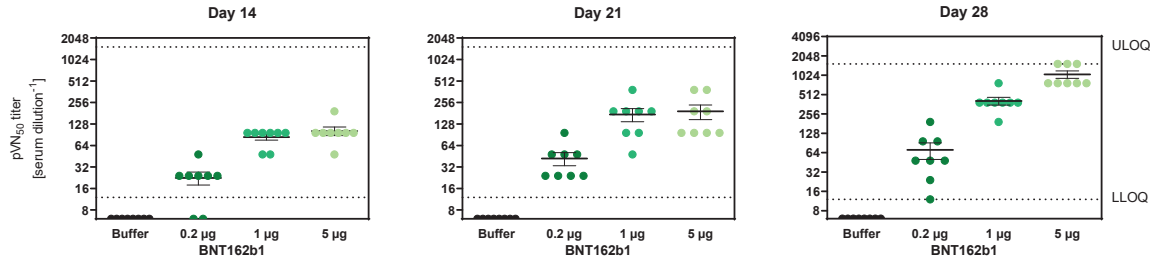


Figure 22: Neutralization of SARS-CoV-2 pseudovirus 14, 21, and 28 d after immunization with BNT162b1

BALB/c mice were immunized IM once with 0.2, 1 and 5 µg BNT162b1 or buffer. On 14, 21, and 28 d after immunization, animals were bled, and the sera were tested for SARS-CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

The summary of antibody titers on day 28 is as follows:

	BNT162b1 0.2 µg	BNT162b1 1 µg	BNT162b1 5 µg
Anti S1 protein total IgG [µg/mL]	68.2 ± 11.9	232.7 ± 40.6	392.7 ± 30.2
Anti RBD protein total IgG [µg/mL]	131.0 ± 23.5	455.4 ± 92.4	990.8 ± 96.7
pVN50 titer [reciprocal dilution]	67.5 ± 21.0	480.0 ± 166.3	960.0 ± 177.8

In a repetitive study (data report R-20-0084), the different antibody titers were confirmed.

4.1.1.3.3 Immunogenicity study of BNT162b2 (modRNA encoding V9)

The immunogenicity of the vaccine candidate BNT162b2 (V9) was investigated (data report R-020-0085).

Four groups of eight female BALB/c mice were immunized on day 0 with doses of 0 (buffer), 0.2 µg, 1 µg or 5 µg per animal of BNT162b2, or with the buffer alone (control group) as outlined in Table 8. Blood was collected on days 7, 14, 21 and 28 after immunization to analyze the antibody immune response by ELISA and pVNT.

The vaccine candidate was highly immunogenic; treatment with all tested BNT162b2 doses induced a strong immune response across the observation period of 28 days. Total IgG ELISA showed that the construct induced a strong, dose-dependent generation of antibodies against the S1 antigen and the RBD (Figure 23). In pVNT analysis, all mice developed functional neutralizing antibodies starting at 14 days after immunization and increasing up to final study day (Figure 24).

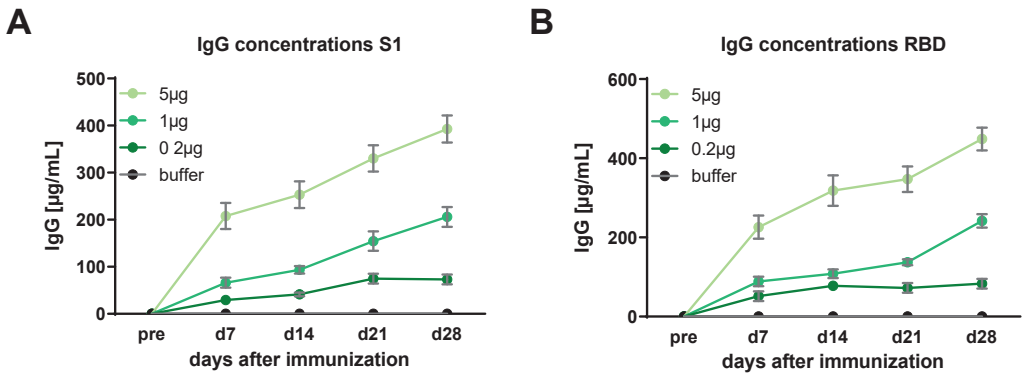


Figure 23: Anti-S IgG response 7, 14, 21, and 28 d after immunization with BNT162b2

BALB/c mice were immunized IM once with 0.2, 1 and 5 µg BNT162b2 or buffer. On 7, 14, 21, and 28 days after immunization, animals were bled and the serum samples were analyzed. For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean ant body concentrations are shown (±SEM). Group size n=8.

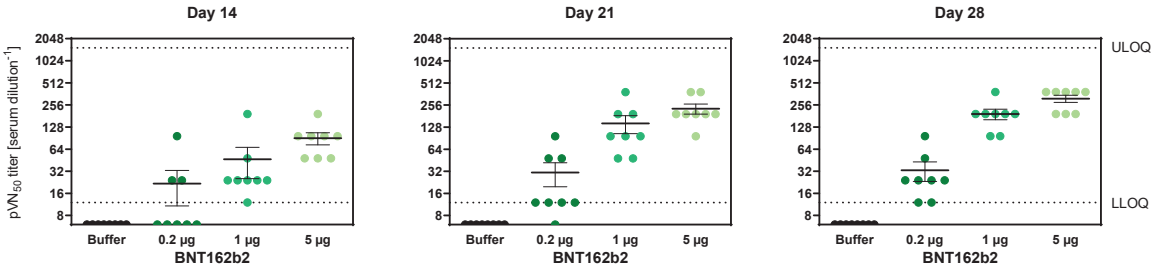


Figure 24: Neutralization of SARS-CoV-2 pseudovirus 14, 21, and 28 d after immunization with BNT162b2

BALB/c mice were immunized IM once with 0.2, 1 and 5 µg BNT162b2 or buffer. On 14, 21, and 28 d after immunization, animals were bled, and the sera were tested for SARS-CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

The summary of antibody titers on day 28 is as follows:

	BNT162b2 0.2 µg	BNT162b2 1 µg	BNT162b2 5 µg
Anti S1 protein total IgG [µg/mL]	73.0 ± 10.4	205.9 ± 21.0	392.7 ± 28.9
Anti RBD protein total IgG [µg/mL]	83.1 ± 12.3	241.7 ± 17.2	448.6 ± 28.6
pVN50 titer [reciprocal dilution]	33.0 ± 9.8	192.0 ± 31.4	312.0 ±35.1

4.1.1.3.4 Immunogenicity study of BNT162b3 (antigen V5TM)

The immunogenicity of the vaccine candidate BNT162b3 was investigated (data report R-020-0145; report pending). The study is currently ongoing and only interim results can be included in this document.

Three groups of eight female BALB/c mice were immunized on day 0 with doses of 0 (buffer), 0.2 µg, or 1 µg per animal and blood was collected on days 7, 14 and 21 to analyze the antibody immune response by ELISA and pVNT.

The vaccine candidate was highly immunogenic and induced a high generation of antigen-specific IgG already at an early timepoint after vaccination (Figure 25). For comparison, 14 days after immunization the 1 µg immunization dose of BNT162b3 induced a mean of 382 µg/mL RBD-specific Ab while the 1µg BNT162b1 immunization dose induced a mean of 93 µg/mL (see Section 4.1.1.3.2). Also in pVNT, a high titer of neutralizing antibodies was detected (Figure 26). For comparison, 14 days after immunization the 1 µg immunization dose of BNT162b3 induced in pVNT a mean titer of 1:186 (reciprocal dilution) while the 1 µg BNT162b1 immunization dose induced a mean titer of 1:84 (see Section 4.1.1.3.2).

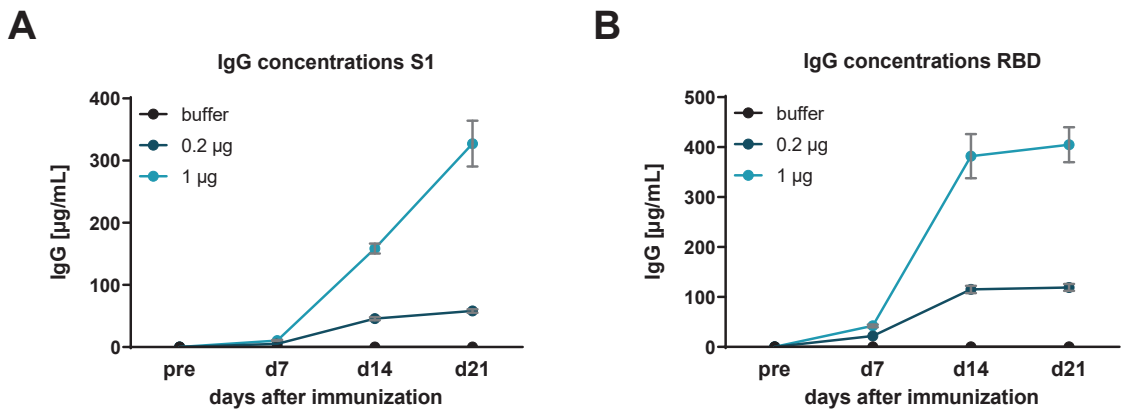


Figure 25: Anti-S IgG response 7, 14, and 21 d after immunization with BNT162b3

BALB/c mice were immunized IM once with 0.2 and 1 BNT162b2 or buffer. On 7, 14, and 21 days after immunization, animals were bled and the serum samples were analyzed. For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean ant body concentrations are shown (±SEM). Group size n=8.

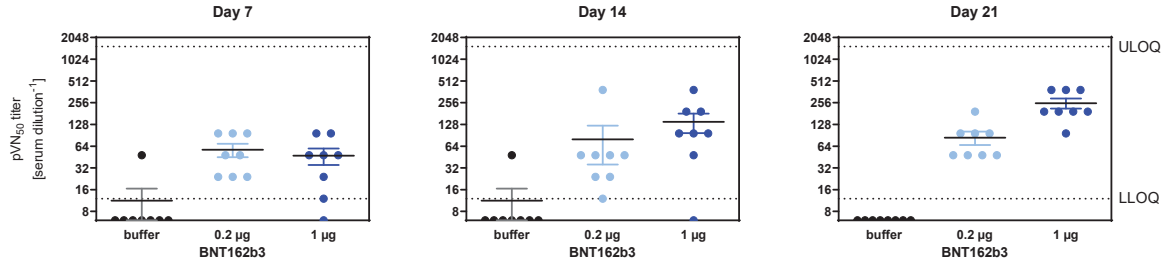


Figure 26: Neutralization of SARS-CoV-2 pseudovirus 7, 14 and 21 d after immunization with BNT162b3

BALB/c mice were immunized IM once with 0.2 and 1 µg BNT162b2 or buffer. On day 7, 14, and 21 after immunization, animals were bled, and the sera were tested for SARS-CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

The study is ongoing and serology will be performed weekly up to day 28 after immunization.

4.1.1.3.5 Immunogenicity study of BNT162c2 (saRNA encoding V9)

The immunogenicity of the LNP-formulated saRNA encoding V9 (vaccine candidate BNT162c2) was tested in mice as outlined in Table 8 (data report R-020-0053).

Four groups of eight female BALB/c mice were immunized on day 0 with doses of 0 (buffer), 0.2 µg, 1 µg or 5 µg per animal and blood was collected on days 7, 14, 21 and 28 after immunization to analyze the antibody immune response by ELISA and pVNT.

The vaccine candidate was highly immunogenic; treatment with all tested BNT162c2 doses induced a strong immune response across the observation period of 28 days after vaccination. Total IgG ELISA results showed that the construct induced a strong, dose-dependent generation of antibodies against the S1 antigen and the RBD (Figure 27). In pVNT analysis, all mice developed functional neutralizing antibodies starting at 14 days after immunization and increasing up to final study day (Figure 28).

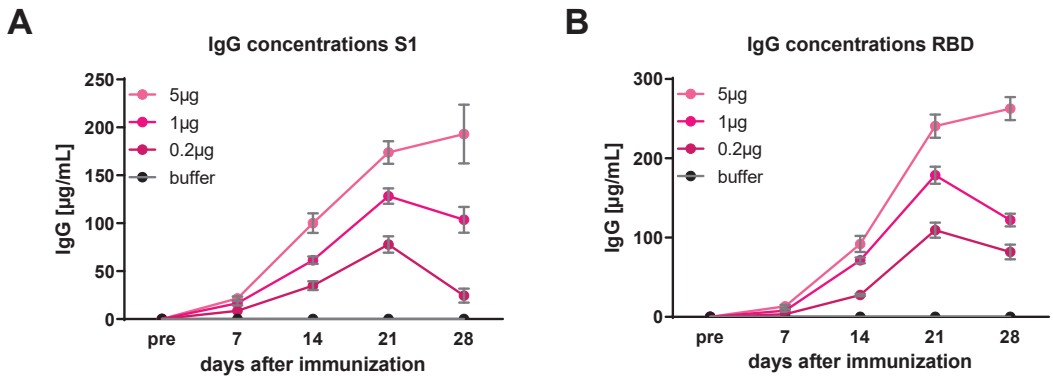


Figure 27: Anti-S IgG response 7, 14, 21, and 28 d after immunization with BNT162c2

BALB/c mice were immunized IM once with 0.2, 1 and 5 µg BNT162c2 or buffer. On 7, 14, 21, and 28 days after immunization, animals were bled and the serum samples were analyzed. For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean ant body concentrations are shown (±SEM). Group size n=8.

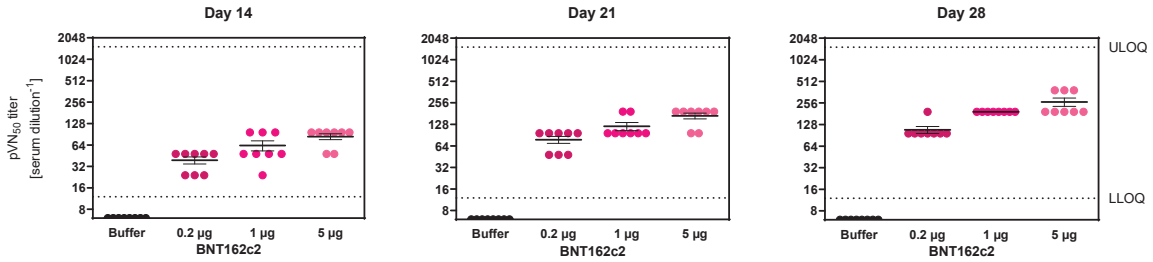


Figure 28: Neutralization of SARS-CoV-2 pseudovirus 14, 21, and 28 d after immunization with BNT162c2

BALB/c mice were immunized IM once with 0.2, 1 and 5 µg BNT162c2 or buffer. On 14, 21, and 28 d after immunization, animals were bled, and the sera were tested for SARS-CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

The summary of antibody titers on day 28 is as follows:

	BNT162c2 0.2 µg	BNT162c2 1 µg	BNT162c2 5 µg
Anti S1 protein total IgG [µg/mL]	72.98 ± 10.3	205.94 ± 21.0	392.74 ± 28.9
Anti RBD protein total IgG [µg/mL]	83.10 ± 12.3	241.73 ± 17.2	410.5 ± 66.3
pVN50 titer [reciprocal dilution]	33.0 ± 9.2	192.0 ± 29.4	448.58 ± 28.6

4.1.1.3.6 Immunogenicity in non-human primates (NHP)

Six rhesus macaques per group were immunized IM with 30 µg or 100 µg of BNT162b1 (modRNA encoding antigen V5) and BNT162b2 (modRNA encoding antigen V8), or with saline (buffer) on days 0 and 21. Of note, BNT162b2 differs from the clinical BNT162b2 candidate with regard to codon-optimization, meaning that both encode the same amino acid sequence but differ in their RNA-sequence.

First, sera were tested for IgG antibodies that bind to the SARS-CoV-2 S1-protein. On day 14 after the first dose virus antigen binding IgG were present in sera of all modRNA-immunized macaques (Figure 29). Geometric mean concentrations (GMCs) of virus antigen binding IgG were highest on day 28 (7 d after the second dose) and day 35 (14 d after the second dose). Second, authentic SARS-CoV-2 50% serum neutralization geometric mean titers (GMTs) were assessed and were detectable 14 d after a single immunization with either dose level of BNT162b1 or modRNA coding for V8. These titers were highest on day 28 and on day 35 (Figure 30).

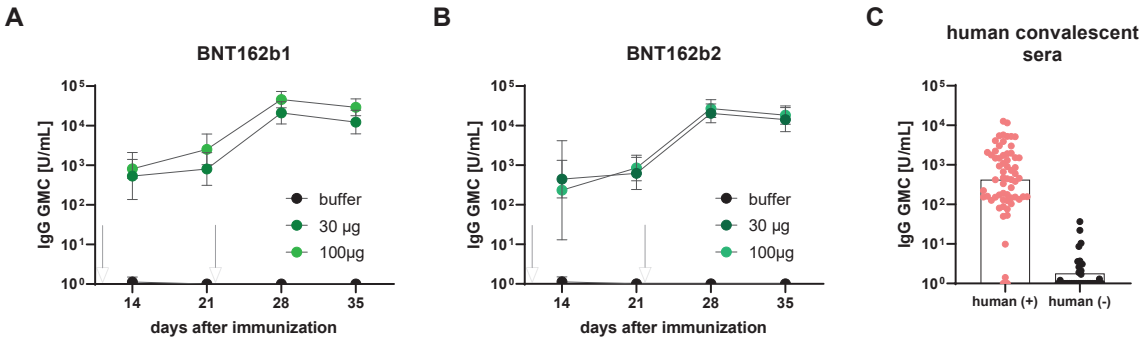


Figure 29: Anti-S IgG response 14, 21, 28, and 35 d after immunization in NHP

Rhesus macaques were immunized IM on day 0 and 21 as indicated by grey arrows with buffer, 30, and 100 µg of (A) BNT162b1 or (B) BNT162b2. On 14, 21, 28, and 35 d after immunization, animals were bled and the serum samples were analyzed for IgG binding a recombinant SARS-CoV-2 RBD. IgG binding a recombinant SARS-CoV-2 RBD. Geometric mean concentrations (GMC±CI) are given. (C) Human COVID-19 convalescent sera (human (+)), drawn 20–40 d after the onset of symptoms with confirmed COVID-19 diagnosis with at least 14 d of asymptomatic convalescence, were tested for IgG binding a recombinant SARS-CoV-2 RBD (sample size: 62) as well as serum samples from healthy donors (sample size: 31). Every single value is included in the graph as well as the geometric mean concentrations (GMCs) indicated by bars.

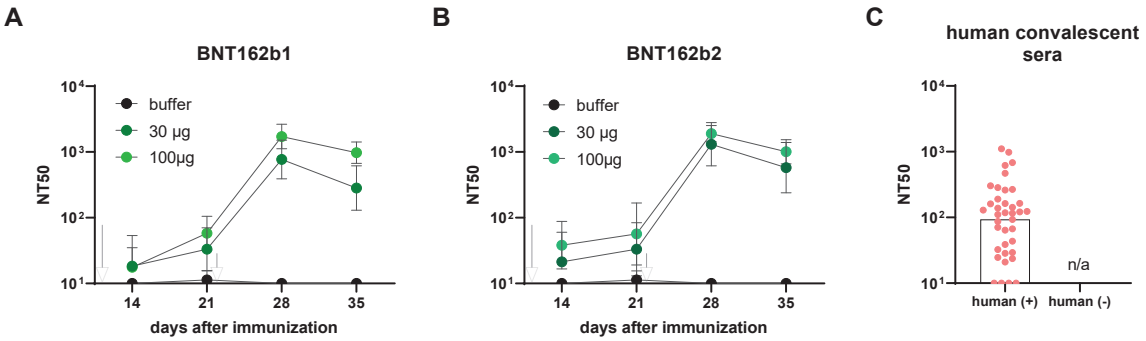


Figure 30: Neutralization of SARS-CoV-2 14, 21, 28, and 35 d after immunization in NHP

Rhesus macaques were immunized IM on day 0 and 21 as indicated by grey arrows with buffer, 30 and 100 µg of (A) BNT162b1 or (B) BNT162b2. On 14, 21, 28, and 35 d after immunization, animals were bled and the serum samples were analyzed for neutralizing antibodies against SARS-CoV-2. Geometric mean ± CI are given for the groups within the observation period. (C) Human COVID-19 convalescent sera (human (+)), drawn 20–40 d after the onset of symptoms with confirmed COVID-19 diagnosis with at least 14 d of asymptomatic convalescence, were tested for neutralizing ant bodies (sample size: 38). Every single value is included in the graph as well as the geometric mean concentration indicated by bar. n/a: not applicable as no samples were tested. All graphs depict the reciprocal titer of sera when 50% of virus infection was inhibited.

On day 28 and day 35, both total IgG concentration as well as the neutralizing geometric mean (GM) titer in rhesus macaques were high. In comparison to human convalescent sera, the NT50 GM titers were very high (Figure 31).

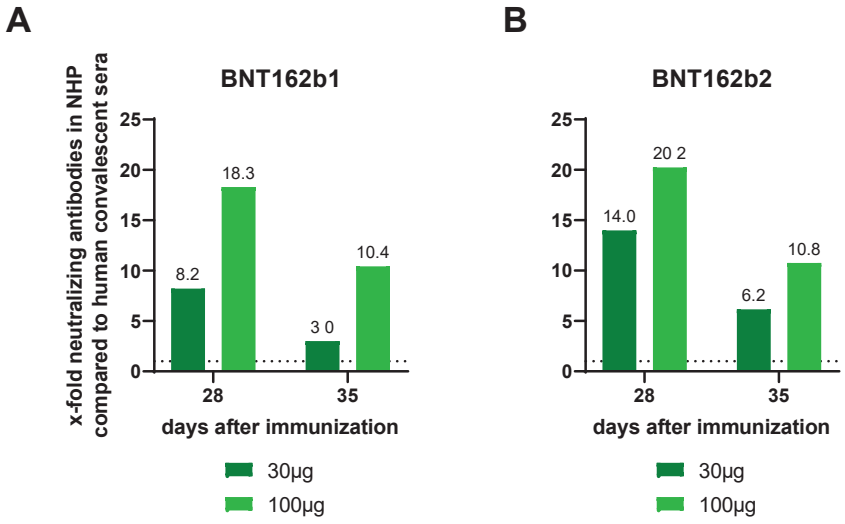


Figure 31: Comparison of the NT50 titer of NHP after immunization and human convalescent sera

The NHP GM titer from Figure 30 were normalized to the GM of the human convalescent serum and x-fold concentration was calculated after (A) BNT162b1 or (B) BNT162b2 immunization. The value "1" stands for the concentration of the human sera (absolute value: 93.6 U/mL) and is indicated via a dotted line.

The rhesus macaque immunogenicity data show strong neutralizing humoral responses to the LNP-formulated modRNAs that exceed those observed in in COVID-19 convalescing humans.

In another (still ongoing) study, six rhesus macaques were immunized IM with 30 µg of BNT162b3 (modRNA encoding antigen V5TM). In parallel, a group of three animals were immunized with saline (buffer) on day 0. Sera were tested for IgG antibodies that bind to the SARS-CoV-2 S1-protein on days 7 and 14 after immunization (Figure 32).

On day 7 after immunization, virus antigen binding IgG were present in the sera of all modRNA-immunized macaques. The neutralization assay revealed neutralizing antibodies in all BNT162b3 immunized NHP 14 d after immunization.

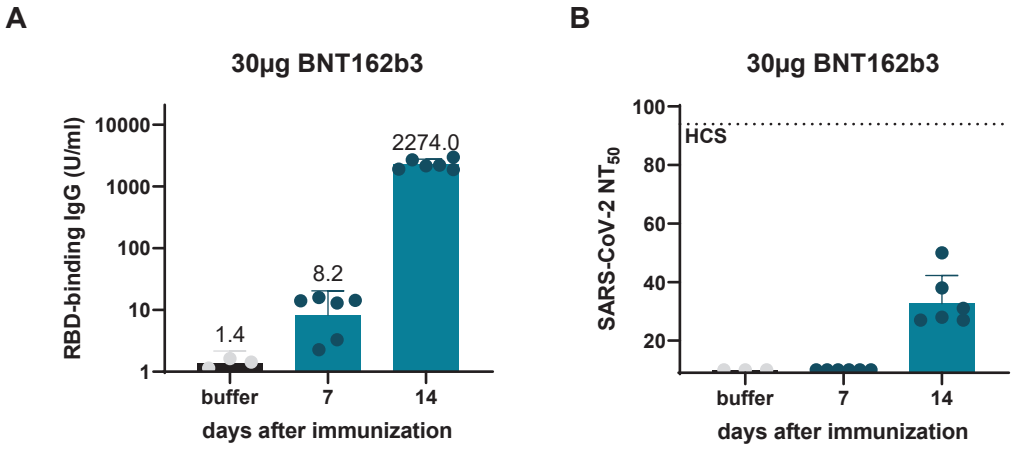


Figure 32: Anti-S IgG response and virus neutralization titer 7 and 14 d after immunization with BNT162b3 in NHP

Rhesus macaques were immunized IM on day 0 with buffer or 30 of BNT162b3. On 7 and 14 d after immunization, animals were bled and the serum samples were analyzed for (A) IgG binding a recombinant SARS-CoV-2 RBD or (B) neutralization antibodies. Geometric mean concentrations (GMC±CI) are given. HCS = human convalescent serum (Geometric mean from Figure 30).

4.1.1.3.7 Immunogenicity of BNT162 vaccine candidates in rats after repeated dosing

In the GLP compliant repeat-dose toxicity study in rats (Section 4.3.1, Study No. 38166), the immunogenicity of the administered RNA vaccines BNT162a1 (uRNA encoding V5), BNT162b1 (modRNA encoding V5), BNT162b2 (modRNA encoding V8), and BNT162a1 (saRNA encoding V5) was investigated. Serum samples were collected from repeatedly dosed main study animals on day 10 (BNT162c1) or day 17 after first immunization (BNT162a1, BNT162b1, and BNT162b2) as well as from recovery cohorts at the end of the study on day 31 (BNT162c1) or day 38 (BNT162a1, BNT162b1, and BNT162b2).The elicited antibody immune response was analyzed by S1 domain (Figure 33 for the main

study and Figure 34 for the recovery cohort, respectively) and RBD sub-domain specific ELISA (Figure 35 for main study and Figure 36 for the recovery cohort, respectively). Samples were also tested in a SARS-CoV2-S pVNT (Figure 37 for the main study and Figure 38 for the recovery cohort, respectively) for determination of a pseudovirus neutralization titer.

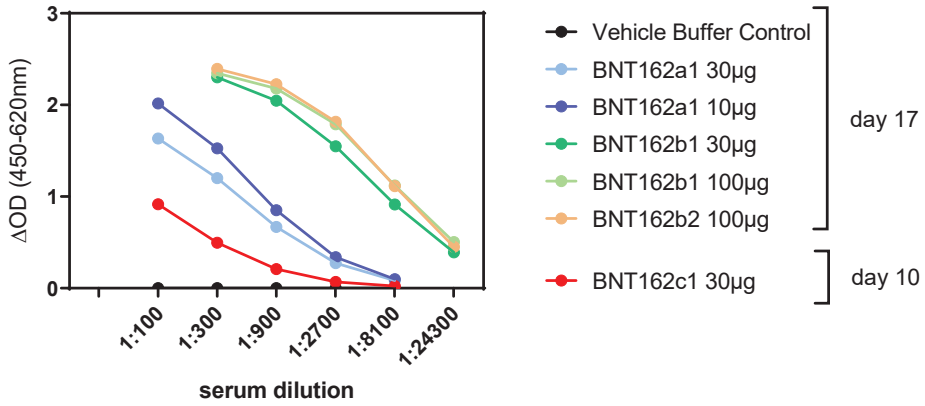


Figure 33: ELISA screening analysis of main study cohort to detect antibody responses directed against the recombinant SARS-CoV-2 S protein S1 domain

Wistar Han rats were immunized IM with three weekly injections of 10 or 30 µg BNT162a1, 30 or 100 µg BNT162b1, 100 µg BNT162b2, or two weekly injections of 30 µg BNT162c1. On day 10 (saRNA coding for V5) or day 17 (all other cohorts) animals were bled and the sera were tested for total amount of anti-S1 antigen specific immunoglobulin G (IgG) measured via ELISA. Different serum dilutions were tested ranging from 1:100 to 1:24300. One point in the graph stands for the ΔOD group mean value at a particular given serum dilution (group size n=20).

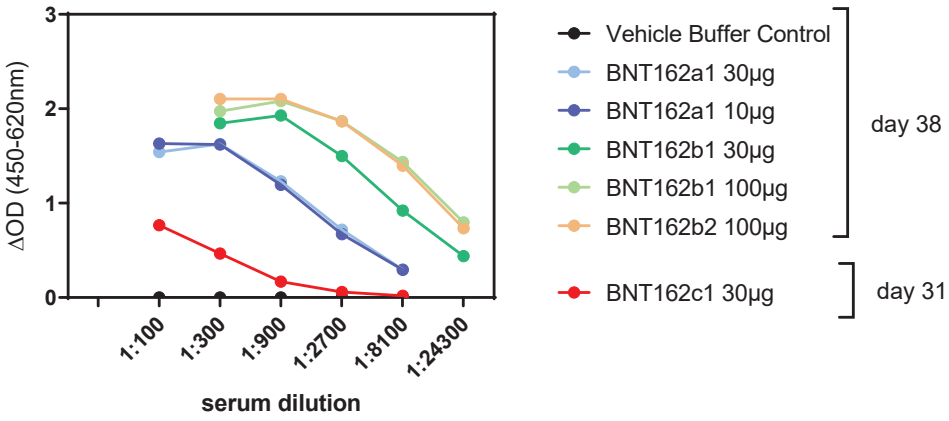


Figure 34: ELISA screening analysis of recovery cohort sera to detect antibody responses directed against the recombinant SARS-CoV-2 S protein S1 domain

ELISA was performed using serum samples collected on day 31 after two immunizations (prime/boost on days 1 and 8) with BNT162c1, or on day 38 after three administrations (prime/boost on days 1/8/15) of BNT162a1, BNT162b1, or BNT162b2 to analyze elicited antibody responses. The serum samples were tested against the S1 protein. Group mean ΔOD values of n=20 mice/group are shown by dots across serum dilutions ranging from 1:100 to 1:24,300.

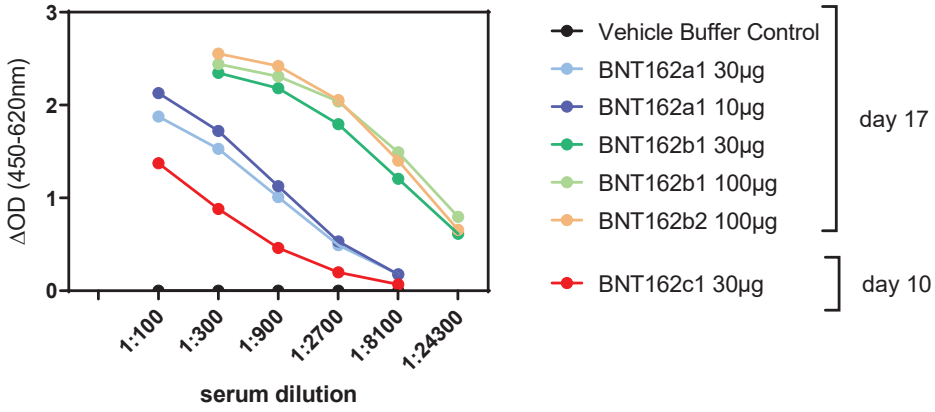


Figure 35: ELISA screening analysis of main study cohort to detect antibody responses directed against the recombinant SARS-CoV-2 S protein RBD domain

Wistar Han rats were immunized IM with three weekly injections of 10 or 30 µg BNT162a1, 30 or 100 µg BNT162b1, 100 µg BNT162b2, or two weekly injections of 30 µg BNT162c1. On day 10 (saRNA coding for V5) or day 17 (all other cohorts) animals were bled and the sera were tested for total amount of anti-RBD antigen specific immunoglobulin G (IgG) measured via ELISA. Different serum dilutions were tested ranging from 1:100 to 1:24300. One point in the graph stands for the ΔOD group mean value at a particular given serum dilution (group size n=20).

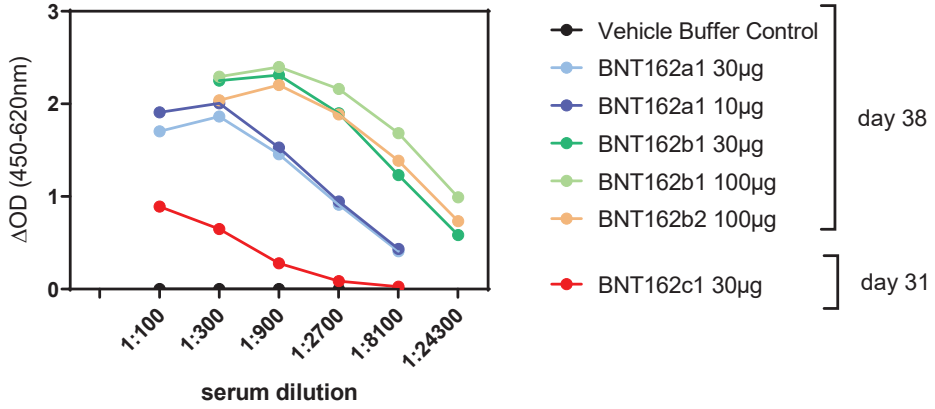


Figure 36: ELISA screening analysis of recovery cohort sera to detect antibody responses directed against the recombinant SARS-CoV-2 S protein RBD domain

ELISA was performed using serum samples collected on day 31 after two immunizations (prime/boost on days 1 and 8) with BNT162c1, or on day 38 after three administrations (prime/boost on days 1/8/15) of BNT162a1, BNT162b1, or BNT162b2 to analyze elicited antibody responses. The serum samples were tested against the RBD domain. Group mean ΔOD values of n=20 rats/group are shown by dots across serum dilutions ranging from 1:100 to 1:24,300.

Treatment of rats with each of the BNT162 vaccine candidates resulted in the formation of antibodies of the IgG isotype against the S1 domain as well as the RBD sub-domain of the SARS-CoV2 S protein (Figure 33, Figure 34, Figure 35, Figure 36). The analysis showed a weak antibody immune response for BNT162c1 treated animals on day 10 and day 31, a

moderate antibody immune response for BNT162a1 treated animals on day 17 and 38, and a strong antibody immune response for both modRNA based vaccines, BNT162b1 and BNT162b2, on days 17 and 38, irrespective of the vaccine antigen used. Whereas for the BNT162b1 cohort the magnitude of immune activation was dose-dependent, the low-dose (10 µg/animal) BNT162a1 treated animals displayed a slightly more pronounced antibody immune response with higher titers of antigen-specific IgG in serum compared to the high-dose (30 µg/animal) treated cohort.

Antibody concentrations in the serum samples were calculated for the individual samples and the IgG concentration against S1 and RBD proteins is given in Table 9. Antibody concentrations against S1 and RBD increased in a dose-dependent manner over time only for the modRNA based vaccine BNT162b1. In rats, the lower concentration of BNT162a1 induced a slightly higher IgG concentration against the two antigens in comparison to the 30 µg of BNT162a1.

Table 9: IgG antibody concentration against the viral antigen in Wistar Han rats

		BNT162a1 30 µg	BNT162a1 10 µg	BNT162b1 100 µg	BNT162b1 30 µg	BNT162b2 100 µg	BNT162c1* 30 µg
17 days after first immunization	**Against S1**	83.0 ± 13.6	149.8 ± 24.6	1844.2 ± 243.4	1502.9 ± 269.9	1755.9 ± 164.1	19.3 ± 3.7
	Against RBD	192.6 ± 35.2	208.3 ± 28.9	2632.6 ± 270.9	2017.0 ± 257.1	2331.4 ± 185.1	56.3 ± 12.0
38 days after first immunization	**Against S1**	47.6 ±5.6	312.0 ±43.0	3432.1 ± 301.3	2137.2 ±392.6	3463.8 ± 522.5	21.5 ± 4.2
	Against RBD	405.7 ±58.9	730 ±135.6	6718.4 ±822.8	4011.9 ±900.0	4898.0 ±873.3	25.2 ±4.9

For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against the S1 protein and RBD. Group mean antibody concentrations are shown (±SEM) that are shown graphically in Figure 33 to Figure 36. * for saRNA encoding V5 group, the days of analysis were d10 and d31, respectively.

Sera of all immunized animals show SARS-CoV-2 pseudovirus neutralization to a varying extent (Figure 37). In-line with ELISA data, a weak neutralizing antibody response is induced by BNT162c1 treatment on day 10 and 31, a moderate response by BNT162a1 treatment on days 17 and 38, and a high viral-neutralization response by BNT162b1 and BNT162b2 treatment on days 17 and day 38 after first immunization.

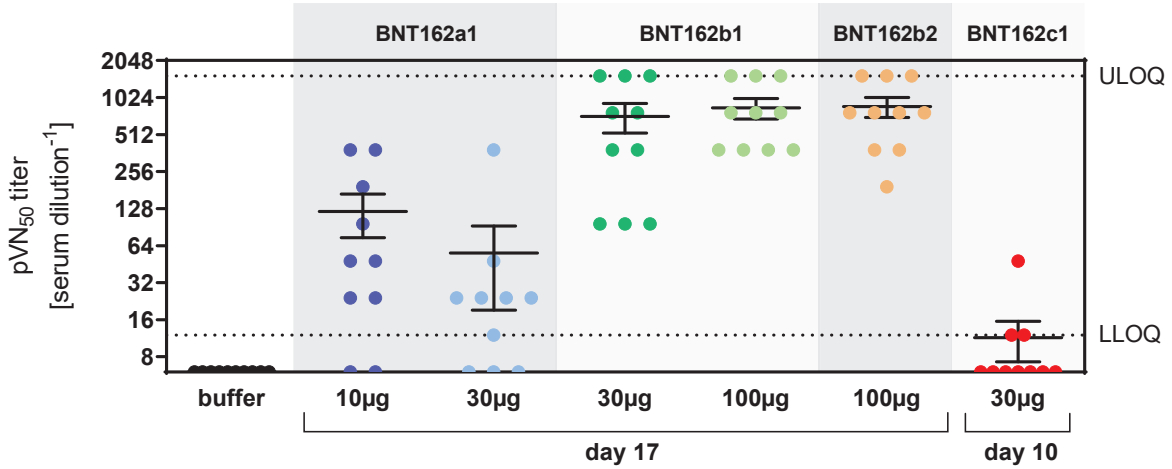


Figure 37: Antibody titer resulting in 50% pseudovirus neutralization activity (pVN_{50})

Wistar Han rats were immunized IM with three weekly injections of 10 or 30 µg BNT162a1, 30 or 100 µg BNT162b1, 100 µg BNT162b2, or two weekly injections of 30 µg BNT162c1. On day 10 (saRNA encoding V5) or day 17 (all other cohorts) animals were bled and the sera were tested for SARS-CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one rat. Every rat sample was measured in duplicate. Group size n=5 male and n=5 female rats. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

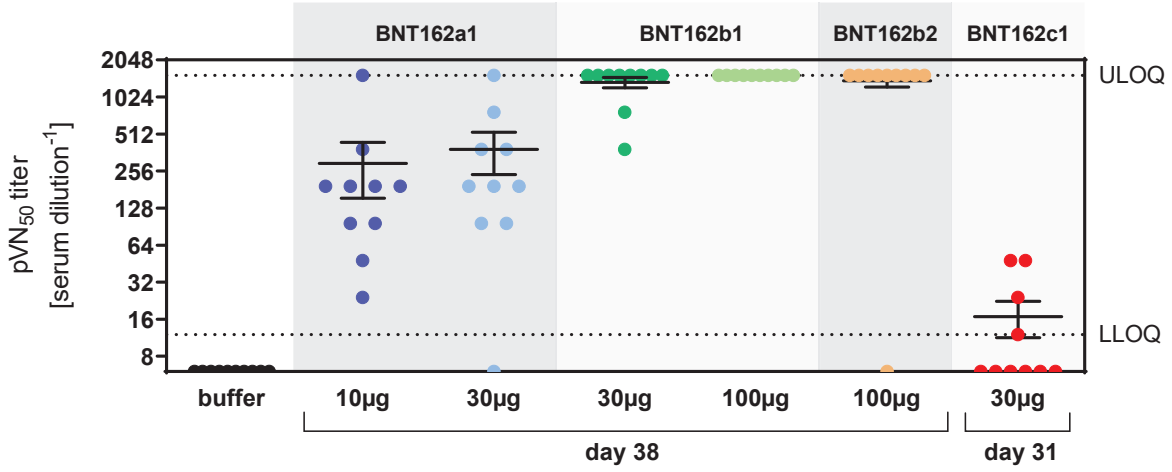


Figure 38: Pseudovirus neutralization activity of recovery cohort sera plotted as pVN50 titer

Serum samples were collected on day 31 (BNT162c1, red dots) or day 38 (all other cohorts) after first immunization of the recovery cohort animals and titers of virus-neutralizing antibodies were determined by pVNT. Individual VNT titers resulting in 50% pseudovirus neutralization (pVN50) are shown by dots; group mean values are indicated by horizontal bars (±SEM, standard error of the mean).

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, see Figure 37 and Figure 38). In contrast, no neutralizing

activity was associated with serum samples generated from vehicle buffer control treated animals. Neutralizing antibody titers in vaccinated animals increased over time with the recorded neutralizing activity being consistent with the ELISA data shown above. Whereas sera from BNT162c1 treated animals display weak neutralizing activity both on days 10 and 31, sera from BNT162a1 treated animals display moderate neutralizing activity on day 17 that is significantly augmented on day 38. The strongest pseudovirus neutralization effect is mediated by sera obtained from BNT162b1- and BNT162b2-treated rats. In case of both modRNA-based vaccines, BNT162b1 and BNT162b2, neutralizing antibody titers resulting in 50% pseudovirus neutralization exceeded the upper limit of quantification (ULOQ) of a reciprocal titer of 1536 in more than 8 out of ten animals on day 38.

The available data demonstrates that all BNT162 vaccine candidates elicited a SARS-CoV-2 S protein specific antibody response directed against the S1 domain and the RBD sub-domain. Antibody responses detected via ELISA directly translated into neutralizing activity as seen in the Vesicular Stomatitis Virus/SARS-CoV2-S pseudovirus neutralization test (pVNT) with BNT162 vaccines showing higher antigen-specific antibody titers also displaying more pronounced virus neutralization effect.

4.1.2 Secondary pharmacodynamics

No secondary pharmacodynamics studies were conducted for the BNT162 vaccine candidates.

4.1.3 Safety pharmacology

No safety pharmacology studies were conducted as they are not considered necessary according to the WHO guideline (WHO Technical Report Series, No. 927, "Annex 1: WHO guidelines on nonclinical evaluation of vaccines", 2005).

4.1.4 Non-clinical pharmacology - Conclusions

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

The currently available data demonstrate that vaccines based on all three RNA platforms (uRNA, modRNA, and saRNA) in conjunction with V5, V8/V9 as well as V5TM including the clinical vaccine candidates, BNT162a1, BNT162b1, BNT162b2, BNT162b3, and BNT162c2 are capable of inducing robust immune responses in mice, rats, and NHPs.

In mice, the antibody response was detected at a very early time point by IgG analysis on 7 d post-immunization. The induction of an antibody response by a very low immunization dose of 0.2 µg with the modRNA platform (BNT162b1, BNT162b2) and the saRNA platform (BNT162c2) indicate high vaccine potency. Also, immune responses by SARS-CoV-2 pseudovirus neutralization are detectable 14 d post-immunization in the mice immunized with intermediate doses.

The summary of neutralization titers after 1 µg immunization of BALB/c with one of the five assigned vaccine candidates is as follows:

pVN50 titer [reciprocal dilution] Day 28	1 µg dose
BNT162a1	6.0 ± 0.0
BNT162b1	480.0 ± 166.3
BNT162b2	192.0 ± 31.4
BNT162c2	192.0 ± 29.4
BNT162b3 (day 21)	252.0 ± 40.3

Within the different vaccine candidates, BNT162b1 induced the highest virus neutralization titer. The BNT162b3 candidate induced an early response of antibodies with following high titer; day 28 results are pending.

Similar results indicating immunogenicity were obtained in an accessory study to the GLP-compliant repeat-dose toxicology study in rats (Study No. 38166). In NHPs, a generation of S-specific, neutralizing antibodies was detected early on and after two immunizations after BNT162b, the overserved titers exceeded human convalescent sera. Results for other vaccine candidates in NHP are pending.

4.2 Non-clinical pharmacokinetics and metabolism

No pharmacokinetic studies were conducted for the BNT162 vaccine candidates as they are considered not necessary according to the WHO guideline (WHO Technical Report Series, No. 927, "Annex 1: WHO guidelines on nonclinical evaluation of vaccines", 2005).

4.2.1 Methods of analysis

Not applicable.

4.2.2 Absorption

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

4.2.3 Distribution

No biodistribution studies were performed with the BNT162 vaccine candidates.

The biodistribution of luciferase as a surrogate marker protein for the antigens encoded in the BNT162b vaccine candidates was assessed using an RNA encoding luciferase formulated comparable to that used for the BNT162 vaccine candidates.

Based on extensive prior experience with RNA therapeutics, we routinely test new drug candidates for their ability to deliver RNA *in vivo* using luciferase-encoding RNA as reporter. Luciferase expression can be detected *in vivo* after injection of luciferin by measuring the luminescence *in vivo*. Using this methodology, we demonstrated that the modRNA, as representative for all three RNA platforms, induces a high and long luciferase expression (Figure 39).

Based on our previous experience, we anticipate that the biodistribution of the antigen encoded by the RNA components of the BNT162 vaccine candidates will be dependent on

the LNP distribution. Therefore, the modRNA results shown below are considered to be representative for all three BNT162 RNA platforms.

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.

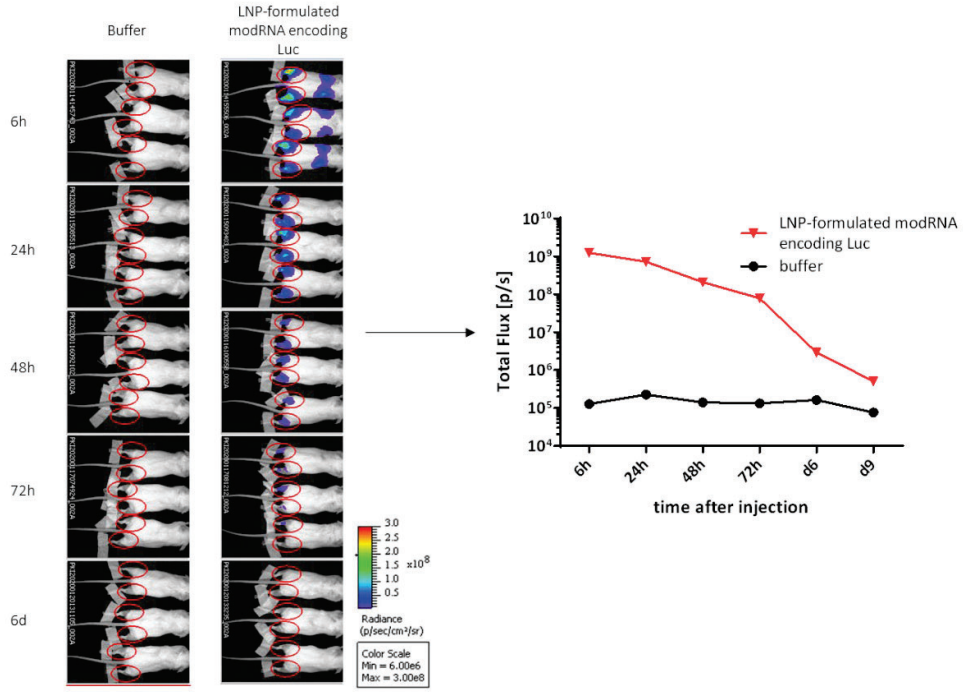


Figure 39: Bioluminescence imaging measurement using the LNP-candidate formulated BNT162b encoding luciferase

BALB/c mice were injected IM with 1 µg of LNP-formulated modRNA encoding luciferase in each hind leg. At time points after injection, the luciferase expression *in vivo* was measured by luciferin application. After 9 d, luciferase expression dropped to background levels.

4.2.4 Metabolism and excretion

RNA, including pseudouridine modified RNA and saRNA, 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.

Proteins encoded by the RNA in the BNT162 vaccine candidates are proteolytically degraded, just like other endogenous proteins. Therefore, no RNA or protein metabolism or excretion studies will be 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 pharmacokinetic profile of the two novel lipids (ALC-0315 and ALC-0159) will be characterized at a later stage of non-clinical development.

For the above-noted reasons, no metabolism or excretion studies were conducted.

4.2.5 Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies were performed.

4.2.6 Non-clinical pharmacokinetics and metabolism - Conclusions

Pharmacokinetic studies were conducted using a luciferase reporter RNA, and protein expression after IM injection was demonstrated *in vivo*. The luciferase biodistribution profile resembles that of similar RNA products developed by BioNTech, some of which have been safely tested at higher doses non-clinically and clinically using IV administration. Although liver parameters will be carefully monitored during the clinical development of the BNT162 vaccines, prior clinical experience with similar RNA products developed by BioNTech indicates that the distribution to the liver does not pose a safety risk.

4.3 Toxicology

To enable the rapid development of a prophylactic vaccine during a public health emergency, as is the case for the current SARS-CoV-2 outbreak, the WHO has published recommendations on the content of a minimum non-clinical safety package to support initiation of clinical testing (see "WHO Technical Report Series, No. 1011", "Annex 2: Guidelines on the quality, safety and efficacy of Ebola vaccines, 2018"). For the BioNTech BNT162 vaccines, this guideline was considered applicable due to the pandemic situation.

4.3.1 Repeat-dose toxicology to support the clinical evaluation of BNT162 vaccine candidates

Toxicology of BNT162 vaccine candidates was studied in a GLP compliant repeat-dose study. The study design was based on guideline recommendations ("WHO Technical Report Series, No. 927", "Annex 1: WHO guidelines on nonclinical evaluation of vaccines, 2005"). The study design is summarized in Table 10.

Table 10: Design of the GLP compliant repeat-dose toxicity study (Study No. 38166)

Test Items	• BNT162a1 (LNP formulated uRNA encoding antigen V5) • BNT162b1 (LNP formulated modRNA encoding antigen V5) • BNT162b2 [V8] (LNP formulated modRNA encoding antigen V8) * • BNT162c1 (LNP formulated saRNA encoding antigen V5)	
Species(age)	Wistar Han rat (10-14 weeks)	
Administrations	Three (BNT162a1, BNT162b1, and BNT162b2 [V8]) or two (BNT162c1) administrations on day 1, 8 and (if applicable) 15 followed by a 3-week recovery period	
Route	Intramuscular into the M. biceps femoris	
Dose groups	**Test Item**	**Dose level**
1	Control = Buffer	/
2	**BNT162a1**	30 µg
3		10 µg
4	**BNT162b1**	30 µg
5		100 µg
6	**BNT162c1**	30 µg
7	**BNT162b2 [V8]**	100 µg
Satellite group	Cytokine response analysis	3/sex/group
Group size	Group 1-7	10 (+ 5 recovery)/sex/group

* The RNA component of the BNT162b2 vaccine variant tested here has a different nucleotide sequence than the RNA component of the BNT162b2 vaccine candidates under clinical investigation, but both RNAs encode the same antigen, i.e., full length SARS-CoV-2 spike protein bearing mutations preserving neutralization-sensitive sites.

A relevant animal model for toxicity assessment of vaccines is one that develops an immune response similar to the expected human response after vaccination, while also allowing administration of the absolute clinical dose (WHO Technical Report Series, No. 927, "Annex 1: WHO guidelines on non-clinical evaluation of vaccines", 2005). Since the rat develops an immune response similar to the expected human response after RNA vaccination and is a commonly used species in vaccine toxicology studies, it was chosen as the animal model for toxicity assessment of the BNT162 vaccines.

The repeat-dose study investigated to what extent any observed side effect is related to:

- the RNA platform (uRNA, modRNA, and saRNA),
- the RNA/LNP formulation for each respective platform,
- the vaccine dose, and/or
- the encoded antigen.

Examples for each of the three RNA platforms (uRNA, modRNA and saRNA) used in the BNT162 vaccine candidates were investigated utilizing the same LNP formulation and therefore the observed safety profiles are considered representative for all candidate vaccines based on these RNA platforms.

Different vaccine doses, covering the highest anticipated clinical doses, were tested for the modRNA and uRNA platforms. For modRNA, the doses tested were 30 µg and 100 µg.

For uRNA, the doses 10 µg and 30 µg were tested. For the saRNA, a 30 µg dose was tested. These studies evaluated the safety and immunogenicity of three different RNA modalities (uRNA, modRNA, and saRNA) formulated in an LNP and administered intramuscularly. Vaccine candidates were administered in a reduced administration schedule once weekly for 3 (BNT162a1, BNT162b1, BNT162b2) or 2 (BNT162c1) doses followed by a 3-week recovery period. All three RNA platforms were evaluated encoding the SARS-CoV-2 RBD subunit antigen. In addition, a modRNA based vaccine (BNT162b2) encoding the full-length p2 mutated S protein was evaluated, allowing identification of antigen specific effects. The RNA component of the BNT162b2 vaccine candidate tested in this study has a different nucleic acid sequence than the RNA component of the clinical BNT162b2 vaccine candidate, but encodes the same antigen and is therefore considered to be representative for the clinical BNT162b2 vaccine candidates. For simplicity, the name BNT162b2 is used in this section.

The study design was based on regulatory guidance for vaccines (EMA Guideline on Repeated Dose Toxicity, 2010; WHO Guidelines on Nonclinical Evaluation of Vaccines, 2005), results of all parameters assessed are summarized in Table 11.

Table 11: Parameters assessed in the repeat-dose toxicity study (Study No. 38166)

Parameter	Time of assessment	Dosing phase	Recovery phase
Mortality	At least twice daily until end of dosing/recovery.	No vaccine-related mortality was observed in any group.	No mortality was observed in any group.
Clinical signs	At least twice daily until end of dosing/recovery.	No systemic clinical signs were observed.	No systemic clinical signs were observed.
Body weight	Twice weekly (prior and one day post each administration) and until the end of dosing/recovery.	Decreased body weights/ overall weight gain in all test-item treated groups compared to buffer control, primarily due to decreases in body weight 24 h after dosing. Body weight gain during the inter-dosing interval was similar to buffer controls.	No difference in body weight was observed between buffer control and immunized groups.
Food consumption	Weekly until the end of dosing/recovery.	A slight reduction by up to 7.2% in test week 1 and 2 in food consumption was seen in animals receiving 30 µg BNT162a1 in comparison with control group.	No difference in food consumption was observed between control and immunized groups.
Local tolerance	+4 h and 24 h post each administration, then every 48 h until end of dosing/recovery.	All immunized animals developed mainly very slight to slight oedema at the injection site 24 h after first dose. Oedema seen after the second and third injection was moderate to severe. In addition, after the second and third dose, mild to severe erythema was seen in many rats in (30 µg BNT162a1, 100 µg BNT162b1 and 100 µg BNT162b2)1 at 6 dafter the second	Very slight to slight oedema for nearly all animals (10 or 30 µg BNT162a1) following the third injection on test day 15. No dose-dependency was observed. All oedema had subsided on test day 35 latest. All animals (30 µg BNT162a1) revealed severe erythema at 4 days after the last injection. In

Parameter	Time of assessment	Dosing phase	Recovery phase
		dose. For rats given a third dose, all findings resolved prior to the third administration. On test days 14 and/or 15, eschar formation at the injection site for 5 male and 6 female animals (30 µg BNT162a1) The injection site appeared to be painful for 4/15 male animals and 12/15 female animals (30 µg BNT162a1) on test day 9 and for one male animal also on test day 10.	the majority, this had subsided by test day 35 latest. Only 2 male and 2 female animals revealed erythema up to test day 33. 6/10 animals treated with 30 µg displayed severe erythema 6 d post last immunization. A single animal displayed erythema until the end of recovery. Apart from this animal, at the end of the recovery, any local skin reactions had subsided.
Body temperature	+4 h and 24 h post each administration, weekly during recovery.	A slight increase of body temperature was noted 24 h post administration compared to 4 h values (approx. 0.9°C) in all animals including controls. It was more pronounced in the treatment groups. For single animals, temperature reached 40°C, but was reduced again 24 h later.	During the recovery period, the body temperature remained at a slightly higher level compared to the buffer control group in all previously test item treated groups.
Cytokines	Prior to and 6 h post each dosing and at the end of dosing.	No vaccine-related changes observed.	Not assessed.
Hematology	3 d post first administration and at the end of dosing/recovery.	Dose-related increases in neutrophils leucocytes, monocytes, basophils and large unstained cells (LUC) were seen with all vaccines on test day 17 (and day 4 for 30 µg BNT162a1) and were greater in females. Decreases in the reticulocyte count (test day 4 only), platelet count, and very slight red cell mass (HGB, HCT and RBC; test day 17 only) were observed.	No differences observed between buffer control and immunized groups.
Clinical chemistry incl. acute phase proteins	3 d post first administration and at the end of dosing/recovery.	The majority of clinical chemistry parameters were not affected. An elevated plasma activity of gamma-glutamyl transpeptidase (GGT) was noted for all test item-treated groups in comparison to the control group. An increase in albumin and a decrease in globulin plasma levels, resulting in an altered albumin/globulin ratio, were observed in all test item treated groups. The changes were within the biological range of normal. Elevated serum levels of the acute phase proteins alpha1-acid glycoprotein and alpha2 macroglobulin were noted for all test item-treated groups in comparison to the control group on test day 4 and test day 10 to 17.	No differences observed between control and immunized groups.

Parameter	Time of assessment	Dosing phase	Recovery phase
Coagulation	At the end of dosing/recovery.	No changes except for an elevation of fibrinogen levels were observed for all vaccinated groups.	No differences observed between control and immunized groups.
Ophthalmology/ Auditory	At the end of dosing/recovery.	No findings in any group.	No findings in any group.
Urinanalysis	At the end of dosing/recovery.	No differences observed between buffer control and immunized groups.	No differences observed between buffer control and immunized groups.
Organ weight	At the end of dosing/recovery.	Spleen weight was increased in all vaccinated animals when compared with buffer control.	No differences observed between buffer control and immunized groups.
Macroscopic pathology	At the end of dosing/recovery.	A thickened injection site was the most common observation in all vaccine treated animals (20/20 for 30 µg BNT162a1, 15/20 for 10 µg BNT162a1, 13/20 for 30 µg BNT162b1, 6/20 for 100 µg BNT162b1, 20/20 in 30 µg BNT162c1 and 18/20 for BNT162b2). Some animals also displayed enlarged iliac lymph nodes and/or enlarged spleens.	No observations were made for the buffer control group, 30 µg BNT 162a1, 10 µg BNT162a1 and 30 µg BNT162c1. Enlarged iliac lymph nodes were observed in some BNT162b treated animals (1/10 for 30 µg BNT162b1, 7/10 for 100 µg BNT162b1, 4/10 for 100 µg BNT162b2).
Histopathology	At the end of dosing/recovery.	Injection sites: oedema, fibrosis, myofiber degeneration, hyperplasia of the epidermis and inflammation (with all BNT162 vaccines) Iliac lymph nodes: increased cellularity of the follicular germinal centers, increased plasma cells (plasmacytosis) with all BNT162 vaccines and inflammation (30 µg BNT162a1, 100 µg BNT162b1, 100 µg BNT162b2 and 30 µg BNT162c1) Bone marrow: minimal to mild increases in the cellularity (all BNT162 vaccines) Spleen: extramedullary hematopoiesis in the spleen (10 µg BNT162a1, 100 µg BNT162b1 and 100 µg BNT162b2) Liver: vacuolation of hepatocytes in the portal regions in either all animals (100 µg BNT162b1 and 100 µg BNT162b2) or females only (10 µg BNT162a1, 30 µg BNT162a, 30 µg BNT162b1 and 30 µg BNT162c1)	The majority of microscopic findings had resolved by the end of recovery. Minimal to mild changes in the iliac lymph nodes and inflammation at the injection site was still present (all BNT162 vaccines).
Dose exposure serology	At the end of dosing/recovery.	Treatment with all BNT162 vaccine candidates resulted in the formation of neutralizing antibodies protecting against pseudovirus infection. No antibody response or neutralization was observed in any of the buffer control animals.	Treatment with all BNT162 vaccine candidates resulted in the formation of antibodies, which, in protected against pseudovirus infection in all groups but 30 µg BNT162c1, where a neutralization titer was only detectable in a few

Parameter	Time of assessment	Dosing phase	Recovery phase
			animals. The strongest responses were seen in animals treated with BNT162b1 and BNT162b2. No antibody response or neutralization was observed in any of the buffer control animals.

4.3.1.1 Mortality and clinical signs

In the repeat-dose toxicity study, no vaccine-related mortality was observed throughout the course of the main study or in the recovery phase. All scheduled administrations for main and recovery animals have been performed. No systemic clinical signs were noted until the end of the study in any group.

4.3.1.2 Local tolerance

Special attention was paid to the local tolerance of vaccines BNT162a1, BNT162b1, BNT162b2, and BNT162c1 at the injection site, in the repeated-dose toxicity study (Section 4.3.1).The injection sites were assessed for erythema/eschar/oedema formation and induration/hardening following palpation. Any reactions such as formation of erythema, oedema or induration of injection site observed were scored with a grading similar to Draize 1959. Occurrence of oedema was scored as described in Table 12.

Table 12: Grading of oedema formation

Oedema formation	Value
No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well defined by definite raising)	2
Moderate oedema (raised approx. 1 mm)	3
Severe erythema (raised more than 1 mm and extending beyond area of exposure)	4

All immunized animals developed mainly very slight (grade 1) to slight (grade 2) oedema at the injection site 24 h after first dose. Oedema was more pronounced after the second and third injection, where moderate to severe oedema formation was observed.

An overview over the oedema frequency after first and second dose is given in Table 13.

Table 13: Frequency of highest oedema score noted post first and second vaccine dose in GLP repeated-dose toxicity study

Group | Time Points		Frequency of highest oedema score/total number of animals				
		0	1	2	3	4
Gr. 1 Control = Buffer	all	30/30	0/30	0/30	0/30	0/30
Gr. 2 30 µg BNT162a1 (uRNA encoding antigen V5)	Post 1. dose	6/30	15/30	9/30	0/30	0/30
	Post 2. dose	1/30	2/30	13/30	14/30	0/30
Gr. 3 10 µg BNT162a1 (uRNA encoding antigen V5)	Post 1. dose	8/30	22/30	0/30	0/30	0/30
	Post 2. dose	0/30	0/30	14/30	16/30	0/30
Gr. 4 30 µg BNT162b1 (modRNA encoding antigen V5)	Post 1. dose	6/30	11/30	13/30	0/30	0/30
	Post 2. dose	1/30	22/30	7/30	0/30	0/30
Gr. 5 100 µg BNT162b1 (modRNA encoding antigen V5)	Post 1. dose	9/30	21/30	0/30	0/30	0/30
	Post 2. dose	0/30	1/30	13/30	16/30	0/30
Gr. 6 30 µg BNT162c1 (saRNA encoding antigen V5)	Post 1. dose	3/30	23/30	4/30	0/30	0/30
	Post 2. dose*	12/30	6/30	1/30	9/30	2/30
Gr. 7 100 µg BNT162b2 (modRNA encoding antigen V8)	Post 1. dose	4/30	26/30	0/30	0/30	0/30
	Post 2. dose	0/30	3/30	14/30	13/30	0/30

* Only recovery animals were scored at 24 h after the second dose.

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 thrird injection, transient observations of severe erythema were seen for all vaccines, except for 30 µg BNT162b1, starting at 96 h after administration. Occasionally these observations of severe erythema continued over several days and/or were associated with wounds or scar tissue in individual animals administered 30 µg BNT162a1 or 30 µg BNT162c1.

The injection site appeared to be painful for 4 of 15 male animals and 12 of 15 female animals treated with 30 µg BNT162a1/animal on test day 9 and for one male animal also on test day 10.

An indurated and/or thickened injection site, partly accompanied by incrustation, was noted for nearly all animals in all treatment groups at macroscopic inspection at necropsy.

The microscopic examination revealed that test item-related injection site reactions were present in all groups and characterized by mostly moderate inflammation (up to marked) in males and moderate inflammation in females. The most severe findings were consistently in animals administered 100 µg BNT162b1 and 100 µg BNT162b2, followed by animals administered 30 µg BNT162a1. The inflammation was characterized by infiltrates of macrophages, granulocytes, and lymphocytes into the muscle, and variably into the dermis and subcutis, at the injection site. Injection site inflammation was associated with mostly moderate oedema, mostly mild myofiber degeneration, occasional muscle necrosis, and mostly mild fibrosis. Skin ulceration (mild and moderate) was identified in some males and

females administered either 10 or 30 µg BNT162a1 and one animal administered 30 µg BNT162c1. Inflammation extended into tissues adjacent to the injection site, including mammary tissue, perineural tissue of sciatic nerve, tissue around the femur / knee and to the draining lymph node (iliac).

Microscopic injection site findings correlated with macroscopic observations of thickening, induration, and incrustation. Injection site findings were consistent with an immune/inflammatory response to intramuscular vaccine administration.

During the recovery period, very slight to slight oedema for nearly all animals treated with either 10 or 30 µg BNT162a1 were observed following the third injection. No dose-dependency was observed. All oedema had subsided by test day 35 at the latest.

All animals immunized with 30 µg BNT162a1 revealed severe erythema at 4 days after the last injection. In the majority, this had subsided by test day 25. Only 2 male and 2 female animals revealed erythema up to test day 33.

6/10 animals immunized with 30 µg BNT162c1 showed severe erythema 6 d post last immunization. In one animal the reaction decreased in severity but was still detectable at the end of recovery.

The local skin reactions and the indurations and/or thickenings noted macroscopically for the muscle at the injection site(s) were resolved at the end of the recovery period. Most of the microscopic findings noted at the injection sites, iliac lymph node, surrounding tissue of the injection sites (surrounding tissue of bone, os femoris with joint; perineural tissue of sciatic nerve; interstitial tissue of mammary gland, and skeletal muscle) partially or fully recovered at the end of the 3-week recovery period. Some inflammatory lesions were still noted at the injection sites and the surrounding tissue of some animals.

At the end of the recovery period, 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 oedema and more rarely erythema. The occurrence of higher 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.

4.3.1.3 Body weight and food consumption

In the repeat-dose toxicity study, the body weight was decreased 24 h after the administrations in all treatment groups compared to pre-dose levels (up to approx. 13%). No reduction was noted for the buffer control Group 1. Body weight gain between the administrations was comparable to the buffer control group and no difference in body weight gain was observed during the recovery period.

A slight reduction in food consumption was seen in 30 µg BNT162a1 treated in comparison with control during treatment, which improved and returned to normal during recovery.

4.3.1.4 Hematology

In the repeat-dose toxicity study, most hematological parameters remained unchanged 3 d after the first dose, 2 d after the last dose and 23 d after the last dose (recovery period).

The most consistent test item-related hematologic changes were dose-related increases in neutrophils, leucocytes, monocytes, basophils and large unstained cells (LUC), which were seen with 30 µg BNT162a1 on test day 4 and with all vaccines on 2 d post last dose. These effects were greater in females relative to males. Other test item-related changes included decreases in the absolute and relative reticulocyte count (test day 4 only), platelet count, and a very slight reduction in red cell mass (hemoglobin [HGB)], HCT and red blood cell [RBC]; test day 17 only), as well as increases in the numbers of.

All changes were considered to be related to the primary pharmacodynamic activity of the vaccines. Increases in leucocytes (most notably neutrophils and LUC), were consistent with an acute phase response secondary to immune activation and inflammation at the injection sites.

Decreases in numbers of reticulocytes, RBC and platelets were associated with increased bone marrow haematopoiesis, consistent with transient, secondary or peripheral effects. Transient reticulocyte decreases (test day 4 only) were possibly secondary to the acute phase response and inflammation. Effects on red cell mass were limited to minimal decreases in RBC, HGB, and HCT on test day 17. Platelet decreases were small in magnitude and likely secondary to inflammation-related platelet activation and consumption. There were no thrombi evident microscopically.

At the end of recovery, no noteworthy change in any hematology parameters was observed.

4.3.1.5 Clinical chemistry and acute phase proteins

In the repeat-dose toxicity study, almost all clinical chemistry parameters were unchanged.

Only a slight increase in γ-glutamyl transpeptidase (GGT) was noted for all treatment groups 3 d after first dose and 2 d after the last dose. There were no changes in alkaline phosphatase (ALKP) and bilirubin and no macroscopic or microscopic findings consistent with cholestasis or hepatobiliary injury to explain the increased GGT.

Further, an increase in albumin plasma levels and a decrease in globulin plasma levels, resulting in an altered albumin/globulin ratio, were observed in all test item treated groups. The changes were within the biological range of normal and are consistent with an acute phase response in albumin and globulin where albumin goes down and globulin goes up with inflammation, and the albumin/globulin ratio decreases.

Acute phase proteins alpha1-acid glycoprotein and alpha2 macroglobulin were measured to assess vaccine-induced inflammatory reactions. The markers were increased in the treatment groups 3 d after the first dose or at the end of the in-life phase.

No changes in any parameter was observed at the end of the recovery period, 23 d post last immunization.

4.3.1.6 Cytokines

No vaccine-related changes were observed. Levels of interferon-γ, Tumor necrosis factor-α, IL-1-β, IL-6, IL-10 were comparable in buffer control and vaccine administered animals during dosing phase.

4.3.1.7 Coagulation

Increases in fibrinogen levels were detected in all vaccinated animals at the end of dosing phase and were consistent with an acute phase response secondary to immune activation and inflammation at the injection sites.

Changes observed in other coagulation parameters with any BNT162 vaccine at the end of dosing phase were within normal laboratory values and are not of toxicological relevance.

No changes in coagulation parameters were observed at the end of the recovery phase, 23 d post last immunization.

4.3.1.8 Ophthalmological and auditory assessments

Prior to, at the end of dosing and recovery period ophthalmological and auditory assessments resulted in detection of no changes.

4.3.1.9 Urine composition

At the end of the in-life and recovery period, urine was collected over a period of 24 h from main study animals. No vaccine-related changes in pH, relative urine volume and specific gravity were observed in any group.

4.3.1.10 Macroscopic pathology

Main study animals were dissected following a randomization scheme 2 d and 23 d after the last administration.

The most common observation in all treatment groups was a thickened injection site and/or induration at the injected muscle (see Table 14 for all findings). This finding is test-item related and is caused by the local inflammation process. Furthermore, enlarged spleen and iliac lymph nodes were noted in a number of animals in the test-item treated groups. The effects on the lymphoid organs are likely the result of the induction of an immune response by the vaccine.

Table 14: Summary of macroscopic vaccine related findings – main study

Group	Findings in male and female animals
1 (Control)	• none
2 (30 µg BNT162a1)	• Thickened / hardened injection site and/or muscle (20/20 animals) • Enlarged spleen (6/20 animals) • Enlarged iliac lymph nodes (2/20 animals)
3 (10 µg BNT162a1)	• Thickened / hardened injection site and/or muscle (15/20 animals) • Enlarged spleen (7/20 animals) • Enlarged iliac lymph nodes (7/20 animals)
4 (30 µg BNT162b1)	• Thickened / hardened injection site and/or muscle (13/20 animals) • Enlarged spleen (2/20 animals) • Enlarged iliac lymph nodes (10/20 animals)
5 (100 µg BNT162b1)	• Thickened / hardened injection site and/or muscle (13/20 animals) • Enlarged spleen (12/20 animals) • Enlarged iliac lymph nodes (15/20 animals)
6 (30 µg BNT162c2)	• Thickened / hardened injection site and/or muscle (20/20 animals) • Enlarged spleen (6/20 animals) • Enlarged iliac lymph nodes (3/20 animals)
7 (100 µg BNT162b2)	• Thickened / hardened injection site and/or muscle (16/20 animals) • Enlarged spleen (9/20 animals) • Enlarged iliac lymph nodes (11/20 animals) • Muscle adhered to sciatic nerve (3/20 animals)

Most effects observed 2 d after the last immunization reversed within the 21 d recovery period. 23 d post last immunization, no macroscopic observations were made for the control group, 30 µg BNT 162a1, 10 µg BNT162a1 and 30 µg BNT162c1. Enlarged iliac lymph nodes were observed in some BNT162b treated animals (1/10 for 30 µg BNT162b1, 7/10 for 100 µg BNT162b1, 4/10 for 100 µg BNT162b2).

4.3.1.11 Organ weight

In the majority of weighed organs no difference in relative and absolute organ weight between vaccinated and buffer control animals were observed. Congruent with the macroscopic observations (Section 4.3.1.9), the average spleen weight was increased in male and female animals vaccinated with the BNT162 vaccine candidates. This effect reversed during the recovery period: 23 d post last immunization no differences between the organ weights of vaccinated animals and control group animals were observed.

4.3.1.12 Histopathology

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.

In the draining (iliac) lymph node, increased cellularity of the follicular germinal centers and increased plasma cells (plasmacytosis) which were variably present for all BNT162-immunized animals.

Minimal to mild increases in the cellularity of bone marrow and extramedullary hematopoiesis in the spleen (which correlated with increased spleen size and weight), and a vacuolation of hepatocytes in the portal regions of the liver were present for all BNT162-immunized animals. The liver findings were not associated with changes in markers of hepatocyte injury (e.g., ALAT). While GGT was elevated in test-item treated animals, it is not a marker of hepatocyte injury.

The majority of the microscopic findings noted at the injection sites and surrounding tissues, iliac lymph node and spleen were partially or completely recovered in all animals at the end of the recovery period. Inflammation at the injection site and surrounding tissues was less severe (minimal to mild) or resolved at the end of the 3-week recovery period, indicating partial or complete recovery. The incidence and the severity of the remaining findings were markedly reduced at the end of the recovery period.

In the iliac lymph node, plasmacytosis was less severe and in fewer groups (30 or 100 µg of BNT162b1 or 100 µg BNT162b2) indicating partial or complete recovery. Macrophage infiltrates were present in the iliac lymph node 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, fully recovered at the end of the 3-week recovery phase.

4.3.1.13 Genotoxicity

The components of all BNT162 vaccine excipients, lipids and RNA, are not suspected to have genotoxic potential. No impurity or component of the delivery system warrants genotoxicity testing. In accordance with the WHO guideline (WHO Technical Report Series, No. 927, "Annex 1: WHO guidelines on nonclinical evaluation of vaccines", 2005), no genotoxicity studies were performed.

4.3.1.14 Carcinogenicity

RNA itself, and the lipids used in the BNT162 vaccines have no carcinogenic or tumorigenic potential. Furthermore, according to ICH S1A (ICH S1A Guideline: "Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals", November 1995), no carcinogenicity studies are required for therapeutics that are not continuously administered.

4.3.1.15 Reproductive and developmental toxicity

Macroscopic and microscopic evaluation of male and female reproductive tissues were included in the GLP repeat-dose toxicity study testing BNT162a1, BNT162b1, BNT162b2, and BNT162c1 (Section 4.3.1). No changes in these tissues were reported.

The vaccine candidates have not been assessed in specific fertility and embryofetal development studies yet.

4.3.2 Immunotoxicology

Immunotoxicity of BNT162a1, BNT162b1, BNT162b2, and BNT162c1, was assessed in the GLP compliant repeated-dose toxicity study in rats (Section 4.3.1). The parameters

measured in the study include: clinical signs/systemic tolerance, body weight, macroscopic and histopathological assessment of lymphatic organs, bone marrow smears, absolute and relative differential blood count, albumin/immunoglobulin ratio, coagulation parameters, and changes in body temperature.

No vaccine-related systemic intolerance or mortality was observed. Almost no changes were observed in the absolute and differential blood count, as described in Section 4.3.1.4. Body weight was decreased 24 h after the administrations in all treatment groups compared to pre-dose (up to approx. 13%), but the relative body weight gain between the administrations was comparable to the control group (Section 4.3.1.3).

An increase of body temperature was noted at 24 h post each administration compared to values 4 h post administration in all groups. This increase was generally higher in immunized rats than in buffer treated animals. Of note, the physiological body temperature of rats is approx. 1°C higher than of humans and body temperatures observed 24 h post injection in rats did not exceed 40.2°C. In general, only individual animals displayed temperatures beyond 40°C, and then only after the second or third immunization. The temperature increase was fully reversible within 48 to 72 h post immunization.

All cytokines assessed displayed high background levels/variability and were similarly elevated in control and vaccinated animals.

4.3.3 Toxicology - Conclusions

The available results of the repeat-dose toxicology demonstrate tolerability of the tested vaccines. Through the entire repeat-dose toxicity study, there were no vaccine-related clinical signs or mortalities observed.

As expected, all vaccines induced a pro-inflammatory response manifested as a reversible reduction in body weight post immunization without affecting body weight gain between immunizations. Increases in typical inflammatory blood parameters such as fibrinogen and acute phase proteins support this hypothesis. The reversible elevation of GGT activity in the absence of increase of specific markers, such as ALKP and bilirubin, and relevant microscopic findings, does not indicate hepatobiliary injury.

Hematological changes were observed: an increase in large unclassified cell and leukocyte (monocyte, basophil and neutrophil) counts, as well as a transient, dose-dependent reduction in reticulocytes after first immunization. The reticulocyte changes have been observed in rats treated with the licensed LNP-small interfering RNA (siRNA) pharmaceutical Onpattro™ (FDA assessment report of Onpattro™ 2018), but have not been observed in patients treated with this compound. The effect is therefore considered species specific. After the last immunization, a slight reduction in red cell mass and platelet numbers was observed. The latter is likely attributable to inflammation, causing specific platelet consumption, which is considered a pharmacodynamics attribute (Davidson 2013; Middleton et al. 2016). All changes observed in blood parameters reversed fully throughout the 3-week recovery period.

As an induction of a local pro-inflammatory environment within the muscle can be considered a mode of action, local reactions were anticipated. The occurrence of higher grade local reactions after boost immunizations is considered to be attributable to the

reduced administration schedule and to the high vaccine dose, in relation to the bodyweight of the rat (approximately up to 0.5 mg/kg).

Macroscopic observations of indurated injection sites and enlarged spleens and/or draining lymph nodes (as described in Section 4.3.1.10) together with a tendency of increased spleen weights in vaccinated animals (Section 4.3.1.11), support the hypothesis that the vaccine candidates generate a pro-inflammatory environment.

Microscopical reversible changes were seen in the spleen, bone marrow and lymph nodes and injection sites with all vaccines. Other microscopic observations were reversible vacuolation of portal hepatocytes present in all vaccinated groups not associated with alterations in hepatic function (e.g., no elevations in ALAT). This change may be related to hepatic clearance of the pegylated lipid in the LNP.

No unexpected changes were observed during the recovery phase. All vaccine induced effects on local tolerance, food consumption and body weight were fully reversible and blood parameter changes were not detectable anymore. Macroscopic and microscopic findings ameliorated, though in some animals treated with BNT162b1 or BNT162b2 iliac lymph nodes were still enlarged and, microscopically, minimal to mild signs of inflammation were still detectable at the injection site and in the draining lymph node. The infiltration of macrophages in the iliac lymph nodes of previously treated recovery animals were regarded as consequence of phagocytosis relating to the inflammatory reactions at the injection sites. This finding corresponds well with the serological observation made in this group: BNT162b1 and BNT162b2 vaccines induced very high neutralizing titers, which were, for some animals, above the upper limit of quantification of the neutralization assay at the end of the recovery period.

5 EFFECTS IN HUMANS

Reference safety information for the BNT162 candidate vaccines is provided in Section 6.2.

5.1 Ongoing and planned clinical trials

For the status of ongoing and planned clinical trials with BNT162 vaccine variants, see Table 15.

Table 15: Status of ongoing and planned clinical trials (as of June 22nd, 2020)

Trial number	Design	Current number dosed (subject age)
BNT162-01 (NCT04380701) Germany	Phase I/II, 2-part, dose escalation trial. Part A is open label and non-randomized. (All subjects receive active vaccine) Part B will be defined in a protocol amendment.	BNT162a1 (age 18-55 years): 0.1 µg 12 subjects prime 0.3 µg 12 subjects prime / 12 boost 3 µg 6 subjects prime BNT162b1 (age 18 to 55 years): 1 µg 12 subjects prime / 11 boost 10 µg 12 subjects prime / 12 boost 30 µg 12 subjects prime / 12 boost 50 µg 12 subjects prime / 11 boost 60 µg 12 subjects prime BNT162b2 (age 18 to 55 years): 1 µg First dosing planned end of June-2020 10 µg 12 subjects prime 30 µg 2 subjects prime BNT162c2 (age 18 to 55 years): 0.1 µg 12 subjects (single dose) 0.3 µg 12 subjects (single dose) 1 µg First dosing planned 23-JUN-2020
BNT162-02 (Pfizer Protocol Number C4591001; NCT NCT04368728) US	Phase I/II, placebo-controlled, randomized, observer-blind, dose-finding trial. (Subjects are randomized: 4 active vaccine to 1 placebo)	BNT162b1 (age 18 to 55 years): 10 µg 15 subjects prime / 15 boost 30 µg 15 subjects prime / 15 boost 100 µg 15 subjects prime BNT162b1 (age 65 to 85 years): 10 µg 15 subjects prime 20 µg 15 subjects prime 30 µg 15 subjects prime BNT162b2 (age 18 to 55 years): 10 µg 15 subjects prime 20 µg 15 subjects prime BNT162b2 (age 65 to 85 years): 20 µg 15 subjects prime 30 µg 15 subjects prime
BNT162-03 China	To be defined.	Enrollment has not started.
BNT162-04 Germany	To be defined.	Enrollment has not started.

Up until June 22nd 2020, a total of 248 subjects (men and women) were vaccinated with BNT162 candidate vaccines in the ongoing clinical trials BNT162-01 and BNT162-02/C4591001: BNT162a1 (75 single-dose [SD] and 42 prime/boost [P/B]), BNT162b1 (105 [SD] and 46 [P/B]), BNT162b2 (44 [SD] and 0 [P/B]), and BNT162c2 (24 [SD]).

5.1.1 German trial BNT162-01 - Preliminary results (status June 22nd, 2020)

For the current status of dosing with BNT162 vaccines candidates by dose level in BNT162-01, see Table 15.

Summary of safety in trial BNT162-01

In the trial BNT162-01, younger adults aged 18 to 55 years were dosed with one of four BNT162 vaccine candidates (BNT162a1, BNT162b1, BNT162b2, and BNT162c2). The most complete experience is available for the vaccine BNT162b1, which has been dosed in 5 cohorts of 12 subjects each (all subjects received active vaccine). Except for those in the highest dose cohort (60 µg), all subjects were dosed twice (i.e., prime and boost).

Note: BNT162a1 has been tested at doses of 0.1 µg, 0.3 µg and 3 µg (starting dose level). In the first 6 subjects treated (sentinel and sub-group 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 trial 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 subjects reported only injection site reactions (pain and tenderness, almost exclusively of mild intensity) and no systemic reactions. Currently, the sponsor has elected to deprioritize further development the BNT162a1 candidate.

Reactogenicity

Local reactions and systemic events are solicited from the subjects and recorded by them in a diary for 7 days following administration of the vaccine. Most subjects in all cohorts experienced the expected reactogenicity, typically starting within 24 h of dosing and resolving within 24 h. The specific, solicited local and systemic reaction are summarized below in Table 16 and Table 17.

Table 16: Number of adults aged 18 to 55 years with local symptoms (diary): BNT162b1

	Number of subjects with local reactions (n=)							
	7 d Post Prime			7 d Post Boost			Total (both)	
	Subjects dosed prime	Any event	Any ≥ severe	Subjects dosed boost	Any event	Any ≥ severe	Any event	Any ≥ severe
BNT162b1	60	51	8	46	39	7	54	13
1 µg	12	6	0	11	7	2	7	2
10 µg	12	10	1	12	10	0	11	1
30 µg	12	11	4	12	11	2	12	5
50 µg	12	12	2	11	11	3	12	4
60 µg	12	12	1				12	1

Any ≥ severe = Any symptom graded 3 (severe) or higher. The highest grade is Grade 4 (potentially life threatening).

Table 17: Number of adults aged 18 to 55 years with systemic symptoms (diary): BNT162b1

	Number of subjects with systemic reactions (n=)							
	7d Post Prime			7d Post Boost			Total (both)	
	Subjects dosed prime	Any event	Any ≥ severe	Subjects dosed boost	Any event	Any ≥ severe	Any event	Any ≥ severe
BNT162b1	60	52	15	46	38	17	57	27
1 µg	12	9	0	12	7	2	11	2
10 µg	12	8	1	11	9	4	10	5
30 µg	12	11	3	12	11	6	12	6
50 µg	12	12	4	11	11	5	12	7
60 µg	12	12	7				12	7

Any ≥ severe = Any symptom graded 3 (severe) or higher. The highest grade is Grade 4 (potentially life threatening).

In local reactions, most subjects reported injection site pain and tenderness, whilst reports of swelling / induration or erythema were scarce. The most common systemic reactions were headache and fatigue, experienced by most subjects. Grade 3 (severe intensity) local reactions were reported for pain, tenderness and swelling. Grade 3 (severe intensity) systemic reactions were fever, headache, myalgia, arthralgia, nausea, vomiting, chills, loss of appetite, malaise and fatigue.

Laboratory findings

A consistent pattern has been seen in the laboratory assessments with elevation of the C-reactive protein with concomitant reduction in the plasma lymphocyte count 24 h after vaccination. These changes are consistent with the known pharmacology of this technology, with the changes in lymphocytes known to represent a reversible compartmental shift from the vascular space to lymphoid organs. These observations have been self-limiting and without clinical consequence. There have been no other consistent findings on laboratory assessments.

Adverse events

Adverse events are collected throughout the trial and graded by the investigators on a 4-point scale (as per this protocol). Most subjects report adverse events (Table 18), >90% of which are related to reactogenicity. 6 subjects had AEs rated as severe in intensity (Grade 3) covering 5 preferred terms: muscle tightness, headache, influenza like illness, injection site discomfort, pyrexia.

Table 18: Summary BNT162b1 TEAE (prime +/- boost) by number of subjects

BNT162b1	Subjects Dosed N =	Number of Subjects with (n=)					
		TEAEs	Mild AE	Moderate AE	Severe AE	SAE	Resolved AE
1 µg	12	11	10	7	2	0	11
10 µg	12	12	12	8	1	0	12
30 µg	12	12	12	9	0	0	12
50 µg	12	12	12	11	2	0	12
60 µg	12	12	12	10	1	0	12
Total	**60**	**59**	**58**	**45**	**6**	**0**	**59**

Summary

For vaccine BNT162b1, generally good tolerability was observed with no SAEs and no unexpected toxicities. To date, there is high acceptance by trial subjects with no withdrawals due to related AEs. Most reported AEs are signs and symptoms of reactogenicity, typical onset within first 24 h post immunization. All AEs / reactogenicity resolve spontaneously, mostly within 24 h. of onset and can be managed with simple measures (e.g., paracetamol). Laboratory assessments suggest a Th1 pattern of immune activation 24 h post dosing. Some dose dependency of tolerability has been observed, with 1 µg dose best tolerated. The possibly of a slight increase in reactogenicity following boost dose is noted, as is some inter-individual variability.

BNT162a1 has been tested at doses of 0.1 µg, 0.3 µg, and 3 µg (starting dose level). In the first 6 subjects treated 3 µg (starting dose level), although formal dose limiting toxicity criteria were not met, the frequency and duration of systemic reactogenicity (predominantly of moderate intensity) led to a recommendation to de-escalate the dose to 0.1 µg and 0.3 µg. At these dose levels, most subjects reported only injection site reactions (pain and tenderness, almost exclusively of mild intensity) and no systemic reactions. Currently, the sponsor has elected to deprioritize further development the BNT162a1 candidate.

Most recently dosing has begun with vaccines BNT162b2 and BNT162c2. The early pattern of reactogenicity with the BNT162c2 candidate at doses <1 µg appears similar or less than that seen with vaccine BNT162b1 at the 1 µg dose. Early indications for tolerability of BNT162b2 at a 10 µg dose are very encouraging with only minimal local reactogenicity in initial reports.

5.1.2 US trial BNT162-02 (C4591001) - Preliminary results (status, June 22nd, 2020)

This trial in the US is conducted by Pfizer, Inc. (New York, US) and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany). The trial has been approved by the US regulatory authorities and trial conduct has started.

The US trial BNT162-02 (Pfizer Protocol Number C4591001, NCT NCT04368728) is "a Phase I/II, placebo-controlled, randomized, observer-blind, dose-finding study to describe the safety, tolerability, immunogenicity, and potential efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy adults. This trial will be developed into a combined Phase I/II/III trial using a protocol amendment, such that the results can support applications for marketing approval globally.

Preliminary results from this trial were published by Mulligan et al. (2020).

Summary of safety in BNT162-02/C4591001

US Trial BNT162-02/C4591001 is a randomized and placebo-controlled trial, in which the trial subjects are randomized 4:1 to receive active vaccine or placebo. The available safety and tolerability data for younger adults aged 18 to 55 years (see Table 19) who have received dose 1 and dose 2 of BNT162b1 were broadly comparable to those in trial BNT162-01 and are briefly summarized below.

Preliminary safety and tolerability data in elderly (aged 65 to 85 years) after dosing with BNT162b1 are presented separately below and are summarized in Figure 41 and Figure 43.

Table 19: Number of adults aged 18 to 55 years dosed in BNT162-02/C4591001 (status, June 22nd, 2020)

	BNT162b1		Placebo	
	Dose 1	Dose 2	Dose 1	Dose 2
18-55 years of age				
10 µg dose level	N=12	N=12	N=3	N=3
30 µg dose level	N=12	N=12	N=3	N=3
100 µg dose level	N=12	Not applicable	N=3	Not applicable

Overall, all dose levels exhibited a tolerability and safety profile consistent with modRNA-based vaccines, and a clear dose level response was observed after dose 1 and dose 2 in younger adults. Reactogenicity was generally higher after the second dose, but the symptoms resolved quickly over the course of a few days. In the 10 µg and 30 µg groups, the only reports of Grade ≥3 (severe) events were 1 case of fatigue in a subject in the 10 µg cohort and 1 case of chills in a single subject in the 30 µg cohort, both after their boost dose. Based on the tolerability profile observed with the 100 µg dose level after the first dose, and the reactogenicity observed in lower dose levels, an internal decision was made not to give a boost dose at 100 µg.

Adverse events were reported by 50.0% (6/12) of subjects who received either 10 µg or 30 µg of BNT162b1, by 58.3% (7/12) of those who received 100 µg of BNT162b1, and by

11.1% (1/9) of placebo recipients. Two subjects reported severe AEs: Grade 3 pyrexia 2 days after vaccination in the 30 µg cohort, and sleep disturbance 1 day after vaccination in the 100 µg cohort. Related AEs were reported by 25% (3/12 in the 10 µg cohorts) to 50% (6/12 each in 30 µg and 100 µg cohorts) of BNT162b1 recipients and by 11.1% (1/9) of placebo recipients. No SAEs were reported. For details, see Table 20.

Table 20: Summary of the AEs reported adults aged 18 to 55 years dosed in BNT162-02/C4591001 (status, June 22nd, 2020)

Adverse event (AE)	10 µg (N = 12) n (%)	30 µg (N = 12) n (%)	100 µg (N = 12) n (%)	Placebo (N = 9) n (%)
Any event	6 (50.0)	6 (50.0)	7 (58.3)	1 (11.1)
Related	3 (25.0)	6 (50.0)	6 (50.0)	1 (11.1)
Severe	0	1 (8.3)	1 (8.3)	0
Life-threatening	0	0	0	0
Any serious adverse event	0	0	0	0
Related	0	0	0	0
Severe	0	0	0	0
Life-threatening	0	0	0	0
Any AE leading to withdrawal	0	0	0	0
Severe	0	0	0	0
Life-threatening	0	0	0	0
Death	0	0	0	0

Summary of safety in elderly subjects (aged 65 to 85 years) in BNT162-02/C4591001

Preliminary safety and tolerability data after the first dose of 10 µg, 20 µg, and 30 µg in adults aged 65 to 85 years (see Table 21) after one dose of BNT162b1 are shown in Figure 41 and Figure 42 (local reactions), Figure 43 and Figure 43 (systemic events).

Table 21: Number of adults aged 65 to 85 years dosed in BNT162-02/C4591001 (status, June 22nd, 2020)

	BNT162b1		Placebo	
	Dose 1	Dose 2	Dose 1	Dose 2
65-85 years of age				
10 µg dose level	N=12	N=0	N=3	N=0
20 µg dose level	N=12	N=0	N=3	N=0
30 µg dose level	N=12	N=0	N=3	N=0

The first dose of BNT162b1 in this age group was generally well tolerated. One episode of severe muscle pain and erythematous rash occurred with mild fever occurred in an 81-year-old man on day 2 after receiving a 20 µg dose, consistent with varicella zoster (shingles). He was prescribed Valacyclovir and this AE was reported as fully resolved within 7 days. The investigator reported this AE as not related to vaccine.

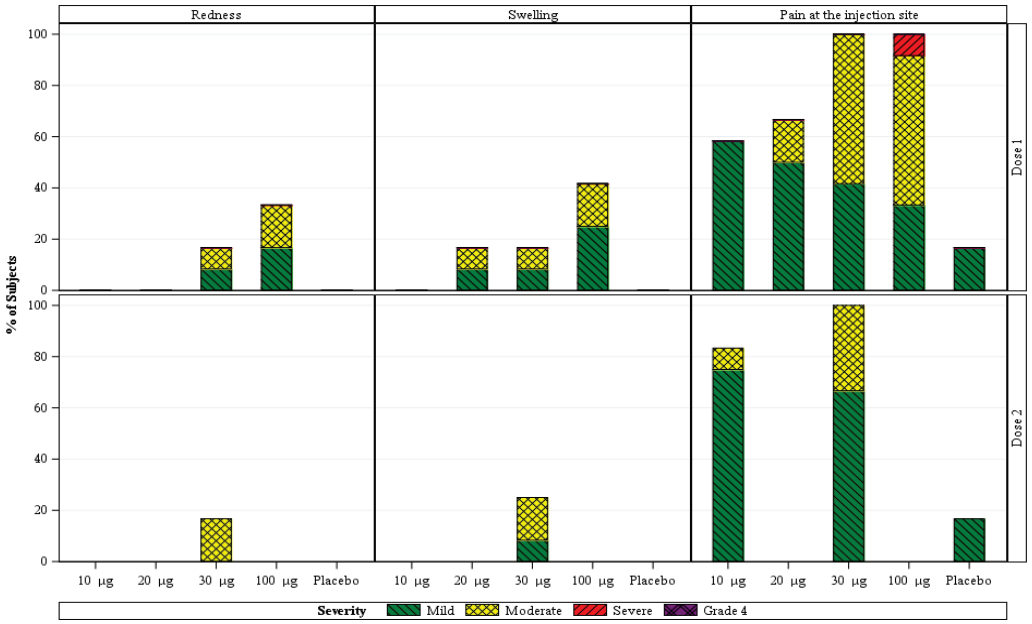


Figure 40: BNT162b1 - Local reactions in younger subjects in BNT162-02/C4591001

Notes: Younger subjects are aged 18 to 55 years. Local reactions after doses 1 & 2 (100 µg group did not receive dose 2). 12 subjects had received dose 1 (i.e., prime) in 20 µg group with 1-3 days of follow-up.

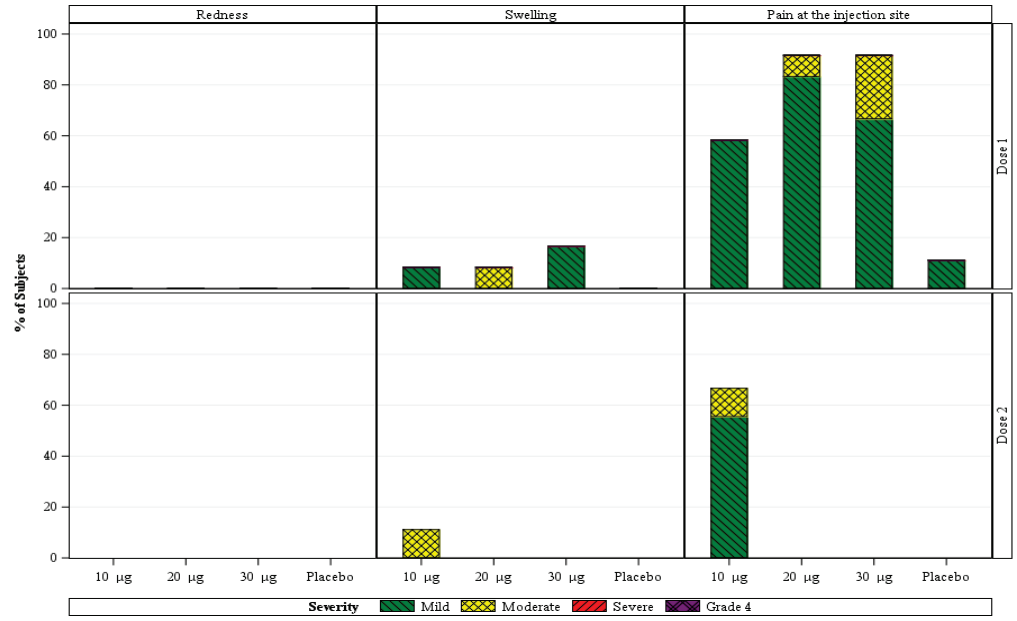


Figure 41: BNT162b1 - Local reactions in elderly subjects in BNT162-02/C4591001

Notes: Elderly subjects are aged 65 to 85 years.

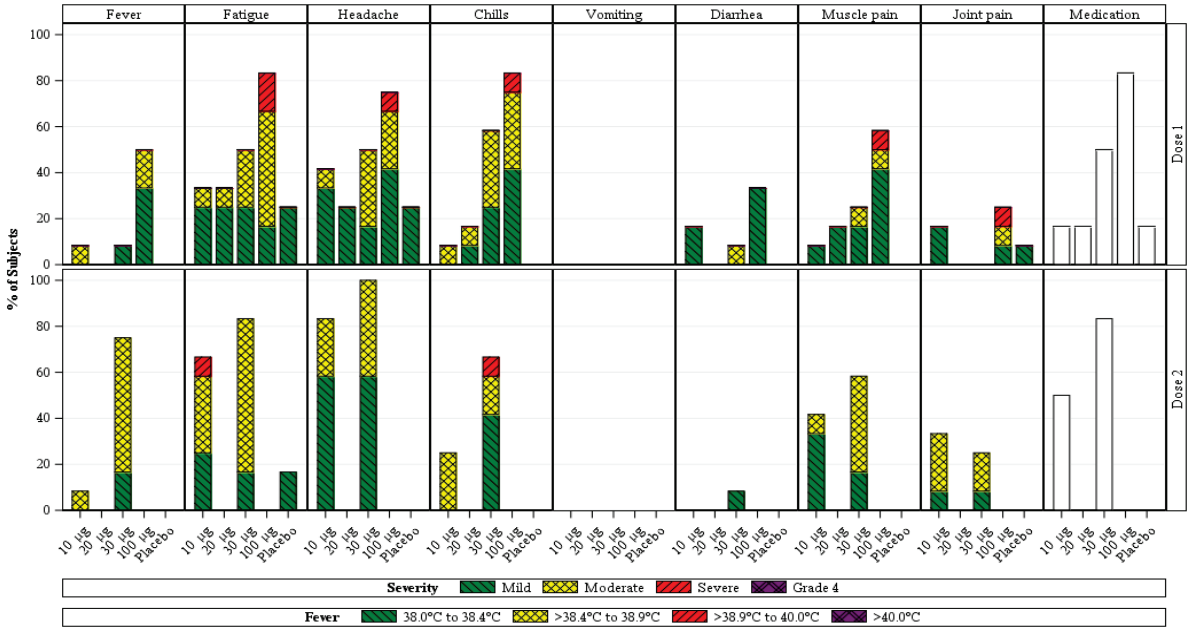


Figure 42: BNT162b1 - Systemic events in younger subjects in BNT162-02/C4591001

Notes: Younger subjects are aged 18 to 55 years. 12 subjects had received dose 1 in 20 µg group with 1-3 days of follow-up. Systemic events after doses 1 & 2. The 100 µg group did not receive dose 2.

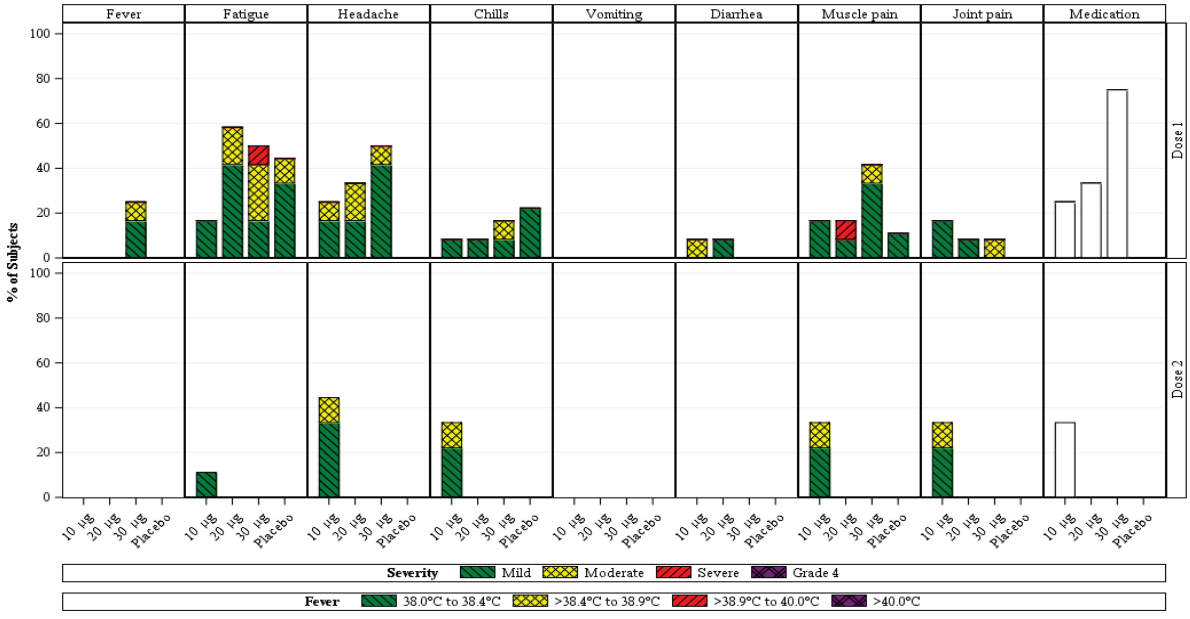


Figure 43: BNT162b1 - Systemic events in elderly subjects in BNT162-02/C4591001

Notes: Elderly subjects are aged 65 to 85 years. Systemic events after doses 1 & 2. 9 subjects had received dose 2 in 10 µg group with 2-3 days of follow-up.

In general terms, the local tolerability of BNT162b1 in elderly subjects seems comparable to that recorded in younger adults. The pattern of systemic reactogenicity appears similar between the two age groups, possibly with a lower overall incidence in the elderly subjects in comparison to the younger adults.

5.1.3 Chinese trial BNT162-03 - Planned

The trial BNT162-03 will be conducted in healthy Chinese adults by Shanghai Fosun Pharmaceutical Development, Inc. (Shanghai, China) and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany).

Currently the trial has not been approved and the concrete trial design is under discussion with the Chinese regulatory authorities to ensure alignment with the rapidly progressing overall clinical development and the adequacy of the Chinese trial for regional extension of the potential registrational data package.

5.1.4 BNT162-04 - Planned

This trial will be conducted and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany) to investigate the safety and immunogenicity of BNT162b3 in healthy adults (men and women). The trial set-up is ongoing. The trial has not been approved by the regulatory authorities or relevant ethical committees, and therefore trial conduct has not started.

5.2 Marketing experience

The BNT162 vaccine candidates have neither been approved for use nor been marketed in any country.

6 SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

For a summary of the relevant non-clinical and clinical information, see Section 1.

All tested vaccine candidates were immunogenic to highly immunogenic in non-clinical model including mouse, rats, and NHPs.

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

The currently available data demonstrate that vaccines based on all three RNA platforms (uRNA, modRNA, and saRNA) in conjunction with V5, V8/V9 as well as V5TM including the clinical vaccine candidates, BNT162a1, BNT162b1, BNT162b2, BNT162b3, and BNT162c2 are capable of inducing robust immune responses in mice, rats, and NHPs.

In mice, the antibody response was detected at a very early time point by IgG analysis on 7 d post-immunization. The induction of an antibody response by a very low immunization dose of 0.2 µg with the modRNA platform (BNT162b1, BNT162b2) and the saRNA platform (BNT162c2) indicate high vaccine potency. Also, immune responses by SARS-CoV-2 pseudovirus neutralization are detectable 14 d post-immunization in the mice immunized with intermediate doses.

Within the different vaccine candidates, BNT162b1 induced the highest virus neutralization titer. The BNT162b3 candidate induced an early response of antibodies with following high titer; day 28 results are pending.

Similar results indicating immunogenicity were obtained in an accessory study to the GLP-compliant repeat-dose toxicology study in rats. In NHPs, a generation of S-specific, neutralizing antibodies was detected early on and after two immunizations after BNT162b, the overserved titers exceeded human convalescent sera. Results for other vaccine candidates in NHP are pending.

Pharmacokinetic studies were conducted using a luciferase reporter RNA, and protein expression after IM injection was demonstrated *in vivo*. The luciferase biodistribution profile resembles that of similar RNA products developed by BioNTech, some of which have been safely tested at higher doses non-clinically and clinically using IV administration. Prior clinical experience with similar RNA products developed by BioNTech indicates that the distribution to the liver does not pose a safety risk.

The available results of the repeat-dose toxicology demonstrate tolerability of the tested vaccines. Through the entire repeat-dose toxicity study, there were no vaccine-related clinical signs or mortalities observed.

As expected, all vaccines induced a pro-inflammatory response manifested as a reversible reduction in body weight post immunization without affecting body weight gain between immunizations. Increases in typical inflammatory blood parameters such as fibrinogen and acute phase proteins support this hypothesis. The reversible elevation of GGT activity in the absence of increase of specific markers, such as ALKP and bilirubin, and relevant microscopic findings, does not indicate hepatobiliary injury.

Hematological changes were observed: an increase in large unclassified cell and leukocyte (monocyte, basophil and neutrophil) counts, as well as a transient, dose-

dependent reduction in reticulocytes after first immunization. The reticulocyte changes have been observed in rats treated with the licensed LNP-small interfering RNA (siRNA) pharmaceutical Onpattro™ (FDA assessment report of Onpattro™ 2018), but have not been observed in patients treated with this compound. The effect is therefore considered species specific. After the last immunization, a slight reduction in red cell mass and platelet numbers was observed. The latter is likely attributable to inflammation, causing specific platelet consumption, which is considered a pharmacodynamics attribute (Davidson 2013; Middleton et al. 2016). All changes observed in blood parameters reversed fully throughout the 3-week recovery period.

As an induction of a local pro-inflammatory environment within the muscle can be considered a mode of action, local reactions were anticipated. The occurrence of higher grade local reactions after boost immunizations is considered to be attributable to the reduced administration schedule and to the high vaccine dose, in relation to the bodyweight of the rat (approximately up to 0.5 mg/kg).

Macroscopic observations of indurated injection sites and enlarged spleens and/or draining lymph nodes together with a tendency of increased spleen weights in vaccinated animals, support the hypothesis that the vaccine candidates generate a pro-inflammatory environment.

Microscopical reversible changes were seen in the spleen, bone marrow and lymph nodes and injection sites with all vaccines. Other microscopic observations were reversible vacuolation of portal hepatocytes present in all vaccinated groups not associated with alterations in hepatic function (e.g., no elevations in ALAT). This change may be related to hepatic clearance of the pegylated lipid in the LNP.

The were no unexpected changes observed during the recovery phase. All vaccine induced effects on local tolerance, food consumption and body weight were fully reversible and blood parameter changes were not detectable anymore. Macroscopic and microscopic findings ameliorated, though in some animals treated with BNT162b1 or BNT162b2 iliac lymph nodes were still enlarged and, microscopically, minimal to mild signs of inflammation were still detectable at the injection site and in the draining lymph node. The infiltration of macrophages in the iliac lymph nodes of previously treated recovery animals were regarded as consequence of phagocytosis relating to the inflammatory reactions at the injection sites. This finding corresponds well with the serological observation made in this group: BNT162b1 and BNT162b2 vaccines induced very high neutralizing titers, which were, for some animals, above the upper limit of quantification of the neutralization assay at the end of the recovery period.

As of June 22nd 2020, a total of 248 subjects (men and women) were vaccinated with BNT162 candidate vaccines in the ongoing clinical trials BNT162-01 and BNT162-02/C4591001: BNT162a1 (75 single-dose [SD] and 42 prime/boost [P/B]), BNT162b1 (105 [SD] and 46 [P/B]), BNT162b2 (44 [SD] and 0 [P/B]), and BNT162c2 (24 [SD]).

In the ongoing trials, the pattern of tolerability is, as anticipated, broadly typical of vaccines administered intramuscularly, consistent with the mode of action of the BNT162 vaccines and the available non-clinical/clinical data, with most subjects reporting flu-like symptoms and injection site reactions. Based on reports in subject diaries, the local tolerability of

BNT162b1 in elderly subjects aged 65 to 85 years was comparable to that recorded for younger subjects aged 18 to 55 years. Based on reports in subject diaries, the pattern of systemic reactogenicity appears similar between the two age groups, possibly with a lower overall incidence in the elderly subjects in comparison to the younger adults at equal doses. Reactogenicity seems slightly more pronounced following the boost (second) dose 21 d after the initial prime dosing. All unsolicited AEs resolved spontaneously or with simple medical management. Most of the unsolicited AEs were mild or moderate in severity. No SAEs were reported within the post-vaccination observation period. No subjects were withdrawn due to related AEs. Preliminary data in elderly subjects show a comparable to lower reactogenicity based on the observed local reactions and system events in similar doses. This observation may indicate a lower innate immune activation capability of elderly.

Preliminary data in younger subjects (aged 18 to 55 years) treated in the ongoing BNT162 trials, backed by non-human primate (rhesus macaque) immunogenicity data, have shown that BNT162b1 is immunogenic in the tested dose range. Immunogenicity in humans aged >55 years is not yet known.

BNT162b3 encodes a membrane-anchored variant of the RBD of the SARS-CoV-2 spike-protein (S protein). The candidate is highly homologous to BNT162b1 and BNT162b2 with regard to the RNA chemistry (modRNA containing pseudo-methyl uridine). As RNA-chemistry defines the innate immune activation pattern and thus potential reactogenicity, tolerability data obtained with the BNT162b1 and BNT162b2 vaccine variants is indicative for tolerability of BNT162b3. BNT162b1 and BNT162b3 encode the same antigen, the difference being that the antigen is presented in a different way to the immune system. BNT162b3 vaccine has shown superior early immunogenicity in mice as well as NHP, and thus may show the superior vaccine performance compared with BNT162b1.

Based on all available non-clinical and clinical data with BNT162 vaccine candidates and on data from non-clinical studies and clinical trials with the same or related RNA components or antigens, the expected adverse reactions after vaccination are expected to be manageable using routine symptom driven standard of care as determined by the investigators.

6.1 Guidance for the investigator

6.1.1 Posology and method of administration

The BNT162 vaccines are intended for IM administration in the upper arm (musculus deltoideus) using single dose and prime/boost regimens.

6.1.2 Restrictions

Currently there are no data available from BioNTech clinical trials justifying restrictions, beyond the standard precautionary restrictions when performing vaccinations and blood draws.

6.1.3 Information relevant to special populations

Currently there are no data available from BioNTech clinical trials on the use of BNT162 vaccines in special populations including the renally/hepatically impaired people, and/or pregnant or breastfeeding women.

Currently there are no data available from BioNTech clinical trials on the use of BNT162 vaccines justifying restrictions and/or dosing adaptions when vaccinating elderly adults. For details of the available human experience in healthy elderly adults, see Section 5.

6.1.4 Special warnings and precautions for use

For specific special warnings and precautions, see the respective trial protocol.

6.2 Reference safety information

Based on the observed adverse drug reactions (ADRs) in the ongoing trials with BNT162 vaccine candidates, the most frequently reported toxicities are flu-like illness and injection site reactions as shown in Table 22.

Table 22: Expected ARs [a] observed for BNT162 vaccine candidates

Description	MedDRA Preferred Terms	Intensity [b]
Systemic reactogenicity	Flu-like illness	Severe
Local reactogenicity	Injection site reaction	Severe

[a] Due to limited clinical data no statement regarding frequency can be provided.

[b] Intensity of AEs or SAEs as graded by the investigator. For further guidance, see guideline "US FDA Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

No SARs are considered expected by the sponsor for regulatory reporting purpose.

6.3 Risks

6.3.1 General risks

The risks linked to the trial-specific procedures are as follows:

- The volume of blood drawn will kept to a minimum.
- All trial-specific procedures will be performed by qualified trial site personnel.

The risks linked to vaccinations in general are as follows:

- Due to the IM route of administration, there is the risk of localized injection site reactions, e.g., erythema, pruritus, pain, tenderness, swelling.
- Due to their immune-modulatory effect, vaccines may cause systemic flu-like reactions such as temporary headache, fatigue, loss of appetite, myalgia, arthralgia, fever, sweating, and chills. Rarely, with certain prophylactic vaccines (e.g., as seen for vaccines using attenuated viruses) severe allergic reaction or a neurological side effects, such as a seizure, were seen. Although these rare side

effects are a concern, the risk of a vaccine causing serious harm or death is considered to be extremely small, in particular for BNT162 vaccines, which are molecularly defined, highly purified and based on RNA, which naturally occurs and is metabolized in the human organism.

6.3.2 Potential risks

As of June 22nd 2020, the pattern of tolerability in the ongoing clinical trials is, as anticipated, broadly typical of vaccines administered intramuscularly, consistent with the mode of action of the BNT162 vaccines and the available non-clinical/clinical data, with most subjects reporting flu-like symptoms and injection site reactions. For details, see Section 5.

Prior clinical experience with similar RNA products developed by BioNTech indicates that the RNA distribution to the liver does not pose a safety risk, nonetheless, liver parameters will be carefully monitored in the planned clinical trials.

Vaccine-related enhanced disease has been reported in the literature from non-clinical studies investigating different vaccine formulations tested to prevent various coronavirus-induced diseases. Such effects have not been documented so far for SARS-CoV-2. No data are currently available to exclude that BNT162 may cause enhanced disease in vaccinated subjects. The planned clinical trials will include monitoring of possible COVID-19-related symptoms in trial subjects.

6.3.3 Identified risks

Based on the sum of the available non-clinical and clinical data, the identified risks linked to the administration of the BNT162 vaccine candidates are: injection site pain, fever, fatigue, headache, chills, and muscle pain.

These risks can be managed using routine symptom driven standard of care.

6.3.4 Risk evaluation summary

The sponsor considers all of the listed risks to be manageable using routine symptom driven standard of care and justified given:

- the urgent need for the development of new prophylactic vaccines,
- the threat posed by the increasing number of globally distributed outbreaks of SARS-CoV-2 infection,
- the potential of the BioNTech platform of RNA-based vaccines:
  - to rapidly deliver high numbers of vaccine doses rapidly in a single production campaign, and
  - to be both well tolerated and effective.

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INVESTIGATOR'S BROCHURE

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Version: 5.0 **Date:** 12 AUG 2020

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Reference safety information for the investigational medicinal products (IMPs) is provided in Section 7.8.2.

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
ALAT	Alanine-aminotransferase
ASAT	Aspartate-aminotransferase
BNT162a	BNT162 RNA-LNP vaccine utilizing uridine 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.)
CI	Confidence intervals
CMV	Cytomegalovirus
COVID-19	Coronavirus Disease 2019
d	Day(s)
EBV	Epstein-Barr virus
Elderly	Individuals aged 65 yrs
ELISA	Enzyme-Linked Immunosorbent Assay
GGT	Gamma (γ)-glutamyl transpeptidase
GLP	Good Laboratory Practice
GMC	Geometric mean concentration
GMT	Geometric mean titer
h	Hour(s)
HA	Hemagglutinin
HCS	COVID-19 human convalescent sera (panel)
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IL	Interleukin
IM	Intramuscular(ly)
IMP	Investigational Medicinal Product
IV	Intravenous(ly)
LNP	Lipid nanoparticle
modRNA	Nucleoside modified messenger RNA
mRNA	Messenger RNA
NCT	ClinicalTrials.gov identifier
NHP	Non-human primates
Older adults	Individuals aged 56 to 85 yrs
P/B	Prime/boost
pVNT	Pseudovirus-based neutralization assay
RBD	Receptor Binding Domain
RNA	Ribonucleic acid
S protein	SARS-CoV-2 sp ke-protein
saRNA	Self-amplifying messenger RNA
SARS-CoV-2	The virus leading to COVID-2019

Abbreviation	Explanation
SD	Single-dose
Th1	Type 1 T helper cells
uRNA	Non-modified uridine messenger RNA
WHO	World Health Organization
Younger adults	Individuals aged 18 to 55 yrs
yr(s)	Year(s)

2 SUMMARY

There is an urgent need for the development of a new prophylactic vaccine given the threat posed by the increasing number of globally distributed outbreaks of Severe Acute Respiratory Syndrome (SARS) -CoV-2 infection and thus its associated disease Coronavirus Disease 2019 (COVID-19).

The development of a ribonucleic acid (RNA)-based vaccine encoding a viral antigen that is translated by the vaccinated organism to protein to induce a protective immune response provides significant advantages over more conventional vaccine approaches.

At BioNTech, 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 non-clinical safety and toxicity of the BNT162 family of lipid nanoparticle (LNP) enveloped uRNA, modRNA, and saRNA vaccine platforms encoding SARS-CoV-2 antigens was tested in a GLP-compliant repeat-dose toxicity study. In this study in Wistar Han rats, administration of the vaccine candidates BNT162a1, BNT162b1, BNT162b2, or BNT162c1 using intramuscular (IM) injections weekly for 2 (BNT162c1) or 3 administrations was tolerated without evidence of systemic toxicity. Non-adverse inflammatory changes at the injection sites and the draining lymph nodes, increased hematopoiesis in the bone marrow and spleen, and clinical pathology changes consistent with an immune response or inflammation in the injection sites were observed. Transient vacuolation of portal hepatocytes unassociated with evidence of hepatocellular damage was observed in dosed animals. The findings in this study are consistent with those typically associated with the IM administration of LNP encapsulated RNA-based vaccines.

BNT162 vaccine candidates based on the uRNA, modRNA, and saRNA formats are currently under investigation in three clinical trials with healthy adults (men and women) aged between 18 and 85 yrs. In these trials, the subjects are either younger adults (aged 18 to 55 yrs), older adults (aged 55 to 85 yrs), or elderly adults (aged 65 to 85 yrs).

As summarized below, as of August 6th, 2020, a total of 1,506 subjects (men and women) were dosed at least once with BNT162 vaccine candidates in the ongoing clinical trials (i.e., BNT162-01, BNT162-02/C4591001, and BNT162-03).

BNT162 vaccine candidate ***Dosing regimen (age group)***	**BNT162a1**	**BNT162b1**	**BNT162b2**	**BNT162c2**	
Phase I					
SD (younger adults)	30	93	199	71	
P/B (younger adults	24	61	121	1	
SD (elderly adults)	0	36	36	0	
P/B (elderly adults)	0	36	36	0	
Phase II/III					
SD (younger and older adults)			1,041*		
Total all adults dosed at least once in Phase I & II/III	**30**	**129**	**1,276***	**71**	**Sum = 1,506**

* Estimated / includes estimated number based on 1.1 verum:placebo assignment.
Years = yrs; Younger adults = adults aged 18 to 55 yrs; Elderly adults = adults aged 65 to 85 yrs.

Preliminary immunogenicity data (status July 24th, 2020) are available from younger and elderly adults dosed with BNT162b1 or BNT162b2. The available immunogenicity data suggest that, by day 21, the BNT162b (i.e., modRNA-based) vaccine candidates induce a robust IgG-binding response to RBD/S1 and neutralizing response specific to SARS-CoV-2. Immunogenicity appears to be substantially increased following the second dose of vaccine.

For BNT162b1, P/B doses of 1, 10, 30, and 50 µg administered 21 d apart elicited antibodies and robust $CD4^+$ and $CD8^+$ T cell responses. All subjects exhibited antibody responses superior to those observed in a COVID-19 convalescent human serum (HCS) panel. The COVID-19 HCS panel is comprised of 38 human COVID-19 HCS sera drawn from individuals aged 18 to 83 yrs, at least 14 d after PCR-confirmed diagnosis, and at a time when the individuals were asymptomatic. The serum donors predominantly had symptomatic infections (35/38), and one had been hospitalized.

For BNT162b2, P/B doses of 10 µg of BNT162b2 administered 21 d apart elicited substantial Th1-type $CD4^+$ and $CD8^+$ T cell responses.

The BNT162b1 and BNT162b2 vaccines-elicited, antigen specific CD8+ and $CD4^+$ T cell responses were comparable to or higher than the memory responses in the same subjects against cytomegalovirus (CMV), Epstein-Barr virus (EBV), influenza virus, and tetanus toxoid.

In the trial BNT162-02/C4591001 (status July 24th, 2020) in younger adults administered BNT162b1 P/B at 10 µg or 30 µg, RBD-binding IgG levels had increased at day 7 to approximately 8- and 46-fold that seen in a COVID-19 HCS panel. After 10 µg or 30 µg BNT162b1 doses, preliminary data show modest increases in SARS-CoV-2 neutralizing titers (geometric mean titers, GMTs) at 21 d after the prime dose. Higher titers were observed at 7 d after the boost dose, reaching 1.8 to 2.8-fold neutralization GMT, compared to that seen in the COVID-19 HCS panel. Similar results were seen for BNT162b2.

Similar results were seen for BNT162b1 and BNT162b2 after administration to younger adults in the trial BNT162-01.

Preliminary safety data are available from the ongoing trials BNT162-01 and BNT162-02/C4591001.

Generally, good tolerability was observed. Overall, many of the reported adverse events (AEs) appear to be similar to reactogenicity events anticipated for intramuscularly (IM)-administered vaccines, typically with an onset within first 24 h post immunization. All AEs / reactogenicity symptoms resolved spontaneously, mostly within 24 h of onset, and were managed with simple measures (e.g., paracetamol). There were no serious adverse events (SAEs) and no unexpected toxicities.

In the trial BNT162-01, BNT162a1 P/B has been tested at doses of 0.1, 0.3, and 3 µg in younger adults. In the first 6 subjects treated with the 3 µg prime dose, the frequency and duration of systemic reactogenicity (predominantly of moderate intensity) led to a decision not to administer the 3 µg boost dose and to defer further dosing with this vaccine candidate.

In the trials BNT162-01 and BNT162-02/C4591001, BNT162b1 P/B dosing has been tested at dose levels between 1 µg and 100 µg in younger adults. Acceptable tolerability was shown after both doses up to 50 µg BNT162b1.

In the trials BNT162-01 and BNT162-02/C4591001, BNT162b2 P/B has been tested at dose levels between 1 µg and 30 µg in younger adults. Acceptable tolerability was shown after both doses at all dose levels.

In the trial BNT162-02/C4591001, overall, P/B dosing with BNT162b1 and BNT162b2 doses of 10 µg to 30 µg showed acceptable tolerability in elderly adults. This tolerability appears to be better than seen in younger adults at the same doses.

BNT162c2 has been tested in younger adults at doses between 0.1 µg and 1 µg. Preliminary data suggest an acceptable tolerability, with a similar or weaker reactogenicity than seen with BNT162b1 at the same dose.

The BNT162 vaccine candidates have neither been approved for use nor been marketed in any country.

3 INTRODUCTION

3.1 Background

The number of SARS-CoV-2 infections and the associated disease, COVID-19, is increasing every day and continues to spread globally. The World Health Organization (WHO) classified the COVID-19 outbreak as pandemic on March 11th, 2020. The WHO Situation Update Report dated August 6th, 2020 noted 18,614,177 confirmed cases with 702,642 deaths globally (WHO Situation Update Report 199).

There are currently no approved vaccines or antiviral drugs to prevent or treat infection with SARS-CoV-2 or its associated disease COVID-2019 (Habibzadeh and Stoneman 2020).

3.2 BioNTech's RNA therapeutics

BioNTech has longstanding and diversified expertise in utilizing messenger RNA (mRNA) to deliver genetic information to cells, where it is used to express proteins for the therapeutic effect. BioNTech has been working in the RNA field for more than a decade and is developing a portfolio of RNA therapies that utilize four different mRNA formats and three different formulations to derive five distinct platforms, each optimized for delivering a particular therapeutic mode-of-action.

These mode-of-actions include using mRNA as a vaccine to induce antibody and T-cell immune responses. Three of these platforms are currently in human testing in oncology indications, primarily as repeatedly administered therapeutic cancer vaccines, where over 613 patients have been dosed to date (data on file). This clinical experience includes a large number of patients who have had long-term exposure, i.e., who have received more than 8 administrations.

RNA is a highly versatile multi-purpose molecule. What makes it attractive as vaccine platform is that it enables timely and effective response to emerging threats. RNA 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.

The production of RNA requires only a single development and manufacturing platform, irrespective of the encoded pathogen antigens. Thus, RNA has the potential of rapid, cost-efficient, high-volume manufacturing and flexible stockpiling (long term storage of low-volume libraries of frozen plasmid and unformulated RNA, which can be rapidly formulated and distributed). BioNTech has expertise in production-process development for various RNA chemistries and formulations.

3.3 Introduction to BioNTech RNA-based vaccines

A LNP-formulated RNA-based vaccine would provide one of the most flexible, scalable, and fastest approaches to provide protection against new, fast spreading, virus infections (Rauch et al. 2018; Sahin et al. 2014).

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

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 an 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: RNA which contains the standard nucleoside uridine (uRNA), nucleoside-modified RNA (modRNA), in which uridine is replaced by the nucleoside pseudo-uridine; and self-amplifying RNA (saRNA), which also contains uridine nucleosides (Figure 1).

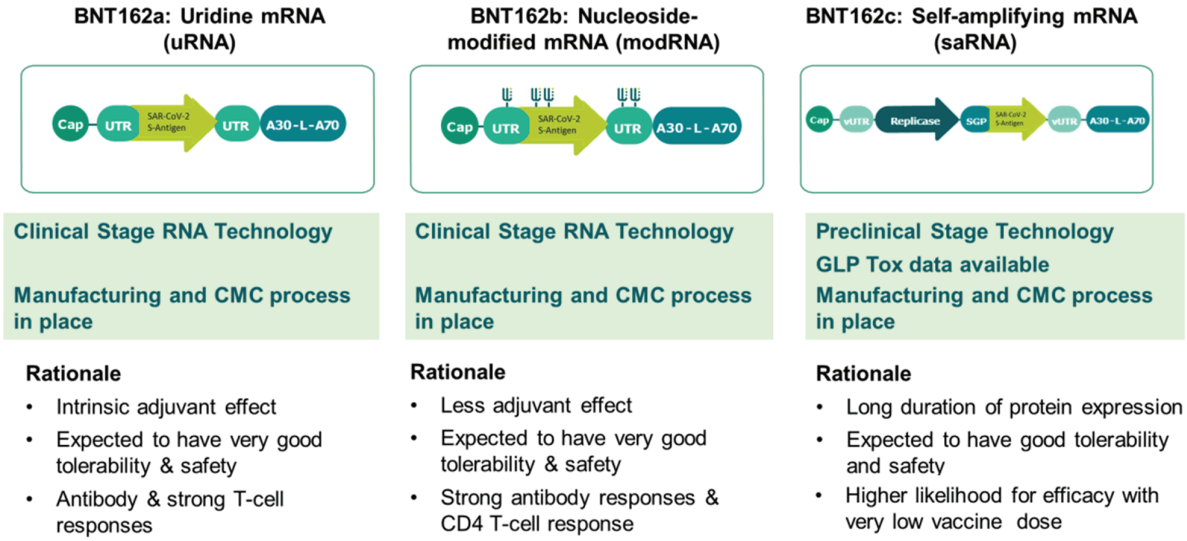


Figure 1: Overview of the three RNA platforms

The RNA vaccine molecules are capped, contain ORFs flanked by the UTR, and have a polyA-tail at the 3' end. The ORF of the uRNA and modRNA vectors encode the vaccine antigen. The saRNA has two ORFs. The first ORF encodes an alphavirus-derived RNA-dependent RNA polymerase (replicase), which upon translation mediates self-amplification of the RNA. The second ORF encodes the vaccine antigen. Abbreviations: A30-L-A70 = poly(A) tail interrupted by a linker; CMC = chemistry, manufacturing and controls; SGP= subgenomic promotor; ORF = open reading frame; UTR = untranslated region; vUTR = viral untranslated region.

The utility of each of these RNA platforms for the development of infectious disease vaccines is supported by various non-clinical studies that demonstrated the efficient induction of potent neutralizing antibody and T-cell responses against a variety of viral

pathogens including influenza, Ebola, human immunodeficiency virus (HIV), and Zika virus (Vogel et al. 2018; Moyo et al. 2018; Pardi et al. 2017).

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 2). 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.

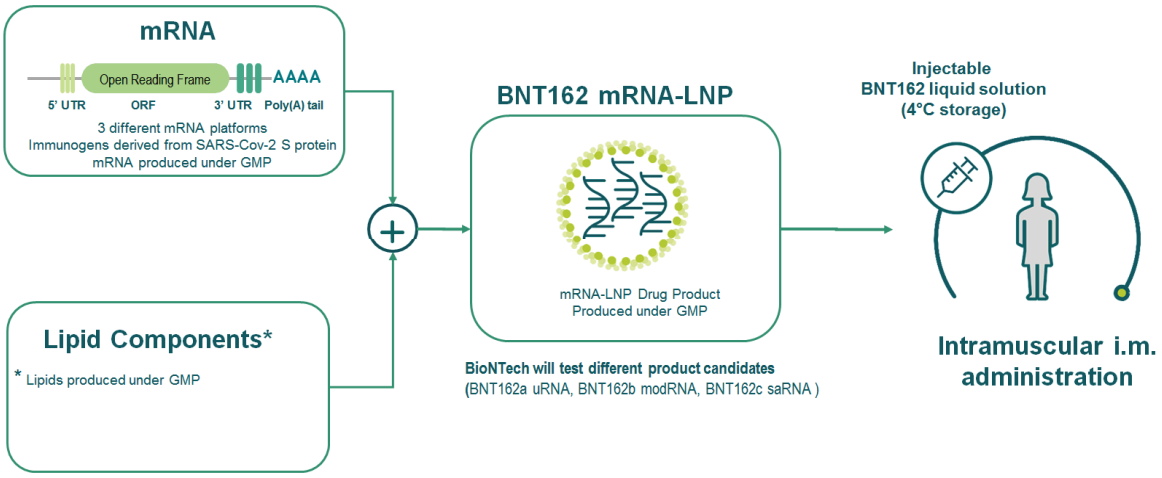


Figure 2: RNA-LNP-based BNT162 vaccines

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 IM injection. Abbreviations: GMP = good manufacturing practice; i.m. = intramuscular; mRNA = messenger RNA; ORF = open reading frame; RNA-LNP = RNA complexed with liposomes; UTR = untranslated region.

The three RNA platforms used in the BNT162 vaccine candidates have complementary strengths (Figure 1): 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 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.

All vaccine candidates may be administered using P/B or prime-only administration regimens (Figure 3).

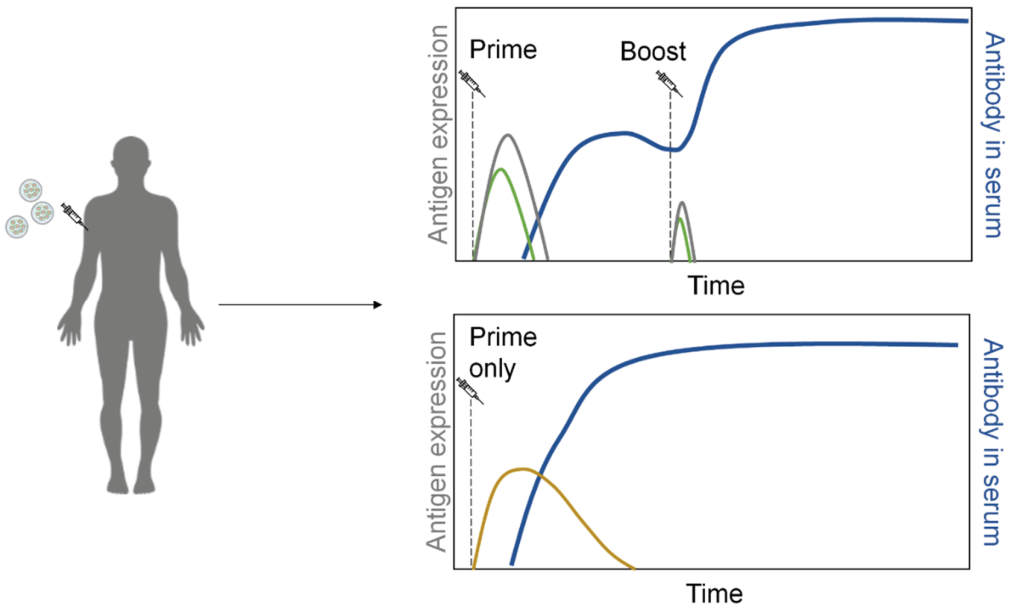


Figure 3: Rationale for the administration schema of BNT162 vaccines

Two different dosing regimens are proposed for the different BNT162 vaccines. While vaccines based on the BNT162a and BNT162b platforms have the highest antigen expression shortly after immunization, a second immunization may be necessary to induce a higher antibody generation (see the upper graph). For vaccines based on the BNT162c platform, due to the self-amplification properties of the saRNA, the antigen expression peaks later and is more prolonged, therefore enabling one immunization to induce a high antibody generation (see the lower graph).

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 spike glycoprotein (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 4 and Figure 5). The 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 receptor-binding domain (RBD) recognizes the host receptor and binds to the target host cell. SARS-CoV and SARS-CoV-2 have similar structural properties and bind to the same host cell receptor, angiotensin converting enzyme 2 (ACE-2) (Zhou et al. 2020). The S protein is not only pivotal for host cell recognition and entry, but also for the induction of virus neutralizing antibodies by the host immune system (Zakhartchouk et al. 2007; Yong et al. 2019).

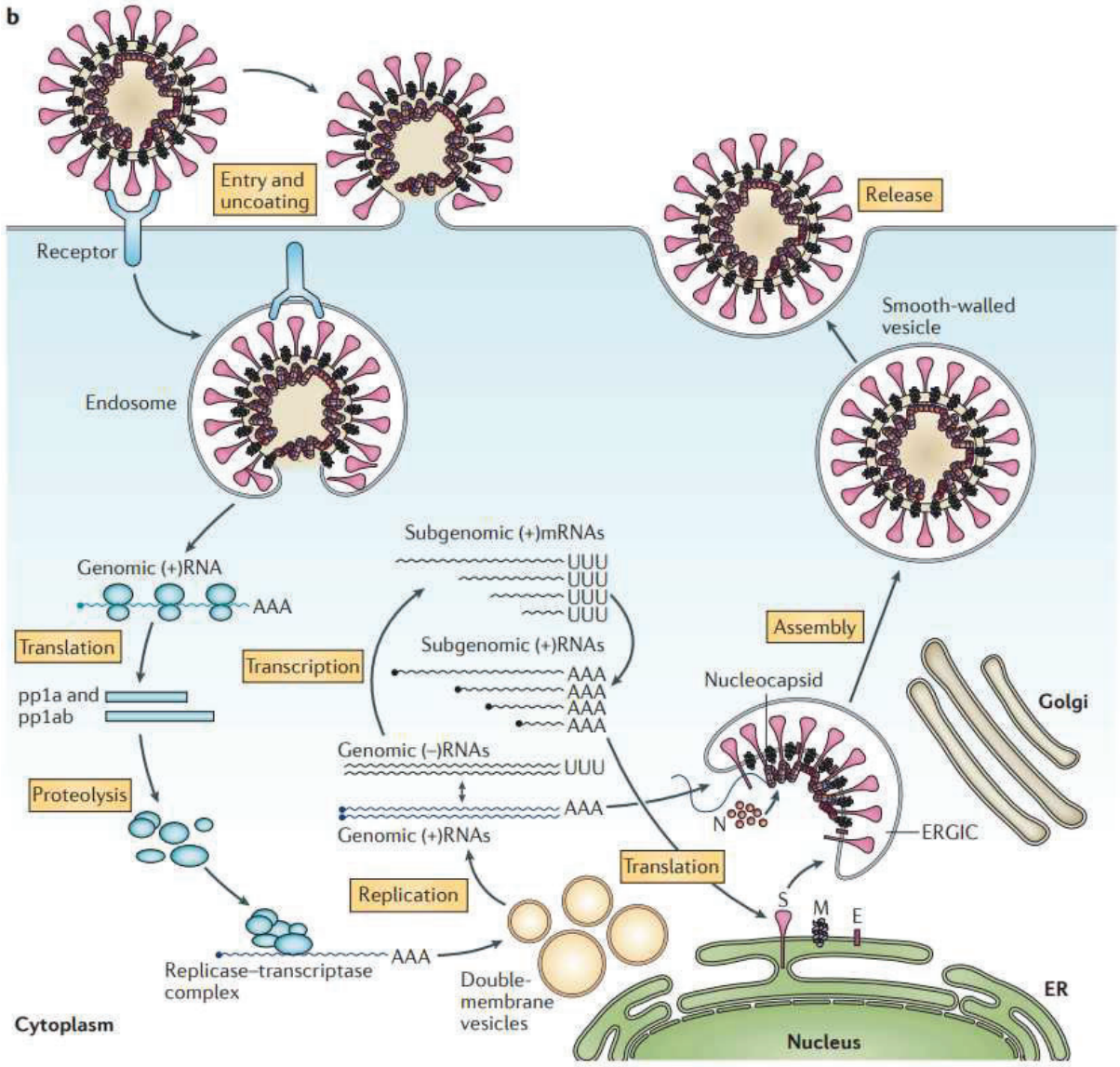


Figure 4: Schematic lifecycle of a Coronavirus

(Source: de Wit et al. 2016)

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).

Targeting the S protein, as well as its S1 cleavage fragment or the RBD alone, with vaccines is sufficient to induce neutralizing immune responses (Al-Amri et al. 2017). The RBD forms membrane distal "heads" on the S protein that are connected to the 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).

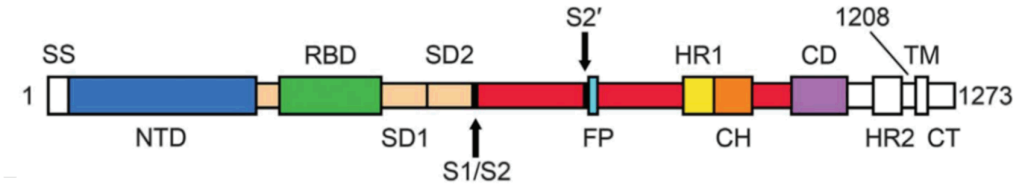


Figure 5: Schematic overview of the organization of the SARS-CoV-2 S glycoprotein

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); source: modified from Wrapp et al. 2020. NTD = N-terminal Domain.

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 (Figure 6).

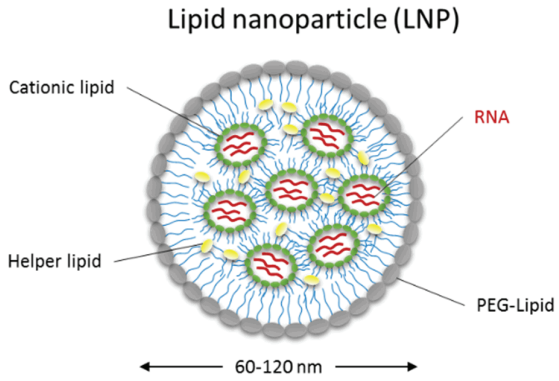


Figure 6: Schematic overview of a LNP

The LNPs are composed of four different lipids in a defined ratio. During mixing of the RNA and the dissolved lipids, the lipids form the nanoparticles encapsulating the RNA. After injection, the LNPs are taken up by the cells, and the RNA is released into the cytosol. In the cytosol, the RNA is translated to the encoded viral antigen.

The antigen may be incorporated into the cellular membrane or secreted into the extracellular environment and induce an adaptive immune response. In addition, as S protein is the antigen that recognizes and drives infection of the host cells, it is a key target of virus neutralizing antibodies. Furthermore, as RNA-expressed S protein is fragmented intracellularly, the resulting peptides can be presented at the cell surface, triggering a specific T cell-mediated immune response with activity against the virus.

3.4 Clinical development

BNT162 vaccine candidates based on the uRNA, modRNA, and saRNA formats are currently under investigation in three clinical trials with healthy subjects (men and women) aged between 18 and 85 yrs. One further clinical trial is planned.

For an overview of the different BNT162 vaccine candidates under clinical investigation, see Table 1.

Table 1: Characteristics of the different BNT162 vaccine candidates in clinical investigation

RNA platform	BNT162 vaccine candidate (Product code)	Encoded antigen	Evaluation in clinical trial
uRNA	BNT162a1	SARS-CoV-2 RBD, a secreted variant	BNT162-01 (GER)
modRNA	BNT162b1	SARS-CoV-2 RBD, a secreted variant	BNT162-01 (GER) and C4591001 (USA) BNT162-03 (CHN)
	BNT162b2	Full length SARS-CoV-2 sp ke protein bearing mutations preserving neutralization-sensitive sites	BNT162-01 (GER) and BNT162-02/C4591001 (USA, BRA, ARG, TUR, GER)
	BNT162b3	SARS-CoV-2 RBD, a membrane-bound variant	BNT162-04 (GER) – trial set up is ongoing
saRNA	BNT162c2	Full length SARS-CoV-2 S protein bearing mutations preserving neutralization-sensitive sites	BNT162-01 (GER)

ARG = Argentina; BRA = Brazil; CHN = China; GER = Germany; modRNA = modified RNA; RBD = receptor binding domain; saRNA = self-amplifying RNA; uRNA = uridine RNA; TUR = Turkey; USA = United States (of America).

The safety and immunogenicity of five BNT162 vaccine candidates (BNT162a1, BNT162b1, BNT162b2, BNT162b3, BNT162c2) are being investigated clinically, as part of a program to develop a prophylactic vaccine to prevent infection with SARS-CoV-2 and thus its associated disease COVID-19.

The clinical program started with the immunization of healthy adults, both men and women, aged between 18 and 55 yrs, and has since then been expanded to include older healthy adults aged between 56 and 85 yrs. If the immunization is found to be well tolerated, immunization will also be investigated in other likely target populations, which will include at risk populations such as immunocompromised populations.

At the time of this update, further dosing with the BNT162a1 has been deferred, the BNT162b2 has entered a Phase II/III evaluation of efficacy, with the intent to support an application for marketing authorization for this candidate, and development of BNT162b1, BNT162b3, and BNT162c2 is ongoing.

4 PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

The following section gives general information about the physical, chemical and pharmaceutical properties of the BNT162 family of prophylactic RNA-based vaccine candidates encoding viral antigens that are translated by the vaccinated organism to protein to induce a protective immune response. The RNA components of the RNA-LNP drug products of the three different RNA platforms for clinical investigation are the non-modified uridine containing mRNA (uRNA), nucleoside modified mRNA (modRNA), and self-amplifying mRNA (saRNA), each encoding 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 1.

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 viral S protein of SARS-CoV-2.

Non-modified uridine mRNA (uRNA)

The active principle of the non-modified messenger RNA (uRNA) drug substance is a single-stranded, 5′-capped mRNA that is translated upon entering the cell. In addition to the sequence encoding the SARS-CoV-2 antigen (i.e., open reading frame), 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).

Nucleoside modified mRNA (modRNA)

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

Self-amplifying mRNA (saRNA)

The active principle of the self-amplifying mRNA (saRNA) drug substance is a single-stranded 5'-capped RNA, which self-amplifies upon 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., open reading frame) and the common structural elements in the uRNA and modRNA, the saRNA vector contains an additional open reading frame, which encodes the Venezuelan equine encephalitis (VEE) virus RNA-dependent RNA polymerase replicase and a subgenomic promotor plus conserved sequence elements supporting replication and translation, but no other VEE virus coding sequences.

The physicochemical properties of the RNA drug substances are listed in Table 2.

Table 2: General properties of uRNA, modRNA and saRNA drug substances

Parameter	Value/Description	
	uRNA/modRNA	saRNA
Appearance	Clear, colorless liquid	
Theoretical length	~1200 to 4500 nucleotides *	~10,000 to 13,000 nucleotides *
Concentration	1.70 ± 0.17 mg/mL; 2.25 ± 0.25 mg/mL **	
Extinction coefficient at 260 nm	25 L/g × cm	
pH	7.0 ± 1.0	

* Depending on the finally selected antigen.
** Depending on batch size.

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 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 composition of RNA drug products for use in the planned clinical trials and the function of the respective components are given in Table 3. The LNP composition is the same for all five BNT162 vaccine candidates.

Table 3: Composition of drug products

Component	Quality standard	Function
Drug substance	In-house	Active
ALC-0315 [1]	In-house	Functional lipid
ALC-0159 [2]	In-house	Functional lipid
DSPC [3]	In-house	Structural lipid
Cholesterol	Ph. Eur.	Structural lipid
Sucrose	NF/Ph. Eur.	Cryoprotectant
NaCl	USP/Ph. Eur.	Buffer
KCl	USP/Ph. Eur.	Buffer
Na_2HPO_4	USP/Ph. Eur.	Buffer
KH_2PO_4	NF/Ph. Eur.	Buffer
Water for injection	Ph. Eur.	Solvent/Vehicle

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

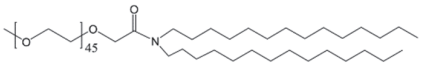
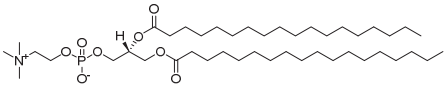
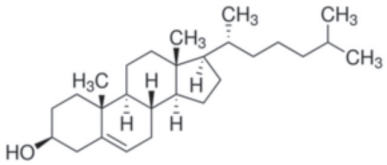
4.2.1 Description of the excipients

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

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 4.

Table 4: 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 (not applicable)	766	$C_{48}H_{95}NO_5$	Liquid (oil) -20ºC	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
ALC-0159 (1849616-42-7)	~2400-2600	$C_{30}H_{60}NO(C_2H_4O)_nOCH_3$ n=45-50	Solid -20ºC	2-[(polyethylene glycol)-2000]-N,N-ditetradecyclacetamide 
DSPC (816-94-4)	790	$C_{44}H_{88}NO_8P$	Solid -20ºC	1,2-Distearoyl-*sn*-glycero-3-phosphocholine 
Cholesterol (57-88-5)	387	$C_{27}H_{46}O$	Solid -20ºC	

CAS = Chemical Abstracts Service; DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine.

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., uRNA (product code: BNT162a1), modRNA (product codes: BNT162b1, BNT162b2, BNT162b3), saRNA (product code: BNT162c2).

IMP administration route: IM injection.

Dosage frequency: Depending on the vaccine, using either SD or P/B regimens.

4.5 Storage and handling of the IMP

Drug product of BNT162 will be provided as a frozen concentrate for solution for injection at a concentration of 0.50 mg/mL. For preparation of solution for injection, the drug product will be thawed and diluted with isotonic sodium chloride solution (0.9% NaCl, saline) by a one-step dilution process. The concentration of the final solution for injection varies depending on the respective dose level to be administered.

Administration has to be performed within 6 h after begin of preparation due to the risk of microbial contamination and considering the multiple-dose approach of the preparation process. In this period of 6 h, two conditions are allowed: room temperature for preparation, handling and transfer as well as 2 to 8°C for storage.

Detailed instruction for storage and handling are given in the respective trials-specific Pharmacy Manuals.

5 NON-CLINICAL STUDIES

RNA vaccines have shown great potential in generating immune responses in animal models and confer protection against various viruses such as Zika, human immunodeficiency virus (HIV), and Influenza virus (Vogel et al. 2018; Moyo et al. 2018; Pardi et al. 2017). Unpublished immunogenicity data from RNA based vaccines against other viruses such as Ebola, Marburg, and Lassa virus indicate that the range of applications for anti-viral RNA vaccines is broad (data on file).

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. For this purpose, mice were immunized once with the vaccine candidate and different immunological read-outs were performed during the individual studies. In serology analysis, antigen binding immunoglobulin G (IgG) responses were detected by an enzyme-linked immunosorbent assay (ELISA) as well as functional antibody responses to the vaccine candidates by a pseudovirus-based neutralization assay (pVNT). Cellular analysis included the T-cell specific response against the antigen.

Table 5 summarizes the nomenclature used for the BNT162 vaccine candidates to facilitate the review of the provided non-clinical information.

Table 5: Nomenclature used for the BNT162 vaccine candidates[§]

RNA platform	Product code	Encoded antigen	Sequence variant *
modRNA	BNT162b1	SARS-CoV-2 RBD, a secreted variant	V5
	BNT162b2	Full length SARS-CoV-2 spike protein bearing mutations preserving neutralization-sensitive sites[#]	V8 and V9 [#]
	BNT162b3	SARS-CoV-2 RBD, a membrane-bound variant	V5TM
saRNA	BNT162c2	Full length SARS-CoV-2 spike protein bearing mutations preserving neutralization-sensitive sites	V9

* Sequence variant refers to the nucleotide sequence of the RNA component encoding the antigen.

[#] 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.

[§] BNT162a1 is not listed here because further dosing with this candidate has been deferred.

5.1 Non-clinical pharmacology

5.1.1 Primary pharmacodynamics

Table 19 summarizes the primary pharmacodynamics studies.

5.1.2 *In vitro* expression of BNT162 RNA encoded antigens

To analyze whether the two SARS-CoV2 derived vaccine antigens V5 (a secreted variant of SARS-CoV-2 RBD) and V8/V9 (the full length SARS-CoV-2 spike protein bearing mutations preserving neutralization-sensitive sites) are robustly translated from the respective RNA drug substances, *in vitro* assays were performed and antigen expression was assessed using Western blots, or immune-fluorescence analysis. All RNA-components expressed the desired antigens.

In vivo expression and co-localization of the antigens with an endoplasmic reticulum marker was shown using immunofluorescence in HEK293T cells expressing BNT162b1 (modRNA encoding V5) and BNT162c2 (saRNA encoding V9), respectively (Figure 7). These results show that both antigens are processed within the endoplasmic reticulum for secretion and/or surface expression, which is a prerequisite for increased bioavailability and improved induction of an immune response.

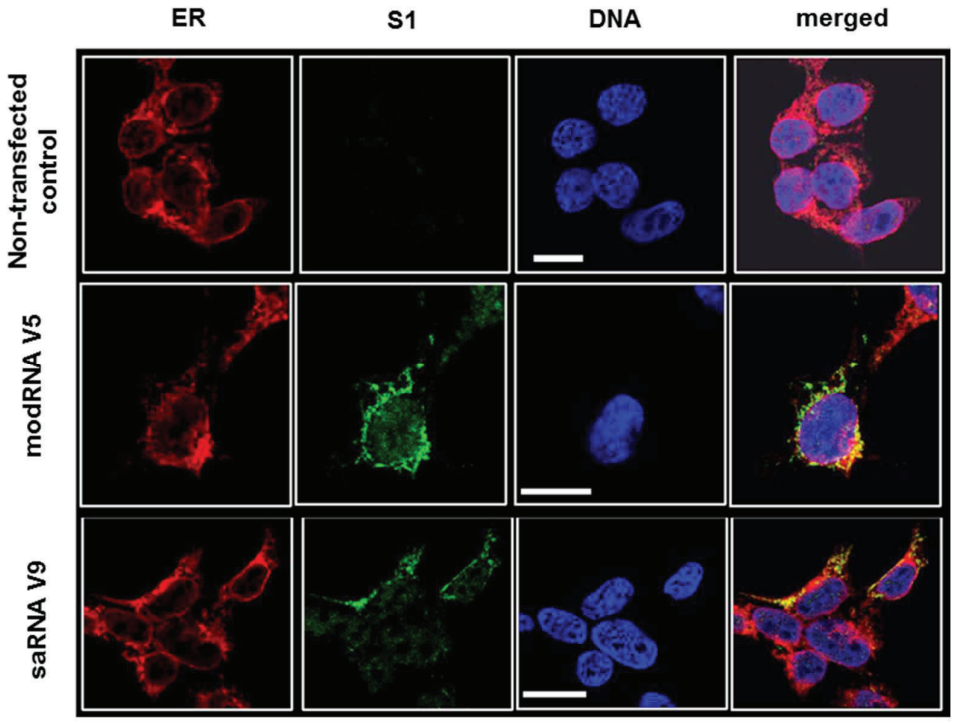


Figure 7: Immunofluorescence staining of cells transfected with BNT162b1 (modRNA encoding V5) and BNT162c2 (saRNA encoding V9)

HEK293T cells were transfected with 2.5 µg of modRNA encoding the secreted, trimerized RBD (V5) or saRNA encoding the membrane anchored, mutated full-length S protein (V9). After 18, cells were fixed and stained for the endoplasmic reticulum (endoplasmic reticulum, red), the S1 protein subdomain (RBD, green) and for deoxyr bonucleic acid (DNA; blue). The merged colored picture shows that both, V5 and V9 co-localize with the endoplasmic reticulum marker localization (scale: 10 µm). A control using non-transfected cells is shown at the top.

As membrane-bound antigens are particularly potent in activating B-cells (Batista and Harwood 2009; Bergtold et al. 2005), an additional vaccine candidate was designed and

included in the development pipeline. The new vaccine candidate, BNT162b3, uses a modRNA encoding a membrane-anchored, trimerized variant of the RBD of the SARS-CoV-2 S protein (V5TM).

To analyze whether the V5TM antigen is expressed by the respective mRNA and transported to the cell surface, *in vitro* assays were performed and antigen expression was assessed by flow cytometry or immune-fluorescence analysis. BNT162b3 was detected on the cell surface while BNT162b1 was only detected intracellularly, demonstrating a functional design of the constructs.

5.1.3 *In vivo* immunogenicity studies in mice

Non-clinical immunogenicity studies were performed for the BNT162 vaccine candidates BNT162a1, BNT162b1 (V5), BNT162b2 (V9), BNT162b3, and BNT162c2.

To benchmark the different vaccine candidates, mice were immunized once and different immunological read-outs were performed similar to the study designs reported in the supportive study section and outlined in Table 6.

Table 6: Study design

Group no	No of animals	Vaccine dose	Immunization day	Dose volume [µL] / route	Blood collection day	End of in-life phase
1	8	buffer	0	20 / IM	7, 14, 21	28
2	8	Low	0	20 / IM	7, 14, 21	28
3	8	Medium	0	20 / IM	7, 14, 21	28
4	8	High	0	20 / IM	7, 14, 21	28

Blood sampling: Blood was collected at 7, 14, 21, and 28 d after immunization to analyze the antibody immune response by ELISA and pVNT.

5.1.3.1 Immunogenicity of BNT162b1 (modRNA encoding V5)

The immunogenicity of BNT162b1 was tested in mice as summarized in Table 6 and in Figure 8.

As shown in Figure 8, total IgG ELISA showed that the expressed antigen is highly immunogenic and induced a dose-dependent generation of antibodies against the S1 antigen and the RBD early after immunization. In the pVNT analysis, all animals displayed a dose-dependent increase in neutralizing titers (Figure 9).

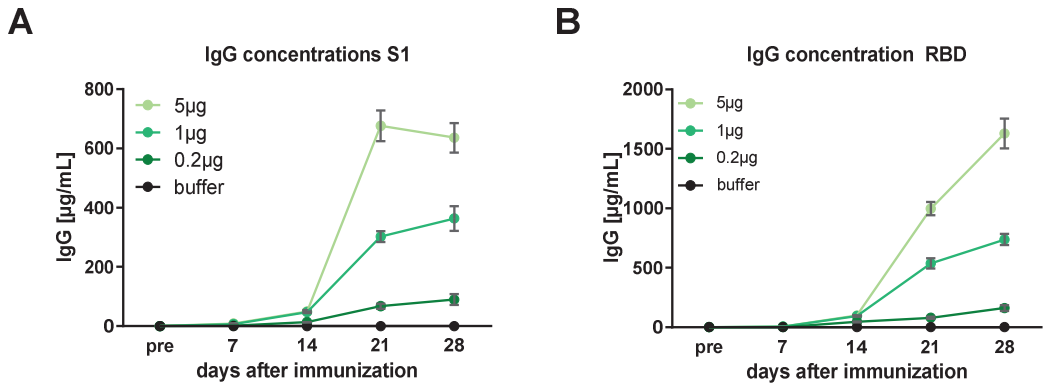


Figure 8: Anti-S IgG response 7, 14, 21, and 28 d after immunization with BNT162b1

BALB/c mice were immunized IM once with 0.2, 1 and 5 µg BNT162b1 or buffer. On 7, 14, 21, and 28 d after immunization, animals were bled and the serum samples were analyzed. For individual ΔOD values, the ant body concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean ant body concentrations are shown (±SEM). Group size n=8.

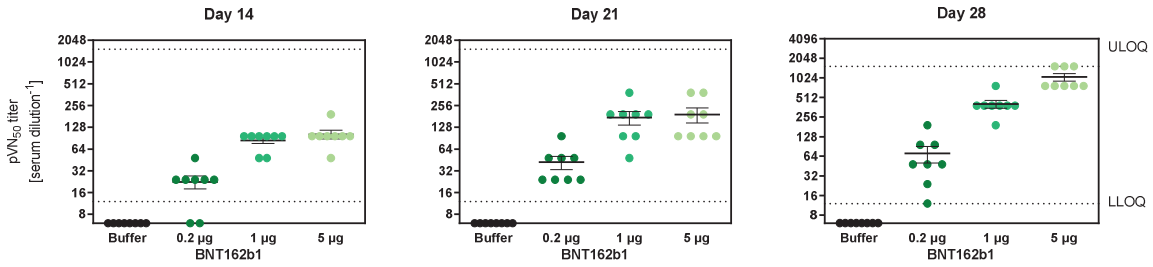


Figure 9: Neutralization of SARS-CoV-2 pseudovirus 14, 21, and 28 d after immunization with BNT162b1

BALB/c mice were immunized IM once with 0.2, 1 and 5 µg BNT162b1 or buffer. On 14, 21, and 28 d after immunization, animals were bled, and the sera were tested for SARS-CoV-2 pseudovirus neutralization. Graphs depict pVN50 serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean + SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

The summary of antibody titers on day 28 is as follows:

	BNT162b1 0.2 µg	BNT162b1 1 µg	BNT162b1 5 µg
Anti S1 protein total IgG [µg/mL]	68.2 ± 11.9	232.7 ± 40.6	392.7 ± 30.2
Anti RBD protein total IgG [µg/mL]	131.0 ± 23.5	455.4 ± 92.4	990.8 ± 96.7
pVN50 titer [reciprocal dilution]	67.5 ± 21.0	480.0 ± 166.3	960.0 ± 177.8

5.1.3.2 Immunogenicity of BNT162b2 (modRNA encoding V9)

The immunogenicity of the BNT162b2 (V9) was investigated in mice as summarized in Table 6, and depicted graphically in Figure 10 and Figure 11.

The expressed antigen was highly immunogenic; treatment with all tested BNT162b2 doses induced a strong immune response across the observation period of 28 days. Total IgG ELISA showed that the construct induced a strong, dose-dependent generation of antibodies against the S1 antigen and the RBD (Figure 10). In pVNT analysis, all mice developed functional neutralizing antibodies starting at 14 d after immunization and increasing up to final study day (Figure 11).

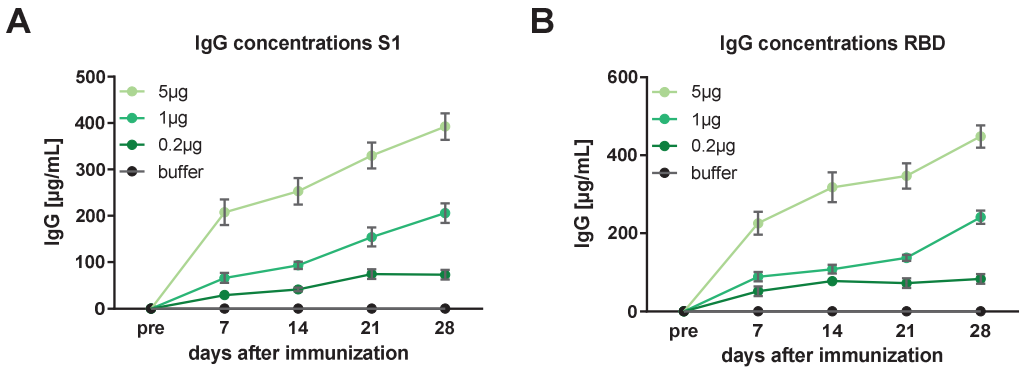


Figure 10: Anti-S IgG response 7, 14, 21, and 28 d after immunization with BNT162b2

BALB/c mice were immunized IM once with 0.2, 1, and 5 µg BNT162b2 or buffer. On 7, 14, 21, and 28 d after immunization, animals were bled and the serum samples were analyzed. For individual ΔOD values, the ant body concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean antibody concentrations are shown (±SEM). Group size n=8.

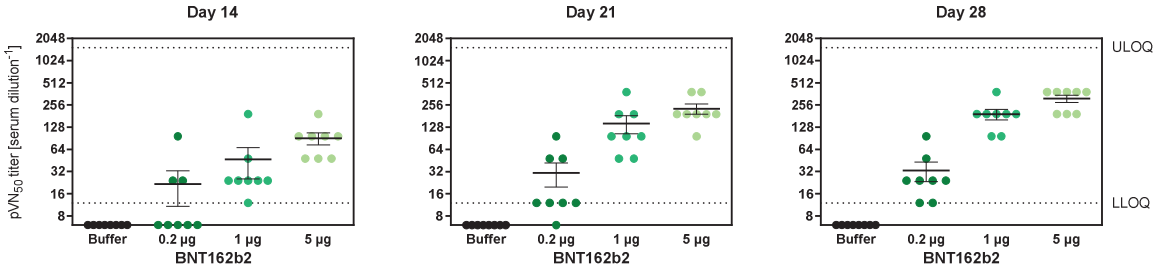


Figure 11: Neutralization of SARS-CoV-2 pseudovirus 14, 21, and 28 d after immunization with BNT162b2

BALB/c mice were immunized IM once with 0.2, 1, and 5 µg BNT162b2 or buffer. On 14, 21, and 28 d after immunization, animals were bled, and the sera were tested for SARS-CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

The summary of antibody titers on day 28 is as follows:

	BNT162b2 0.2 µg	BNT162b2 1 µg	BNT162b2 5 µg
Anti S1 protein total IgG [µg/mL]	73.0 ± 10.4	205.9 ± 21.0	392.7 ± 28.9
Anti RBD protein total IgG [µg/mL]	83.1 ± 12.3	241.7 ± 17.2	448.6 ± 28.6
pVN50 titer [reciprocal dilution]	33.0 ± 9.8	192.0 ± 31.4	312.0 ±35.1

5.1.3.3 Immunogenicity of BNT162b3 (modRNA encoding V5TM)

The immunogenicity of the BNT162b3 (V5TM) was investigated by immunizing mice with a single immunization using a low and medium dose as described in Table 6.

The antibody immune response was investigated using ELISA and pVNT.

The expressed antigen was highly immunogenic and induced a high titer of antigen-specific IgG already at an early time point after vaccination (see Figure 12). For comparison, 14 d after immunization the 1 µg immunization dose of BNT162b3 induced a mean of 382 µg/mL RBD-specific antibodies while the 1 µg BNT162b1 immunization dose induced a mean of 93 µg/mL (see Section 5.1.3.1). Also in pVNT (see Figure 13), a high titer of neutralizing antibodies was detected early on. For comparison, 14 d after immunization the 1 µg immunization dose of BNT162b3 induced in pVNT a mean titer of 1:186 (reciprocal dilution) while immunization with 1 µg BNT162b1 induced a mean titer of 1:84 (see Section 5.1.3.1).

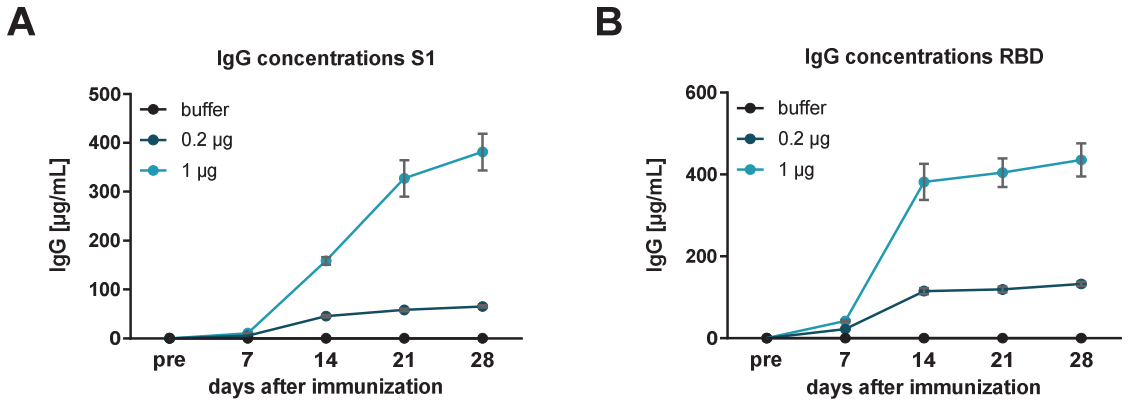


Figure 12: Anti-S IgG response 7, 14, 21 and 28 d after immunization with BNT162b3

BALB/c mice were immunized IM once with 0.2 and 1 BNT162b2 or buffer. On 7, 14, 21 and 28 d after immunization, animals were bled and the serum samples were analyzed. For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean ant body concentrations are shown (±SEM). Group size n=8.

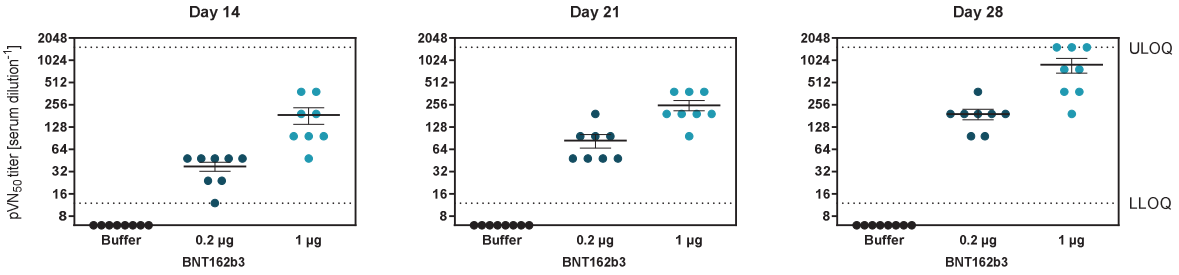


Figure 13: Neutralization of SARS-CoV-2 pseudovirus 14, 21, and 28 d after immunization with BNT162b3

BALB/c mice were immunized IM once with 0.2, and 1 µg BNT162b3 or buffer. On 14, 21, and 28 d after immunization, animals were bled, and the sera were tested for SARS-CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

The summary of antibody titers on day 28 is as follows:

	BNT162b3 0.2 µg	BNT162b3 1 µg
Anti S1 protein total IgG [µg/mL]	65.3 ± 2.3	381.3 ± 37.9
Anti RBD protein total IgG [µg/mL]	132.6 ± 5.3	435.7 ± 40.7
pVN50 titer [reciprocal dilution]	192.0 ± 31.4	888.0 ± 201.8

5.1.3.4 Immunogenicity of BNT162a and BNT162c candidates

The immunogenicity of different BNT162a1 (LNP-formulated uRNA encoding V5), BNT162c1 (LNP-formulated saRNA encoding V5) and BNT162c2 (LNP-formulated saRNA encoding V9) was tested in mice as summarized in Table 6.

The expressed antigen was immunogenic and all tested doses were immunogenic. While BNT162c2 induced a strong neutralization capacity, immune responses to BNT162a1 were weak.

The summary of antibody titers immunizing with 5 µg of the vaccine candidate on day 28 is as follows:

	BNT162a1 5 µg	**BNT162c1** 5 µg	**BNT162c2 5 µg**
Anti S1 protein total IgG [µg/mL]	15.6 ± 3.0	217.7 ± 10.8	392.74 ± 28.9
Anti RBD protein total IgG [µg/mL]	24.2 ± 2.9	531.9 ± 35.1	410.5 ± 66.3
pVN50 titer [reciprocal dilution]	7.5 ± 0.9	87.0 ± 8.4	448.58 ± 28.6

5.1.4 *In vivo* immunogenicity in non-human primates

5.1.4.1 Immunogenicity of BNT162b1 (modRNA encoding V5) and BNT162b2 (modRNA encoding V9) and BNT162b3 (modRNA encoding V5TM)

Six rhesus macaques (non-human primates, NHP) per group were immunized IM with 30 µg or 100 µg of BNT162b1 (V5) or BNT162b2 (V9), 30 µg 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-protein. On day 14 after the first dose of BNT162b1 and on day 7 after BNT162b2 or BNT162b3, virus antigen binding IgG were present in sera of modRNA-immunized macaques (Figure 14).

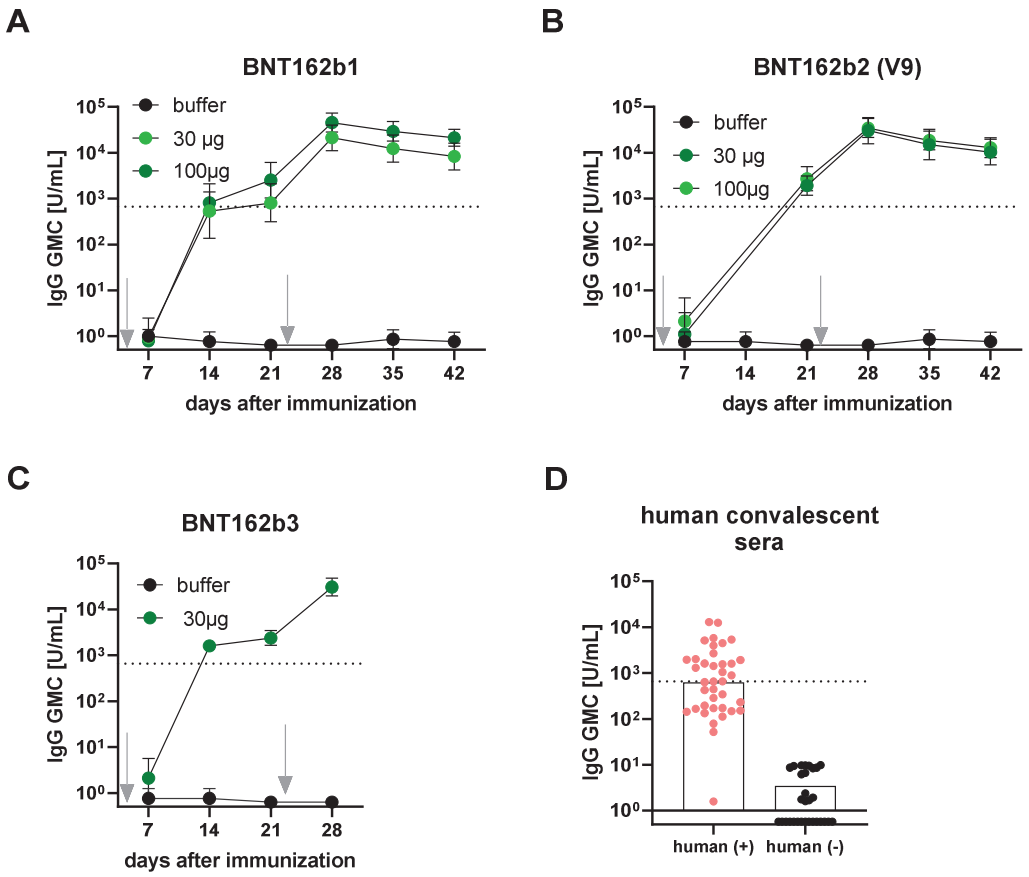


Figure 14: Anti-S IgG response after immunization with the different BNT162b candidates in NHP

Rhesus macaques were immunized IM on day 0 and 21 as indicated by grey arrows with buffer, 30, and 100 µg of (A) BNT162b1 or (B) BNT162b2 (V9) or (C) 30 µg BNT162b3. Weekly after immunization, animals were bled and the serum samples were analyzed for IgG binding a recombinant SARS-CoV-2 S1 protein (note that for BNT162b2 (V9), the analysis is pending. Geometric mean concentrations (GMC±CI) are given. (D) Human COVID-19 convalescent sera (human (+)), drawn 20–40 d after the onset of symptoms with confirmed COVID-19 diagnosis with at least 14 d of asymptomatic convalescence, were tested for IgG binding a recombinant SARS-CoV-2 S1 (sample size: 62) as well as serum samples from healthy donors (sample size: 31). Every single value is included in the graph as well as the geometric mean concentrations (GMCs) indicated by bars. The dotted line in the different graphs gives the GMC of the tested human convalescent sera.

Geometric mean concentrations (GMCs) of virus antigen binding IgG were highest on day 28 (7 d after the second dose). Second, authentic SARS-CoV-2 50% serum neutralization geometric mean titers (GMTs) were detectable 14 d after a single immunization with either dose level of BNT162b1 or BNT162b2 (V9). Please note that the BNT162b3 study is still ongoing and therefore, not all time points were yet analyzed.

On day 28 and day 35, both total IgG concentration as well as the neutralizing titer in rhesus macaques were high in comparison to human convalescent sera (Figure 15).

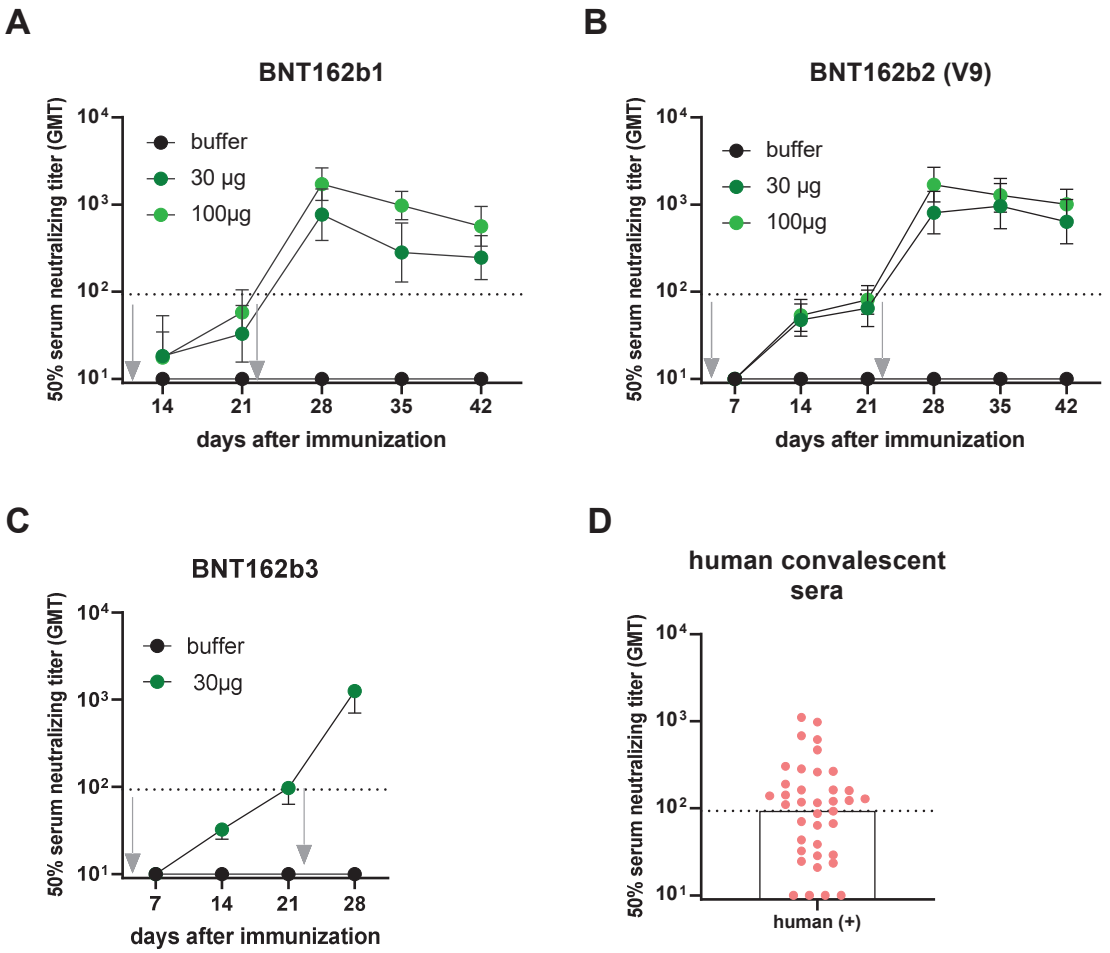


Figure 15: NT50 titer after immunization with the different BNT162b candidates in NHP

Rhesus macaques were immunized IM on day 0 and 21 as indicated by grey arrows with buffer, 30, and 100 µg of (A) BNT162b1 or (B) BNT162b2 (V9) or (C) 30 µg BNT162b3. Weekly after immunization, animals were bled and the serum samples were analyzed for neutralizing ant bodies. Geometric mean concentrations (GMC±CI) are given. (D) Human COVID-19 convalescent sera (human (+)), drawn 20–40 d after the onset of symptoms with confirmed COVID-19 diagnosis with at least 14 d of asymptomatic convalescence, were tested for neutralizing ant bodies (sample size: 62). Every single value is included in the graph as well as the geometric mean concentrations (GMCs) indicated by bars. The dotted line in the different graphs gives the GMC of the tested human convalescent sera.

The rhesus macaque immunogenicity data show strong humoral, neutralizing humoral responses to the LNP-formulated modRNAs that exceed those observed in in COVID-19 convalescing humans.

5.1.5 *In vivo* immunogenicity in rats

5.1.5.1 *In vivo* immunogenicity of BNT162 vaccine candidates after repeated dosing

In the GLP compliant repeat-dose toxicity study in rats (Section 5.3.1, Study No. 38166), the immunogenicity of the administered RNA vaccines BNT162a1 (uRNA encoding V5), BNT162b1 (modRNA encoding V5), BNT162b2 (modRNA encoding V8), and BNT162a1 (saRNA encoding V5) were investigated. Serum samples were collected from 10 repeatedly dosed main study animals per group on day 10 (BNT162c1) or day 17 after first immunization (BNT162a1, BNT162b1, and BNT162b2) as well as from recovery cohorts consisting of 5 animals 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 antibodies of the IgG against the S1 domain as well as the RBD sub-domain of the SARS-CoV2 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 in the serum samples for the individual samples and the IgG concentration against S1 and RBD proteins are given in Table 7. Antibody concentrations against S1 and RBD increased in a dose-dependent manner over time in animals treated with BNT162b1, but not for BNT162a1, BNT162b2, or BNT162a.

Table 7: IgG antibody concentration [µg/mL] against the viral antigen in Wistar Han rats

		BNT162a1 30 µg	BNT162a1 10 µg	BNT162b1 100 µg	BNT162b1 30 µg	BNT162b2 100 µg	BNT162c1* 30 µg
17 days after first immunization	**Against S1**	83.0 ± 13.6	149.8 ± 24.6	1844.2 ± 243.4	1502.9 ± 269.9	1755.9 ± 164.1	19.3 ± 3.7
	Against RBD	192.6 ± 35.2	208.3 ± 28.9	2632.6 ± 270.9	2017.0 ± 257.1	2331.4 ± 185.1	56.3 ± 12.0
38 days after first immunization	**Against S1**	47.6 ±5.6	312.0 ±43.0	3432.1 ± 301.3	2137.2 ±392.6	3463.8 ± 522.5	21.5 ± 4.2
	Against RBD	405.7 ±58.9	730 ±135.6	6718.4 ±822.8	4011.9 ±900.0	4898.0 ±873.3	25.2 ±4.9

For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against the S1 protein and RBD. * for saRNA encoding V5 group, the days of analysis were days 10 and 31, respectively.

Sera of all immunized animals show SARS-CoV-2 pseudovirus neutralization to a varying extent. In-line with ELISA data, a weak neutralizing antibody response is induced by BNT162c1 treatment on day 10 and 31and a high viral-neutralization response by BNT162b1 and BNT162b2 treatment on days 17 and day 38 after first immunization.

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, see Figure 16). Neutralizing antibody titers in vaccinated animals increased over time with the recorded neutralizing activity being consistent with the ELISA data shown above. Whereas sera from BNT162c1 treated animals display weak neutralizing activity both on days 10 and 31, and a strong pseudovirus neutralization effect is mediated by sera obtained from BNT162b1- and BNT162b2-treated rats. For BNT162b1 and BNT162b2, the neutralizing antibody titers resulting in 50% pseudovirus neutralization exceeded the upper limit of quantification (ULOQ) of a reciprocal titer of 1536 in more than 8 out of 10 animals on day 38.

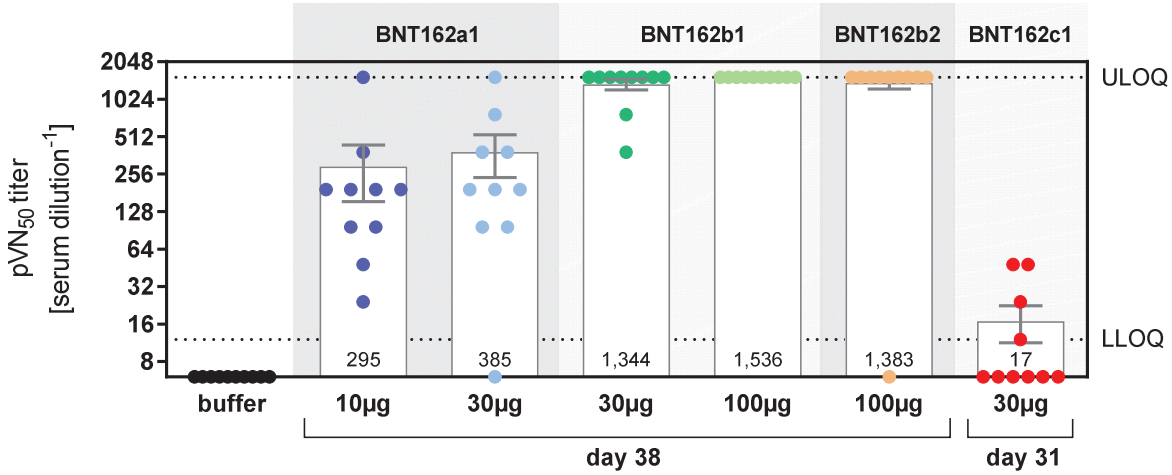


Figure 16: Pseudovirus neutralization activity of recovery cohort sera plotted as pVN50 titer

Serum samples were collected on day 31 (BNT162c1, red dots) or day 38 (all other cohorts) after first immunization of the recovery cohort animals and titers of virus-neutralizing ant bodies were determined by pVNT. Individual VNT titers resulting in 50% pseudovirus neutralization (pVN50) are shown by dots; group mean values are indicated by horizontal bars and are included at the bottom of bars (±SEM, standard error of the mean).

5.1.6 Secondary pharmacodynamics

No secondary pharmacodynamics studies were conducted for the BNT162 vaccine candidates.

5.1.7 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, "Annex 1: WHO guidelines on nonclinical evaluation of vaccines", 2005).

5.1.8 Non-clinical pharmacology - Conclusions

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

The available data demonstrate that BNT162b1, BNT162b2, BNT162b3, and BNT162c2 are capable of inducing robust immune responses in mice, (except for BNT162c2) rats and NHPs.

In mice, the antibody response was detected at a very early time point by IgG analysis on 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, and BNT162c2, indicates a high vaccine potency. Also, (pseudovirus) neutralizing antibody responses are detectable 14 d post-immunization in mice immunized with intermediate doses.

The neutralization titers in mice after 1 µg immunization with the vaccine candidates were as follows:

pVN50 titer [reciprocal dilution] Day 28	1 µg dose
BNT162b1	480
BNT162b2	192
BNT162c2	192
BNT162b3	888

The virus neutralization titers in NHPs after 30 µg immunization with the vaccine candidates were as follows:

pVN50 titer [reciprocal dilution] Day 28	30 µg dose
BNT162b1	768
BNT162b2	809
BNT162b3	1262

Overall, all BNT162b candidates were highly immunogenic with BNT162b3 inducing the highest virus neutralization titer.

Though BNT162b3 was not included in a toxicological report yet, similar results indicating immunogenicity were obtained in an accessory study to the GLP-compliant repeat-dose toxicology study in rats with the other candidates.

5.2 Non-clinical pharmacokinetics and metabolism

No pharmacokinetic studies were conducted for the BNT162 vaccine candidates as they are considered not necessary according to the WHO guideline (WHO Technical Report Series, No. 927, "Annex 1: WHO guidelines on nonclinical evaluation of vaccines", 2005).

5.2.1 Methods of analysis

Not applicable.

5.2.2 Absorption

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

5.2.3 Distribution

No biodistribution studies were performed with the BNT162 vaccine candidates. Instead, biodistribution of the RNA-LNP formulation comparable to BNT162 vaccine candidates was assessed using luciferase as a surrogate marker in place of the antigens encoded in the BNT162b vaccines. Luciferase expression can be detected *in vivo* after injection of luciferin by measuring the luminescence *in vivo*.

Using modRNA as representative for all three RNA platforms, injection of modRNA lead to a high and long expression of luciferase *in vivo* (Figure 17). 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.

It is anticipated that the biodistribution of the antigen encoded by the RNA components of the BNT162 vaccine candidates will be dependent on the LNP distribution. Therefore, the modRNA results obtained are considered to be representative for all three BNT162 RNA platforms.

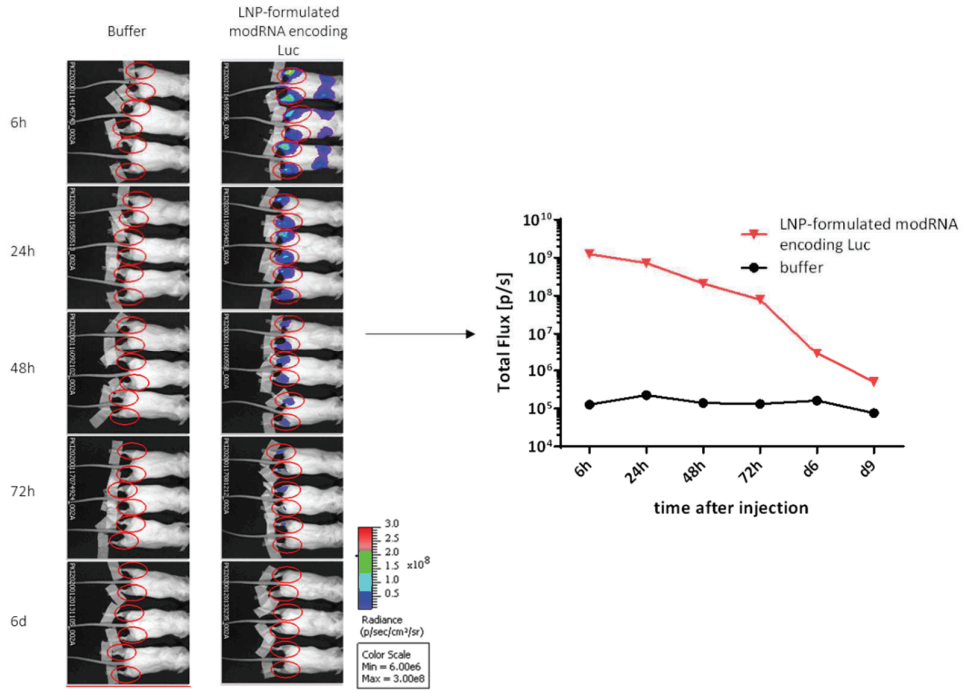


Figure 17: Bioluminescence imaging measurement using the LNP-candidate formulated BNT162b encoding luciferase

BALB/c mice were injected IM with 1 µg of LNP-formulated modRNA encoding luciferase in each hind leg. At time points after injection, the luciferase expression *in vivo* was measured by luciferin application. After 9 d, luciferase expression dropped to background levels.

5.2.4 Metabolism and excretion

RNA, including pseudouridine modified RNA and saRNA, 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 pharmacokinetic profile of the two novel lipids (ALC-0315 and ALC-0159) is currently being characterized.

5.2.5 Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies were performed.

5.2.6 Non-clinical pharmacokinetics and metabolism - Conclusions

Pharmacokinetic studies were conducted using a luciferase reporter RNA, and protein expression after IM injection was demonstrated *in vivo*. Expression of the luciferase reporter was observed at the site of injection and, to a lesser extent, in the liver.

5.3 Toxicology

To enable the rapid development of prophylactic vaccines during a public health emergencies, as is the case for the current SARS-CoV-2 outbreak, the WHO has published recommendations on the content of a minimum non-clinical safety package to support initiation of clinical testing (see "WHO Technical Report Series, No. 1011", "Annex 2: Guidelines on the quality, safety and efficacy of Ebola vaccines, 2018"). This guideline is considered applicable for the BNT162 vaccines due to the pandemic situation.

5.3.1 Repeat-dose toxicology to support the clinical evaluation of BNT162 vaccine candidates

Toxicology of BNT162 vaccine candidates was studied in a GLP compliant repeat-dose study. The study design was based on guideline recommendations ("WHO Technical Report Series, No. 927", "Annex 1: WHO guidelines on nonclinical evaluation of vaccines, 2005"). The study design is summarized in Table 8.

Table 8: Design of the GLP compliant repeat-dose toxicity study (Study No. 38166)

Test Items	• BNT162a1 (LNP formulated uRNA encoding antigen V5) • BNT162b1 (LNP formulated modRNA encoding antigen V5) • BNT162b2 [V8] (LNP formulated modRNA encoding antigen V8) * • BNT162c1 (LNP formulated saRNA encoding antigen V5)	
Species(age)	Wistar Han rat (10-14 weeks)	
Administrations	Three (BNT162a1, BNT162b1, and BNT162b2 [V8]) or two (BNT162c1) administrations on day 1, 8 and (if applicable) 15 followed by a 3-week recovery period	
Route	Intramuscular into the *M. biceps femoris*	
Dose groups	**Test Item**	**Dose level**
1	Control = Buffer	/
2	**BNT162a1**	30 µg
3		10 µg
4	**BNT162b1**	30 µg
5		100 µg
6	**BNT162c1**	30 µg
7	**BNT162b2 [V8]**	100 µg
Satellite group	Cytokine response analysis	3/sex/group
Group size	Group 1-7	10 (+ 5 recovery)/sex/group

* The RNA component of the BNT162b2 vaccine variant tested here has a different nucleotide sequence than the RNA component of the BNT162b2 vaccine candidates under clinical investigation, but both RNAs encode the same antigen, i.e., full length SARS-CoV-2 spike protein bearing mutations preserving neutralization-sensitive sites.

A relevant animal model for toxicity assessment of vaccines is one that develops an immune response similar to the expected human response after vaccination, while also allowing administration of the absolute clinical dose (WHO Technical Report Series, No. 927, "Annex 1: WHO guidelines on non-clinical evaluation of vaccines", 2005). Since the rat develops an immune response similar to the expected human response after RNA vaccination and is a commonly used species in vaccine toxicology studies, it was chosen as the animal model for toxicity assessment of the BNT162 vaccines.

The repeat-dose study investigated potential toxicity related to:

- the RNA platform (uRNA, modRNA, and saRNA),
- the vaccine dose, and/or
- the encoded antigen.

Examples for each of the three RNA platforms (uRNA, modRNA and saRNA) used in the BNT162 vaccine candidates were investigated utilizing the same LNP formulation, and therefore the observed safety profiles are considered representative for all candidate vaccines.

The repeat-dose nonclinical toxicity study in rats evaluated the safety and immunogenicity of the three different RNA modalities (uRNA, modRNA, and saRNA) formulated in LNPs and administered intramuscularly. Different vaccine doses, covering the highest anticipated clinical doses, were tested for the modRNA and uRNA platforms. For modRNA, the doses tested were 30 µg and 100 µg. For uRNA, the doses 10 µg and 30 µg were tested. For the saRNA, a 30 µg dose was tested. Vaccine candidates were administered once weekly for 3 (BNT162a1, BNT162b1, BNT162b2) or 2 (BNT162c1) doses followed by a 3-week recovery period. The SARS-CoV-2 RBD subunit antigen (V5) was evaluated using all three RNA platforms. In addition, a modRNA based vaccine (BNT162b2) encoding the full-length P2 mutated S protein (V8) was evaluated, allowing identification of antigen specific effects. The RNA component of the BNT162b2 vaccine candidate tested clinically has been codon optimized to improve the immune response, but is otherwise not different from the candidate tested here. For simplicity, the name BNT162b2 is used in this section.

The study design was based on regulatory guidance for vaccines (EMA Guideline on Repeated Dose Toxicity, 2010; WHO Guidelines on Nonclinical Evaluation of Vaccines, 2005), results of all parameters assessed are summarized in Table 9.

Table 9: Outcomes for parameters assessed in the repeat-dose toxicity study (Study No. 38166)

Parameter	Time of assessment	Dosing phase	Recovery phase
Mortality	At least twice daily until end of dosing/recovery.	No vaccine-related mortality was observed in any group.	No mortality was observed in any group.
Clinical signs	At least twice daily until end of dosing/recovery.	No systemic clinical signs were observed.	No systemic clinical signs were observed.
Body weight	Twice weekly (prior and one day post each administration) and until the end of dosing/recovery.	Decreased body weights / overall weight gain in all test-item treated groups compared to buffer control, primarily due to decreases in body weight 24 h after dosing. Body weight gain during the inter-dosing interval was similar to buffer controls.	No difference in body weight was observed between buffer control and immunized groups.
Food consumption	Weekly until the end of dosing/recovery.	A slight reduction by up to 7.2% in test week 1 and 2 in food consumption was seen in animals receiving 30 µg BNT162a1 in comparison with control group.	No difference in food consumption was observed between control and immunized groups.
Body temperature	+4 h and 24 h post each administration, weekly during recovery.	A slight increase of body temperature was noted 24 h post administration compared to 4 h values (approx. 0.9°C) in all animals including controls. It was more pronounced in the treatment groups. For single animals, temperature reached 40°C, but was reduced again 24 h later.	During the recovery period, the body temperature remained at a slightly higher level compared to the buffer control group in all previously test item treated groups.

Parameter	Time of assessment	Dosing phase	Recovery phase
Local tolerance	+4 h and 24 h post each administration, then every 48 h until end of dosing/recovery.	The majority of immunized animals developed very slight to slight oedema at the injection site 24 h after first dose. Oedema seen after the second and third injection was most often very slight to moderate, with occasional instances of severe odema. In addition, after the second and third dose, mild to severe erythema was seen in many rats (30 µg BNT162a1, 100 µg BNT162b1 and 100 µg BNT162b2) 6 d after the second dose. For rats given a third dose, all findings resolved prior to the third administration. On test days 14 and/or 15, eschar formation at the injection site for 5 male and 6 female animals (30 µg BNT162a1) was seen. The injection site appeared to be painful for 4/15 male animals and 12/15 female animals (30 µg BNT162a1) on test day 9 and for one male animal also on test day 10.	Very slight to slight oedema for nearly all animals following the third injection on test day 15. No dose-dependency was observed. All oedema had subsided on test day 35 latest. All animals (30 µg BNT162a1) revealed severe erythema at 4 days after the last injection. In the majority, this had subsided by test day 35 latest. Only 2 male and 2 female animals revealed erythema up to test day 33. 6/10 animals treated with 30 µg displayed severe erythema 6 d post last immunization. A single animal displayed erythema until the end of recovery. Apart from this animal, at the end of the recovery, any local skin reactions had subsided.
Cytokines	Prior to and 6 h post each dosing and at the end of dosing.	No vaccine-related changes observed.	Not assessed.
Clinical chemistry incl. acute phase proteins	3 d post first administration and at the end of dosing/recovery.	The majority of clinical chemistry parameters were not affected. An elevated plasma activity of GGT was noted for all test item-treated groups in comparison to the control group. An increase in albumin and a decrease in globulin plasma levels, resulting in an altered albumin/globulin ratio, were observed in all test item treated groups. The changes were within the biological range of normal. Elevated serum levels of the acute phase proteins alpha1-acid glycoprotein and alpha2 macroglobulin were noted for all test item-treated groups in comparison to the control group on test day 4 and test days 10 to 17.	No differences observed between control and immunized groups.
Hematology	3 d post first administration and at the end of dosing/recovery.	Dose-related increases in neutrophils leucocytes, monocytes, basophils and large unstained cells were seen with all vaccines on test day 17 (and day 4 for 30 µg BNT162a1) and were greater in females. Decreases in the reticulocyte count (test day 4 only), platelet count, and very slight red cell mass (HGB, HCT and RBC; test day 17 only) were observed.	No differences observed between buffer control and immunized groups.

Parameter	Time of assessment	Dosing phase	Recovery phase
Coagulation	At the end of dosing/recovery.	No changes except for an elevation of fibrinogen levels were observed for all vaccinated groups.	No differences observed between control and immunized groups.
Ophthalmology / Auditory	At the end of dosing/recovery.	No findings in any group.	No findings in any group.
Urinalysis	At the end of dosing/recovery.	No differences observed between buffer control and immunized groups.	No differences observed between buffer control and immunized groups.
Organ weight	At the end of dosing/recovery.	Spleen weight was increased in all vaccinated animals when compared with buffer control.	No differences observed between buffer control and immunized groups.
Macroscopic pathology	At the end of dosing/recovery.	A thickened injection site was the most common observation in all vaccine treated animals (20/20 for 30 µg BNT162a1, 15/20 for 10 µg BNT162a1, 13/20 for 30 µg BNT162b1, 6/20 for 100 µg BNT162b1, 20/20 in 30 µg BNT162c1 and 18/20 for BNT162b2). Some animals also displayed enlarged iliac lymph nodes and/or enlarged spleens.	No observations were made for the buffer control group, 30 µg BNT 162a1, 10 µg BNT162a1 and 30 µg BNT162c1. Enlarged iliac lymph nodes were observed in some BNT162b treated animals (1/10 for 30 µg BNT162b1, 7/10 for 100 µg BNT162b1, 4/10 for 100 µg BNT162b2).
Histopathology	At the end of dosing/recovery.	Injection sites: oedema, fibrosis, myofiber degeneration, hyperplasia of the epidermis and inflammation (with all BNT162 vaccines) Iliac lymph nodes: increased cellularity of the follicular germinal centers, increased plasma cells (plasmacytosis) with all BNT162 vaccines and inflammation (30 µg BNT162a1, 100 µg BNT162b1, 100 µg BNT162b2 and 30 µg BNT162c1) Bone marrow: minimal to mild increases in the cellularity (all BNT162 vaccines) Spleen: extramedullary hematopoiesis in the spleen (10 µg BNT162a1, 100 µg BNT162b1 and 100 µg BNT162b2) Liver: vacuolation of hepatocytes in the portal regions in either all animals (100 µg BNT162b1 and 100 µg BNT162b2) or females only (10 µg BNT162a1, 30 µg BNT162a, 30 µg BNT162b1 and 30 µg BNT162c1)	The majority of microscopic findings had resolved by the end of recovery. Minimal to mild changes in the iliac lymph nodes and inflammation at the injection site was still present (all BNT162 vaccines).

Parameter	Time of assessment	Dosing phase	Recovery phase
Dose exposure serology	At the end of dosing/recovery.	Treatment with all BNT162 vaccine candidates resulted in the formation of neutralizing antibodies protecting against pseudovirus infection. No ant body response or neutralization was observed in any of the buffer control animals.	Treatment with all BNT162 vaccine candidates resulted in the formation of antibodies, which, in protected against pseudovirus infection in all groups but 30 µg BNT162c1, where a neutralization titer was only detectable in a few animals. The strongest responses were seen in animals treated with BNT162b1 and BNT162b2. No antibody response or neutralization was observed in any of the buffer control animals.

d = day(s); GGT = Gamma (γ)-glutamyl transpeptidase; HGB = hemoglobin; HCT = hematocrit; RBC = Red blood cells.

5.3.1.1 Mortality and clinical signs

In the repeat-dose toxicity study, no vaccine-related mortality was observed throughout the course of the main study or in the recovery phase. All scheduled administrations for main and recovery animals have been performed. No systemic clinical signs were noted until the end of the study in any group.

5.3.1.2 Local tolerance

Special attention was paid to the local tolerance of vaccines BNT162a1, BNT162b1, BNT162b2, and BNT162c1 at the injection site in the repeat-dose toxicity study (Section 5.3.1).The injection sites were assessed for erythema/eschar/oedema formation and induration/hardening following palpation. Any reactions such as formation of erythema, oedema or induration of injection site observed were scored with a grading similar to Draize 1959. Occurrence of oedema was scored as described in Table 10.

Table 10: Grading of oedema formation

Oedema formation	Value
No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well defined by definite raising)	2
Moderate oedema (raised approx. 1 mm)	3
Severe erythema (raised more than 1 mm and extending beyond area of exposure)	4

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

An overview over the oedema frequency after first and second dose is given in Table 11.

Table 11: Frequency of highest oedema score noted post first and second vaccine dose in GLP repeated-dose toxicity study (Study No. 38166)

Group | Time Points		Frequency of highest oedema score/total number of animals				
		0	1	2	3	4
Gr. 1 Control = Buffer	all	30/30	0/30	0/30	0/30	0/30
Gr. 2 30 µg BNT162a1 (uRNA encoding antigen V5)	Post 1. dose	6/30	15/30	9/30	0/30	0/30
	Post 2. dose	1/30	2/30	13/30	14/30	0/30
Gr. 3 10 µg BNT162a1 (uRNA encoding antigen V5)	Post 1. dose	8/30	22/30	0/30	0/30	0/30
	Post 2. dose	0/30	0/30	14/30	16/30	0/30
Gr. 4 30 µg BNT162b1 (modRNA encoding antigen V5)	Post 1. dose	6/30	11/30	13/30	0/30	0/30
	Post 2. dose	1/30	22/30	7/30	0/30	0/30
Gr. 5 100 µg BNT162b1 (modRNA encoding antigen V5)	Post 1. dose	9/30	21/30	0/30	0/30	0/30
	Post 2. dose	0/30	1/30	13/30	16/30	0/30
Gr. 6 30 µg BNT162c1 (saRNA encoding antigen V5)	Post 1. dose	3/30	23/30	4/30	0/30	0/30
	Post 2. dose*	12/30	6/30	1/30	9/30	2/30
Gr. 7 100 µg BNT162b2 (modRNA encoding antigen V8)	Post 1. dose	4/30	26/30	0/30	0/30	0/30
	Post 2. dose	0/30	3/30	14/30	13/30	0/30

* Only recovery animals were scored at 24 h after the second dose.

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. Occasionally these observations of severe erythema continued over several days and/or were associated with wounds or scar tissue in individual animals administered 30 µg BNT162a1 or 30 µg BNT162c1.

The injection site appeared to be painful for 4 of 15 male animals and 12 of 15 female animals treated with 30 µg BNT162a1/animal on test day 9 and for one male animal also on test day 10.

An indurated and/or thickened injection site, partly accompanied by incrustation, was common in animals from all treatment groups at macroscopic inspection at necropsy.

The microscopic examination revealed test item-related injection site inflammation in all groups which was mostly moderate (up to marked) in males and moderate in females. The most severe findings were seen in animals administered 100 µg BNT162b1 and 100 µg BNT162b2, followed by animals administered 30 µg BNT162a1. The inflammation was characterized by infiltrates of macrophages, granulocytes, and lymphocytes into the muscle, and variably into the dermis and subcutis, at the injection site. Injection site inflammation was associated with mostly moderate oedema, mostly mild myofiber degeneration, occasional muscle necrosis, and mostly mild fibrosis. Skin ulceration (mild and moderate) was identified in some males and females administered either 10 or 30 µg

BNT162a1 and one animal administered 30 µg BNT162c1. Inflammation extended into tissues adjacent to the injection site, including mammary tissue, perineural tissue of sciatic nerve, tissue around the femur / knee and to the draining lymph node (iliac).

Microscopic injection site findings correlated with macroscopic observations of thickening, induration, and incrustation. Injection site findings were consistent with an immune/inflammatory response to intramuscular vaccine administration.

During the recovery period, very slight to slight oedema for nearly all animals and severe oedema in some BNT162c1 dosed animals were observed following the last injection. No dose-dependency was observed. All oedema had subsided by test day 35 at the latest.

All animals immunized with 30 µg BNT162a1 revealed severe erythema 4 days after the last injection. In the majority, this had subsided by test day 25. Only 2 male and 2 female animals revealed erythema up to test day 33.

6/10 animals immunized with 30 µg BNT162c1 showed severe erythema 6 d post last immunization. In one animal the reaction decreased in severity but was still detectable at the end of recovery.

The local skin reactions and the indurations and/or thickenings noted macroscopically for the muscle at the injection site(s) were resolved at the end of the recovery period. Most of the microscopic findings noted at the injection sites, iliac lymph node, surrounding tissue of the injection sites (surrounding tissue of bone, os femoris with joint; perineural tissue of sciatic nerve; interstitial tissue of mammary gland, and skeletal muscle) partially or fully recovered at the end of the 3-week recovery period. Some inflammatory lesions were still noted at the injection sites and the surrounding tissue of some animals.

At the end of the recovery period, 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 oedema 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.

5.3.1.3 Body weight and food consumption

In the repeat-dose toxicity study, the body weight was decreased 24 h after the administrations in all treatment groups compared to pre-dose levels (up to approx. 13%). No reduction was noted for the buffer control Group 1. Body weight gain between the administrations was comparable to the buffer control group and no difference in body weight gain was observed during the recovery period.

A slight reduction in food consumption was seen in 30 µg BNT162a1 treated in comparison with control during treatment, which improved and returned to normal during recovery.

5.3.1.4 Hematology

In the repeat-dose toxicity study, most hematological parameters remained unchanged 3 d after the first dose, 2 d after the last dose and 23 d after the last dose (recovery period).

The most consistent test item-related hematologic changes were dose-related increases in neutrophils, leucocytes, monocytes, basophils and large unstained cells, which were seen with 30 µg BNT162a1 on test day 4 and with all vaccines on 2 d after the last dose. These effects were greater in females relative to males. Other test item-related changes included decreases in the absolute and relative reticulocyte count (test day 4 only), platelet count, and a very slight reduction in red cell mass (hemoglobin, hematocrit, and red blood cell; test day 17 only).

All changes were considered to be related to the primary pharmacodynamic activity of the vaccines. Increases in leucocytes (most notably neutrophils and red blood cells), were consistent with an acute phase response secondary to immune activation and inflammation at the injection sites. Decreases in numbers of reticulocytes, red blood cells, and platelets were associated with increased bone marrow haematopoiesis, consistent with transient, secondary or peripheral effects.

At the end of recovery, no noteworthy change in any hematology parameter was observed.

5.3.1.5 Clinical chemistry and acute phase proteins

In the repeat-dose toxicity study, almost all clinical chemistry parameters were unchanged.

Only a slight increase in γ-glutamyl transpeptidase (GGT) was noted for all treatment groups 3 d after first dose and 2 d after the last dose. There were no changes in alkaline phosphatase (ALKP) and bilirubin levels and no macroscopic or microscopic findings consistent with cholestasis or hepatobiliary injury to explain the increased GGT.

Further, a decrease in albumin plasma levels and an increase in globulin plasma levels, resulting in an altered albumin/globulin ratio, were observed in all test item treated groups. The changes were within the biological range of normal and are consistent with an acute phase response in albumin and globulin where albumin goes down and globulin goes up with inflammation, and the albumin/globulin ratio decreases.

Acute phase proteins alpha1-acid glycoprotein and alpha2 macroglobulin were measured to assess vaccine-induced inflammatory reactions. The markers were increased in the treatment groups 3 d after the first dose or at the end of the main study phase.

No changes in any parameter was observed at the end of the recovery period, 23 d post last immunization.

5.3.1.6 Cytokines

No vaccine-related changes were observed. Levels of IFN-γ, TNF-α, IL-1-β, IL-6, IL-10 were comparable in buffer control and vaccine administered animals during dosing phase.

5.3.1.7 Coagulation

Increases in fibrinogen levels were detected in all vaccinated animals at the end of dosing phase and were consistent with an acute phase response secondary to immune activation and inflammation at the injection sites.

Changes observed in other coagulation parameters with any BNT162 vaccine at the end of dosing phase were within normal laboratory values and are not of toxicological relevance.

No changes in coagulation parameters were observed at the end of the recovery phase, 23 d post last immunization.

5.3.1.8 Ophthalmological and auditory assessments

Prior to, at the end of dosing and recovery period ophthalmological and auditory assessments resulted in detection of no changes.

5.3.1.9 Urinalysis

At the end of the in-life and recovery period, urine was collected over a period of 24 h from main study animals. No vaccine-related changes in pH, relative urine volume and specific gravity were observed in any group.

5.3.1.10 Macroscopic pathology

Main study animals were dissected following a randomization scheme 2 d and 23 d after the last administration.

The most common observation in all treatment groups was a thickened injection site and/or induration at the injected muscle (see Table 12 for all findings). This finding is test-item related and is caused by the local inflammation process. Furthermore, enlarged spleen and iliac lymph nodes were noted in a number of animals in the test-item treated groups. The effects on the lymphoid organs are likely the result of the induction of an immune response by the vaccine.

Table 12: Summary of macroscopic vaccine related findings – main study (Study No. 38166)

Group	Findings in male and female animals
1 (Control)	• None
2 (30 µg BNT162a1)	• Thickened / hardened injection site and/or muscle (20/20 animals) • Enlarged spleen (6/20 animals) • Enlarged iliac lymph nodes (2/20 animals)
3 (10 µg BNT162a1)	• Thickened / hardened injection site and/or muscle (15/20 animals) • Enlarged spleen (7/20 animals) • Enlarged iliac lymph nodes (7/20 animals)
4 (30 µg BNT162b1)	• Thickened / hardened injection site and/or muscle (13/20 animals) • Enlarged spleen (2/20 animals) • Enlarged iliac lymph nodes (10/20 animals)

Group	Findings in male and female animals
5 (100 µg BNT162b1)	• Thickened / hardened injection site and/or muscle (13/20 animals) • Enlarged spleen (12/20 animals) • Enlarged iliac lymph nodes (15/20 animals)
6 (30 µg BNT162c2)	• Thickened / hardened injection site and/or muscle (20/20 animals) • Enlarged spleen (6/20 animals) • Enlarged iliac lymph nodes (3/20 animals)
7 (100 µg BNT162b2)	• Thickened / hardened injection site and/or muscle (16/20 animals) • Enlarged spleen (9/20 animals) • Enlarged iliac lymph nodes (11/20 animals) • Muscle adhered to sciatic nerve (3/20 animals)

Most effects observed 2 d after the last immunization reversed within the 21 d recovery period. At 23 d post last immunization, there were no macroscopic observations for the control group, for 10 and 30 µg BNT162a1, and for 30 µg BNT162c1. Enlarged iliac lymph nodes were observed in some BNT162b treated animals (1/10 for 30 µg BNT162b1, 7/10 for 100 µg BNT162b1, and 4/10 for 100 µg BNT162b2).

5.3.1.11 Organ weight

In the majority of weighed organs, no difference in relative and absolute organ weight between vaccinated and buffer control animals were observed. Congruent with the macroscopic observations (Section 5.3.1.9), the average spleen weight was increased in male and female animals vaccinated with the BNT162 vaccine candidates. This effect reversed during the recovery period: 23 d post last immunization no differences between the organ weights of vaccinated animals and control group animals were observed.

5.3.1.12 Histopathology

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.

In the draining (iliac) lymph node, increased cellularity of the follicular germinal centers and increased plasma cells (plasmacytosis) which were variably present for all BNT162-immunized animals.

Minimal to mild increases in the cellularity of bone marrow and extramedullary hematopoiesis in the spleen (which correlated with increased spleen size and weight), and a vacuolation of hepatocytes in the portal regions of the liver were present for all BNT162-immunized animals. The liver findings were not associated with changes in markers of hepatocyte injury (e.g., alanine-aminotransferase [ALAT]). While GGT was elevated in test-item treated animals, it is not a marker of hepatocyte injury.

The majority of the microscopic findings noted at the injection sites and surrounding tissues, iliac lymph node and spleen were partially or completely recovered in all animals at the end of the recovery period. Inflammation at the injection site and surrounding tissues was less severe (minimal to mild) or resolved at the end of the 3-wk recovery period,

indicating partial or complete recovery. The incidence and the severity of the remaining findings were markedly reduced at the end of the recovery period.

In the iliac lymph node, plasmacytosis was less severe and present in fewer groups (30 or 100 µg of BNT162b1 or 100 µg BNT162b2) indicating partial or complete recovery. Macrophage infiltrates were present in the iliac lymph node at the end of the 3-wk 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, fully recovered at the end of the 3-wk recovery phase.

5.3.1.13 Genotoxicity

The components of all BNT162 vaccines (lipids and RNA), are not suspected 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, "Annex 1: WHO guidelines on nonclinical evaluation of vaccines", 2005), no genotoxicity studies were performed.

5.3.1.14 Carcinogenicity

RNA itself, and the lipids used in the BNT162 vaccines have no carcinogenic or tumorigenic potential. Furthermore, according to ICH S1A (ICH S1A Guideline: "Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals", November 1995), no carcinogenicity studies are required for therapeutics that are not continuously administered. Therefore, no carcinogenicity studies were performed.

5.3.1.15 Reproductive and developmental toxicity

Macroscopic and microscopic evaluation of male and female reproductive tissues were included in the GLP repeat-dose toxicity study testing BNT162a1, BNT162b1, BNT162b2, and BNT162c1 in rat (Section 5.3.1). No changes in these tissues were reported.

Specific fertility and embryofetal development studies are ongoing.

5.3.2 Immunotoxicology

No dedicated immunotoxicity study was conducted, however immunotoxicity of BNT162a1, BNT162b1, BNT162b2, and BNT162c1, was assessed in the GLP compliant repeated-dose toxicity study in rats (Section 5.3.1). The parameters measured in the study include: clinical signs/systemic tolerance, body weight, macroscopic and histopathological assessment of lymphatic organs, bone marrow smears, absolute and relative differential blood count, albumin/immunoglobulin ratio, coagulation parameters, and changes in body temperature.

No vaccine-related systemic intolerance or mortality was observed. Almost no changes were observed in the absolute and differential blood count, as described in Section 5.3.1.4. Body weight was decreased 24 h after the administrations in all treatment groups compared to pre-dose (up to approx. 13%), but the relative body weight gain between the administrations was comparable to the control group (Section 5.3.1.3).

An increase of body temperature was noted at 24 h post each administration in all groups. This increase was generally higher in immunized rats than in buffer treated animals. Of note, the physiological body temperature of rats is approx. 1°C higher than of humans and body temperatures observed 24 h post injection in rats did not exceed 40.2°C. In general, only individual animals displayed temperatures beyond 40°C, and then only after the second or third immunization. The temperature increase was fully reversible within 48 to 72 h post immunization.

All cytokines assessed displayed high background levels/variability and were similarly elevated in control and vaccinated animals.

5.3.3 Toxicology - Conclusions

The repeat-dose toxicology study in rats demonstrated tolerability of the tested vaccines. There were no vaccine-associated adverse findings or mortalities observed.

As expected, all vaccines induced a pro-inflammatory response which was evident in clinical signs, clinical pathology findings, and macro and microscopic findings. Increases in typical inflammatory blood parameters such as fibrinogen and acute phase proteins support this hypothesis. The reversible elevation of GGT activity in the absence of increase of specific markers, such as alkaline phosphatase and bilirubin, and relevant microscopic findings, suggests hepatobiliary injury is not involved. Hematological changes observed included an increase in large unclassified cell and leukocyte (monocyte, basophil and neutrophil) counts, as well as a transient, dose-dependent reduction in reticulocytes after first immunization. Similar reticulocyte changes have been observed in rats treated with the licensed LNP-small interfering RNA (siRNA) pharmaceutical OnpattroTM (FDA assessment report of Onpattro™ 2018), but have not been observed in NHPs or patients treated with this compound. The effect is therefore considered species specific. After the last immunization, a slight reduction in red cell mass and platelet numbers was observed. The latter is likely attributable to inflammation, causing specific platelet consumption, which is considered a pharmacodynamics attribute (Davidson 2013; Middleton et al. 2016). All changes observed in blood parameters reversed fully throughout the 3-week recovery period.

Secondary test-item related findings manifested as a reversible reduction in body weight post immunization without affecting body weight gain between immunizations.

Inflammation at the injection site was an anticipated response to the administered RNA-LNP and expressed antigen. Injection site reactions were greater after the boost dose(s), and the accelerated dosing schedule of once weekly may have exacerbated these reactions compared to the anticipated clinical dosing regimen.

Macroscopic observations of enlarged spleens and draining lymph nodes correlated with increased germinal center cellularity and increased hematopoiesis (as described in Sections 5.3.1.10 and 5.3.1.12) together with a tendency of increased spleen weights in vaccinated animals (Section 5.3.1.11). In addition, macroscopic injection site findings also correlated with microscopic inflammation, consistent with an immune response to the administered vaccine.

Vacuolation in portal hepatocytes was present in all vaccinated animals and was unassociated with evidence of hepatocyte injury (e.g., no elevations in ALAT or aspartate-aminotransferase [ASAT]). This change may be related to hepatic clearance of the pegylated lipid in the LNP.

No unexpected changes were observed during the recovery phase. All vaccine induced effects on local tolerance, food consumption and body weight were fully reversible and clinical pathology changes were partially or completely reversed at the end of the recovery phase. Most macroscopic and microscopic findings ameliorated or were also partially or completely resolved at the end of the recovery period, though some animals treated with BNT162b1 or BNT162b2 had enlarged iliac lymph nodes at the end of the recovery period. Microscopically, minimal to mild inflammation was also present at the injection site and in the draining lymph node in some animals. The infiltration of macrophages in the iliac lymph nodes of previously treated recovery animals were regarded as consequence of phagocytosis relating to the inflammatory reactions at the injection sites.

6 EFFECTS IN HUMANS

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

6.1 Ongoing and planned clinical trials

For the status of ongoing and planned clinical trials, see Table 13.

Table 13: Status of ongoing and planned clinical trials (as of August 6th, 2020)

Trial number	Design	Current number dosed (subject age)
BNT162-01 (NCT04380701) Germany	Phase I/II, 2-part, dose escalation trial. Part A is open label and non-randomized. (All subjects receive active vaccine) Part B will be defined in a protocol amendment.	<u>BNT162a1 (age 18-55 yrs):</u> 0.1 µg 12 subjects prime / 12 boost 0.3 µg 12 subjects prime / 12 boost 3 µg 6 subjects prime / 0 boost (Further dosing with BNT162a1 has been deferred) <u>BNT162b1 (age 18 to 55 yrs):</u> 1 µg 12 subjects prime / 12 boost 3 µg 12 subjects prime / 0 boost 10 µg 12 subjects prime / 11 boost 20 µg 12 subjects prime / 0 boost 30 µg 12 subjects prime / 12 boost 50 µg 12 subjects prime / 11 boost 60 µg 12 subjects prime / 0 boost <u>BNT162b2 (age 18 to 55 yrs):</u> 1 µg 12 subjects prime / 8 boost 3 µg 10 subjects prime / 0 boost 10 µg 12 subjects prime / 11 boost 20 µg 12 subjects prime / 12 boost 30 µg 12 subjects prime / 12 boost <u>BNT162c2 P/B (age 18 to 55 yrs):</u> 0.1 µg 12 subjects prime / 1 boost 0.3 µg 11 subjects prime / 0 boost <u>BNT162c2 SD (age 18 to 55 yrs):</u> 0.1 µg 12 subjects (single dose) 0.3 µg 12 subjects (single dose) 0.6 µg 12 subjects (single dose) 1 µg 12 subjects (single dose)

Trial number	Design	Current number dosed (subject age)
BNT162-02 / C4591001 (NCT NCT04368728) US, Argentina, Brazil, Turkey, Germany	Phase I/II/III, placebo-controlled, randomized, observer-blind, dose-finding and efficacy trial. (Phase 1: Subjects are randomized: 4:1 active:placebo. Phase 2/3: Subjects are randomized: 1:1 active:placebo)	<u>Phase I</u> BNT162b1 (age 18 to 55 yrs): 10 µg 15 subjects prime / 15 boost 20 µg 15 subjects prime / 15 boost 30 µg 15 subjects prime / 15 boost 100 µg 15 subjects prime / 0 boost BNT162b1 (age 65 to 85 yrs): 10 µg 15 subjects prime / 15 boost 20 µg 15 subjects prime / 15 boost 30 µg 15 subjects prime / 15 boost BNT162b2 (age 18 to 55 yrs): 10 µg 15 subjects prime / 15 boost 20 µg 15 subjects prime / 15 boost 30 µg 15 subjects prime / 15 boost BNT162b2 (age 65 to 85 yrs): 10 µg 15 subjects prime / 15 boost 20 µg 15 subjects prime / 15 boost 30 µg 15 subjects prime / 15 boost <u>Phase II/III</u> BNT162b2 (age 18 to 85 yrs): 30 µg 2083 subjects prime
BNT162-03 China (NCT to be obtained)	Phase I, randomized, placebo-controlled, observer-blind trial. (Subjects are randomized: 1:1:1 high-, low-dose groups and placebo group)	BNT162b1 (age 18 to 55 yrs): 10 µg 24 subjects prime 20 µg 24 subjects prime Placebo 24 subjects prime BNT162b1 (age >55 yrs): Enrollment has not started.
BNT162-04 (NCT to be obtained) Germany	Phase I/II, 2-part, dose escalation trial. Part A is open label and non-randomized. (All subjects receive active vaccine) Part B will be defined in a protocol amendment.	<u>BNT162b3 (age 18-55 yrs):</u> Enrollment has not started. <u>BNT162b3 (age 18 to 55 yrs):</u> Enrollment has not started.

Note: For the BNT162-02/C4591001 trial, the term "stage" was replaced by "phase" by an amendment.
NCT = ClinicalTrials.gov identify identifier.

6.1.1 BNT162-01 - Preliminary results

For the current status of dosing with BNT162 vaccines candidates by dose level in BNT162-01, see Table 13.

Two trial subjects allocated to dosing with BNT162b1 discontinued from the trial, one each at the 50 µg ('private reason') and 10 µg dose levels ('unable to further participate in the trial').

This section presents preliminary and unaudited data.

6.1.1.1 Summary of immunogenicity in trial BNT162-01

Immunogenicity data for older adults after dosing with BNT162b1 or BNT162b2 were not available at the time of preparation of this summary.

6.1.1.1.1 Summary of immunogenicity (status July 1st, 2020)

Two doses of BNT162b1 of 1, 10, 30, and 50 µg of BNT162b1 administered 21 d apart in younger adults elicited antibodies and a robust $CD4^+$ and $CD8^+$ T cell responses.

All subjects exhibited strong antibody responses with RBD-binding IgG concentrations clearly above those observed in a COVID-19 HCS panel. Day 43 SARS-CoV-2 neutralizing geometric mean titers (GMTs) were in the range of 0.7-fold (1 µg) to 3.3-fold (50 µg) compared to those of the COVID-19 HCS panel.

The COVID-19 HCS panel is comprised of 38 human COVID-19 HCS sera drawn from individuals aged 18 to 83 yrs, at least 14 d after PCR-confirmed diagnosis, and at a time when the individuals were asymptomatic. The serum donors predominantly had symptomatic infections (35/38), and one had been hospitalized. The sera were obtained from Sanguine Biosciences (Sherman Oaks, CA), the MT Group (Van Nuys, CA), and Pfizer Occupational Health and Wellness (Pearl River, NY).

For detailed immunogenicity data after dosing with BNT162b1 and BNT162b2, see the data from the trial BNT162-02 given in Section 6.1.2.1.1 (for BNT162b1) and Section 6.1.2.1.2 (for BNT162b2).

6.1.1.1.2 T cell responses (status July 24th, 2020)

To evaluate the T cell phenotype elicited by immunization of humans with BNT162b2, IFNγ ELISpot was performed on peripheral blood mononuclear cells (PBMCs) obtained from younger adults dosed P/B with either BNT162b1 or BNT162b2.

6.1.1.1.3 IFNγ ELISpot analysis - BNT162b1

Vaccine elicited T cell responses were determined using CD4- or CD8-depleted PBMC obtained from subjects prior to the prime dose and on day 29 (7 d after the boost dose). Until June 30, IFNγ ELISpot data readouts have been generated for 20 subjects dosed with BNT162b1 (1 from the 1 µg, 8 from the 10 µg, 6 from the 30 µg, and 5 from the 50 µg cohort).

Post-dose RBD-specific *ex vivo* CD4$^+$ and CD8$^+$ T cell responses were detected in 20/20 (100%) and 17 / 20 (85%) subjects, respectively. All responses were absent in the pre-dosing samples and are considered BNT162b1 induced (Figure 18).

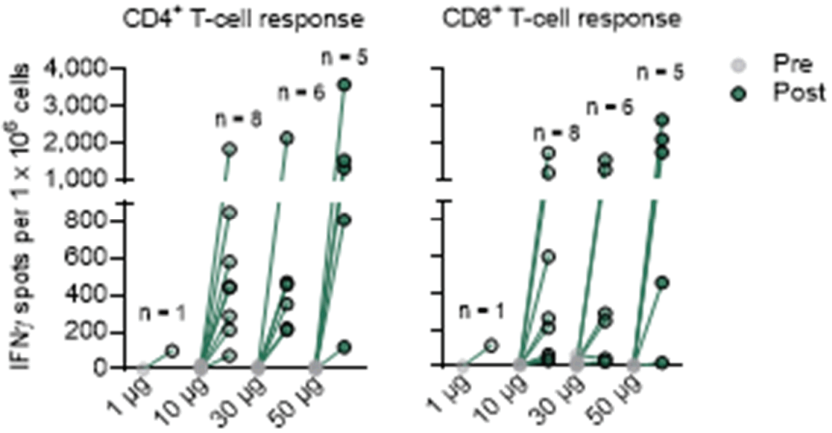


Figure 18: IFNγ ELISpot data for 20 subjects dosed with BNT162b1

T cell response analysis was performed in a GCLP compliant manner using a validated *ex-vivo* IFNγ ELISpot assay. All tests were performed in duplicate and included negative and positive controls (medium only and anti-CD3). In addition, peptide epitopes derived from CMV, EBV and influenza virus were used. CD4- or CD8-depleted PBMCs were stimulated for 16-20 h in pre-coated ELISPOT plates (Mabtech) with overlapping peptides covering the whole sequence of RBD encoded by BNT162b1. For analysis of *ex vivo* T-cell responses, bound IFNγ was visualized by an alkaline phosphatase conjugated secondary ant body. Plates were scanned using a Robot ELISPOT Reader and analyzed by ImmunoCapture V6.3 or AID ELISPOT 7.0 software. Spot counts were summarized as mean values for each duplicate. T-cell responses stimulated by peptides were compared to effectors incubated with medium only as negative control using an ELISPOT data analysis Tool (EDA), based on two statistical tests (distribution free resampling) according to Moodie et al. 2006 and 2010, thus providing sensitivity while maintaining control over false positive rate. The figure shows background-subtracted spot counts from duplicates prior to dosing (Pre) and on day 29 per 10^6 cells. No significant changes were observed in the pre / day 29 T cell responses against positive controls.

The strength of BNT162b1 vaccine-induced antigen specific CD8+ and CD4$^+$ T cells against SARS-CoV-2 can be considered as high to very high, respectively when compared to prevalent immune responses in the same subjects against CMV, EBV and Influenza virus (Figure 19 and Figure 20).

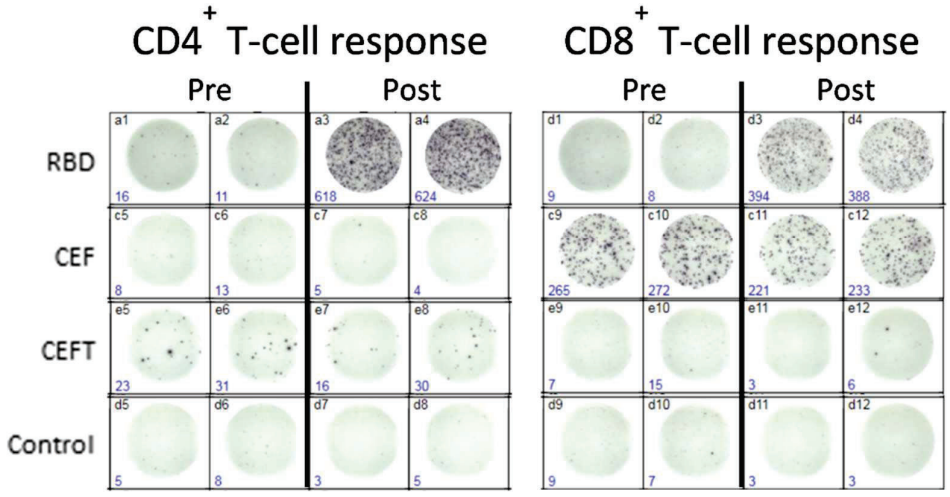


Figure 19: Exemplary CD4⁺ and CD8⁺ ELISpot data

Immune response analysis was performed as descr bed above using PBMC obtained prior treatment and on day 29 after first injection from a subject dosed with 10 µg BNT162b1. HLA class I and class II peptide epitopes CEF (CMV, EBV, Influenza, HLA class I epitope mix), and CEFT (CMV, EBV, Influenza, Tetanus, HLA class II cell epitope mix) were used as benchmarking controls to assess CD8⁺ and CD4⁺ T cell reactivity.

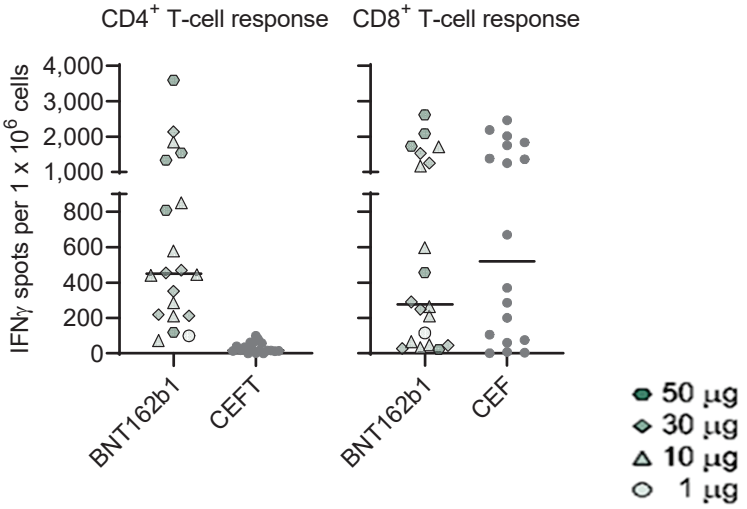


Figure 20: Comparison of vaccine immune responses induced vs. pre-valent virus and tetanus epitope T cells in 20 subjects dosed with BNT162b1

IFNγ spot counts in post-vaccine blood samples obtained from subjects who received either 1, 10, 30 or 50 µg of BNT162 prime/boost vaccine. CEF (CMV, EBV, Influenza, HLA class I epitope mix), and CEFT (CMV, EBV, Influenza, Tetanus, HLA class II cell epitope mix) were used as benchmarking controls to assess CD8+ and CD4+ T cell reactivity.

Evaluation of antigen-specific cytokine secretion in vaccine induced T cells

The functional cytokine profile of RBD-specific T cells was determined in 6 dosed subjects (2 from the 10 µg and 4 subjects from the 30 µg cohort) by intracellular staining (ICS) after stimulation of PBMCs. T cells were stimulated in the presence of epitopes covering the vaccine antigen and subsequently stained with antibodies against INFγ, IL-2, IL-4 as representative cytokines to define Th1 and Th2 immune responses. Post-dose RBD-specific CD4+ T cells characterized in 6 subjects demonstrated a Th1-dominant cytokine profile (INFγ/IL-2 positive CD4 T cells) and no IL-4 secretion (Figure 21).

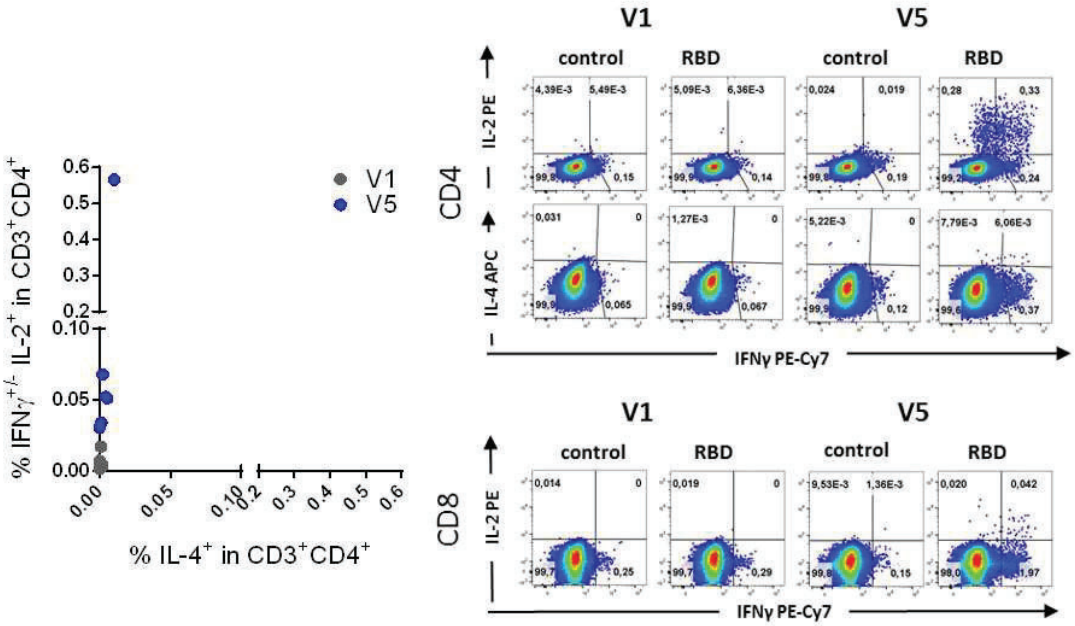


Figure 21: Intracellular cytokine staining data for 6 subjects dosed with BNT162b1

Frequency of Th1 (IFNγ+/- IL2+) and Th2 (IL-4+) cytokine-producing $CD3^+$ $CD4^+$ T cells in response to RBD peptide stimulation measured by intracellular cytokine staining (ICS) from samples collected before (v1; grey) and after dosing (v5; blue, left panel). In right panel exemplary ICS stainings for $CD4^+$ and $CD8^+$ T cells are shown for a dosed subject from the 10 µg cohort. PBMCs were thawn and rested for 4 h in OpTmizer medium in the presence of 2 µg/mL DNAse I (Roche). Next, PBMCs were harvested and stimulated with SARS-CoV-2 RBD domain pool (2 µg/mL/peptide; pool consists of 15-mers overlapping by 11 aa) in the presence of GolgiPlug (BD) for 18 h at 37°C. Stimulation controls were performed with DMSO (unstimulated) or anti-CD3 (1:1000) and 1 µM PepMix CEFX-2 (JPT) as positive controls, respectively. Afterwards cells were first stained for surface markers (CD3 BV421 (clone UCHT1), CD4 BV480 (clone RPA-T4) and CD8-BB515 (RPA-T8); all from BD) and live dead stain (fixable viability dye eFluor780, Thermo Fisher) for 20 min at 4°C. Fixation and permeabilization was performed using Cytofix/Cytoperm Kit (BD). Intracellular staining was performed with CD3 BV421, CD4 BV480, CD8-BB515, IFNγ PE-Cy7 (clone B27), IL-2 PE (clone MQ1-17H12) and IL-4 APC (clone MP4-25D2) in 1x Perm/Wash buffer for 30 min at 4°C. Samples were measured on a FACS VERSE. Flow Cytometry data were analyzed with FlowJo 10.5.3.

These preliminary data confirm prior results obtained in humans dosed with modRNA (nucleoside-modified) platforms, which indicate that modRNA does induce substantial Th1 type $CD4^+$ and $CD8^+$ T cell responses. Evaluation of additional subjects is ongoing.

6.1.1.1.4 IFNγ ELISpot analysis - BNT162b2

Vaccine-elicited T cell responses were determined using CD4- or CD8-depleted PBMCs obtained from subjects prior to Dose 1 and on day 29 (7 d after Dose 2). IFNγ ELISpot data were generated for 5 subjects dosed with 10 µg of BNT162b2 at days 1 and 22.

Post-dose spike-specific *ex vivo* $CD4^+$ and $CD8^+$ T cell responses were detected in 5/5 (100%) subjects, respectively. All responses were minimal or undetectable in the pre-dose samples. The responses are considered vaccine induced (Figure 22, Figure 23, Figure 24).

The BNT162b2 vaccine-elicited, antigen specific $CD8^+$ and $CD4^+$ T cell responses stimulated by S peptide pool 1 (N-terminal portion of the spike, which includes the RBD) and S peptide pool 2 (C-terminal portion of the spike) were comparable to or higher than the memory responses in the same subjects against CMV, EBV, influenza virus, and tetanus toxoid (Figure 24).

The data indicate that modRNA elicits substantial Th1-type $CD4^+$ and $CD8^+$ T cell responses. Evaluation of additional subjects is ongoing.

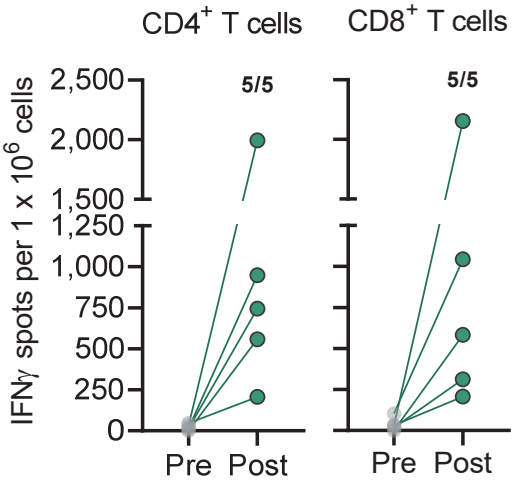


Figure 22: IFNγ ELISpot data for 5 subjects dosed with 10 µg BNT162b2 (BNT162-01)

Background-subtracted spot counts from duplicates prior to dosing (Pre) and on day 29 (Post - 7 d post boost) per 106 cells. T cell response analysis was performed in a GCLP-compliant manner using a validated *ex vivo* IFNγ ELISpot assay. All tests were performed in duplicate and included negative and positive controls (medium only and anti-CD3). In addition, peptide epitopes derived from cytomegalovirus (CMV), Epstein Barr virus (EBV), and influenza virus were used as positive controls. CD4- or CD8-depleted PBMCs were stimulated for 16-20 h in pre-coated ELISpot plates (Mabtech) with overlapping peptides covering the N-terminal portion and C-terminal portion of the sp ke glycoprotein. For analysis of ex vivo T-cell responses, bound IFNγ was visualized by an alkaline phosphatase-conjugated secondary antibody. Plates were scanned using a Robot ELISPOT Reader and analyzed by ImmunoCapture V6.3 or AID ELISPOT 7.0 software. Spot counts were summarized as mean values for each duplicate. T cell counts were calculated as the sum of spot counts detected after stimulation with S pool 1 and S pool 2. T-cell responses stimulated by peptides were compared to effectors incubated with medium only as negative control using an ELISpot data analysis Tool (EDA), based on two statistical tests (distribution free resampling) according to Moodie et al, 2006 and 2010, thus providing sensitivity while maintaining control over false positive rate. No significant changes were observed between the pre- and day 29 T cell responses against the positive control peptides from CMV, EBV, and influenza virus (not shown).

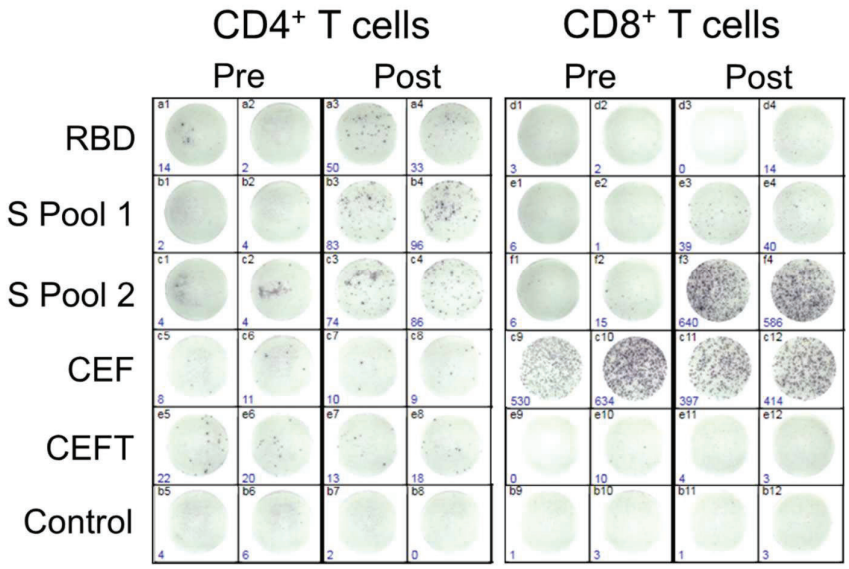


Figure 23: Example of CD4+ and CD8+ IFNγ ELISpot data (BNT162-01)

IFNγ ELISpot was performed as in Figure 22 using PBMCs obtained from a subject prior to immunization and on day 29 after dose 1 of 10 µg BNT162b2 (7 d post dose 2). HLA class I and class II peptide pools CEF (cytomegalovirus [CMV], Epstein Barr virus [EBV] (7 d post dose 2), and influenza virus, HLA class I epitope mix) and CEFT (CMV, EBV, influenza virus, and tetanus toxoid HLA class II cell epitope mix) were used as benchmarking controls to assess CD8+ and CD4+ T cell reactivity.

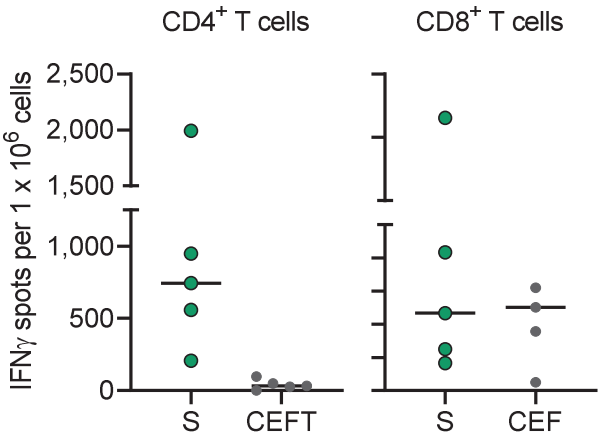


Figure 24: Comparison of BNT162b2-elicited and benchmark INFγ ELISpot responses (BNT162-01)

IFNγ spot counts from day 29 (7 d post dose 2) PBMC samples obtained from 5 subjects who were dosed with 10 µg of BNT162b2 on days 1 and 22. CEF (cytomegalovirus [CMV], Epstein Barr virus [EBV], and influenza virus HLA class I epitope mix), and CEFT (CMV, EBV, influenza virus, and tetanus toxoid HLA class II cell epitope mix) were used as reactivity. Horizontal lines indicate median values.

6.1.1.2 Summary of safety in trial BNT162-01 (status July 1st, 2020)

In the trial BNT162-01, younger adults aged 18 to 55 yrs were dosed with one of four BNT162 vaccine candidates (BNT162a1, BNT162b1, BNT162b2, and BNT162c2). By July 1st 2020, the most complete experience was available for the vaccine BNT162b1, which has been dosed in 5 cohorts of 12 subjects each (all subjects received active vaccine). Except for those in the highest dose cohort (60 µg), all subjects were dosed P/B.

6.1.1.2.1 BNT162a1 - Summary of safety

BNT162a1 has been tested at doses of 0.1, 0.3, and 3 µg (starting dose level). In the first 6 subjects treated (sentinel and sub-group 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 trial SRC, 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 subjects reported only injection site reactions (pain and tenderness, almost exclusively of mild intensity) and no systemic reactions. No SAEs were reported and no subjects have withdrawn due to an AE.

In the first 6 subjects treated with the BNT16a1 3 µg prime dose, the frequency and duration of systemic reactogenicity (predominantly of moderate intensity) led to a decision not to administer the 3 µg boost dose and to defer further dosing with this vaccine candidate.

6.1.1.2.2 BNT162b1 - Summary of safety

The following summary reflects the preliminary data status on July 1st, 2020. At the time of preparation of this summary, the overall assessment of safety data following dosing with BNT162b1 has not changed.

Local reactions and systemic events are solicited from the subjects and recorded by them in a diary for 7 d following administration of the vaccine. Most subjects in all cohorts experienced the expected reactogenicity, typically starting within 24 h of dosing and resolving within 24 h. The specific, solicited local and systemic reaction are summarized below in Table 14 and Table 15.

Table 14: BNT162b1 in younger adults - Number of subjects with local symptoms (diary)

	Number of subjects with local reactions (n=)								
	7 d Post Prime			7 d Post boost			Total (both)	
	Subjects dosed prime	Any event	Any ≥ severe	Subjects dosed boost	Any event	Any ≥ severe	Any event	Any ≥ severe
BNT162b1	60	51	8	46	39	7	54	13
1 µg	12	6	0	11	7	2	7	2
10 µg	12	10	1	12	10	0	11	1
30 µg	12	11	4	12	11	2	12	5
50 µg	12	12	2	11	11	3	12	4
60 µg	12	12	1				12	1

Table 15: BNT162b1 in younger adults - Number of subjects with systemic symptoms (diary)

	Number of subjects with systemic reactions (n=)							
	7 d Post Prime			7 d Post boost			Total (both)	
	Subjects dosed prime	Any event	Any ≥ severe	Subjects dosed boost	Any event	Any ≥ severe	Any event	Any ≥ severe
BNT162b1	60	52	15	46	38	17	57	27
1 µg	12	9	0	12	7	2	11	2
10 µg	12	8	1	11	9	4	10	5
30 µg	12	11	3	12	11	6	12	6
50 µg	12	12	4	11	11	5	12	7
60 µg	12	12	7				12	7

In local reactions, most subjects reported injection site pain and tenderness, whilst reports of swelling / induration or erythema were scarce. The most common systemic reactions were headache and fatigue, experienced by most subjects. Grade 3 (severe intensity) local reactions were reported for pain, tenderness and swelling. Grade 3 (severe intensity) systemic reactions were fever, headache, myalgia, arthralgia, nausea, vomiting, chills, loss of appetite, malaise, and fatigue.

A consistent pattern has been seen in the laboratory assessments with elevation of the C-reactive protein with concomitant reduction in the plasma lymphocyte count 24 h after dosing. These changes are consistent with the know pharmacology of this technology, with the changes in lymphocytes known to represent a reversible compartmental shift from the vascular space to lymphoid organs. These observations have been self-limiting and without clinical consequence. There have been no other consistent findings on laboratory assessments. There were no laboratory assessments findings considered clinically significant.

Adverse events are elicited throughout the trial, collected in the clinical trial database and graded by the investigators on a 4-point scale (as per this protocol). Most subjects reported AEs (see Table 16).

Table 16: BNT162b1 in younger adults - TEAE (prime +/- boost) by number of subjects

BNT162b1	Subjects dosed N =	Number of subjects with (n=)					
		TEAEs	Mild AE	Moderate AE	Severe AE	SAE	Resolved AE
1 µg	12	11	10	7	2	0	11
10 µg	12	12	12	8	1	0	12
30 µg	12	12	12	9	0	0	12
50 µg	12	12	12	11	2	0	12
60 µg	12	12	12	10	1	0	12
Total	60	59	58	45	6	0	59

AE = adverse events; n or N = number; SAE = Serious adverse event; TEAE = Treatment emergent adverse event.

For BNT162b1, generally good tolerability was observed with no SAEs and no unexpected toxicities. To date, there was high acceptance by trial subjects with no withdrawals due to related AEs. Most reported AEs were signs and symptoms of reactogenicity, typical onset within first 24 h post immunization. All AEs / reactogenicity resolved spontaneously, mostly within 24 h of onset and can be managed with simple measures (e.g., paracetamol). Laboratory assessments suggested a Th1 pattern of immune activation 24 h post dosing.

Some dose dependency of tolerability has been observed, with 1 µg dose best tolerated. The possibly of a slight increase in reactogenicity following boost dose is noted, as is some inter-individual variability.

The observed poor tolerability after BNT162b1 prime doses at 60 µg, led to a decision not to administer the boost doses. Acceptable tolerability was shown after both the prime and boost doses at 50 µg BNT162b1.

6.1.1.2.3 BNT162b2 - Summary of safety

The following summary reflects the preliminary data status on July 1st, 2020. At the time of preparation of this summary, the overall assessment of safety data following dosing with BNT162b2 has not changed.

Local reactions and systemic events are solicited from the subjects and recorded by them in a diary for 7 d following administration of the vaccine. Most subjects in all cohorts experienced the expected reactogenicity, typically starting within 24 h of dosing and resolving within 24 h. The specific, solicited local and systemic reaction are summarized below in Table 17 and Table 18 respectively.

Table 17: BNT162b2 in younger adults - Number of subjects with local symptoms (diary)

	Number of subjects with local reactions (n=)					
	7 d Post Prime			7 d Post Boost		
BNT162b2	Subjects dosed prime	Any event	Any ≥ severe	Subjects dosed boost	Any event	Any ≥ severe
1 µg	9	2	0	-	-	-
10 µg	12	12	0	7	0	0
20 µg	10	9	0	-	-	-
30 µg	12	10	0	-	-	-

Table 18: BNT162b2 in younger adults - Number of subjects with systemic symptoms (diary)

	Number of subjects with systemic reactions (n=)					
	7 d Post Prime			7 d Post Boost		
BNT162b2	Subjects dosed prime	Any event	Any ≥ severe	Subjects dosed boost	Any event	Any ≥ severe
1 µg	9	5	0	-	-	-
10 µg	12	12	0	7	3	1
20 µg	10	7	1	-	-	-
30 µg	12	9	0	-	-	-

In local reactions, most subjects reported injection site pain and/or tenderness, whilst reports of swelling / induration or erythema were minimal. The most common systemic reactions were headache and fatigue, chills and myalgia. No reports of Grade 3 (severe intensity) local reactions were reported to date, whilst three Grade 3 (severe intensity) systemic reactions were reported, of headache, myalgia and malaise, each on one day of recording. The overall local and systemic reactogenicity profiles show a more favorable reactogenicity profile for the BNT162b2 vaccine candidate compared to BNT162b1.

No unexpected laboratory findings have been noted for BNT162b2 whilst a similar but lesser pattern of changes to lymphocytes and CRP, in a dose dependent manner, to candidate BNT162b1 have been noted, with minimal effect seen at the 1 µg dose level.

Adverse events are elicited throughout the trial, collected and graded by the investigators on a 4-point scale (as per the trial protocol). Most subjects reported AEs, >95% of which are related to reactogenicity, except in the 1 µg dose group where 4 out of 9 subjects only reported AEs to date.

For vaccine BNT162b2, only initial reports are available, however the pattern of tolerability seems consistent with that described previously for candidate BNT162b1 in the nature, pattern of onset, duration and outcome of reactions. The vast majority of reports are expected reactogenicity. By informal comparison the tolerability of BNT162b2 at least as good as that recorded for BNT162b1 at equivalent dose levels.

6.1.1.2.4 BNT162c2 - Summary of safety

BNT162c2 has been tested at doses of 0.1, 0.3, and 1 µg. Minimal reactogenicity was reported with any local reactions (chiefly pain) being mild or moderate and present in 4, 7, and 11 subjects in each dose cohort respectively. Systemic reactions showed little dose dependency overall with 7, 7, and 8 subjects reporting any systemic reaction by respective dose cohort. 2 subjects each in the 0.3 and 1.0 µg cohorts reported severe local reactions. All reported events were self-limiting or simply managed. No SAEs were reported and no subjects have withdrawn due to an AE. At the time of preparation of this summary, the overall assessment of safety data following dosing with BNT162c2 has not changed.

6.1.2 BNT162-02 / C4591001 - Preliminary results

The trial BNT162-02 (Pfizer trial code C4591001; NCT 04368728) is a Phase I/II/III, placebo-controlled, randomized, observer-blind, dose-finding trial to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy adults. In this trial the subjects are randomized 4:1 (Phase I part) and 1:1 (Phase II/III part) to active vaccine or placebo (Mulligan et al. 2020).

For the current status of dosing with BNT162 vaccines candidates by dose level in BNT162-02, see Table 13.

6.1.2.1 Summary of immunogenicity in BNT162-02 (status July 24th, 2020)

6.1.2.1.1 *BNT162b1* - Summary of immunogenicity

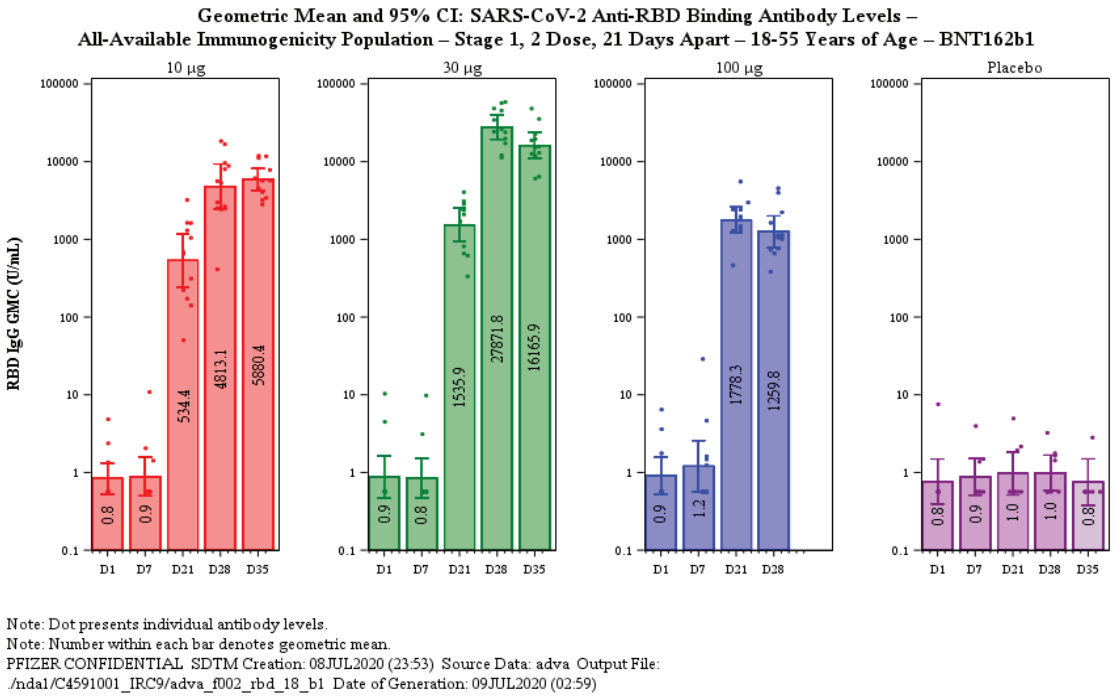
As shown for BNT162b1 in Figure 25 for younger adults and Figure 26 for elderly adults, substantial RBD-binding IgG was induced by Day 21 in all dosed subjects.

Geometric mean concentrations (GMC) in dosed subjects were similar to or higher than the GMC of a panel of 38 COVID-19 human convalescent sera (HCS; samples drawn ≥14 d after PCR-confirmed diagnosis) (Mulligan et al. 2020). The panel had a RBD-binding IgG GMC of 602 U/mL, whereas the BNT162b1 P/B at 30 µg resulted in peak RBD-binding IgG GMCs of 27,871 U/mL (approximately 46.3-times higher) and 7,527 U mL (approximately 12.5-times higher) in younger and elderly adults, respectively.

As shown in Figure 27 for younger adults and Figure 28 for elderly adults, all BNT162b1 groups showed modest increases in SARS-CoV-2 neutralization GMTs after a single dose.

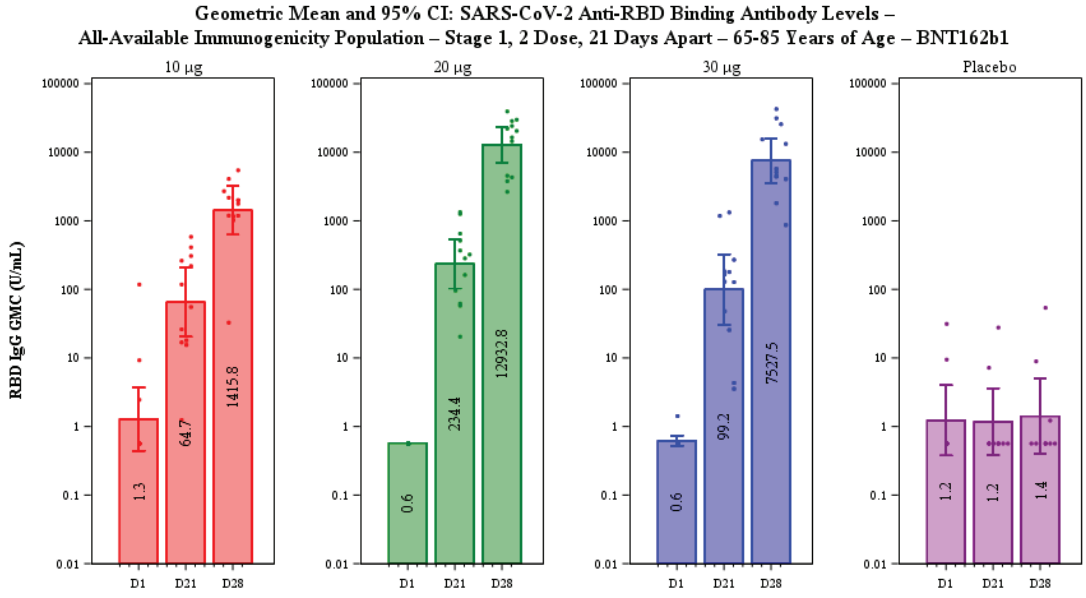
For younger adults, the GMT in the 30 µg group was approximately 2.3-times that of the 10 µg group; GMTs in 30 µg and 100 µg groups were similar, suggesting there may be little benefit in doses above 30 µg. The second doses of 10 µg and 30 µg resulted in a substantial booster response, with Day 28 GMTs approximately 13.2-times and 9.3-times those on Day 21, respectively (note: 100 µg group did not receive a second dose). Similar results were observed in elderly adults.

The GMTs in younger adults dosed with 10 µg and 30 µg BNT162b1 were 1.8-times and 2.8-times that of the COVID-19 HCS panel GMT, respectively (Mulligan et al. 2020).



Note: Dot presents individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 08JUL2020 (23:53) Source Data: adva Output File:
./nda1/C4591001_IRC9/adva_f002_rbd_18_b1 Date of Generation: 09JUL2020 (02:59)

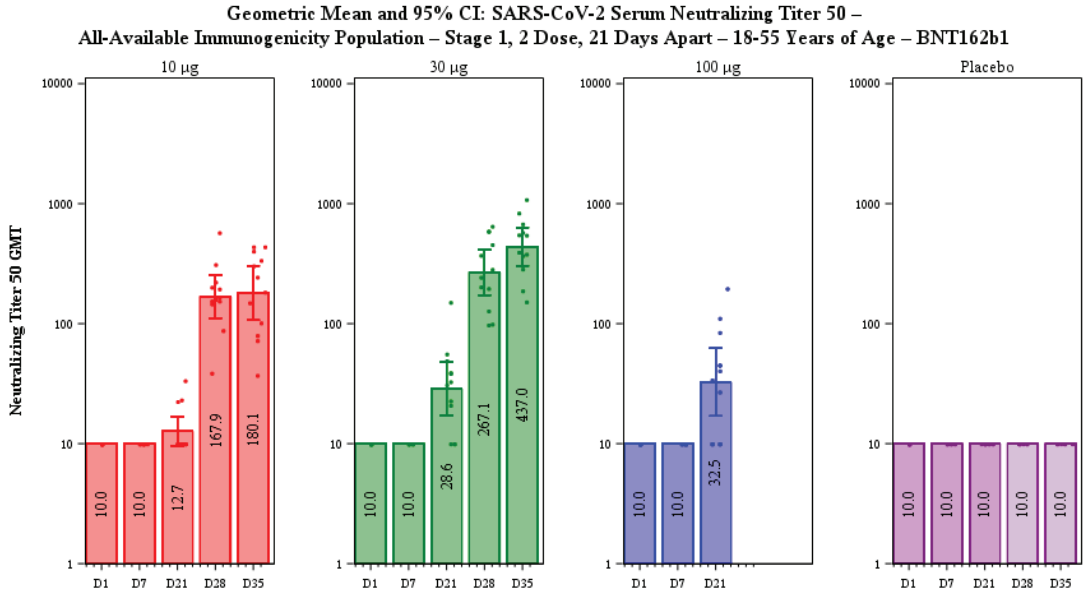
Figure 25: BNT162b1 in younger adults: RBD-binding IgG GMCs (BNT162-02)



Note: Dot presents individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 21JUL2020 (13:28) Source Data: adva Output File:
./nda1/C4591001_Phase1_22JUL2020/adva_f002_rbd_65_b1 Date of Generation: 21JUL2020 (15:30)

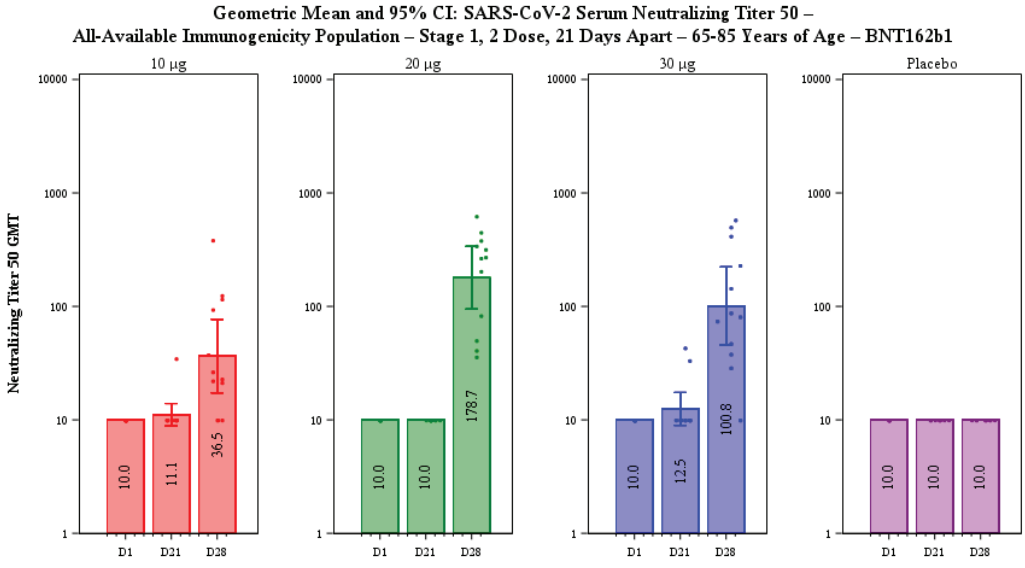
Figure 26: BNT162b1 in elderly adults: RBD-binding IgG GMCs (BNT162-02)

On this page, each data point represents a serum sample; each vertical bar represents a geometric mean with 95% CI. Numbers within bars are GMC or GMT for the group. Note that trial subjects in the 100 µg group only received 1 dose of vaccine.



Note: Dot presents individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 08JUL2020 (23:53) Source Data: adva Output File:
./nda1/C4591001_IRC9/adva_f002_sars_50_18_b1 Date of Generation: 09JUL2020 (09:48)

Figure 27: BNT162b1 in younger adults: 50% SARS-CoV-2 neutralizing GMTs (BNT162-02)



Note: Dot presents individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 21JUL2020 (13:28) Source Data: adva Output File:
./nda1/C4591001_Phase1_22JUL2020/adva_f002_sars_50_65_b1 Date of Generation: 21JUL2020 (15:35)

Figure 28: BNT162b1 in elderly adults: 50% SARS-CoV-2 neutralizing GMTs (BNT162-02)

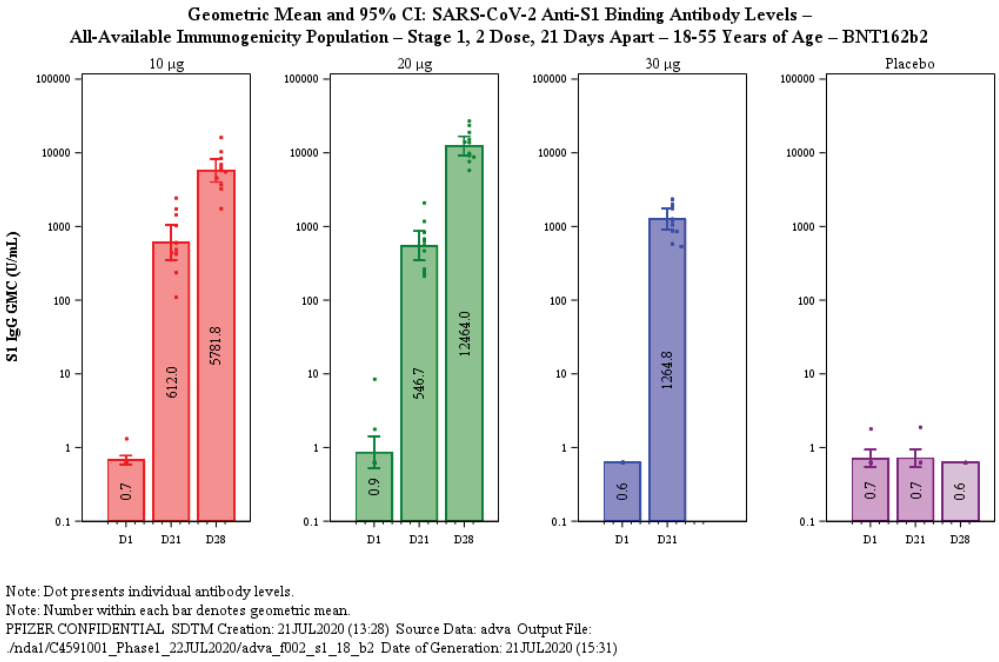
On this page, each data point represents a serum sample; each vertical bar represents a geometric mean with 95% CI. Numbers within bars are GMC or GMT for the group. Note that trial subjects in the 100 µg group only received 1 dose of vaccine.

6.1.2.1.2 BNT162b2 - Summary of immunogenicity

As shown for BNT162b2 in Figure 29 for younger adults and Figure 30 for elderly adults, substantial S1-binding IgG was induced by Day 21 in all dosed subjects.

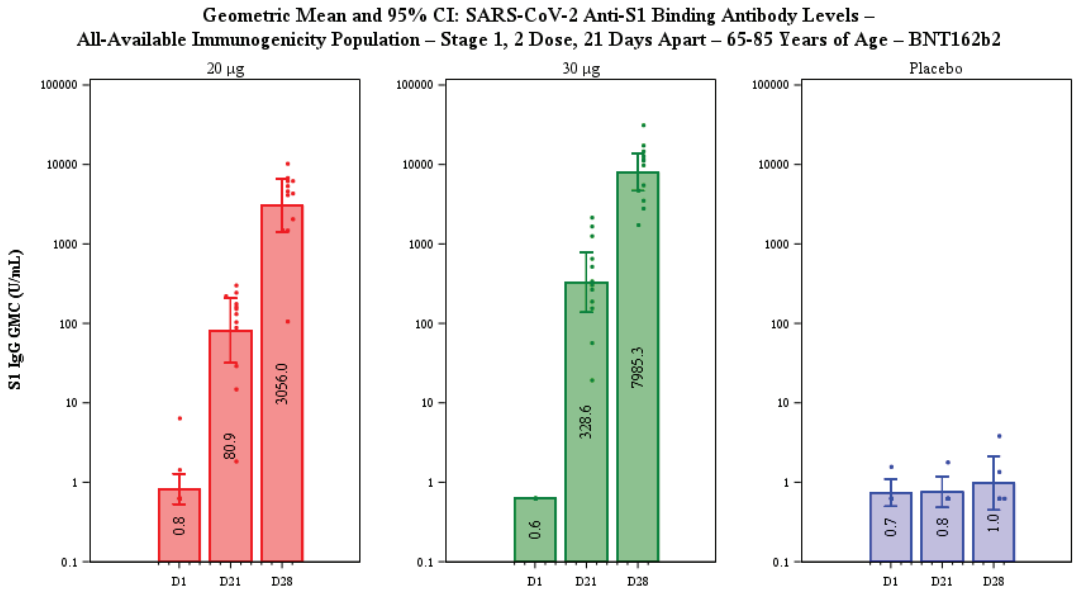
As seen for BNT162b2 in Figure 31 for younger adults and Figure 32 for elderly adults, all BNT162b1 groups showed modest increases in SARS-CoV-2 neutralization GMTs after a single dose.

For younger adults, the GMT in the 20 µg group was approximately 2.3-times that of the 10 µg group. The second doses of 30 µg resulted in a substantial booster response, with Day 28 GMTs approximately 19.2-times and 12.6-times those on Day 21, in younger and elderly adults respectively.



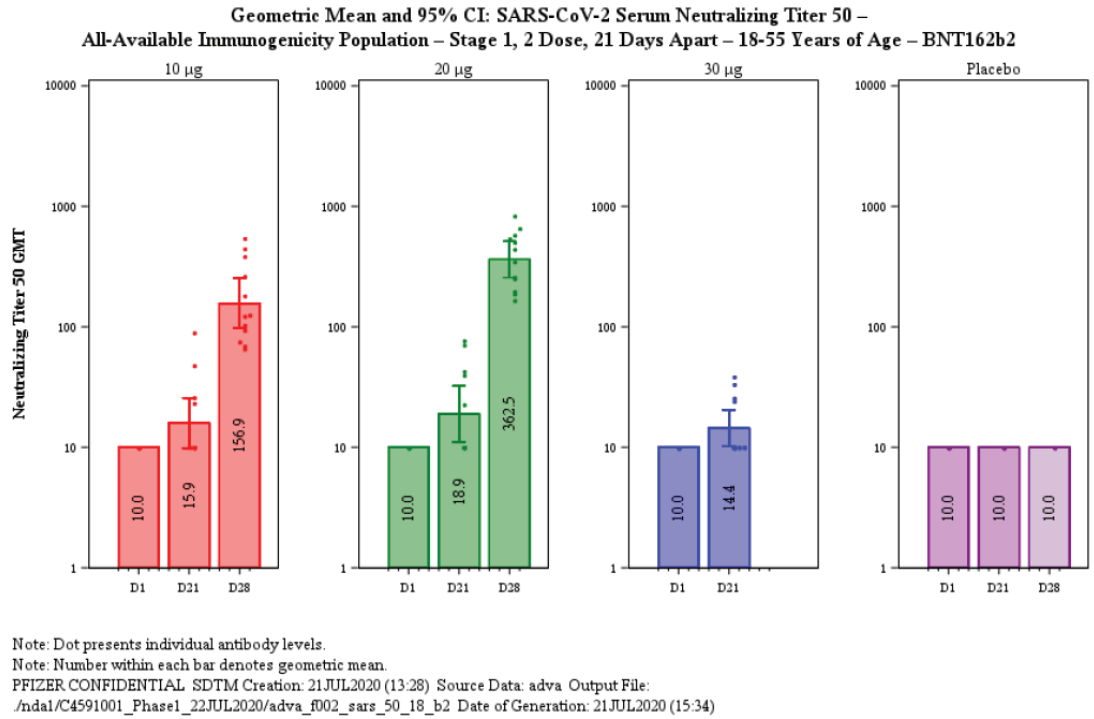
Note: Dot presents individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 21JUL2020 (13:28) Source Data: adva Output File:
./ndal/C4591001_Phase1_22JUL2020/adva_f002_s1_18_b2 Date of Generation: 21JUL2020 (15:31)

Figure 29: BNT162b2 in younger adults: S1-binding IgG GMCs (BNT162-02)



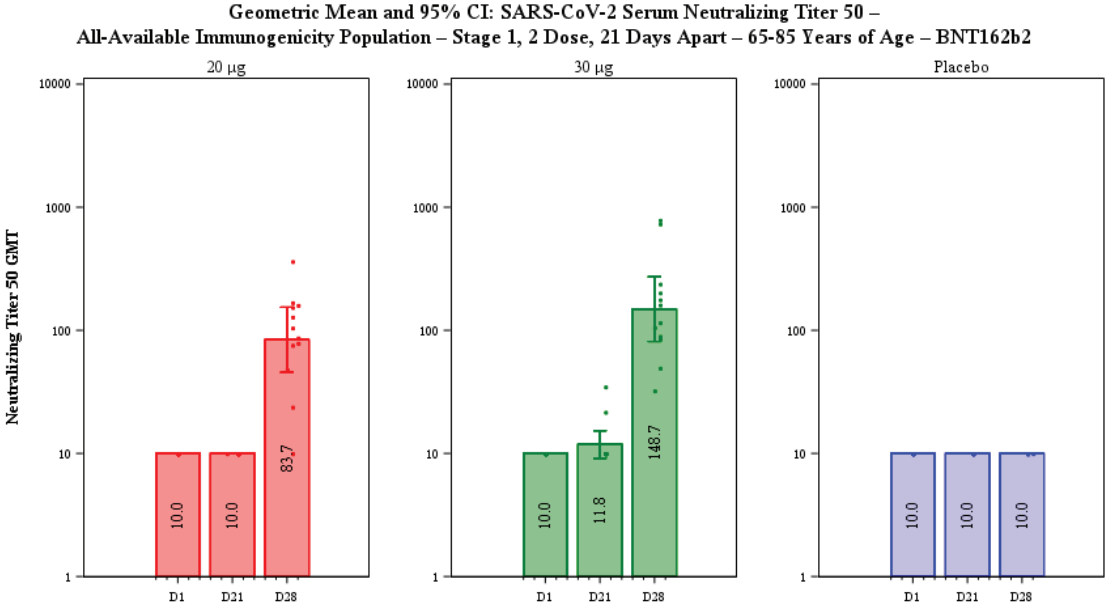
Note: Dot presents individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 21JUL2020 (13:28) Source Data: adva Output File:
./ndal/C4591001_Phase1_22JUL2020/adva_f002_s1_65_b2 Date of Generation: 21JUL2020 (15:33)

Figure 30: BNT162b2 in elderly adults: S1-binding IgG GMCs (BNT162-02)



Note: Dot presents individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 21JUL2020 (13:28) Source Data: adva Output File:
./ndal/C4591001_Phase1_22JUL2020/adva_f002_sars_50_18_b2 Date of Generation: 21JUL2020 (15:34)

Figure 31: BNT162b2 in younger adults: 50% SARS-CoV-2 neutralizing GMTs (BNT162-02)



Note: Dot presents individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 21JUL2020 (13:28) Source Data: adva Output File:
./ndal/C4591001_Phase1_22JUL2020/adva_f002_sars_50_65_b2 Date of Generation: 21JUL2020 (15:35)

Figure 32: BNT162b2 in elderly adults: 50% SARS-CoV-2 neutralizing GMTs (BNT162-02)

6.1.2.2 Summary of safety in BNT162-02 (status July 24th, 2020)

Data for BNT162b1 P/B dosing in younger and elderly adults are available for the 10 µg, 20 µg, and 30 µg dose levels post-Dose 1 and Dose 2. Based on the tolerability profile observed with the 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 elderly adults dosed with BNT162b1 P/B were broadly comparable to those in trial BNT162-01 and are briefly summarized below.

Overall, the dose levels 10 µg, 20 µg, and 30 µg exhibited a tolerability and safety profile consistent with modRNA-based vaccines. The tolerability in elderly adults appears to be better than seen in younger adults at the same doses.

6.1.2.2.1 BNT162b1 - Summary of safety

Local reactions - BNT162b1

For the dose levels 10 µg to 30 µg, pain at the injection site was the most frequent prompted local reaction, increasing in frequency and/or severity with increasing dose level. All prompted local reactions were mild or moderate in severity (see Figure 33). There were no events graded Grade 4. In both younger and elderly adults, reactogenicity increased with increasing dose level and increased after Dose 2 compared to Dose 1.

Systemic reactions - BNT162b1

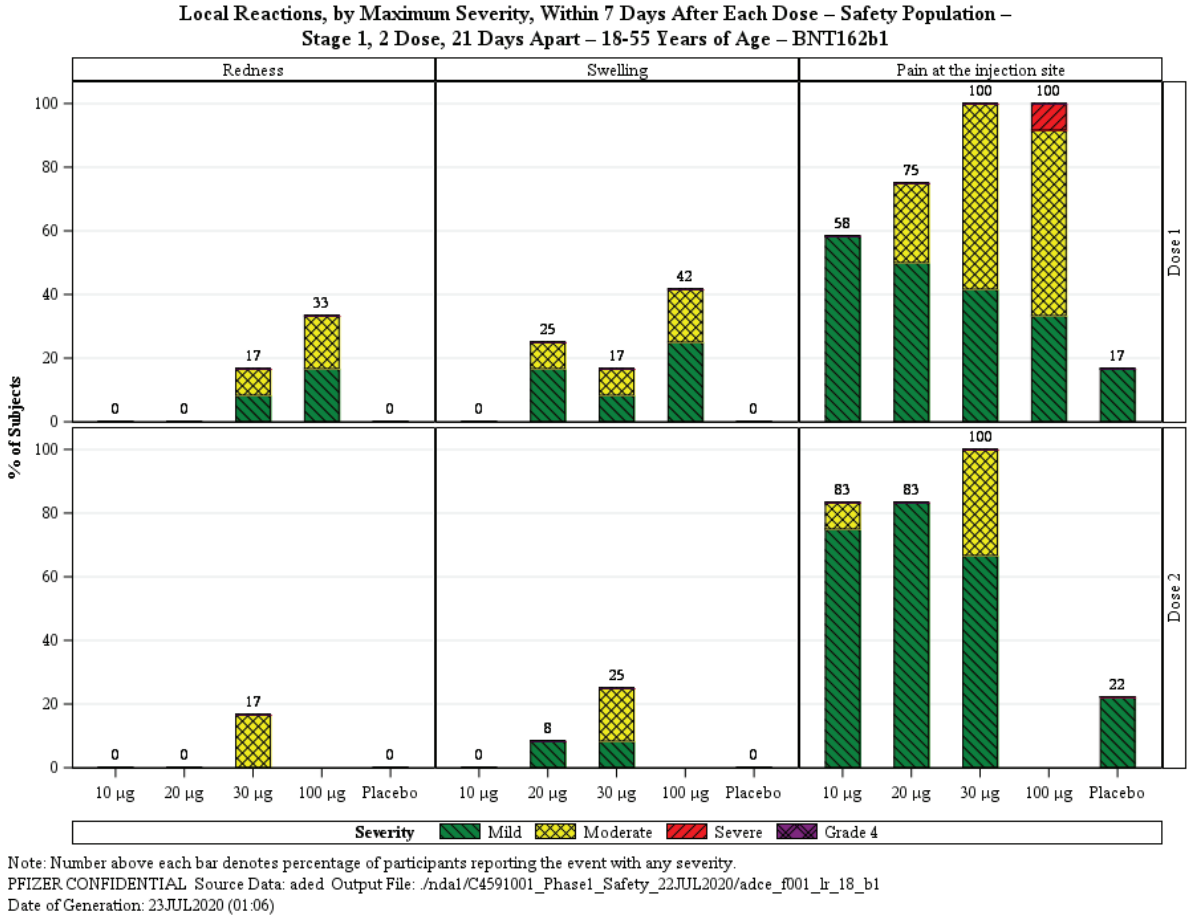
For the dose levels 10 µg to 30 µg, the three most frequent prompted systemic reactions were fatigue, headache, and chills (Figure 34). All systemic reactions were mild or moderate, arose within the first 1 to 2 d after dosing, and were short-lived. Systemic reactions were infrequent in placebo recipients except for fatigue post-Dose 1, the frequency of which was similar in the active and placebo groups. There were no events graded Grade 4. In both younger and elderly adults, reactogenicity increased with increasing dose level and increased after Dose 2 compared to Dose 1.

Adverse events & laboratory assessments - BNT162b1

For elderly adults who were dosed with BNT162b1, one severe AE was reported for a trials subject 2 d post-dose 2 of 20 µg. This subject experienced herpes zoster, which was considered unrelated to the treatment by the investigator. No SAEs were reported.

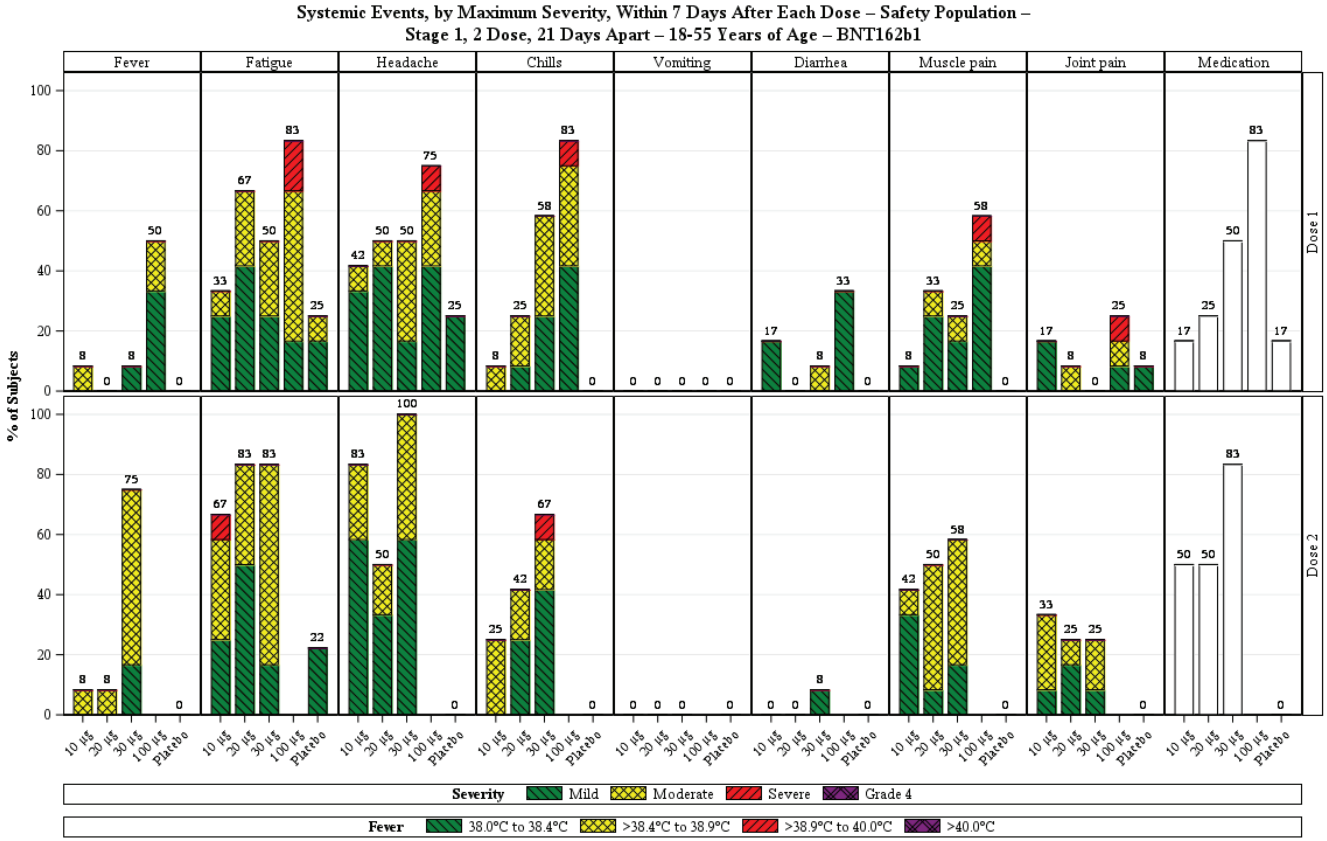
The observed poor tolerability after BNT162b1 Dose 1 at 100 µg, led to a decision not to administer Doe 2 at this dose level. Acceptable tolerability was shown after Doses 1 and 2 at 30 µg BNT162b1.

Most laboratory changes in younger and elderly adults were decreases in lymphocyte count post-dose 1. One Grade 3 decrease in lymphocyte count was reported for 1 trial subject at the 30 µg dose level. One Grade 4 decrease in lymphocyte count was reported for 1 trial subject at the 10 µg dose level. Decreases in lymphocytes after the first dose were transient and returned to normal 6 to 8 d after dosing. No other change in routine clinical laboratory values or abnormalities were observed for the majority of trial subjects after the first dose of BNT162b1.



Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL Source Data: aded Output File: ./ndal/C4591001_Phase1_Safety_22JUL2020/adce_f001_lr_18_b1
Date of Generation: 23JUL2020 (01:06)

Figure 33: BNT162b1 in younger adults: Local reactions after doses 1 and 2 (BNT162-02)



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 Source Data: aded Output File: /ndal/C4591001_Phase1_Safety_22JUL2020/adce_f001_se_18_b1
Date of Generation: 23JUL2020 (01:08)

Figure 34: BNT162b1 in younger adults: Systemic events after doses 1 and 2 (BNT162-02)

6.1.2.2.2 BNT162b2 - Summary of safety

Data for BNT162b2 P/B dosing in younger and elderly adults are available for the 10 µg, 20 µg, and 30 µg dose levels post-dose 1 and dose 2.

Local reactions - BNT162b2

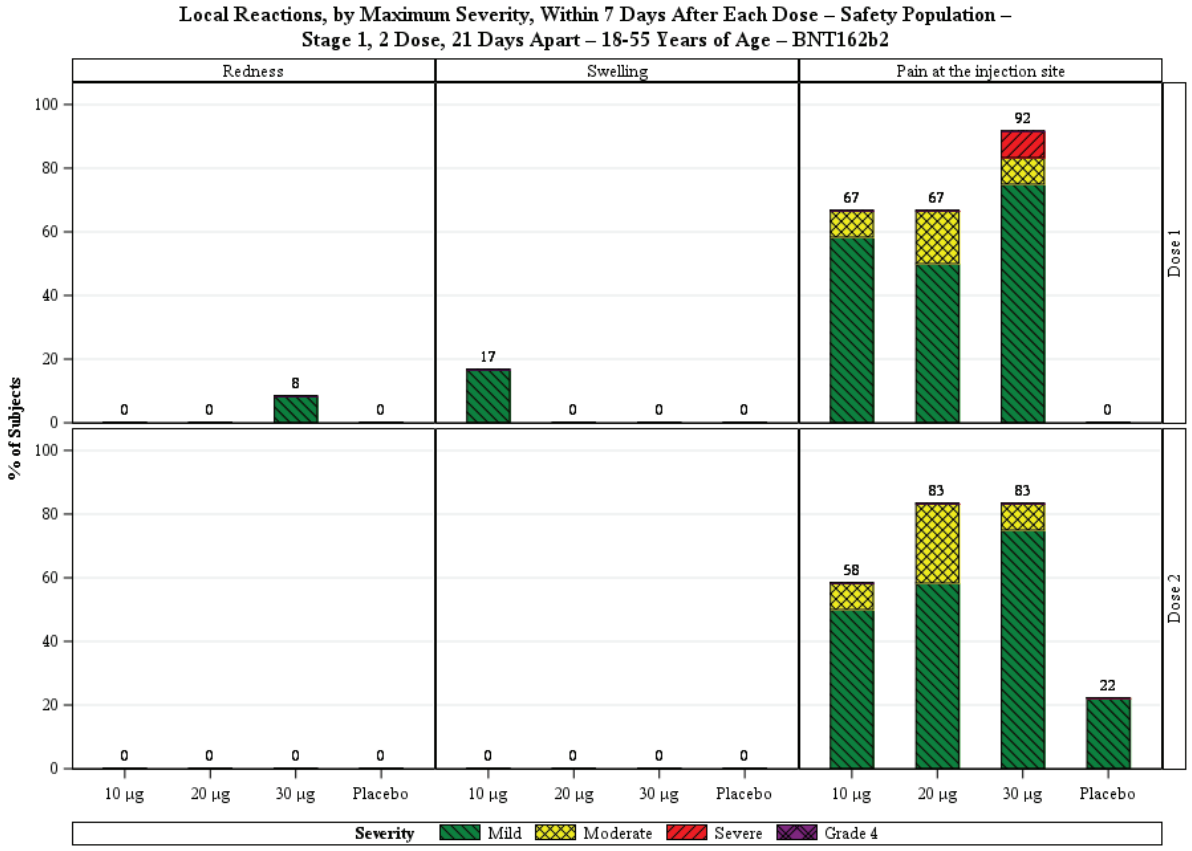
As shown in Figure 35 (younger adults) and Figure 36 (elderly adults), pain at the injection site was the most frequent prompted local reaction, increasing in frequency. Dose level- and dose number-dependent increases in reactogenicity were minimal to modest in either age group. The majority of prompted local reactions were mild in severity.

Systemic reactions - BNT162b2

As shown in Figure 37 (younger adults) and Figure 38 (elderly adults), the most frequent prompted systemic reactions in subjects receiving BNT162b2 were fatigue and headache and fatigue in the placebo group. Systemic reactions were mild or moderate, arose within the first 1 to 2 d after dosing, and were short-lived. Dose level- and dose number-dependent increases in reactogenicity were minimal to modest in either age group.

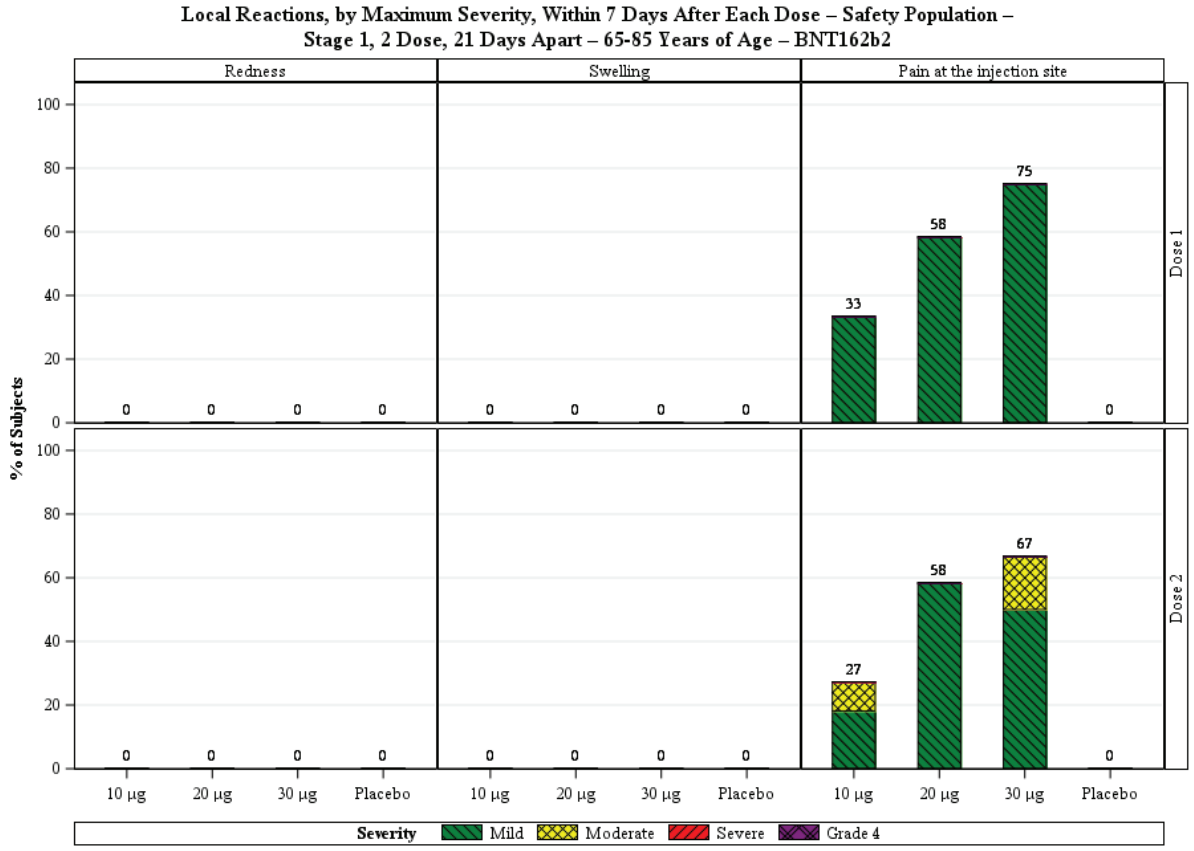
Adverse events & laboratory assessments - BNT162b2

At the time of the data cut, AEs had been reported by only one elderly adult in each of the 20 µg and 30 µg groups who were dosed with BNT162b2. With few exceptions, there were no changes in most of the routine clinical laboratory values, or abnormalities observed, for the majority of trial subjects after the first dose of BNT162b2. Two trial subjects in the 20 µg group had a transitory Grade 2 decrease in neutrophil count 1 to 3 d post-dose 1. Most laboratory changes were decreases in lymphocyte count post-dose 1, which reverted to Grade ≤1 by 6 to 8 d after dosing.



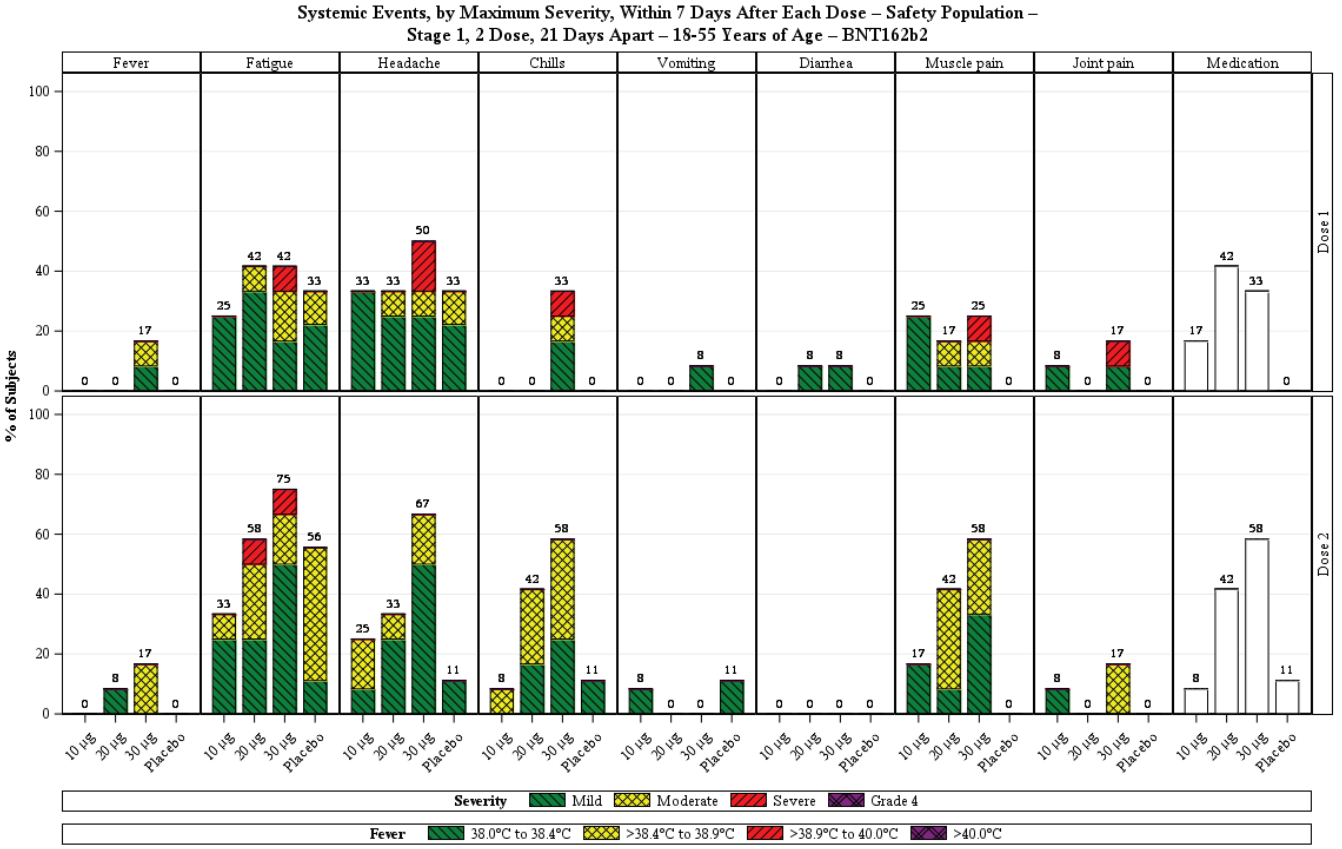
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL Source Data: aded Output File: ./nda1/C4591001_Phase1_Safety_22JUL2020/adce_f001_lr_18_b2
Date of Generation: 23JUL2020 (01:07)

Figure 35: BNT162b2 in younger adults: Local reactions after doses 1 and 2 (BNT162-02)



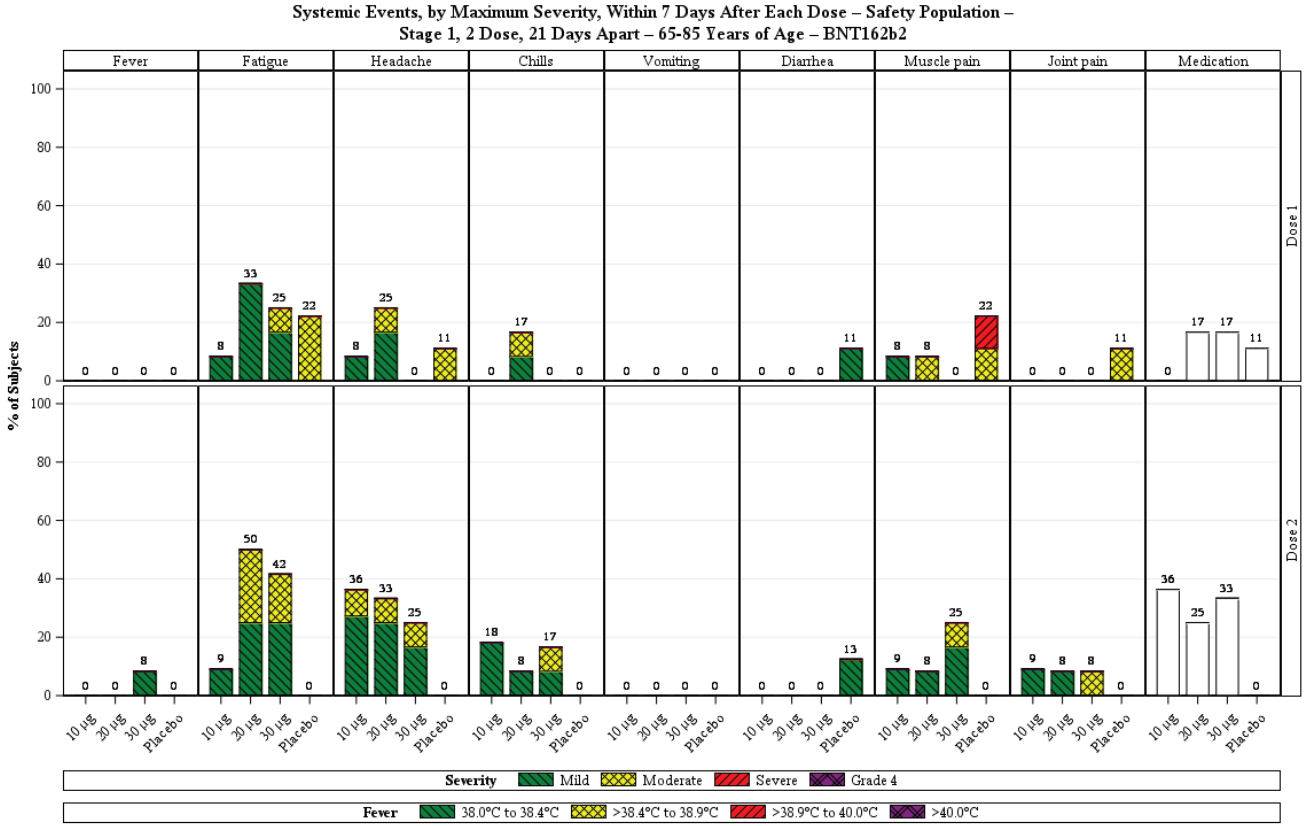
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL Source Data: aded Output File: ./nda1/C4591001_Phase1_Safety_22JUL2020/adce_f001_lr_65_b2
Date of Generation: 23JUL2020 (01:08)

Figure 36: BNT162b2 in elderly adults: Local reactions after doses 1 and 2 (BNT162-02)



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 Source Data: aded Output File: /nda1/C4591001_Phase1_Safety_22JUL2020/adce_f001_se_18_b2
Date of Generation: 23JUL2020 (01:09)

Figure 37: BNT162b2 in younger adults: Systemic events after doses 1 and 2 (BNT162-02)



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 Source Data: aded Output File: ./ndal/C4591001_Phase1_Safety_22JUL2020/adce_f001_se_65_b2
Date of Generation: 23JUL2020 (01:10)

Figure 38: BNT162b2 in elderly adults: Systemic events after doses 1 and 2 (BNT162-02)

6.1.2.3 Conclusions from Phase I data (BNT162-02)

The available immunogenicity data from Phase I trial subjects suggest that the BNT162b (i.e., modRNA-based) vaccine candidates induce a robust IgG-binding response to RBD/S1 and neutralizing response specific to SARS-CoV-2. Immunogenicity appears to be substantially increased following the second dose of vaccine.

The reactogenicity, AEs, and laboratory results reported in the clinical studies thus far are in line with those commonly associated with vaccination, particularly with mRNA-based vaccines. The observed reactogenicity has generally been mild or moderate and short-lived. No unexpected AEs or SAEs have been reported. Reactogenicity was generally higher after the second dose, but symptoms resolved quickly over the course of a few days.

6.1.2.4 Selection of the BNT162b2 candidate and dose for Phase II/III

The rationale for the selection of the BNT162b2 candidate and dose for investigation Phase II/III is summarized below.

While the local tolerability profiles of BNT162b1 and BNT162b2 are, in general, similar between the 2 candidates, the overall systemic reactogenicity profiles (particularly in elderly adults) clearly show a more favorable reactogenicity profile for the BNT162b2 vaccine candidate compared to BNT162b1 while, overall, the immune response data were similar between the two candidates. Since development of a safe COVID-19 vaccine is the Sponsor's highest priority, the favorable tolerability profile was the major driver for choosing BNT162b2.

When selecting the dose level for BNT162b2, the Sponsor put more weight on the SARS - CoV-2 neutralizing antibody response level in the elderly adults to maximize the neutralizing antibody responses in this age group, which is at highest risk of severe disease. Comparing the neutralizing antibody levels in the 20 µg and 30 µg older adult cohorts, the 30 µg dose level was favored, as the neutralizing antibody levels were clearly higher than those in the 20 µg cohort (Figure 28). As a reminder, the 38 human COVID-19 HCS sera drawn from individuals aged 18 to 83 yrs, at least 14 d after PCR-confirmed diagnosis, and at a time when the individuals were asymptomatic. The serum donors predominantly had symptomatic infections (35/38), and one had been hospitalized.

In addition, S1-IgG antibody binding concentrations in both elderly (Figure 30, post-dose 2) and younger (Figure 29, post-dose 1) adult cohorts also favored the selection of the 30 µg dose level.

Preliminary human T cell data that are being generated in the BNT162b2-01 trial have confirmed the robust $CD4^+$ and $CD8^+$ expected for the RNA platform.

With these considerations, the Sponsor has selected to use BNT162b2 at the 30 µg dose level to proceed into Phase II/III because this dose and candidate provides 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.

6.1.3 BNT162-03 in Chinese adults

The trial BNT162-03 is being conducted in healthy Chinese adults by Shanghai Fosun Pharmaceutical Development, Inc. (Shanghai, China) and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany).

This is a Phase I, randomized, placebo-controlled, observer-blind trial investigating the safety and immunogenicity of SARS-CoV-2 RNA vaccine (BNT162b1) in healthy Chinese adults aged 18 to 55 yrs (younger adults) and >55 yrs (older adults). The trial has been approved by the Chinese regulatory authorities and dosing has started.

6.1.4 BNT162-04 for BNT162b3

The trial BNT162-04 will be conducted and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany).

This is 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. Trial approval has been requested and trial set up is ongoing.

6.2 Marketing experience

The BNT162 vaccine candidates have neither been approved for use nor been marketed in any country.

7 SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

For a summary of the relevant non-clinical and clinical information, see Section 2.

7.1 Mode of action and intended indications

The BNT162 vaccine candidates use an RNA to deliver genetic information to cells, where it is used to express proteins for the therapeutic effect.

The intended initial indication is as vaccine for the prevention of COVID-19 in adults aged 18 yrs or older.

7.2 Posology and method of administration

The BNT162 vaccines are intended for IM administration in the upper arm (deltoid muscle) using two doses 21 day apart (P/B regimen). For BNT162c2, optionally a single dose regimen is also under investigation. The vaccine should not be injected into areas where there may be a major nerve trunk.

7.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in Section 4.2.1.

7.4 Special warnings and precautions for use

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Do not inject vaccine intravenously, intradermally, subcutaneously, orally or by any route other than intramuscular.

The vaccine should be administered with caution to individuals with a bleeding disorder or receiving anticoagulant therapy since bleeding may occur following an IM administration to these subjects.

Syncope (fainting) can occur following, or even before, any injection, including vaccination. Procedures should be in place to prevent injury from fainting and manage syncopal reactions.

Immune response to BNT162 may be insufficient in immunocompromised individuals, including those individuals receiving immunosuppressant therapy.

Currently there are no data available on the use of BNT162 vaccine candidates in pediatric age groups.

There is no data on the use of BNT162 in individuals older than 85 yrs of age, individuals younger than 18 yrs of age, or individuals with renal or hepatic impairment.

For trial-specific special warnings and precautions, see the respective trial protocol.

7.5 Interaction with other medicinal products and other forms of interaction

There are no data on the concomitant administration of BNT162 with other vaccines.

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 with other medicinal products are consider unlikely.

The immune response to BNT162 may be insufficient in immunocompromised individuals, including those individuals receiving immunosuppressant therapy.

7.6 Fertility, pregnancy, and lactation

Currently there are no data available on the use of BNT162 vaccine candidates in pregnant or breastfeeding women. It is not known whether BNT162 vaccines are excreted in human milk.

Macroscopic and microscopic evaluation of male and female reproductive tissues were included in the GLP repeat-dose toxicity study testing of BNT162a1, BNT162b1, BNT162b2, and BNT162c1 performed in rats. No changes in these tissues were reported.

BioNTech is currently conducting a developmental and reproductive toxicity study of BNT162 vaccines.

7.7 Effects on ability to drive and use machines

The BNT162 vaccine candidates are 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 adverse reactions (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-marketing 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. ARs in this section may be non-serious or serious.

The ARs identified for BNT162 vaccines at this time are: injection site pain, fever, fatigue, headache, chills, and muscle pain.

7.8.2 Reference safety information for assessment of expectedness of serious adverse reactions

The Reference Safety Information (RSI) is used for the assessment of expectedness for regulatory reporting of serious adverse reactions that are reported in clinical trials. The RSI does not represent a comprehensive overview of the safety profile of BNT162 which is

presented in Section 7.8.1. No serious adverse reactions are considered expected by the sponsor for regulatory reporting purpose.

7.9 Overdose

There is currently no data about overdose with BNT162 vaccine candidates, including accidental overdose in clinical trials.

7.10 Drug abuse and dependence

There is currently no data about drug abuse and dependence with BNT162 vaccine candidates. However, BNT162 is not expected to cause drug abuse or dependence.

7.11 Evolving safety information

7.11.1 Clinical safety

7.11.1.1 Patient exposure

For a summary of subject exposure to BNT162 vaccine candidates in ongoing clinical trials, see Table 13.

7.11.1.2 Specific adverse events of note

See Section 7.8.1.

7.11.1.3 Known drug class effects and other human experience

The AEs reported in the ongoing clinical trials reported appear similar to anticipated reactogenicity events for vaccines administered intramuscularly. In addition to specific solicited reactogenicity events collected from subjects, the events flu-like symptoms and injection site reactions have been reported. For details, see Section 6.

Prior clinical experience with similar RNA products developed by BioNTech (see Section 5.2.3) indicates that the RNA distribution to the liver does not pose a safety risk, nonetheless, liver parameters will be carefully monitored in the planned clinical trials.

Vaccine-related enhanced disease for vaccines against related coronaviruses (SARS-CoV1 and MERS) has been reported only in animal models (Lambert et al. 2020; Graham 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. No data are currently available to exclude that BNT162 may cause enhanced disease in vaccinated subjects. The planned clinical trials will include monitoring of possible COVID-19-related symptoms in trial subjects.

7.11.2 Non-clinical findings of note

All tested non-clinical and clinical vaccine candidates were immunogenic to highly immunogenic in non-clinical models. The available data demonstrate that BNT162b1, BNT162b2, BNT162b3, and BNT162c2 are capable of inducing robust immune responses in mice, (except for BNT162c2) rats and NHPs.

The repeat-dose toxicology study in rats demonstrated tolerability of the tested vaccines. There were no vaccine associated adverse findings or mortalities observed.

As expected, all vaccines induced a pro-inflammatory response which was evident in clinical signs, clinical pathology findings, and macro and microscopic findings. Increases in typical inflammatory blood parameters such as fibrinogen and acute phase proteins support this hypothesis. The reversible elevation of GGT activity in the absence of increase of specific markers, such as alkaline phosphatase and bilirubin, and relevant microscopic findings, does not indicate hepatobiliary injury. Hematological changes observed included an increase in large unclassified cell and leukocyte (monocyte, basophil and neutrophil) counts, as well as a transient, dose-dependent reduction in reticulocytes after first immunization. Similar reticulocyte changes have been observed in rats treated with the licensed LNP-small interfering RNA (siRNA) pharmaceutical OnpattroTM (FDA assessment report of OnpattroTM 2018), but have not been observed in NHPs or patients treated with this compound. The effect is therefore considered species specific. After the last immunization, a slight reduction in red cell mass and platelet numbers was observed. The latter is likely attributable to inflammation, causing specific platelet consumption, which is considered a pharmacodynamics attribute (Davidson 2013; Middleton et al. 2016). All changes observed in blood parameters reversed fully throughout the 3-wk recovery period.

Secondary test-item related findings manifested as a reversible reduction in body weight post immunization without affecting body weight gain between immunizations.

Inflammation at the injection site was an anticipated response to the administered RNA-LNP and expressed antigen. Injection site reactions were greater after the boost dose(s), and the accelerated dosing schedule of once weekly may have exacerbated these reactions compared to the anticipated clinical dosing regimen.

Macroscopic observations of enlarged spleens and draining lymph nodes correlated with increased germinal center cellularity and increased hematopoiesis (as described in Section 5.3.1.10 and 5.3.1.12) together with a tendency of increased spleen weights in vaccinated animals (Section 5.3.1.11). In addition, macroscopic injection site findings also correlated with microscopic inflammation, consistent with an immune response to the vaccine.

Vacuolation in portal hepatocytes was present in all vaccinated animals and was unassociated with evidence of hepatocyte injury (e.g., no elevations in ALAT or ASAT). This change may be related to hepatic clearance of the pegylated lipid in the LNP.

No unexpected changes were observed during the recovery phase. All vaccine induced effects on local tolerance, food consumption and body weight were fully reversible and clinical pathology changes were partially or completely reversed at the end of the recovery phase. Most macroscopic and microscopic findings ameliorated or were also partially or completely resolved at the end of the recovery period, though some animals treated with BNT162b1 or BNT162b2 had enlarged iliac lymph nodes at the end of the recovery period. Microscopically, minimal to mild inflammation was also present at the injection site and in the draining lymph node in some animals. The infiltration of macrophages in the iliac lymph

nodes of previously treated recovery animals were regarded as consequence of phagocytosis relating to the inflammatory reactions at the injection sites.

7.12 Overall conclusions

All tested BNT162 vaccine candidates (BNT162b1, BNT162b2, BNT162b3, and BNT162c2) were immunogenic to highly immunogenic in non-clinical models.

The available results from the repeat-dose toxicology study demonstrate tolerability of the tested vaccines. There were no vaccine-related clinical signs or mortalities observed. As expected, all vaccines induced a pro-inflammatory response, which was evident in clinical signs, clinical pathology findings, and macro and microscopic findings. Secondary test-item related findings manifested as a reversible reduction in body weight post immunization without affecting body weight gain between immunizations.

The were no unexpected changes observed during the recovery phase. All vaccine induced effects on local tolerance, food consumption, clinical pathology and body weight were either fully reversible. Macroscopic and microscopic changes had either recovered completely or were partially present at the end of recovery.

The BNT162 vaccine candidates have not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility or embryonic/fetal development.

The AEs reported in the ongoing clinical trials appear similar to anticipated reactogenicity events for vaccines administered intramuscularly. The identified risks linked to the administration of the BNT162 vaccine candidates are: injection site pain, fever, fatigue, headache, chills, and muscle pain.

The sponsor considers the risks related to administration BNT162 vaccine candidates identified at this time to be manageable using symptom directed treatment. The safety profile of the vaccine is not fully known at this time however continued clinical investigation is justified given:

- the urgent need for the development of new prophylactic vaccines for COVID-19,
- the threat posed by the increasing number of globally distributed outbreaks of SARS-CoV-2 infection,
- the potential of the BioNTech platform of RNA-based vaccines:
    - to rapidly deliver high numbers of vaccine doses rapidly in a single production campaign, and
    - to be both well tolerated and effective.

The results of non-clinical and on-going clinical studies support that BNT162 vaccine has an acceptable safety profile and is well tolerated when administered to adults 18-85 yrs of age.

The safety and immunogenicity data support a favorable benefit-risk profile, supporting continued clinical development of BNT162 vaccine.

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9 APPENDICES

Table 19: Tabular summaries of non-clinical studies - primary pharmacodynamic effects

Study number	Study Type	Species / Test System	Product code		Dose [µg]	Results	Cross reference
BNT162 vaccine studies (clinical candidates)							
R-20-0074	*In vitro* antigen expression and localization	HEK293T cells	BNT162a1 BNT162b1 BNT162b2 BNT162c2	uRNA V5 modRNA V5 modRNA V9 saRNA V9	1, 2, 5	All tested items expressed the encoded S protein derived antigen.	Section 5.1.2
R-20-0040 and R-20-0140	*In vivo* immunogenicity	Mice BALB/c	BNT162a1	uRNA V5	1, 5, 10	Immunogenicity was shown in all tested doses.	n.a.
R-20-0042 and R-20-0084	*In vivo* immunogenicity	Mice BALB/c	BNT162b1	modRNA V5	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 5.1.3.1
VAC-2020-NIRC-COVID-1681	*In vivo* immunogenicity	NHP Maccaca mulatta	BNT162b1	modRNA V5	30, 100	Immunogenicity was shown in all tested doses.	Section 5.1.4
R-20-0085	*In vivo* immunogenicity	Mice BALB/c	BNT162b2	modRNA V9	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 5.1.3.2
R-20-0145	*In vivo* immunogenicity	Mice BALB/c	BNT162b3	modRNA V5TM	0.2, 1	Immunogenicity was shown in all tested doses.	Section 5.1.3.3
COVID-Rh-2020-01	*In vivo* immunogenicity	Non-human primate (NHP) Maccaca mulatta	BNT162b3	modRNA V5TM	30	Immunogenicity was shown.	Section 5.1.4
R-20-0053	*In vivo* immunogenicity	Mice BALB/c	BNT162c2	saRNA V9	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 5.1.3.4

Study number	Study Type	Species / Test System	Product code		Dose [µg]	Results	Cross reference
Supportive studies (non-clinical candidates)							
R-20-0074	*In vitro* antigen expression and localization	HEK293T cells	BNT162a2 BNT162b2 BNT162c1 BNT162c2	uRNA V8 modRNA V8 saRNA V5 saRNA V8	1, 2.5	All tested items expressed the encoded S protein derived antigen.	Section 5.1.2
R-20-0073	In vivo immunogenicity	Mice BALB/c	-	modRNA encoding a non-SARS-CoV-2 antigen (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.
VAC-2020-NIRC-COVID-1681	*In vivo* immunogenicity	NHP Maccaca mulatta	BNT162b2	modRNA V8	30, 100	Immunogenicity was shown in all tested doses.	Section 5.1.4
R-20-0072	*In vivo* distribution	Mice BALB/c	-	modRNA encoding luciferase	2	The surrogate of the BNT162b platform was expressed in mice with distr bution in the muscle (injection site) and liver.	Section 5.2.3

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.

INVESTIGATOR'S BROCHURE

BNT162/PF-07302048

Version: 6.0 **Date:** 29 JAN 2021

Sponsor: BioNTech SE
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55131 Mainz,
Germany

Reference safety information (RSI) 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 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

For a summary of the key changes introduced when preparing version 6.0, see Section 10.

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
~	Approximately
[^{3}H]-CHE	Radiolabeled [Cholesteryl-1,2-3H(N)]-Cholesteryl Hexadecyl Ether
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
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.)
CI	Confidence intervals
COVID-19	Coronavirus Disease 2019
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
GD	Gestation day
GGT	Gamma (γ)-glutamyl transpeptidase
GLP	Good Laboratory Practice
GMC	Geometric mean concentration
GMT	Geometric mean titer
h	Hour(s)
HA	Hemagglutinin
HCS	COVID-19 human convalescent sera (panel)
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IL	Interleukin
IM	Intramuscular(ly)
IMM	Immunogenicity set - All participants who received at least one dose of IMP and have at least one post-baseline immunogenicity assessment
IMP	Investigational Medicinal Product
IFN	Interferon
IV	Intravenous(ly)
LNP	Lipid nanoparticle
LUC	Luciferase (from firefly *Pyractomena lucifera*)
MERS	Middle East respiratory syndrome
modRNA	Nucleoside-modified messenger RNA

Abbreviation	Explanation
mRNA	Messenger RNA
NCT	ClinicalTrials.gov identifier
NHP	Non-human primates
Older adults	Individuals aged 56 to 85 yrs
ORF	Open reading frame
PBMC	Peripheral blood mononuclear cells
P/B	Prime/boost
PK	Pharmacokinetics
PT	Preferred term
pVNT	Pseudovirus-based neutralization assay
RBC	Red blood cells
RBD	Receptor Binding Domain
RNA	Ribonucleic acid
RSI	Reference safety information
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 9000 x g
SAE	Serious adverse event
saRNA	Self-amplifying messenger RNA
SAR(s)	Serious adverse reaction(s)
SARS	Severe acute respiratory syndrome
SARS-CoV-2	The virus leading to COVID-2019
SD	Single dose
SOC	Standard organ class
TEAE	Treatment-emergent adverse event
Th1	Type 1 T helper cells
uRNA	Non-modified uridine messenger RNA
US	United States (of America)
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
VE	Vaccine efficacy
VEE	Venezuelan equine encephalitis
WBC	White blood cells
WHO	World Health Organization
x	Fold
Younger adults	Individuals aged 18 to 55 yrs
yr(s)	Year(s)

2 SUMMARY

There is an urgent need for the development of a prophylactic vaccine given the threat posed by the increasing number of globally distributed outbreaks of Severe Acute Respiratory Syndrome (SARS) -CoV-2 infection and thus its associated disease Coronavirus Disease 2019 (COVID-19).

The development of a ribonucleic acid (RNA)-based vaccine encoding a viral antigen that is translated by the vaccinated organism to protein to induce a protective immune response provides significant advantages over more conventional vaccine approaches.

At BioNTech, there are three different RNA platforms under development, namely non-modified uridine-containing mRNA (uRNA), nucleoside-modified mRNA (modRNA), and self-amplifying mRNA (saRNA). Different vaccine variants based on the SARS-CoV-2 spike (S) protein were generated and three variants thereof were defined, namely a (i) soluble, trimerized receptor binding domain, (ii) full length SARS-CoV-2 S protein bearing mutations preserving neutralization-sensitive sites as well as (iii) membrane-bound, trimerized receptor binding domain. 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, etc. 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.

BNT162b2 was selected for further development and has been authorized for emergency use or been given conditional marketing authorization in numerous countries worldwide. Since then, BNT162b2 has been administered to millions of individuals worldwide. Further clinical investigation of BNT162b2 is ongoing to expand the studied populations.

For BNT162a1, BNT162b1, BNT162b3, and aBNT162c2, all planned vaccine administration to trial participants has been completed and the dosed participants are now in follow-up.

The non-clinical safety of BNT162a1, BNT162b1, BNT162b2, BNT162c1, and BNT162b3 was tested in Good Laboratory Practice (GLP)-compliant repeat-dose toxicity studies in Wistar Han rats. Administration of these candidates using intramuscular (IM) injections weekly for two (BNT162c1 only) or three doses was tolerated without evidence of systemic toxicity. Non-adverse inflammatory changes at the injection sites and the draining lymph nodes, increased hematopoiesis in the bone marrow and spleen, and clinical pathology changes consistent with an immune response or inflammation in the injection sites were observed. Transient vacuolation of portal hepatocytes unassociated with evidence of hepatocellular damage was observed in dosed animals. The findings are consistent with those typically associated with the IM administration of LNP-enveloped RNA-based vaccines.

In a developmental and reproductive toxicity study, dosing of BNT162b1, BNT162b2 or BNT162b3 to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg RNA/immunization) was associated with non-adverse effects after each dose administration. However, there were no effects on mating performance,

fertility, or any ovarian or uterine parameters in the F0 female rats and no effects on embryo-fetal or postnatal survival, growth, or development in the F1 offspring.

Single doses of each of the BNT162 LNP-enveloped RNA-based vaccines induced neutralizing antibodies and T-cell responses in a dose-dependent manner in mice. In a non-human primate (NHP) study, BNT162b1 and BNT162b2 induced neutralizing antibodies and T-cell responses after two immunizations. After challenge infection with SARS-CoV-2, both candidates reduced the viral replication in NHPs, with BNT162b2 fully inhibiting a viral infection in the lung. During the development of BNT162b1 and BNT162b2, a third modRNA (BNT162b) vaccine candidate, BNT162b3, was introduced that induced early and high neutralizing titers both in mouse and NHP.

Five BNT162 vaccine candidates based on the uRNA, modRNA, and saRNA formats are currently under clinical investigation. As of 10 JAN 2021 more than 26,000 male and female trial participants were dosed at least once with a BNT162 candidate in the ongoing clinical studies (30 with BNT162a1; 252 with BNT162b1; 24,554 with BNT162b2; 84 with BNT162b3 84; 96 with BNT162c2).

Reported immunogenicity data in humans are only available for BNT162b1 and BNT162b2 after prime/boost (P/B) dosing, i.e., dosing twice, with ~21 d between doses. Data are available from participants aged 18 to 85 yrs.

In the study BNT162-01, both vaccine candidates elicited robust IgG binding response to receptor binding domain (RBD)/S1 S-protein subunit. SARS-CoV-2 neutralizing titers were seen at ~21 d after Dose 1. Substantially increased titers were seen at ~7 d after Dose 2, which then mostly decreased by ~21 d after Dose 2. Similar immunogenicity results were seen for BNT162b1 and BNT162b2 in the study BNT162-02/C4591001 and for BNT162b1 in the study BNT162-03 with Chinese participants. The observed kinetics of the BNT162b1 and BNT162b2 induced neutralizing antibody response is typical of antigen-activated B cells undergoing proliferation, followed by rebound contraction with a gradual decline in numbers before stabilization of the immune response.

In the study BNT162-01, BNT162b1 and BNT162b2 induced poly-functional and pro-inflammatory $CD4^+/CD8^+$ T-cell responses in almost all participants. The detection of IFNγ and IL-2, but no or only minor IL-4 production, indicates a favorable type 1 helper T (Th1) profile. No notable age-related differences were observed.

Reported safety data are available from the clinical studies with BNT162b1 and BNT162b2. Only preliminary data are available for BNT162a1, BNT162b3, and BNT162c2. Generally, good tolerability was observed for all vaccine candidates. Overall, many of the reported treatment-emergent adverse events (TEAEs) were reactogenicity events anticipated for IM administered vaccines. Generally, the TEAEs had an onset within the first 24 h post-immunization, resolved spontaneously (mostly within 24 h of onset), and were managed with simple measures (e.g., paracetamol).

BNT162b1 (reported data):

In the BNT162-01 study BNT162b1 was tested at doses ≤ 60 µg in participants aged 18 to 55 yrs and at doses ≤ 30 µg in participants aged 56 to 85 yrs. BNT162b1 showed an acceptable tolerability after two BNT162b1 doses ≤ 50 µg in participants aged 18 to 55 yrs

and after two BNT162b1 doses ≤ 30 µg (the highest dose tested) in participants aged 56 to 85 yrs. Similar tolerability was seen for BNT162b1 in the study BNT162-02/C4591001 and in the study BNT162-03 with Chinese adults. In these two studies, a generally good safety and tolerability profile was reported after two doses of BNT162b1 at doses ≤ 30 µg. To date, there were only a few serious adverse events (SAEs), no AEs of special interest (AESI), and only a few AE resulting in participant withdrawal after dosing with BNT162b1.

BNT162b2 (reported data) - Phase 1:

In the BNT162-01 study, two doses of BNT162b2 have been tested at dose levels of ≤ 30 µg in participants aged 18 to 85 yrs. Preliminary data suggest an acceptable tolerability was shown after both doses at all dose levels in all ages.

BNT162b2 (reported data, 14 NOV 2020) - Phase 2/3:

In the Phase 2/3 part of the BNT162-02/C4591001 study, safety data from ~38,000 participants aged ≥ 16 yrs randomized 1:1 to vaccine or placebo with a median of 2 months of follow-up after the second dose suggest a favorable safety profile, with no specific safety concerns. Available safety data from all participants enrolled through the 14 NOV 2020 data cutoff (N=43,252, which includes late enrollment of additional adolescent and adult participants), was consistent with the safety profile for the ~38,000 participants with median follow-up of 2 months and also did not raise specific safety concerns. The most common solicited adverse reactions (ARs) were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%); severe ARs occurred in ≤ 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in participants aged ≥ 55 yrs (≤ 2.8%) as compared to younger participants (≤ 4.6%). The frequency of SAEs was low (< 0.5%), without meaningful imbalances between study arms. Among non-serious unsolicited AEs, there was a numerical imbalance of four cases of Bell's palsy in the vaccine group compared with no cases in the placebo group, though the four cases in the vaccine group do not represent a frequency above that expected in the general population. Otherwise, there were no notable patterns or numerical imbalances between treatment groups for specific categories of non-serious AEs (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2. 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.

Reported efficacy data is available from one clinical study with BNT162b2. In the Phase 2/3 part of the BNT162-02/C4591001 study, the primary efficacy endpoint is incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before or during the 2-dose vaccination regimen. In a mid-November analysis of 36,621 participants randomized 1:1 to vaccine or placebo who were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to 7 d after completion of the vaccination regimen, efficacy in preventing confirmed COVID-19 occurring at least 7 d after the second dose of vaccine was 95.0%, with eight

COVID-19 cases in the vaccine group and 162 COVID-19 cases in the placebo group. Therefore, the criteria for primary efficacy were met. Subgroup analyses of the primary efficacy endpoint 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.

BNT162a1 (preliminary data):

In the study BNT162-01 in participants aged 18 to 55 yrs, two doses of either 0.1 or 0.3 µg BNT162a1 showed generally acceptable tolerability. However, the frequency and duration of systemic reactogenicity (predominantly of moderate intensity) after the first 3 µg dose led to the decision not to administer the second 3 µg dose and to defer further dosing with BNT162a1. To date, there were no SAE, no AESI, and no AE resulting in participant withdrawal after dosing with BNT162a1.

BNT162c2 (preliminary data):

In the BNT162-01 study in participants aged 18 to 55 yrs, single BNT162c2 doses ≤ 1 µg and two BNT162c2 doses ≤ 3 µg showed generally acceptable tolerability, with a similar or weaker reactogenicity than seen with BNT162b1 or BNT162b2 at the same doses. To date, there were no SAE, no AESI, and no AE resulting in participant withdrawal after dosing with BNT162c2.

BNT162b3 (preliminary data):

In the BNT162-04 study, two doses of BNT162b3 have been tested at doses ≤ 20 µg in participants aged 18 to 85 yrs and at doses ≤ 20 µg in participants aged 18 to 85 yrs. An acceptable tolerability was seen after both doses at these dose levels. However, the tolerability observed after the first 30 µg dose in participants aged 18 to 55 yrs led to the decision not to administer the second 30 µg dose. To date, there were no SAEs, no AESIs, and no AE resulting in participant withdrawal after dosing with BNT162b3.

Post-marketing experience:

Pharmacovigilance data after BNT162b2 administration to millions of individuals worldwide confirms the favorable safety profile with no specific safety concerns identified in the Phase 2/3 part of the BNT162-02/C4591001 study. Anaphylactic reactions have been reported in the post-authorization setting; they were not observed in association with the vaccine in the clinical study. The benefit-risk profile of BNT162b2 remains positive.

The BNT162 vaccine candidates BNT162a1, BNT162b1, BNT162b3, and BNT162c2 have neither been approved for use nor been marketed in any country.

3 INTRODUCTION

3.1 Background

The number of SARS-CoV-2 infections and the associated disease, COVID-19, is increasing every day and continues to spread globally. The World Health Organization (WHO) classified the COVID-19 outbreak as pandemic on March 11th, 2020.

3.2 BioNTech's RNA therapeutics

BioNTech has longstanding and diversified expertise in utilizing messenger RNA (mRNA) to deliver genetic information to cells, where it is used to express proteins for the therapeutic effect.

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.

The production of RNA requires only a single development and manufacturing platform, irrespective of the encoded pathogen antigens. Thus, RNA has the potential of rapid, cost-efficient, high-volume manufacturing and flexible stockpiling (long term storage of low-volume libraries of frozen plasmid and unformulated RNA, which can be rapidly formulated and distributed). BioNTech has expertise in production-process development for various RNA chemistries and formulations.

3.3 Introduction to BioNTech RNA-based vaccines

An LNP-formulated RNA-based vaccine would provide one of the most flexible, scalable, and fastest approaches to provide protection against new, fast spreading, virus infections (Rauch et al. 2018; Sahin et al. 2014).

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

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: RNA which contains the standard nucleoside uridine (uRNA), nucleoside-

modified RNA (modRNA), in which uridine is replaced by the nucleoside pseudouridine; and self-amplifying RNA (saRNA), which also contains uridine nucleosides (Figure 1).

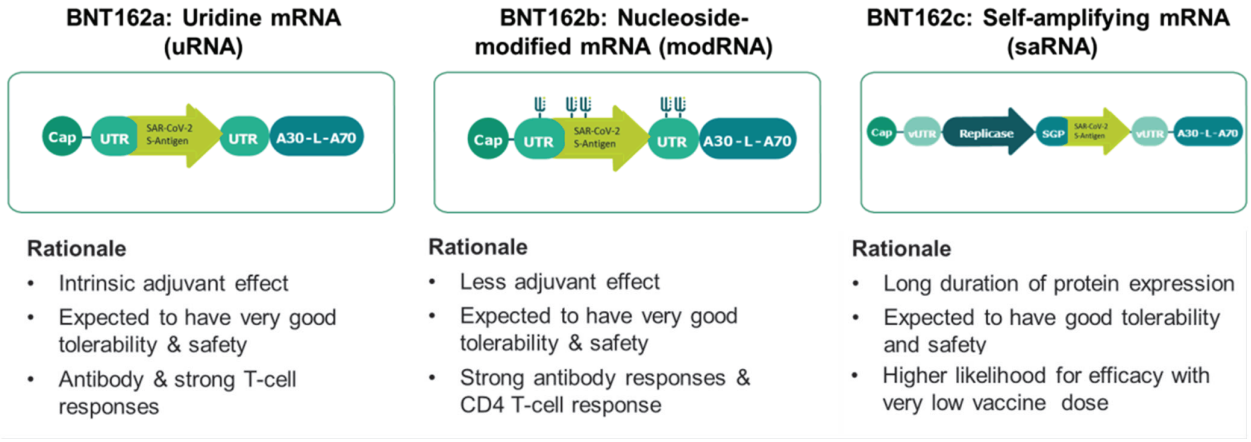


Figure 1: Overview of the three RNA platforms

The RNA vaccine molecules are capped, contain ORFs flanked by the UTR, and have a polyA-tail at the 3' end. The ORF of the uRNA and modRNA vectors encode the vaccine antigen. The saRNA has two ORFs. The first ORF encodes an alphavirus-derived RNA-dependent RNA polymerase (replicase), which upon translation mediates self-amplification of the RNA. The second ORF encodes the vaccine antigen. Abbreviations: A30-L-A70 = poly(A) tail interrupted by a linker; CMC = chemistry, manufacturing and controls; SGP = subgenomic promoter; ORF = open reading frame; UTR = untranslated region; vUTR = viral untranslated region.

The three RNA platforms used in the BNT162 vaccine candidates have complementary strengths (Figure 1): 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. For details on the physical, chemical, and pharmaceutical properties of the drug substance, see Section 4.1.

The utility of each of these RNA platforms for the development of infectious disease vaccines is supported by various non-clinical studies that demonstrated the efficient induction of potent neutralizing antibody and T-cell responses against a variety of viral pathogens including influenza, Ebola, human immunodeficiency virus (HIV), and Zika virus (Vogel et al. 2018; Moyo et al. 2018; Pardi et al. 2017).

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 2). 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.

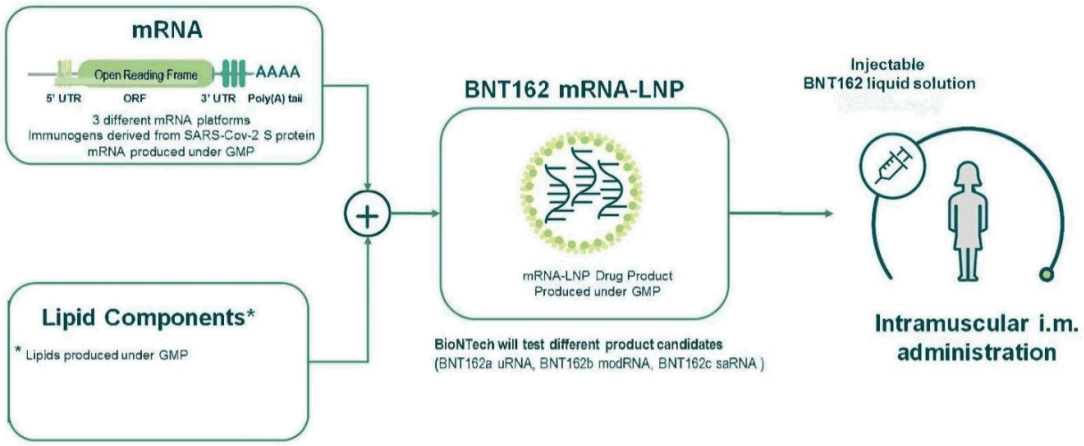


Figure 2: RNA-LNP-based BNT162 vaccines

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 IM injection. Abbreviations: GMP = good manufacturing practice; i.m. = intramuscular; mRNA = messenger RNA; ORF = open reading frame; RNA-LNP = RNA complexed with liposomes; UTR = untranslated region.

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.

All vaccine candidates may be administered using two dose or single dose administration regimens (Figure 3).

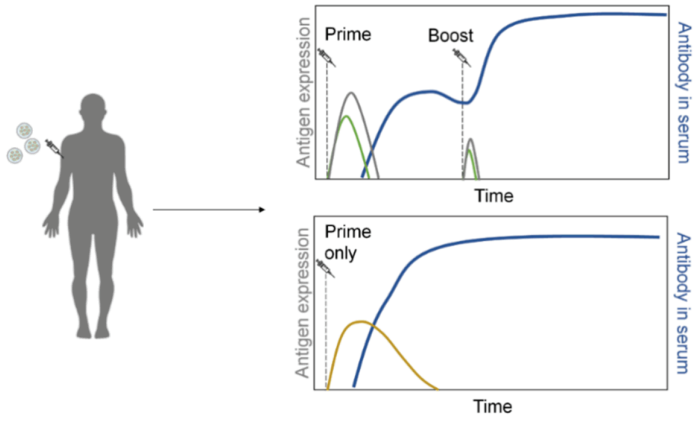


Figure 3: Rationale for the administration schema of BNT162 vaccines

Two different dosing regimens are proposed for the different BNT162 vaccines. While vaccines based on the BNT162a and BNT162b platforms have the highest antigen expression shortly after immunization, a second immunization may be necessary to induce a higher antibody generation (see the upper graph). For vaccines based on the BNT162c platform, due to the self-amplification properties of the saRNA, the antigen expression peaks later and is more prolonged, therefore potentially enabling one immunization to induce a strong antibody response (see the lower graph). Green line = BNT162a (uRNA); gray line = BNT162b (modRNA); yellow line = BNT162c; blue line = antibody in serum (saRNA).

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 spike glycoprotein (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 4 and Figure 5). 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. SARS-CoV and SARS-CoV-2 have similar structural properties and bind to the same host cell receptor, the human angiotensin converting enzyme 2 (hACE-2) (Zhou et al. 2020). The S protein is not only pivotal for host cell recognition and entry, but also for the induction of virus neutralizing antibodies by the host immune system (Zakhartchouk et al. 2007; Yong et al. 2019).

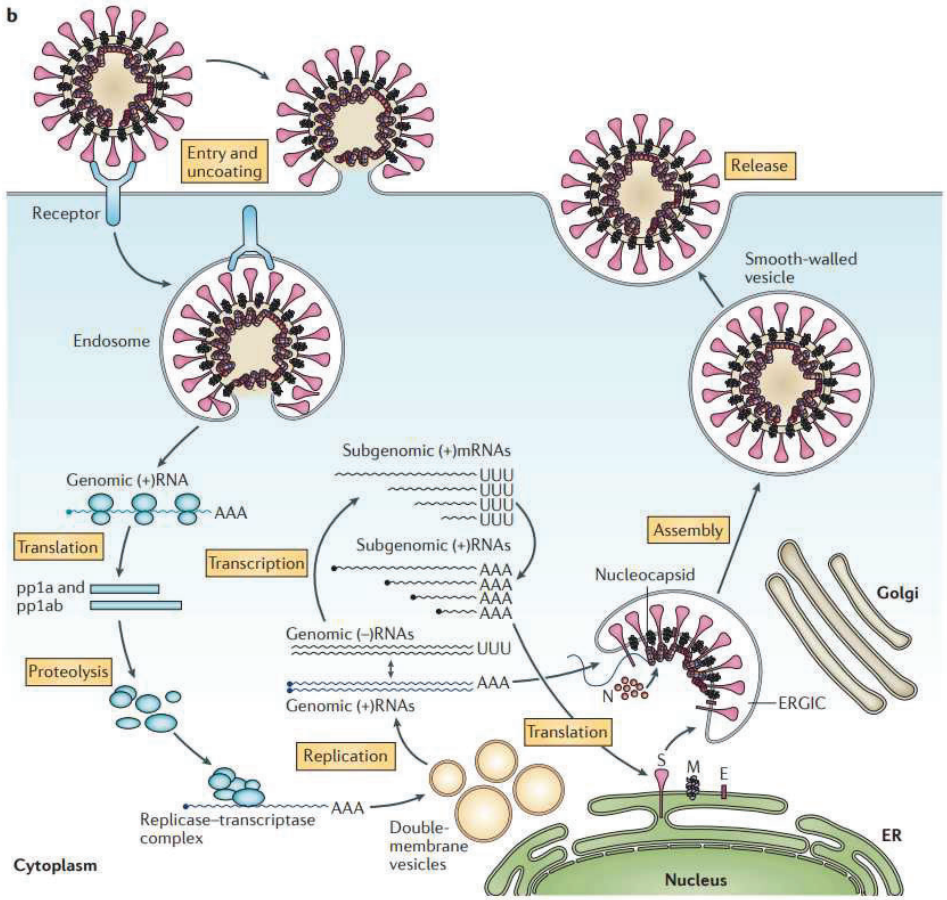


Figure 4: Schematic lifecycle of a coronavirus

(Source: de Wit et al. 2016)

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).

Targeting the S protein, as well as its S1 cleavage fragment or the RBD alone, with vaccines is sufficient to induce neutralizing immune responses (Al-Amri et al. 2017). The RBD forms membrane distal "heads" on the S protein that are connected to the 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).

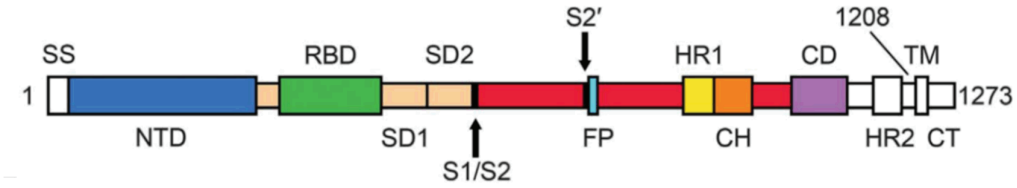


Figure 5: Schematic overview of the organization of the SARS-CoV-2 S glycoprotein

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); source: modified from Wrapp et al. 2020. NTD = N-terminal domain.

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 (Figure 6).

The LNPs are composed of four different lipids in a defined ratio. During mixing of the RNA and the dissolved lipids, the lipids form the nanoparticles encapsulating the RNA. After injection, the LNPs are taken up by the cells, and the RNA is released into the cytosol. In the cytosol, the RNA is translated to the encoded viral antigen.

The antigen may be incorporated into the cellular membrane or secreted into the extracellular environment and induce an adaptive immune response. In addition, as S protein is the antigen that recognizes and drives infection of the host cells, it is a key target of virus neutralizing antibodies. Furthermore, as RNA-expressed S protein is fragmented intracellularly, the resulting peptides can be presented at the cell surface, triggering a specific T-cell-mediated immune response with activity against the virus.

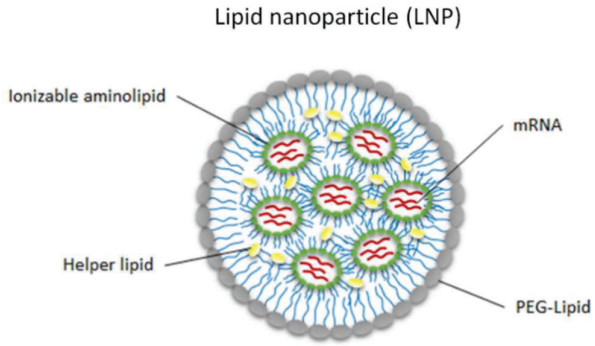


Figure 6: Schematic overview of a LNP encapsulating RNA

3.4 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 1.

BNT162b2 was selected for further development and has been authorized for emergency use or been given conditional marketing authorization in numerous countries worldwide. Since then, BNT162b2 has been administered to millions of individuals worldwide. Further clinical investigation of BNT162b2 is ongoing to expand the studied populations.

For BNT162a1, BNT162b1, BNT162b3, and aBNT162c2, all planned vaccine administration to trial participants has been completed and the dosed participants are now in follow-up.

Table 1: Characteristics of the different BNT162 vaccine candidates in clinical investigation

RNA platform	BNT162 vaccine candidate (Product code)	Encoded antigen	Sequence variant*
uRNA	BNT162a1	SARS-CoV-2 RBD, a secreted variant	V5
modRNA	BNT162b1	SARS-CoV-2 RBD, a secreted variant	V5
	BNT162b2	Full length SARS-CoV-2 spike protein bearing mutations preserving neutralization-sensitive sites	V8 and V9[#]
	BNT162b3	SARS-CoV-2 RBD, a membrane-bound variant	V5TM
saRNA	BNT162c2	Full length SARS-CoV-2 S protein bearing mutations preserving neutralization-sensitive sites	V9

* Sequence variant refers to the nucleotide sequence of the RNA component encoding the antigen.

[#] 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.

modRNA = nucleoside-modified RNA; RBD = receptor binding domain; saRNA = self-amplifying RNA; uRNA = uridine-containing RNA.

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 encoding viral antigens that are translated by the vaccinated organism to protein to induce a protective immune response. 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 1.

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 viral S protein of SARS-CoV-2.

Non-modified uridine 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).

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.

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 (VEE) virus RNA-dependent RNA polymerase replicase and a subgenomic promoter plus conserved sequence elements supporting replication and translation, but no other VEE virus coding sequences.

The physicochemical properties of the RNA drug substances are listed in Table 2.

Table 2: General properties of uRNA, modRNA and saRNA drug substances

Parameter	Value/Description	
	uRNA/modRNA	saRNA
Appearance	Clear, colorless liquid	
Theoretical length	~1,200 to 4,500 nucleotides *	~10,000 to 13,000 nucleotides *
Concentration	1.70 ± 0.17 mg/mL; 2.25 ± 0.25 mg/mL **	
Extinction coefficient at 260 nm	25 L/g × cm	
pH	7.0 ± 1.0	

* Depending on the finally selected antigen.
** Depending on batch size.

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 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 composition of RNA drug products for use in the planned clinical studies and the function of the respective components are given in Table 3. The LNP composition is the same for all five BNT162 vaccine candidates.

Table 3: Composition of drug products

Component	Quality standard	Function
Drug substance	In-house	Active
ALC-0315 [1]	In-house	Functional lipid
ALC-0159 [2]	In-house	Functional lipid
DSPC [3]	In-house	Structural lipid
Cholesterol	Ph. Eur.	Structural lipid
Sucrose	NF/Ph. Eur.	Cryoprotectant
NaCl	USP/Ph. Eur.	Buffer
KCl	USP/Ph. Eur.	Buffer
Na_2HPO_4	USP/Ph. Eur.	Buffer
KH_2PO_4	NF/Ph. Eur.	Buffer
Water for injection	Ph. Eur.	Solvent/Vehicle

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

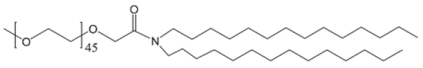
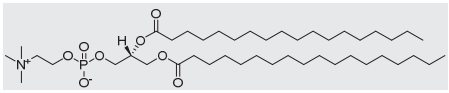
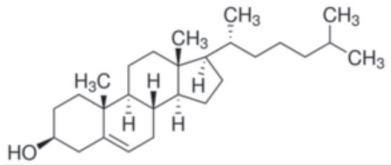
4.2.1 Description of the excipients

All excipients used in the formulation of the drug product are listed in Table 3.

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 4.

Table 4: 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 (not applicable)	766	$C_{48}H_{95}NO_5$	Liquid (oil) -20°C	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
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., uRNA (product code: BNT162a1), modRNA (product codes: BNT162b1, BNT162b2, BNT162b3), saRNA (product code: BNT162c2).

IMP administration route:	IM injection.
Dosage frequency:	Depending on the vaccine, using either single dose or two-dose regimens.

4.5 Storage and handling of the IMP

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

Administration has to be performed within 6 h at ambient temperatures (2 to 25°C) after the dilution is prepared due to the risk of microbial contamination and considering the multiple-dose approach of the preparation process.

Detailed instructions for storage and handling are given in the respective study-specific Pharmacy Manual.

5 NON-CLINICAL STUDIES

RNA vaccines have shown great potential in generating immune responses in animal models and confer protection against various viruses such as Zika virus, HIV, and influenza virus (Vogel et al. 2018; Moyo et al. 2018; Pardi et al. 2017). Unpublished immunogenicity data from RNA-based vaccines against other viruses such as the Ebola, Marburg, and Lassa viruses indicate that the range of applications for anti-viral RNA vaccines is broad (data on file).

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. For this purpose, BALB/c mice were immunized once with the vaccine candidate and different immunological read-outs were performed. In serology analysis, antigen binding immunoglobulin G (IgG) responses were detected by an enzyme-linked immunosorbent assay (ELISA) as well as functional antibody responses to the vaccine candidates using a pseudovirus-based neutralization assay (pVNT). Cellular analysis included the T-cell specific response against the antigen.

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 developmental and reproductive toxicity (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 1 summarizes the nomenclature used for the BNT162 vaccine candidates to facilitate the review of the provided non-clinical information.

5.1 Non-clinical pharmacology

5.1.1 Primary pharmacodynamics

Table 24 summarizes the primary pharmacodynamics studies.

5.1.1.1 *In vitro* expression of BNT162 RNA encoded antigens

To analyze whether the two SARS-CoV-2 derived vaccine antigens V5 (a secreted variant of SARS-CoV-2 RBD) and V9 (the full length SARS-CoV-2 spike protein bearing mutations preserving neutralization-sensitive sites) are robustly translated from the respective RNA drug substances, *in vitro* assays were performed and antigen expression was assessed using western blots, or immunofluorescence analysis. All RNAs expressed the desired antigens.

In vitro expression and co-localization of the antigens with an endoplasmic reticulum marker was shown using immunofluorescence in HEK293T cells expressing BNT162b1 (modRNA encoding V5) RNA or BNT162b2 (modRNA encoding V9) RNA, respectively (Figure 7).

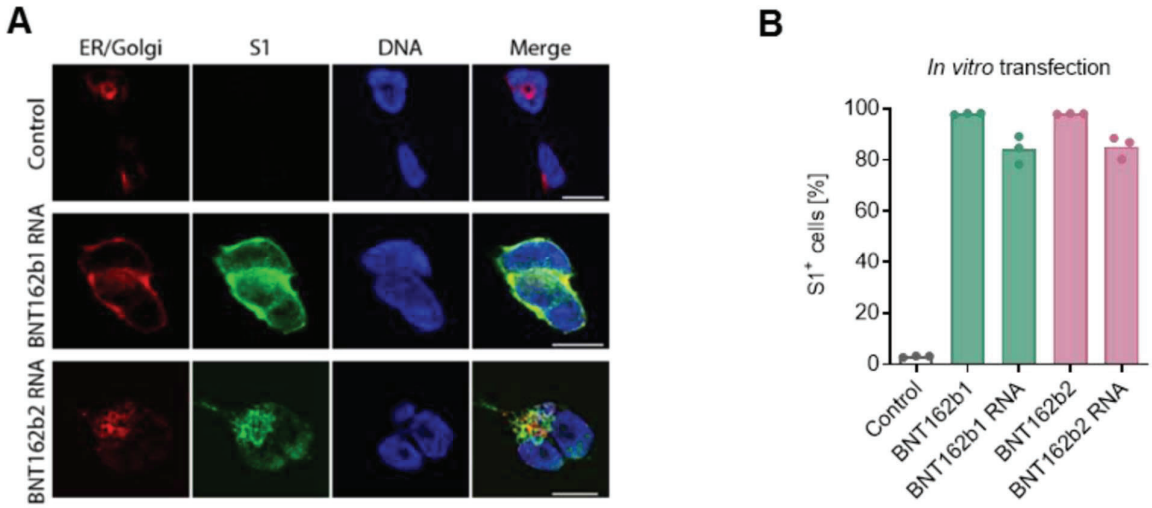


Figure 7: Immunofluorescence staining of cells transfected with BNT162b1 or BNT162b2 and flow cytometry analysis of cells transfected with BNT162b1 or BNT162b2

(A) HEK293T cells were transfected with 2.5 µg of BNT162b1 RNA (V5) or BNT162b2 RNA (V9). After 18 h, cells were fixed and stained for the endoplasmic reticulum (ER, red), the S1 protein subdomain (RBD, green) and for deoxyr bonucleic acid (DNA; blue). The merged colored picture shows that both BNT162b1 and BNT162b2 co-localize with the ER marker localization (scale: 10 µm bar). A control using non-transfected cells is shown for comparison. (B) Detection of BNT162b1-encoded secreted, trimerized RBD (V5) and BNT162b2-encoded membrane anchored, mutated full length S protein (V9) in fixed and permeabilized HEK293T cells by S1-specific antibody staining and flow cytometry. HEK293T cells were transfected with 1 µg R boJuice transfection reagent-mixed BNT162b1 RNA or BNT162b2 RNA or with the vaccine candidates BNT162b1 (LNP-formulated BNT162b1 RNA) or BNT162b2 (LNP-formulated BNT162b2 RNA) by incubation for 18 h.

These results show that both antigens are processed within the endoplasmic reticulum for secretion and/or surface expression, which is a prerequisite for increased bioavailability and improved induction of an immune response. Robust expression of the trimerized RBD

or P2 S was detectable by flow cytometry after transfection of HEK293T cells with BNT162b1 RNA or BNT162b2 RNA, respectively, formulated as the drug product or mixed with a transfection reagent (Figure 7B).

As membrane-bound antigens are particularly potent in activating B cells (Batista and Harwood 2009; Bergtold et al. 2005), an additional vaccine candidate was designed and included in the development pipeline. The vaccine candidate, BNT162b3, uses a modRNA encoding a membrane anchored, trimerized variant of the RBD of the SARS-CoV-2 S protein (V5TM).

To analyze whether the V5TM antigen is expressed by the respective RNA and transported to the cell surface, *in vitro* assays were performed and antigen expression was assessed by flow cytometry or immunofluorescence analysis. BNT162b3 was detected on the cell surface while BNT162b1 was only detected intracellularly, demonstrating a functional design of the constructs (Figure 8).

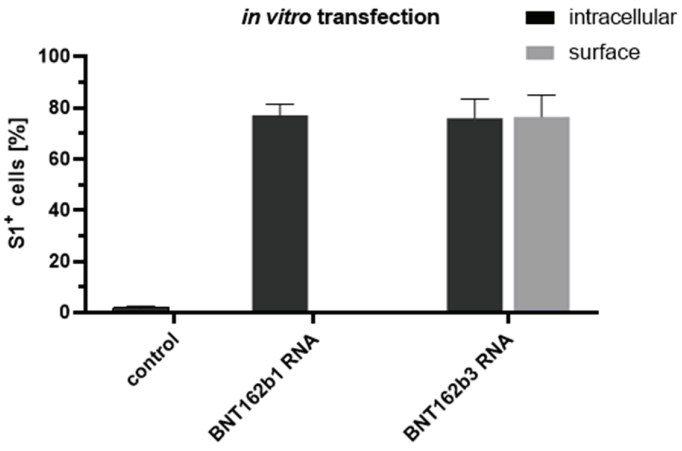


Figure 8: Intracellular and surface expression flow cytometry analysis of cells transfected with BNT162b1 or BNT162b3

Detection of BNT162b1-encoded secreted, trimerized RBD (V5) and BNT162b3-encoded membrane anchored RBD (V5TM) in HEK293T cells by S1-specific antibody staining and flow cytometry. HEK293T cells were transfected with 1 µg R boJuice transfection reagent-mixed BNT162b1 RNA or BNT162b3 RNA by incubation for 18 h. For the cell surface staining, cells were fixed; for the intracellular staining, cells were fixed and permeabilized prior to the antibody staining.

5.1.1.2 *In vivo* immunogenicity studies in mice

Non-clinical immunogenicity studies were performed for the BNT162 vaccine candidates BNT162a1, BNT162b1 (V5), BNT162b2 (V9), BNT162b3, and BNT162c2.

To benchmark the different vaccine candidates, mice were immunized once and different immunological read-outs were performed similar to the study designs reported in the supportive study section and outlined in Table 5.

Table 5: Study design

Group number	No of animals	Vaccine dose	Immunization day	Dose volume (µL) / route	Blood collection day	End of in-life phase
1	8	Buffer	0	20 / IM	7, 14, 21	28
2	8	Low	0	20 / IM	7, 14, 21	28
3	8	Medium	0	20 / IM	7, 14, 21	28
4	8	High	0	20 / IM	7, 14, 21	28

Blood sampling: Blood was collected for analysis using the antibody immune response by ELISA and pseudovirus-based neutralization assay.

5.1.1.2.1 Immunogenicity of BNT162b1 (modRNA encoding V5)

The immunogenicity of BNT162b1 was tested in mice as summarized in Table 5.

As shown in Figure 9, total IgG ELISA showed that the expressed antigen is highly immunogenic and induced a dose-dependent generation of antibodies against the S1 antigen and the RBD early after immunization. In the pVNT analysis, all animals displayed a dose-dependent increase in neutralizing titers (Figure 10).

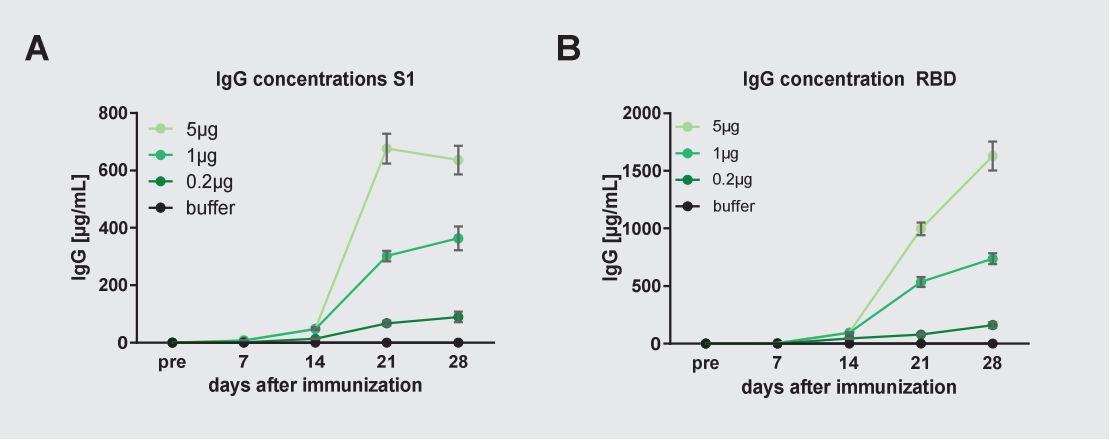


Figure 9: Anti-S and anti-RBD IgG responses at 7, 14, 21, and 28 d after immunization with BNT162b1

BALB/c mice were immunized IM once with 0.2, 1 and 5 µg BNT162b1 or buffer. On 7, 14, 21, and 28 d after immunization, animals were bled and the serum samples were analyzed. For individual ΔOD values, the ant body concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean ant body concentrations are shown (±SEM). Group size n=8.

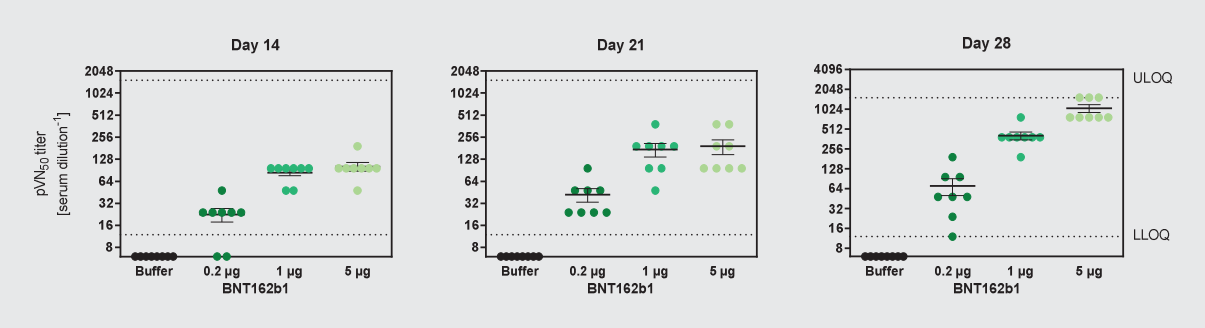


Figure 10: Neutralization of SARS-CoV-2 pseudovirus at 14, 21, and 28 d after immunization with BNT162b1

BALB/c mice were immunized IM once with 0.2, 1 and 5 µg BNT162b1 or buffer. On 14, 21, and 28 d after immunization, animals were bled, and the serum samples were tested for SARS-CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs denotes data for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ = lower limit of quantification; ULOQ = upper limit of quantification.

The summary of antibody titers on Day 28 is as follows:

	BNT162b1 0.2 µg	BNT162b1 1 µg	BNT162b1 5 µg
Anti-S1 protein total IgG [µg/mL]	68.2 ± 11.9	232.7 ± 40.6	392.7 ± 30.2
Anti-RBD protein total IgG [µg/mL]	131.0 ± 23.5	455.4 ± 92.4	990.8 ± 96.7
pVN_{50} titer [reciprocal dilution]	67.5 ± 21.0	480.0 ± 166.3	960.0 ± 177.8

5.1.1.2.2 Immunogenicity of BNT162b2 (modRNA encoding V9)

The immunogenicity of BNT162b2 (V9) was investigated in mice as summarized in Table 5.

The expressed antigen was highly immunogenic; treatment with all tested BNT162b2 doses induced a strong immune response across the observation period of 28 d. Total IgG ELISA showed that the construct induced a strong, dose-dependent generation of antibodies against the S1 antigen and the RBD (Figure 11). In pVNT analysis, all mice developed functional neutralizing antibodies starting at 14 d after immunization and increasing up to the final study (Figure 12).

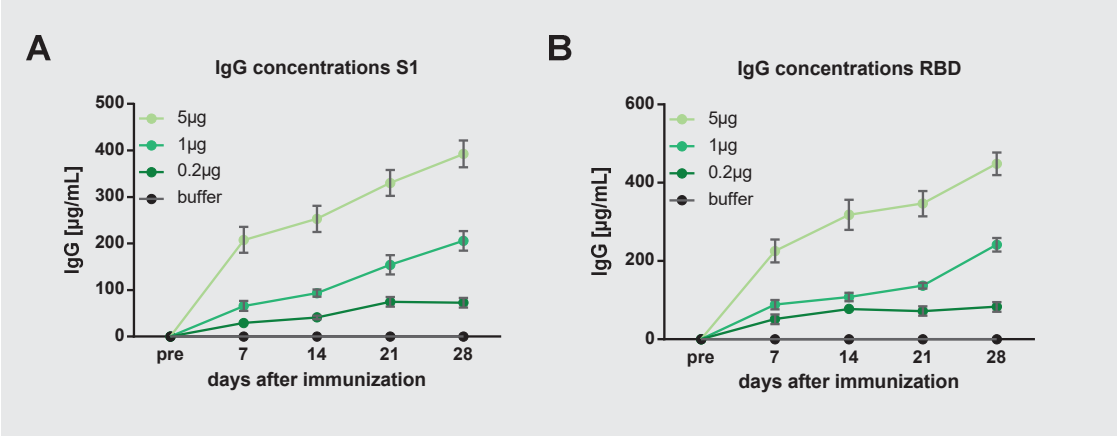


Figure 11: Anti-S and anti-RBD IgG responses at 7, 14, 21, and 28 d after immunization with BNT162b2

BALB/c mice were immunized IM once with 0.2, 1, and 5 µg BNT162b2 or buffer. On 7, 14, 21, and 28 d after immunization, animals were bled and the serum samples were analyzed. For individual ΔOD values, the ant body concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean ant body concentrations are shown (±SEM). Group size n=8.

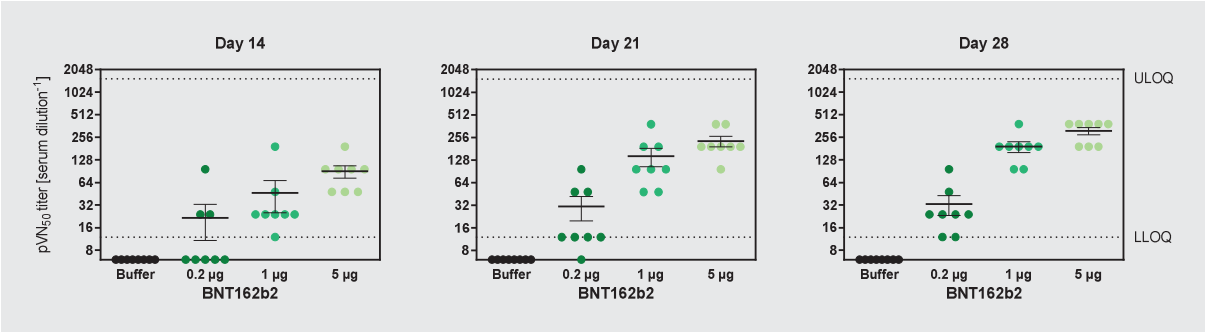


Figure 12: Neutralization of SARS-CoV-2 pseudovirus 14, 21, and 28 d after immunization with BNT162b2

BALB/c mice were immunized IM once with 0.2, 1, and 5 µg BNT162b2 or buffer. On 14, 21, and 28 d after immunization, animals were bled, and the sera were tested for SARS-CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs denotes data for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ = lower limit of quantification; ULOQ = upper limit of quantification.

The summary of antibody titers on Day 28 is as follows:

	BNT162b2 0.2 µg	BNT162b2 1 µg	BNT162b2 5 µg
Anti-S1 protein total IgG [µg/mL]	73.0 ± 10.4	205.9 ± 21.0	392.7 ± 28.9
Anti-RBD protein total IgG [µg/mL]	83.1 ± 12.3	241.7 ± 17.2	448.6 ± 28.6
pVN_{50} titer [reciprocal dilution]	33.0 ± 9.8	192.0 ± 31.4	312.0 ±35.1

5.1.1.2.3 Immunogenicity of BNT162b3 (modRNA encoding V5TM)

The immunogenicity of the BNT162b3 (V5TM) was investigated by immunizing mice with a single immunization using a low and medium dose as described in Table 5.

The antibody immune response was investigated using ELISA and pVNT.

The expressed antigen was highly immunogenic and induced a high titer of antigen-specific IgG already at an early time point after vaccination (see Figure 13). For comparison, 14 d after immunization the 1 µg immunization dose of BNT162b3 induced a mean of 382 µg/mL RBD-specific antibodies while the 1 µg BNT162b1 immunization dose induced a mean of 93 µg/mL (see Section 5.1.1.2.1). Also, in pVNT (see Figure 14), a high titer of neutralizing antibodies was detected early on. For comparison, 14 d after immunization the 1 µg immunization dose of BNT162b3 induced in pVNT a mean titer of 1:186 (reciprocal dilution) while immunization with 1 µg BNT162b1 induced a mean titer of 1:84 (see Section 5.1.1.2.1).

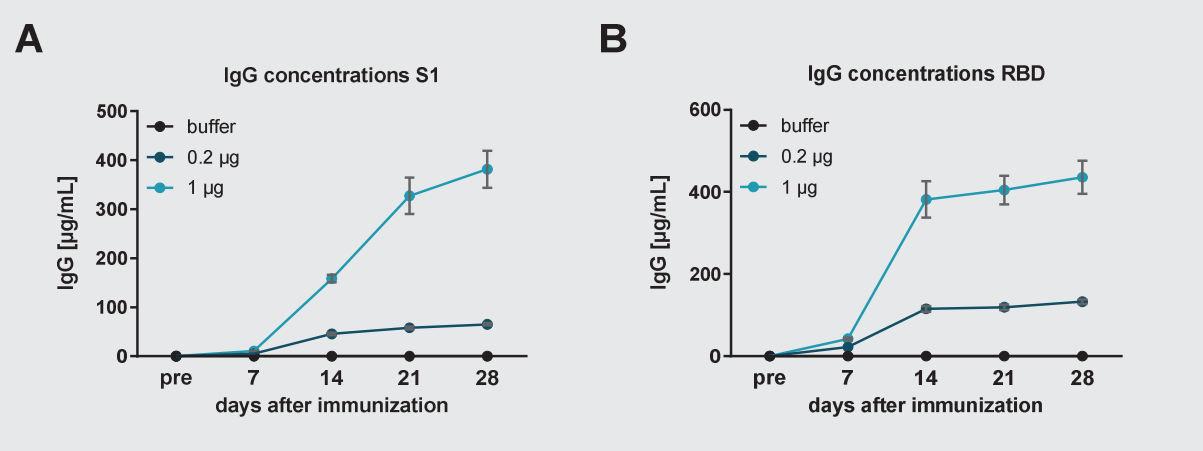


Figure 13: Anti-S and anti-RBD IgG response 7, 14, 21, and 28 d after immunization with BNT162b3

BALB/c mice were immunized IM once with 0.2 and 1 BNT162b3 or buffer. On 7, 14, 21 and 28 d after immunization, animals were bled and the serum samples were analyzed. For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean ant body concentrations are shown (±SEM). Group size n=8.

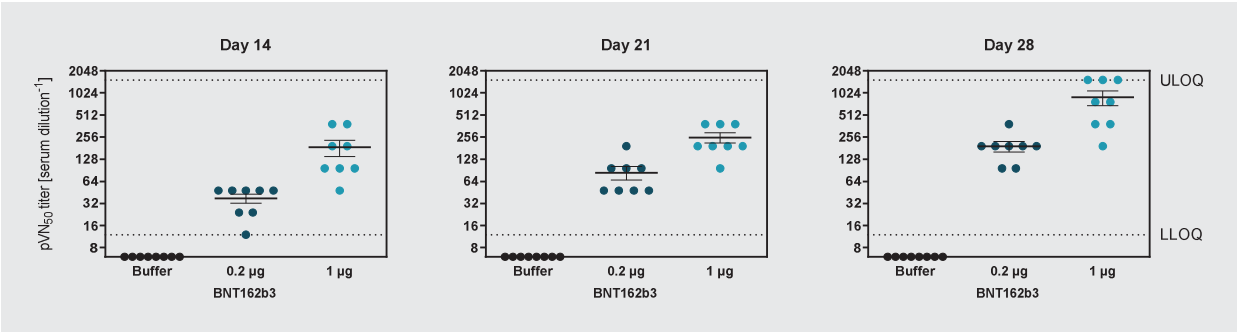


Figure 14: Neutralization of SARS-CoV-2 pseudovirus 14, 21, and 28 d after immunization with BNT162b3

BALB/c mice were immunized IM once with 0.2, and 1 µg BNT162b3 or buffer. On 14, 21, and 28 d after immunization, animals were bled, and the serum samples were tested for SARS-CoV-2 pseudovirus neutralization. Graphs depict pVN_{50} serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point in the graphs denotes data one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is shown by horizontal bars with whiskers for each group. LLOQ = lower limit of quantification; ULOQ = upper limit of quantification.

The summary of antibody titers on Day 28 is as follows:

	BNT162b3 0.2 µg	BNT162b3 1 µg
Anti-S1 protein total IgG [µg/mL]	65.3 ± 2.3	381.3 ± 37.9
Anti-RBD protein total IgG [µg/mL]	132.6 ± 5.3	435.7 ± 40.7
pVN_{50} titer [reciprocal dilution]	192.0 ± 31.4	888.0 ± 201.8

5.1.1.2.4 Immunogenicity of BNT162a and BNT162c candidates

The immunogenicity of BNT162a1 (LNP-formulated uRNA encoding V5), BNT162c1 (LNP-formulated saRNA encoding V5) and BNT162c2 (LNP-formulated saRNA encoding V9) was tested in mice as summarized in Table 5.

The expressed antigen was immunogenic and all tested doses were immunogenic. While BNT162c2 induced a strong neutralization capacity, immune responses to BNT162a1 were weaker.

The summary of antibody titers after immunization with 5 µg of the vaccine candidate on Day 28 is as follows:

	BNT162a1 5 µg	BNT162c1 5 µg	BNT162c2 5 µg
Anti-S1 protein total IgG [µg/mL]	15.6 ± 3.0	217.7 ± 10.8	392.74 ± 28.9
Anti-RBD protein total IgG [µg/mL]	24.2 ± 2.9	531.9 ± 35.1	410.5 ± 66.3
pVN_{50} titer [reciprocal dilution]	7.5 ± 0.9	87.0 ± 8.4	448.58 ± 28.6

5.1.1.3 *In vivo* immunogenicity in rats

5.1.1.3.1 In vivo immunogenicity of BNT162 vaccine candidates after repeated dosing (Study 38166)

In a GLP-compliant repeat-dose toxicity study in rats (Section 5.3.1, Study No. 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 in the serum samples and the IgG concentrations against S1 and RBD proteins are given in Table 6. Antibody concentrations against S1 and RBD increased, for BNT162b1 in a dose-dependent manner, over time in animals.

Table 6: IgG antibody concentration (µg/mL) against the viral antigen in Wistar Han rats

		BNT162a1 30 µg	BNT162a1 10 µg	BNT162b1 100 µg	BNT162b1 30 µg	BNT162b2 100 µg	BNT162c1* 30 µg
17 d after first immunization	**Against S1**	83.0 ± 13.6	149.8 ± 24.6	1844.2 ± 243.4	1502.9 ± 269.9	1755.9 ± 164.1	19.3 ± 3.7
	Against RBD	192.6 ± 35.2	208.3 ± 28.9	2632.6 ± 270.9	2017.0 ± 257.1	2331.4 ± 185.1	56.3 ± 12.0
38 d after first immunization	**Against S1**	47.6 ±5.6	312.0 ±43.0	3432.1 ± 301.3	2137.2 ±392.6	3463.8 ± 522.5	21.5 ± 4.2
	Against RBD	405.7 ±58.9	730 ±135.6	6718.4 ±822.8	4011.9 ±900.0	4898.0 ±873.3	25.2 ±4.9

For individual ΔOD values, the antibody concentrations in the serum samples were calculated. The serum samples were tested against the S1 protein and RBD. * for saRNA encoding V5 group, the analysis days were Days 10 and 31, respectively.

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, see Figure 15).

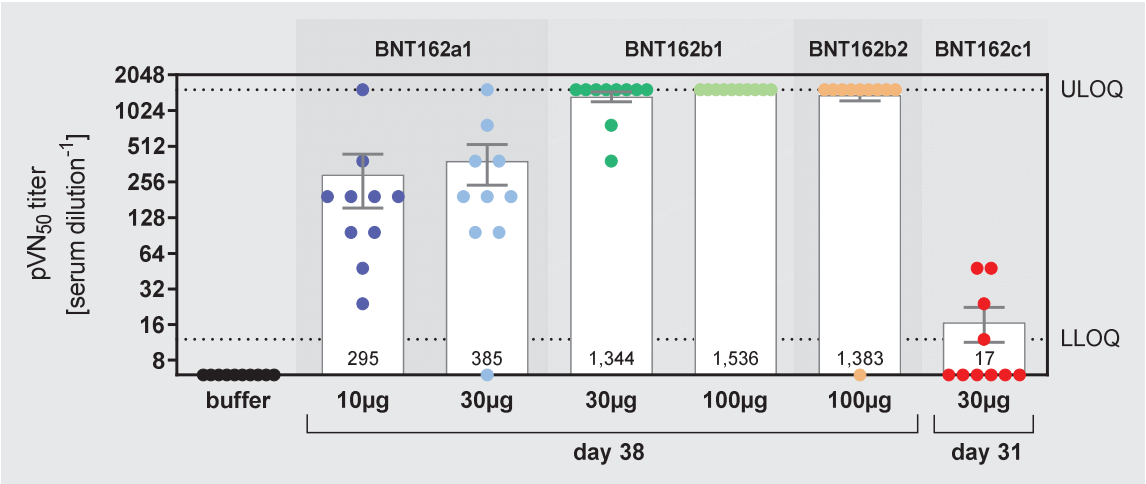


Figure 15: Pseudovirus neutralization activity of recovery cohort sera plotted as pVN_{50} titer

Serum samples were collected on Day 31 (BNT162c1, red dots) or Day 38 (all other cohorts) after first immunization of the recovery cohort rats and titers of virus neutralizing ant bodies were determined by pseudovirus-based neutralization assay (pVNT). Individual pVNT titers resulting in 50% pseudovirus neutralization (pVN_{50}) are shown by dots; group mean values are indicated by horizontal bars and are included at the bottom of bars (±SEM, standard error of the mean).

Neutralizing antibody titers in vaccinated animals increased over time with the recorded neutralizing activity being consistent with the ELISA data shown above. Whereas sera from BNT162c1 treated rats displayed weak neutralizing activity both on Days 10 and 31, 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 (ULOQ) 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 3rd 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 study. SARS-CoV-2 neutralizing antibody responses were not observed in animals prior to vaccine administration or in saline-administered control animals. In a DART study, female rats were administered four total IM doses of BNT162b2 (V9) 21 and 14 d prior to mating and on gestation day (GD) 9 and GD20. Serum samples were collected from females prior to vaccine administration, just prior to mating (M0), at the end of GD21, and at the end of lactation (lactation day 21) and offspring (fetuses on GD21 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 all maternal females as well as in 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.

5.1.1.4 *In vivo* immunogenicity and SARS-CoV-2 challenge in non-human primates

5.1.1.4.1 Immunogenicity of BNT162b1 (modRNA encoding V5) and BNT162b2 (modRNA encoding V9) and BNT162b3 (modRNA encoding V5TM)

In a study with rhesus macaques (i.e., NHP), six animals per group were immunized IM with 30 µg or 100 µg of BNT162b1 (V5) or BNT162b2 (V9), 30 µg 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 (Figure 16).

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 (HCS) 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 (Figure 17). 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.

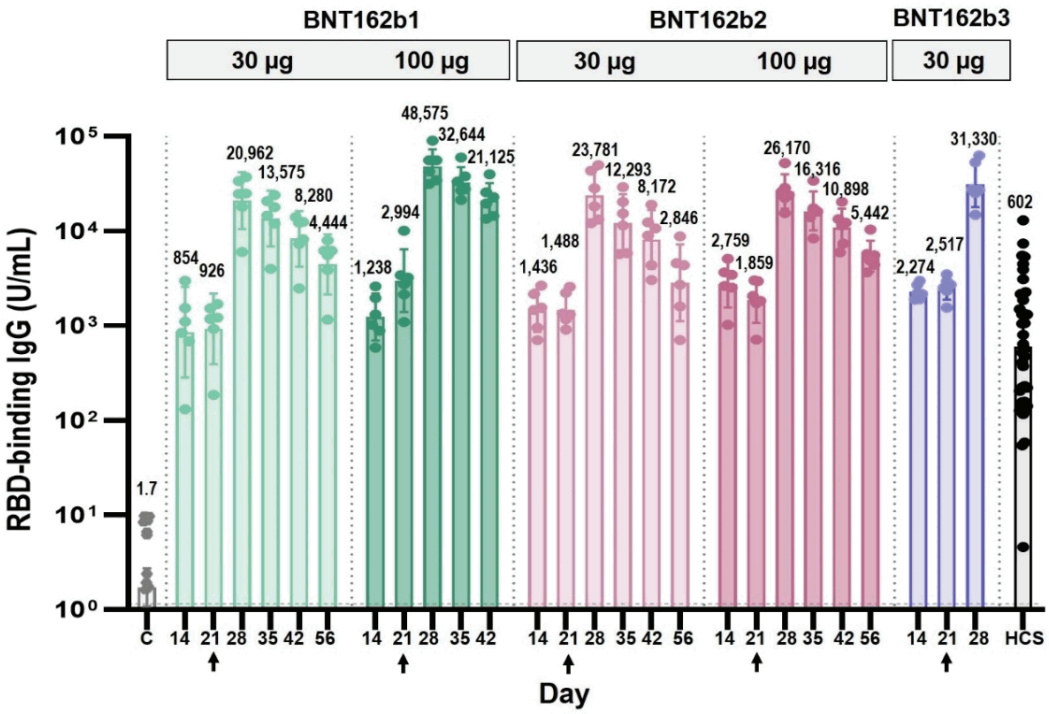


Figure 16: Anti-RBD IgG responses after immunization with the different BNT162b candidates in NHP

Rhesus macaques were immunized IM on Days 0 and 21 as indicated by arrows with buffer, 30, and 100 µg of BNT162b1, BNT162b2 (V9) or BNT162b3. Weekly after immunization, animals were bled and the serum samples were analyzed for IgG binding a recombinant SARS-CoV-2 S1 protein. GMC±CI of RBD-binding IgG are shown. Human COVID-19 convalescent sera (HCS), drawn 20–40 d after the onset of symptoms with confirmed COVID-19 diagnosis with at least 14 d of asymptomatic convalescence, were tested for IgG binding a recombinant SARS-CoV-2 RBD. Values for each animal are included in the graph and the GMC is indicated above each bar. The dotted horizontal line indicates the lower limit of quantification. CI = confidence interval; GMC = geometric mean concentration.

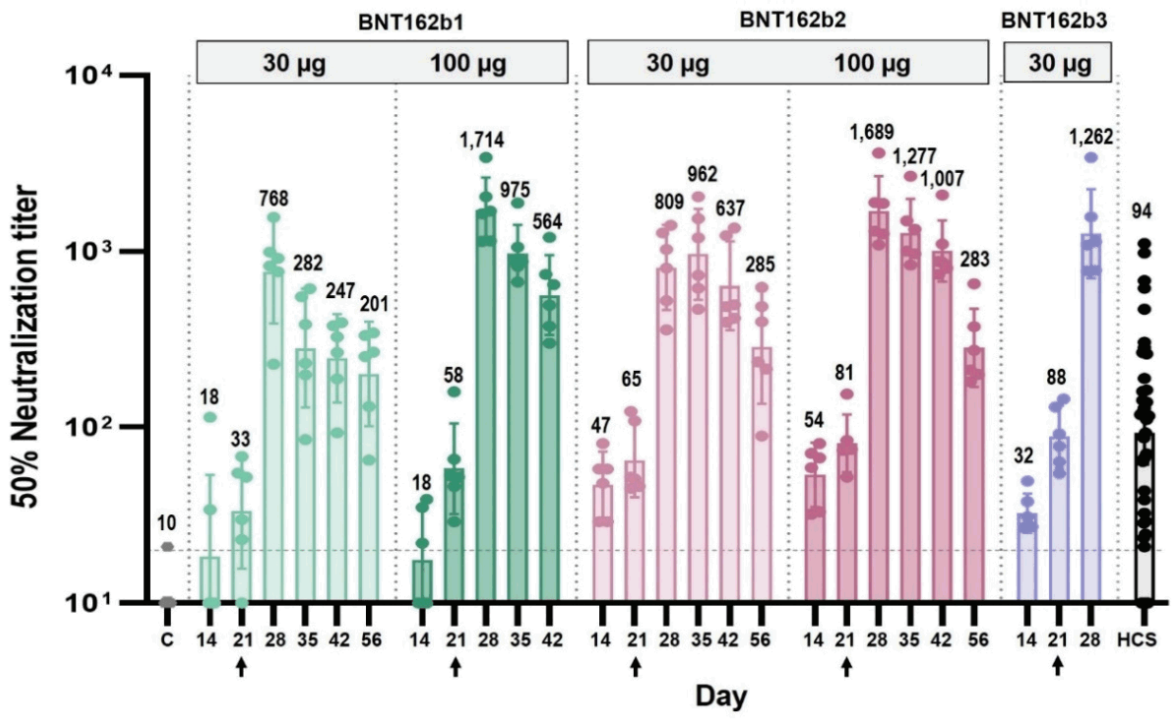


Figure 17: 50% neutralization titers after immunization with different BNT162b candidates in NHP

Rhesus macaques were immunized IM on Days 0 and 21 as indicated by arrows with buffer, 30, and 100 µg of BNT162b1 or BNT162b2 (V9) or 30 µg BNT162b3. Weekly after immunization, animals were bled and the serum samples were analyzed for neutralizing antibodies. Geometric mean titers (GMTs) are shown. Human COVID-19 convalescent sera (HCS), drawn 20 to 40 d after the onset of symptoms with confirmed COVID-19 diagnosis with at least 14 d of asymptomatic convalescence, were tested for neutralizing antibodies (sample size: 32). Values for each animal are included in the graph and the geometric mean 50% neutralizing titer is indicated above each bar. The dotted horizontal line gives the lower detection limit.

For BNT162b2 immunized rhesus macaques, S-specific T-cell responses were analyzed using peripheral blood mononuclear cells (PBMCs) collected 42 d after first immunization. ELISpot demonstrated strong IFNγ but minimal IL-4 responses (Figure 18), 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 1.05×10^6 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 six age-matched macaques (sentinels) were mock-challenged with cell culture medium. Bronchoalveolar lavage (BAL) 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; Figure 19). Viral RNA was detected in BAL fluid from control macaques on Day 3, and to lesser extent in samples from BNT162b1immunized animals. At no time point sampled was viral RNA detected in BAL fluid from the BNT162b2-immunized and SARS-CoV-2 challenged macaques.

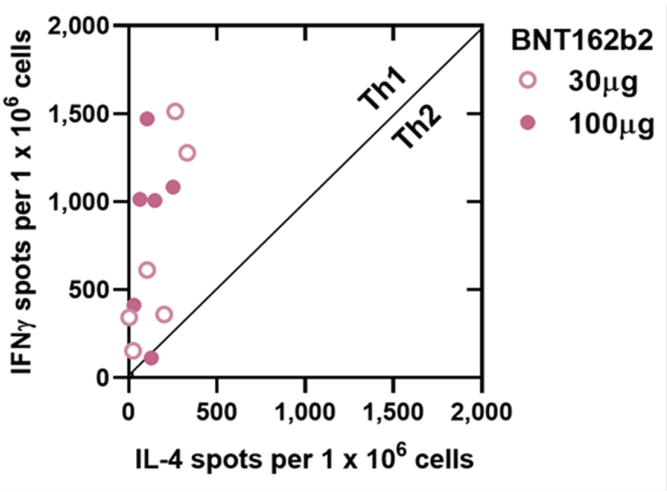


Figure 18: Scatterplot of IL-4 vs. IFNγ ELISpot of rhesus macaque PBMCs after BNT162b2 immunization

Rhesus macaques (n=6 per group) were immunized on Days 0 and 21 with 30 µg or 100 µg BNT162b2. PBMCs for ELISpot were obtained on Day 42 and were stimulated with a full length overlapping S peptide pool.

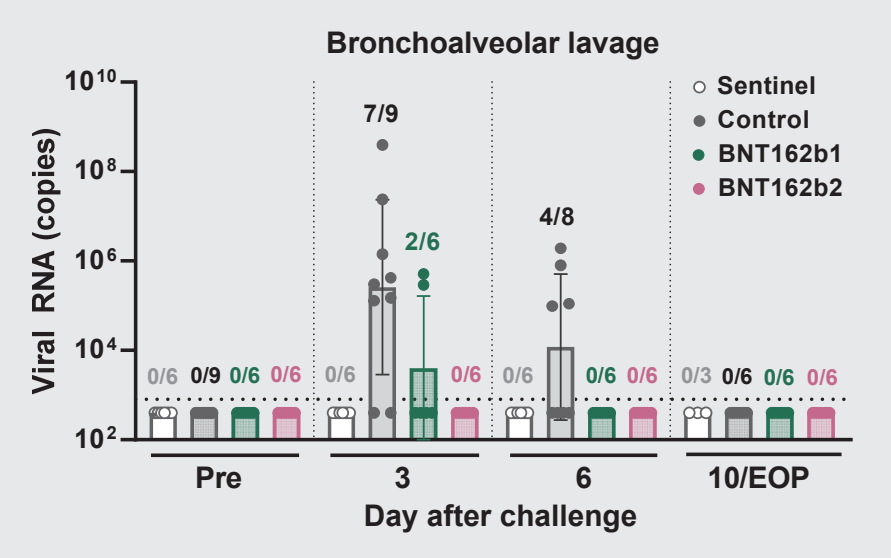


Figure 19: Virological evidence of protection of rhesus macaques from challenge with infectious SARS-CoV-2

Rhesus macaques immunized with 100 µg of BNT162b1 or BNT162b2 (n=6 each) or mock immunized with saline challenge (Control, n=9) were challenged with 1.05×10^6 total plaque forming units (PFU) of SARS-CoV-2. Additional macaques (Sentinel, n=6) were mock-challenged with cell culture medium. Viral RNA in bronchoalveolar lavage (BAL) fluid was measured. Heights of bars indicate geometric mean viral RNA copies; whiskers indicate geometric standard deviations. Each symbol represents one animal. Dotted lines indicate the lower limit of detection (LLOD). Values below the LLOD were set to ½ the LLOD.

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 (Figure 20). 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.

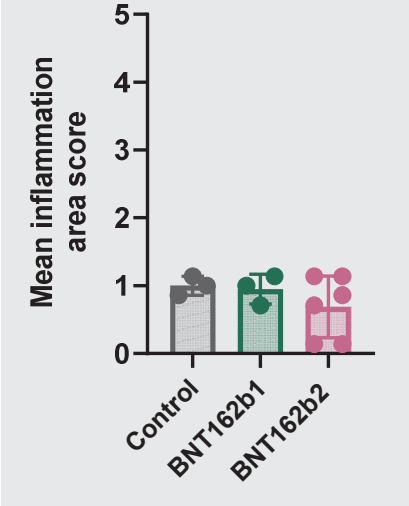


Figure 20: Pulmonary histopathology in rhesus macaques after immunization with BNT162b1 or BNT162b2 and challenge with infectious SARS-CoV-2

Rhesus macaques were immunized with BNT162b1, BNT162b2, or saline (control) and challenged with SARS-CoV-2. Two blinded veterinary pathologists performed microscopic evaluation of formalin fixed, hematoxylin and eosin stained lung tissue sections from each of seven lobes from each macaque that had been necropsied on Days 7 or 8. Inflammation scores were assigned by consensus between the pathologists on a scale of 1 to 5 based on the area of involvement. Each dot represents an individual animal and is the mean inflammation area score from the seven lung lobes.

5.1.2 Secondary pharmacodynamics

No secondary pharmacodynamics studies were conducted for the BNT162 vaccine candidates.

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, "Annex 1: WHO guidelines on non-clinical evaluation of vaccines", 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 BNT162b2 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 21.

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	$t_{½}$ (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	1030	1020	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.

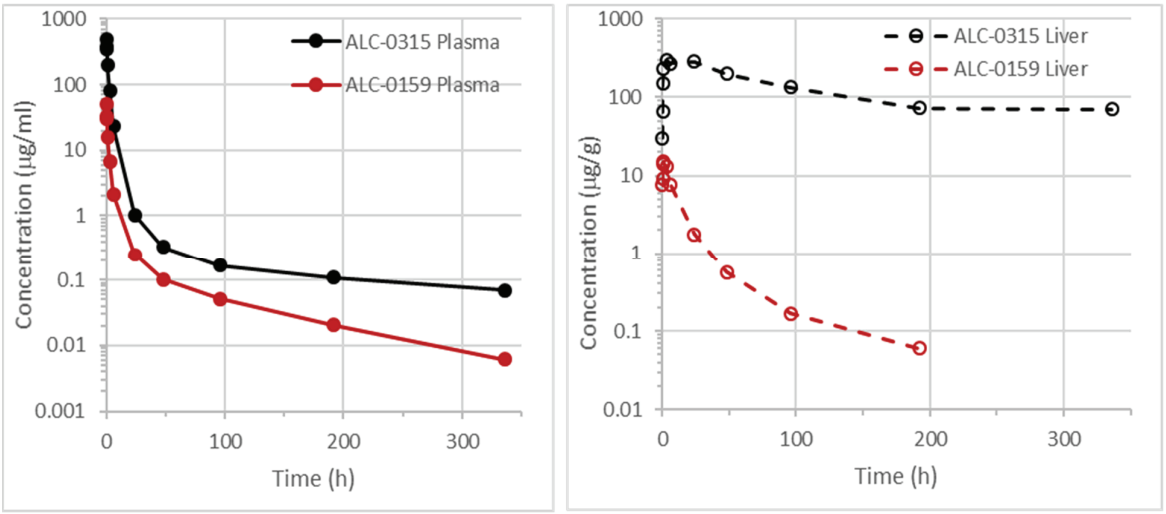


Figure 21: Plasma and liver concentrations of ALC-0315 and ALC-0159 in Wistar Han rats after IV administration of 1 mg/kg LNPs containing RNA encoding the luciferase surrogate marker

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 the RNA-LNP formulation comparable to BNT162 vaccine candidates was assessed in mice using luciferase as a surrogate marker in place of the antigens encoded in the BNT162b vaccines (Study R-20-0072). Luciferase expression can be detected after injection of luciferin by measuring the luminescence *in vivo*.

Using modRNA as representative for all three RNA platforms, injection of RNA led to a high and long expression of luciferase *in vivo* in mice (Figure 22). 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.

It is anticipated that the biodistribution of the antigen encoded by the RNA components of the BNT162 vaccine candidates will be dependent on the LNP distribution. Therefore, the modRNA results obtained are considered to be representative for all three BNT162 RNA platforms.

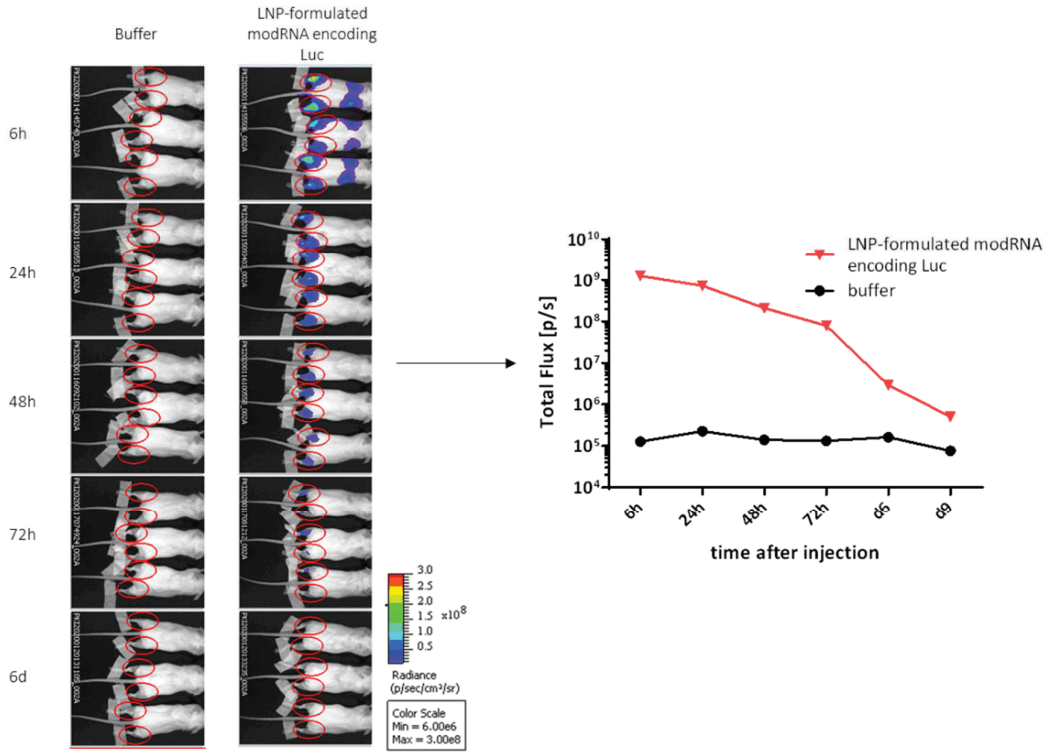


Figure 22: Bioluminescence imaging measurement of the luciferase expression after injection of the LNP-formulated modRNA encoding luciferase

BALB/c mice were injected IM with 1 µg of LNP-formulated modRNA encoding luciferase in each hind leg. At time points after injection, the luciferase expression *in vivo* was measured by luciferin application. After 9 d, luciferase expression dropped to background levels.

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 at 50 µg RNA/animal (Study 185350). The greatest mean concentration of LNP was found remaining in the injection site at each time point in both sexes. Outside the injection site, low levels of radioactivity were detected in most tissues, with the greatest levels in plasma observed 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. Total recovery (% of injected dose) of LNP, for combined male and female animals, outside of the injection site was greatest in the liver (up to 18%) and was much less in the spleen (≤ 1.0%), adrenal glands (≤ 0.11%) and ovaries (≤ 0.095%). The mean concentrations and tissue distribution pattern 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 (aminolipid) 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 23 and Figure 24).

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 23). No excretion studies have been conducted with BNT162b2 for the reasons described above.

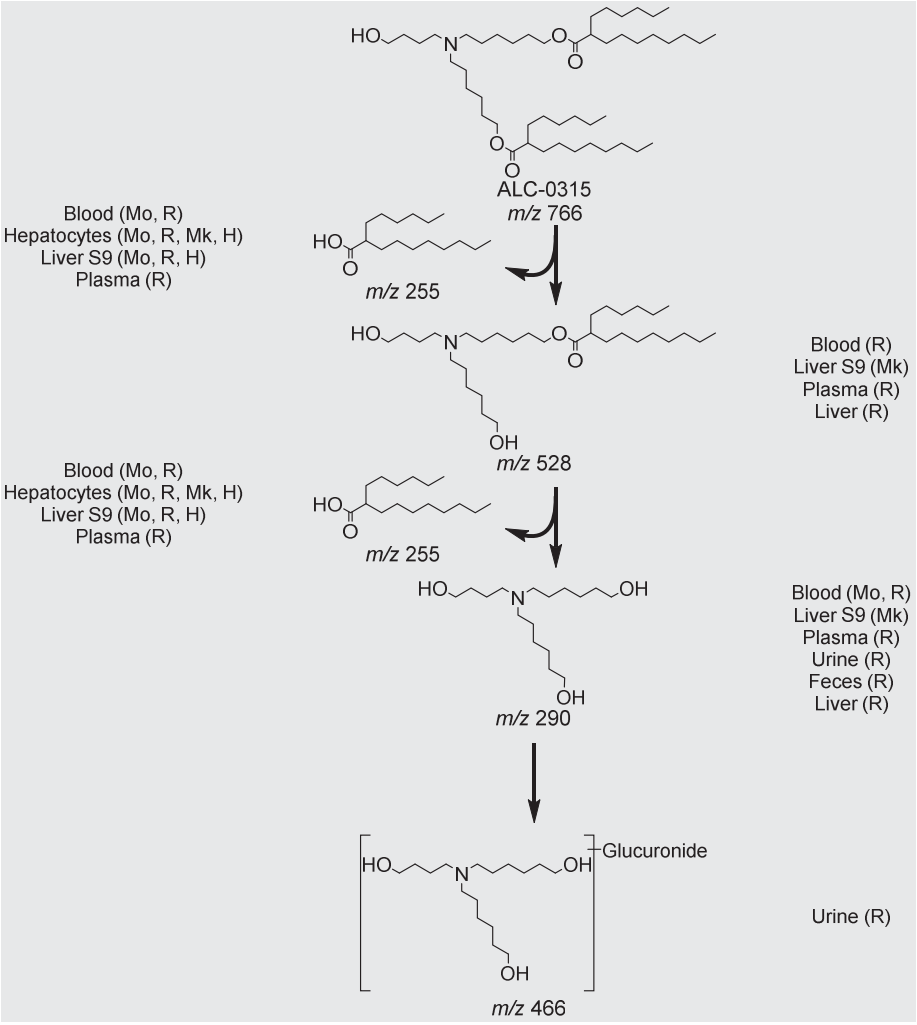


Figure 23: Proposed biotransformation pathway of ALC-0315 in various species

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

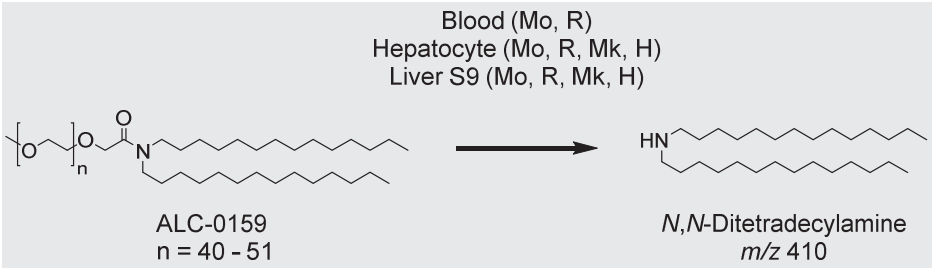


Figure 24: Proposed biotransformation pathway of ALC-0159 in various species

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, a non-exchangeable, non-metabolizable lipid marker. The greatest 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 includes 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 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 (RDW), 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 to support the clinical evaluation 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 nucleoside-modified RNA 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 3 administrations 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 macroscopic changes at the injection sites, spleen, and the draining lymph nodes, increased hematopoiesis in the bone marrow and spleen, periportal hepatocyte vacuolation and clinical pathology changes consistent with an immune response. 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, 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 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 30 µg 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 macroscopic changes at the injection sites, spleen, and the draining lymph nodes, increased hematopoiesis in the bone marrow and spleen, liver vacuolation and clinical pathology changes consistent with an immune response. 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 (maximum increase post each dose) compared with control animals was noted on Day 1 (up to 0.54°C), Day 8 (up to 0.98°C), and Day 15 (up to 1.03°C) post-dose.

BNT162b2 (V9)-related injection site edema and erythema were noted 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, "Annex 1: WHO guidelines on non-clinical evaluation of vaccines", 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 (ICH S1A Guideline: "Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals", 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 (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/oedema formation and induration/hardening following palpation.

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

No dedicated immunotoxicity study was conducted, however immunotoxicity was assessed in the GLP-compliant repeated dose toxicity studies in rats (Section 5.3.1).

No vaccine-related systemic intolerance or mortality was observed. Some changes were observed in the absolute and differential blood count (Sections 5.3.1 and 5.3.2). Body weight was decreased 24 h after the administrations in all treatment groups compared to pre-dose, but the relative body weight gain between the administrations was comparable to the control group.

Vaccine-administered animals generally had higher body temperatures compared with buffer 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. The temperature increase was fully reversible within 48 to 72 h post-dose.

All cytokines assessed in Study 38166 (Section 5.3.1.1) were similarly elevated in control and vaccinated animals.

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).

6 EFFECTS IN HUMANS

The RSI for the BNT162 candidate vaccines is provided in Section 7.8.2.

6.1 Ongoing and planned clinical studies

For the status of the ongoing clinical studies, see Table 8. For an overview of the planned clinical studies, see Table 25. For a summary of the number of participants dosed at least once with each BNT162 candidate in the ongoing clinical studies, see Table 9.

Table 8: Status of the ongoing clinical studies (as of 20 JAN 2021)

Study number / Study status	Design	Number of subjects given active BNT162 vaccine Dose 1 / Dose 2 (by subject age)
BNT162-01 (NCT 04380701) Germany This study is conducted and sponsored by BioNTech. For BNT162a1, BNT162b1, and aBNT162c2, all planned vaccine administration to trial participants has been completed and the dosed participants are now in follow-up. For BNT162b2, three expansion cohorts (Cohorts 11 to 13) are ongoing. Cohort 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. Cohort 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. Cohort 13 is investigating safety and long term immune responses in immunocompromised adults after two 30 µg BNT162b2 doses given ~21 d apart.	Phase 1/2, 2-part, dose escalation study. Part A is open label and non-randomized. Part B was cancelled. (All subjects receive active vaccine)	<u>BNT162a1 P/B (age 18 to 55 yrs):</u> 0.1 µg 12 Dose 1 / 12 Dose 2 0.3 µg 12 Dose 1 / 12 Dose 2 3 µg 6 Dose 1 / 0 Dose 2 (Further dosing with BNT162a1 has been deferred) <u>BNT162b1 P/B (age 18 to 55 yrs):</u> 1 µg 12 Dose 1 / 12 Dose 2 3 µg 12 Dose 1 / 12 Dose 2 10 µg 12 Dose 1 / 11 Dose 2 20 µg 12 Dose 1 / 11 Dose 2 30 µg 12 Dose 1 / 12 Dose 2 50 µg 12 Dose 1 / 11 Dose 2 60 µg 12 Dose 1 / Not administered <u>BNT162b1 P/B (age 56 to 85 yrs):</u> 10 µg 12 Dose 1 / 12 Dose 2 20 µg 12 Dose 1 / 11 Dose 2 30 µg 12 Dose 1 / 12 <u>BNT162b2 P/B (age 18 to 55 yrs):</u> 1 µg 12 Dose 1 / 11 Dose 2 3 µg 12 Dose 1 / 12 Dose 2 10 µg 12 Dose 1 / 11 Dose 2 20 µg 12 Dose 1 / 12 Dose 2 30 µg 12 Dose 1 / 12 Dose 2 <u>BNT162b2 P/B (age 56 to 85 yrs):</u> 10 µg 12 Dose 1 / 12 Dose 2 20 µg 12 Dose 1 / 12 Dose 2 30 µg 12 Dose 1 / 12 Dose 2 <u>BNT162b2 P/B (age 18 to 85 yrs):</u> Cohort 11: 3 µg/30 µg 30 Dose 1 / 30 Dose 2 Cohort 12: 30 µg 57 Dose 1 / 42 Dose 2 Cohort 13: 30 µg 3 Dose 1 / 2 Dose 2

Study number / Study status	Design	Number of subjects given active BNT162 vaccine Dose 1 / Dose 2 (by subject age)
		BNT162c2 SD (age 18 to 55 yrs): 0.1 µg 12 (single dose) 0.3 µg 12 (single dose) 0.6 µg 12 (single dose) 1 µg 12 (single dose) BNT162c2 P/B (age 18 to 55 yrs): 0.1 µg 12 Dose 1 / 12 Dose 2 0.3 µg 12 Dose 1 / 12 Dose 2 1 µg 12 Dose 1 / 12 Dose 2 3 µg 12 Dose 1 / 11 Dose 2
BNT162-02 / C4591001 (NCT 04368728) US, Argentina, Brazil, Turkey, Germany, South Africa This study is conducted by Pfizer and sponsored by BioNTech. For Phase 1, all planned vaccine administration to trial participants has been completed and the dosed participants are now in follow-up. For Phase 2/3 enrollment is complete	Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study. (Phase 1: Subjects are randomized: 4 active vaccine to 1 placebo) (Phase 2/3: Subjects are randomized: 1 active vaccine to 1 placebo)	**Phase 1** BNT162b1 P/B (age 18 to 55 yrs): 10 µg 12 Dose 1 / 12 Dose 2 20 µg 12 Dose 1 / 12 Dose 2 30 µg 12 Dose 1 / 12 Dose 2 100 µg 12 Dose 1 / Not administered BNT162b1 P/B (age 65 to 85 yrs): 10 µg 12 Dose 1 / 12 Dose 2 20 µg 12 Dose 1 / 12 Dose 2 30 µg 12 Dose 1 / 12 Dose 2 BNT162b2 P/B (age 18 to 55 yrs): 10 µg 12 Dose 1 / 12 Dose 2 20 µg 12 Dose 1 / 12 Dose 2 30 µg 12 Dose 1 / 12 Dose 2 BNT162b2 P/B (age 65 to 85 yrs): 10 µg 12 Dose 1 / 12 Dose 2 20 µg 12 Dose 1 / 12 Dose 2 30 µg 12 Dose 1 / 12 Dose 2 **Phase 2/3 30 µg BNT162b2 P/B** Age 18 to 85 yrs: 23,221 Dose 1 / 22,365 Dose 2 * Age 12 to 15 yrs: 1,121 at least Dose 1 * Age 16 to 17 yrs: 377 at least Dose 1 * * Based on 1:1 randomization BNT162b2:placebo

Study number / Study status	Design	Number of subjects given active BNT162 vaccine Dose 1 / Dose 2 (by subject age)
BNT162-03 (NCT 04523571) China This study is conducted by Shanghai Fosun Pharmaceutical Development, Inc. and sponsored by BioNTech. All planned vaccine administration to trial participants has been completed and the dosed participants are now in follow-up.	Phase 1, randomized, placebo-controlled, observer-blind study. (Subjects are randomized to active vaccine or placebo)	<u>BNT162b1 P/B (age 18 to 55 yrs):</u> 10 µg 24 Dose 1 / 24 Dose 2 30 µg 24 Dose 1 / 24 Dose 2 <u>BNT162b1 P/B (age 65 to 85 yrs):</u> 10 µg 24 Dose 1 / 23 Dose 2 30 µg 24 Dose 1 / 23 Dose 2
BNT162-04 (NCT 04537949) Germany This study is conducted and sponsored by BioNTech. Except for at the 30 µg dose level, all planned vaccine administration to trial participants has been completed and the dosed participants are now in follow-up.	Phase 1/2, 2-part, dose escalation study. Part A is open label and non-randomized. (All subjects receive active vaccine) Part B will be defined in a protocol amendment.	<u>BNT162b3 P/B (age 18 to 55 yrs):</u> 3 µg 12 Dose 1 / 12 Dose 2 10 µg 12 Dose 1 / 12 Dose 2 20 µg 12 Dose 1 / 12 Dose 2 30 µg 12 Dose 1 / 12 Dose 2 <u>BNT162b3 P/B (age 56 to 85 yrs):</u> 3 µg 12 Dose 1 / 12 Dose 2 10 µg 12 Dose 1 / 12 Dose 2 20 µg 12 Dose 1 / 12 Dose 2 30 µg 6 Dose 1 / 0 Dose 2
BNT162-05 / C4591005 (NCT 04588480) Japan This study is conducted by Pfizer and sponsored by BioNTech. Enrollment is ongoing.	Phase 1/2, placebo-controlled, randomized, observer-blind study. (Subjects are randomized: 3 active vaccine to 1 placebo)	<u>BNT162b2 P/B (age 20 to 64 yrs):</u> 30 µg 97 Dose 1 / 95 Dose 2 <u>BNT162b2 P/B (age 65 to 85 yrs):</u> 30 µg 22 Dose 1 / 22 Dose 2
BNT162-06 (NCT 04649021) China This study is conducted by Shanghai Fosun Pharmaceutical Development, Inc. and sponsored by BioNTech. The treatment phase is ongoing.	Phase 2, randomized, placebo-controlled, observer-blinded study. (Subjects are randomized: 3 active vaccine to 1 placebo)	<u>BNT162b2 P/B (age 18 to 55 yrs):</u> 30 µg 388 Dose 1 / 386 Dose 2 <u>BNT162b2 P/B (age 56 to 85 yrs):</u> 30 µg 330 Dose 1 / 327 Dose 2 * Based on 3:1 randomization BNT162b2:placebo

Note: For the BNT162-02/C4591001 study, the term "stage" was replaced by "phase" by an amendment.
NCT = ClinicalTrials.gov identify identifier; P/B = prime/boost regimen, i.e., two dose-regimen; SD = single dose regimen.

Table 9: Number of participants dosed at least once with a BNT162 candidate in the ongoing clinical studies

BNT162 vaccine candidate *Phase (age group)*	BNT162a1	BNT162b1	BNT162b2	BNT162b3	BNT162c2
Phase 1					
Aged 18 to 55 yrs	30	180	484	48	96
Aged 56 to 85 yrs	0	120	424	36	0
Phase 2 or 3					
Aged 12 to 15 yrs	NA	NA	1,121*	NA	NA
Aged 16 to 17 yrs	NA	NA	377*	NA	NA
Aged 18 yrs or older	NA	NA	23,221*	NA	NA
Total all adults dosed at least once in Phase 1 or 2 or 3	30	300	25,814*	90	96
Sum for all BNT162 vaccines = 26,330*					

* Estimated / includes estimated number based on 1.1 active vaccine:placebo assignment.
NA = not applicable; Years = yrs.

6.1.1 BNT162-01 - Results (status 28 NOV 2020)

This is a multi-site, Phase 1/2, dose escalation study 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.

Two age group of participants were studied in this study, younger adults (18 to 55 yrs of age) and older adults (56 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.

The dose regimens tested per vaccine in this study are summarized in Table 10.

Table 10: Dose regimens tested per vaccine in the BNT162-01 study

BNT162 vaccine candidate / regimen	Participants aged 18 to 55 yrs	Participants aged 56 to 85 yrs
BNT162a1 P/B	0.1 to 3 µg [a]	Not tested
BNT162b1 P/B	1 to 60 µg [b]	10 to 30 µg
BNT162b2 P/B	1 to 30 µg	10 to 30 µg
BNT162c2 P/B	0.1 to 3 µg	Not tested
BNT162c2 single dose	0.1 to 3 µg	Not tested

a) The second planned dose at 3 µg was not given.
b) The second planned dose at 60 µg was not given.
P/B = two doses given ~21 d apart.

This study is ongoing clinically. The treatment phase has been completed for all dose escalation cohorts for all BNT162 vaccine variants in younger adults and in older adults. The participants are now in the follow-up phase. Currently, three expansion cohorts with BNT162b2 administration are ongoing. One cohort 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. The second expansion cohort 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. The third expansion cohort is investigating safety and long term immune responses in immunocompromised adults after two 30 µg BNT162b2 doses given ~21 d apart.

For an overview of the number of adults immunized per dose level and age group, see Table 8.

This section presents data from the clinical study report (CSR) dated 28 NOV 2020 which summarizes data available for BNT162b1 and BNT162b2 collected up until Visit 8 (the first follow-up visit at ~63 d after the second dose) of the BNT162-01 study which included younger adults (aged 18 to 55 yrs) and older adults (aged 56 to 85 yrs).

Due to prioritization of BNT162b1 and BNT162b2 reporting, only preliminary and unaudited reactogenicity and tolerability data are available for the other two IMPs investigated in the study BNT162-01, i.e., BNT162a1 and BNT162c2.

6.1.1.1 Immunogenicity and cell mediated responses in study BNT162-01 (status 28 NOV 2020)

The available immunogenicity and cell mediated responses data from the BNT162-01 study can be summarized as follows:

- Independent of age, participants dosed with BNT162b2 (1 to 30 µg) showed a strong antibody response. Virus neutralizing activity was detected after Dose 1 and showed a substantial booster response by 7 d after Dose 2 (Day 29) for dose level groups ≥ 3 µg. On Day 43, neutralizing GMTs in the younger participant dose groups decreased for the 3, 20, and 30 µg dose levels. Thereafter, GMTs remained stable up to Day 85 (63 d after Dose 2) for younger adult dose groups 10, 20, and 30 µg BNT162b2 and were comparable or even superior to those of a study independent COVID-19 HCS panel.
- After dosing with ≥ 30 µg BNT162b1 and BNT162b2, all participants showed seroconversion by either 7 d or 21 d after the second dose (Day 29 or Day 43). All participants immunized with 30 µg BNT162b2 remained seropositive throughout the follow-up until Day 85.
- The observed kinetics of the BNT162b1 and 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 before stabilization of the immune response.
- Two doses of BNT162b1 and BNT162b2 induced strong SARS-CoV-2 RBD-specific $CD4^+$ and $CD8^+$ T-cell responses in 98% and 77% of dosed participants, respectively. The T-cell responses elicited by BNT162b2 were directed against additional epitopes of the S antigen outside RBD, indicating the induction of multi-epitopic responses by BNT162b2. The magnitude of the T-cell responses did not show clear dose dependency.
- BNT162b1 and BNT162b2 induced poly-functional and pro-inflammatory $CD4^+$/$CD8^+$ T-cell responses in almost all participants. The detection of IFNγ and

IL-2, but no or only minor IL-4 production, indicates a favorable Th1 profile. No notable age-related differences were observed.

6.1.1.1.1 Immunogenicity - functional antibody responses

Data for functional neutralizing antibody titers are available up until Day 43 for BNT162b1-dosed younger participants aged 18 to 55 yrs dosed with 1, 10, 30, 50, and 60 µg on Days 1 (all dose levels) and 22 (all dose levels except 60 µg) (n=12 per group). For BNT162b2-dosed participants, functional neutralizing antibody titers are available for younger participants aged 18 to 55 yrs dosed with 1, 3, 10, 20, and 30 µg, and older participants aged 56 to 85 yrs dosed with 20 µg on Days 1 and 22 (n=12 per group).

For BNT162b2-dosed participants, functional antibody data for younger participants is available up until Day 50 for dose groups 1 µg and 3 µg, and up until Day 85 for dose groups 10, 20, and 30 µg. For the older participants, data is available up until Day 29.

For virus neutralizing antibody GMTs (neutralizing GMTs) and 95% confidence intervals for participants aged 18 to 55 yrs after dosing with BNT162b1, see Figure 25 (50% neutralizing titer).

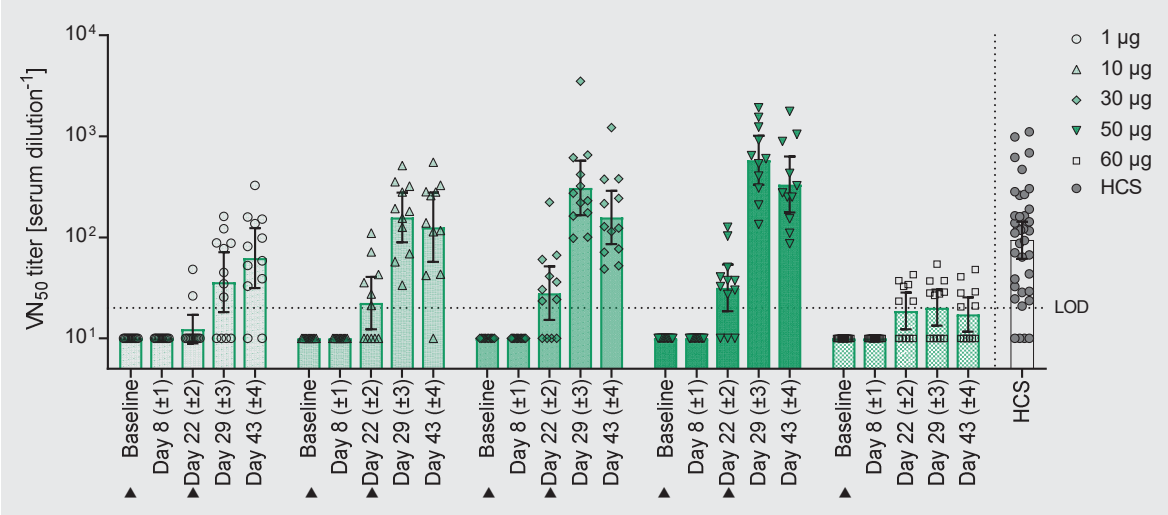


Figure 25: BNT162b1 – Functional 50% SARS-CoV-2 neutralizing antibody titers (VN_{50}) – IMM

VN_{50} titers with 95% confidence intervals are shown for younger participants (aged 18 to 55 yrs) immunized with 1, 10, 30, 50, or 60 µg BNT162b1. Values smaller than the limit of detection (LOD) are plotted as 0.5*LOD. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). Dose 2 was not performed in the 60 µg dose group. The dotted horizontal line represents the LOD. IMM = Immunogenicity set; VN_{50} = 50% SARS-CoV-2 neutralizing ant body titers; HCS = human COVID-19 convalescent serum.
Source: Report R-20-0253.

For neutralizing GMTs and 95% confidence intervals for younger participants aged 18 to 55 yrs and older participants aged 56 to 85 yrs after dosing with BNT162b2, see Figure 26 (50% neutralizing titer).

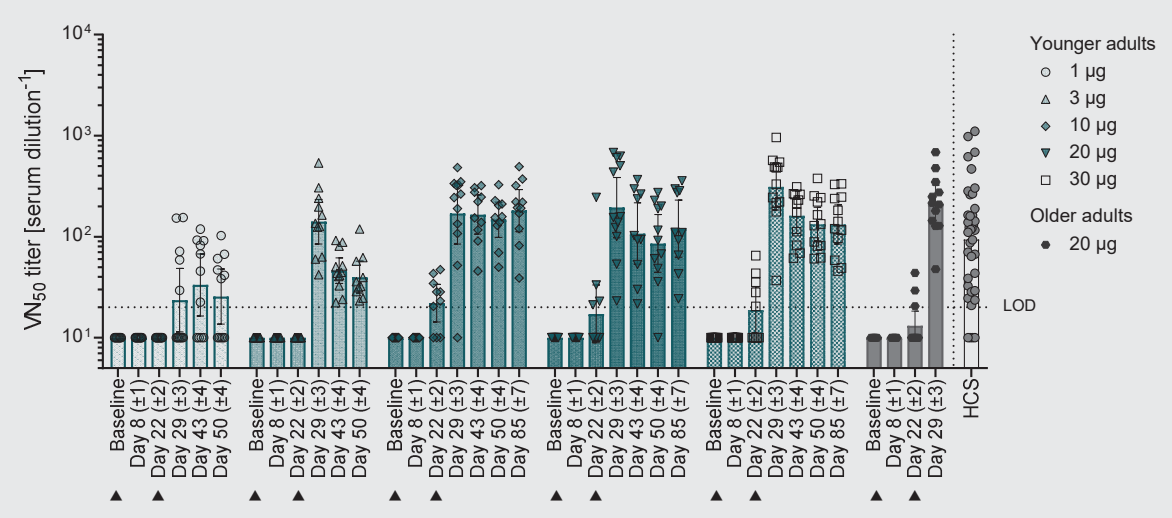


Figure 26: BNT162b2 – Functional 50% SARS-CoV-2 neutralizing antibody titers (VN_{50}) – IMM

VN_{50} titers with 95% confidence intervals are shown for younger adults (aged 18 to 55 yrs) immunized with 1, 3, 10, 20, or 30 µg BNT162b2, and older adults (aged 56 to 85 yrs) immunized with 20 µg BNT162b2. Values smaller than the limit of detection (LOD) are plotted as 0.5*LOD. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). The dotted horizontal line represents the LOD. IMM = Immunogenicity set; VN_{50} = 50% SARS-CoV-2 neutralizing ant body titers; HCS = human COVID-19 convalescent serum.
Source: Report R-20-0253.

Fold increase from baseline in functional antibody titer data is displayed in Figure 27 (BNT162b1) and Figure 28 (BNT162b2).

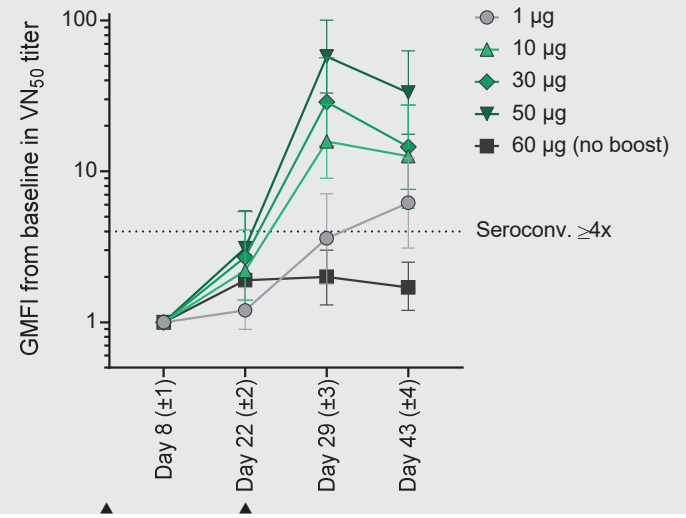


Figure 27: BNT162b1 – Fold increase from baseline in functional 50% SARS-CoV-2 neutralizing antibody titers (VN_{50}) – IMM

Geometric means fold increase (GMFI) from baseline in VN_{50} titer with 95% confidence intervals are shown for younger participants (aged 18 to 55 yrs) immunized with 1, 10, 30, 50, or 60 µg BNT162b1. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). Dose 2 was not performed in the 60 µg dose group. The dotted horizontal line represents the threshold for seroconversion (fold increase ≥ 4). IMM = Immunogenicity set; VN_{50} = 50% SARS-CoV-2 neutralizing antibody titers.
Source: Report R-20-0253.

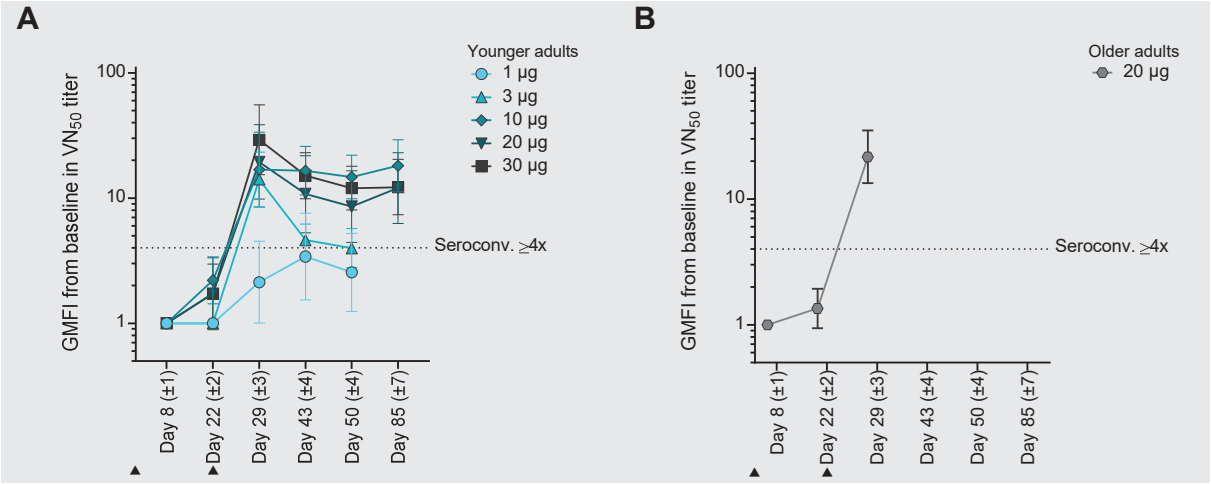


Figure 28: BNT162b2 – Fold increase from baseline in functional 50% SARS-CoV-2 neutralizing antibody titers (VN_{50}) – IMM

Geometric means fold increase (GMFI) from baseline in VN_{50} titer with 95% confidence intervals are shown for (**A**) younger participants (aged 18 to 55 yrs) immunized with 1, 3, 10, 20, or 30 µg BNT162b2, and (**B**) older participants (aged 56 to 85 yrs) immunized with 20 µg BNT162b2. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). The dotted horizontal line represents the threshold for seroconversion (fold increase ≥ 4). IMM = Immunogenicity set; VN_{50} = 50% SARS-CoV-2 neutralizing antibody titers.
Source: Report R-20-0253.

Participants dosed with BNT162b1 showed a strong dose-dependent antibody response. On Day 22, at 21 d after Dose 1, virus neutralizing antibody GMTs (neutralizing GMTs) had increased in a dose-dependent manner for the 1, 10, 30, and 50 µg dose groups. At 7 d after Dose 2 (Day 29), neutralizing GMTs showed a strong, dose level dependent booster response. In the 60 µg dose group, which was only dosed once, neutralizing GMTs remained at a lower level, indicating that a booster dose is necessary to increase functional antibody titers.

On Day 43 (21 d after the Dose 2 of BNT162b1), neutralizing GMTs decreased (with exception of the 1 µg dose level). Day 43 virus neutralizing GMTs were 0.7-fold (1 µg) to 3.6-fold (50 µg) those of a COVID-19 HCS panel.

The COVID-19 HCS panel is comprised of 38 human COVID-19 HCS sera drawn from individuals aged 18 to 85 yrs, at least 14 d after confirmed diagnosis, and at a time when the individuals were asymptomatic. The serum donors predominantly had symptomatic infections (35/38), and one had been hospitalized. The sera were obtained from Sanguine Biosciences (Sherman Oaks, CA), the MT Group (Van Nuys, CA), and Pfizer Occupational Health and Wellness (Pearl River, NY).

Participants dosed with BNT162b2 showed a strong IMP-induced antibody response. Virus neutralizing GMTs were detected at 21 d after Dose 1 (Day 22) and had increased substantially in younger adults (aged 18 to 55 yrs) immunized with ≥ 3 µg BNT162b2, and older participants (aged 56 to 85 yrs) immunized with 20 µg BNT162b2 by 7 d after Dose 2 (Day 29). Day 29 virus neutralizing GMTs were comparable between the younger and older adult 20 µg dose level cohorts. The lowest tested dose of 1 µg BNT162b2 elicited only a minimal neutralizing response in participants aged 18 to 55 yrs.

On Day 43 (21 d after Dose 2 of BNT162b2), virus neutralizing GMTs in the younger adult cohorts decreased for the 3, 20, and 30 µg dose levels. Thereafter, neutralizing GMTs in between Days 29 and 43, neutralizing GMTs remained stable up to Day 85 (63 d after Dose 2) for younger adult dose groups 10, 20, and 30 µg and were 1.3-fold to 1.9-fold those of a COVID-19 HCS panel.

Seroconversion is defined as a minimum of a 4-fold increase of antibody GMT as compared to baseline. The frequency of participants with seroconversion is displayed in Figure 29 (BNT162b1) and Figure 30 (BNT162b2).

All participants dosed with Dose 1 at ≥ 30 µg BNT162b1 or BNT162b2 seroconverted either by 7 d or 21 d after Dose 2 (Day 29 or Day 43). All participants dosed with 30 µg BNT162b2 remained seropositive throughout the follow-up until Day 85.

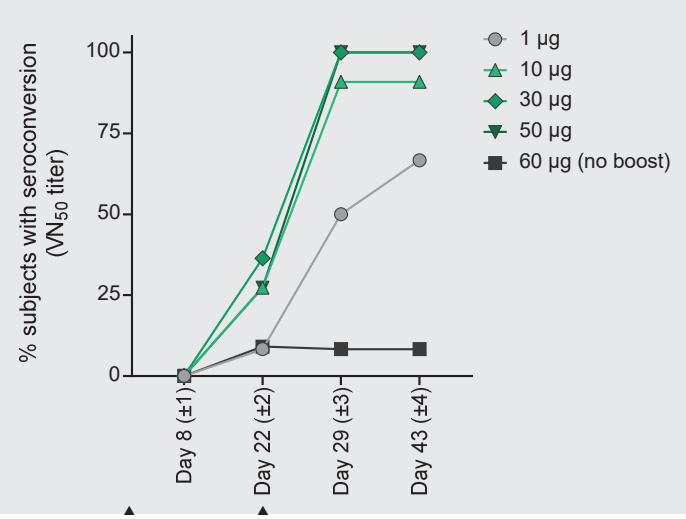


Figure 29: BNT162b1 – Frequency of participants with SARS-CoV-2 neutralizing titer seroconversion – IMM

Seroconversion with regard to 50% SARS-CoV-2 neutralizing ant body titers (VN_{50}) is shown for younger participants (aged 18 to 55 yrs) immunized with 1, 10, 30, 50, or 60 µg BNT162b1. Seroconversion is defined as a minimum of a 4-fold increase of functional ant body response as compared to baseline. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). Dose 2 was not performed in the 60 µg dose group. IMM = Immunogenicity set.

Source: Report R-20-0253.

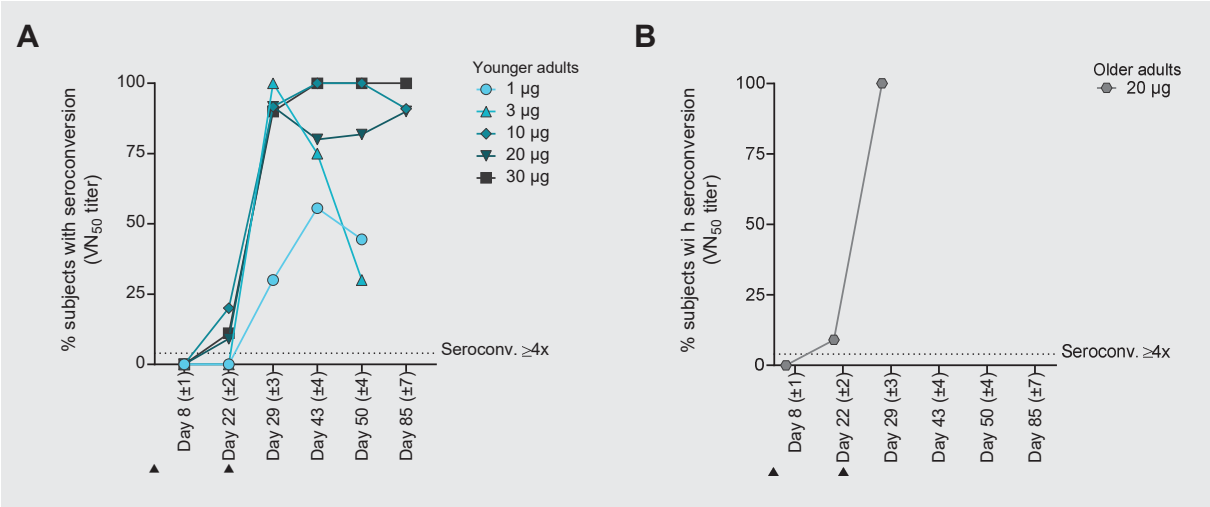


Figure 30: BNT162b2 – Frequency of participants with SARS-CoV-2 neutralizing titer seroconversion – IMM

Seroconversion with regard to 50% SARS-CoV-2 neutralizing antibody titers (VN_{50}) is shown for (**A**) younger participants (aged 18 to 55 yrs) dosed with 1, 3, 10, 20, or 30 µg BNT162b2, and (**B**) older participants (aged 56 to 85 yrs) dosed with 20 µg BNT162b2. Seroconversion is defined as a minimum of 4-fold increase of functional antibody response as compared to baseline. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). IMM = Immunogenicity set.

Source: Report R-20-0253.

6.1.1.1.2 Immunogenicity - binding antibody concentrations

Binding antibody concentration data is available up until Day 43 for BNT162b1-dosed younger participants aged 18 to 55 yrs dosed with 1, 10, 30, 50, or 60 µg on Days 1 (all dose levels) and 22 (all dose levels except 60 µg) (n=12 per group).

For BNT162b2-dosed participants, data is available for younger participants aged 18 to 55 yrs dosed with 1, 3, 10, 20, or 30 µg, and older participants aged 56 to 85 yrs dosed with 20 µg on Days 1 and 22 (n=12 per group). Binding antibody concentration data for younger participant dose groups is available up until Day 50 for dose groups 1 µg and 3 µg, and up until Day 85 for dose groups 10, 20, and 30 µg. For the BNT162b2-dosed older participants, data is available up until Day 29.

The fold increase from baseline in binding antibody concentrations after dosing with BNT162b1 or BNT162b2 is summarized in Figure 31 and Figure 32.

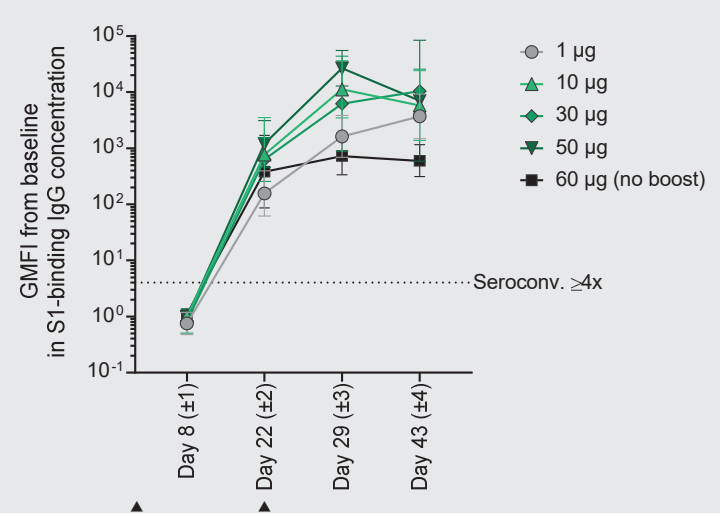


Figure 31: BNT162b1 – Fold increase from baseline in S1-binding antibody concentrations – IMM

Geometric means fold increase (GMFI) from baseline in S1-binding ant body concentrations with 95% confidence intervals are shown for younger participants (aged 18 to 55 yrs) immunized with 1, 10, 30, 50, or 60 µg BNT162b1. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). Dose 2 was not performed in the 60 µg dose group. The dotted horizontal line represents the threshold for seroconversion (fold increase ≥ 4). IMM = Immunogenicity set.

Source: Report R-20-0253.

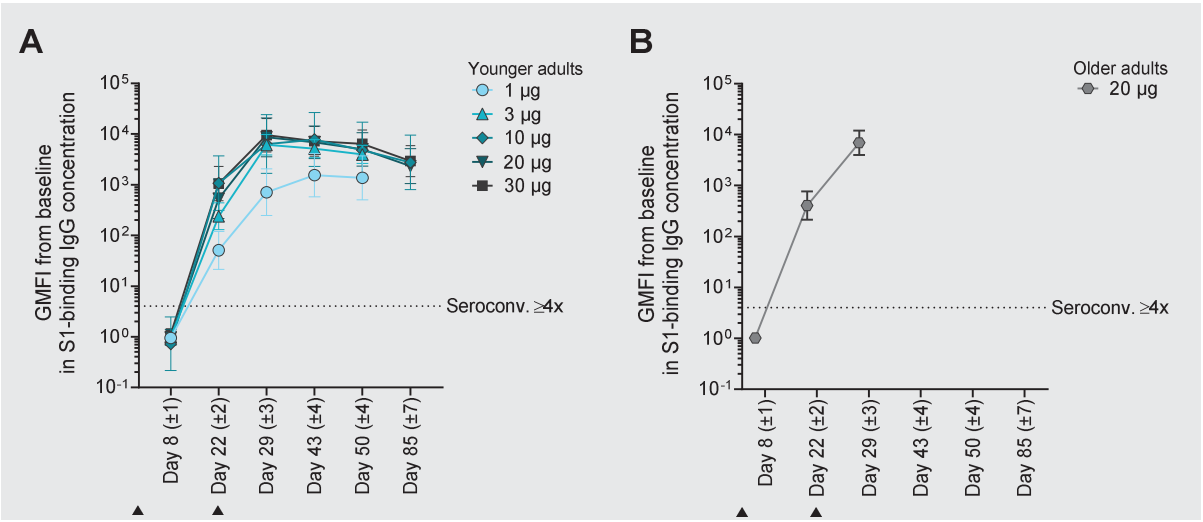


Figure 32: BNT162b2 – Fold increase from baseline in S1-binding antibody concentrations – IMM

Geometric means fold increase (GMFI) from baseline in S1-binding ant body concentrations with 95% confidence intervals are shown for (**A**) younger participants (aged 18 to 55 yrs) immunized with 1, 3, 10, 20, or 30 µg BNT162b2, and (**B**) older participants (aged 56 to 85 yrs) immunized with 20 µg BNT162b2. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). The dotted horizontal line represents the threshold for seroconversion (fold increase ≥ 4). IMM = Immunogenicity set.

Source: Report R-20-0253.

Participants dosed with BNT162b1 showed a strong dose-dependent antibody response against the SARS-CoV-2 spike (S) protein S1 subunit at 21 d after Dose 1 (Day 22). At 7 d after Dose 2 (Day 29), S1-binding immunoglobulin G (IgG) GMCs showed a strong, dose-dependent booster response. In the 60 µg dose group, which was only dosed once, S1-

binding IgG GMCs remained at a lower level, indicating that a booster dose is necessary to increase antibody concentrations.

At 21 d after the Dose 2 of BNT162b1 (Day 43), S1-binding IgG GMCs decreased (with exception of the 1 µg dose group), but were clearly above those of a COVID-19 HCS panel for all doses tested.

BNT162b2 dosed participants showed a strong BNT162b2-induced S1-binding IgG response at 21 d after Dose 1 (Day 22) with evidence of a dose-dependent response only between the 1 µg and 10 µg dose levels. S1-binding IgG GMCs showed a substantial booster response by 7 d after Dose 2 (Day 29). Day 29 S1-binding IgG GMCs were comparable between the younger and older participants at the 20 µg dose level.

Across all dose level cohorts, antibody levels decreased post peak, typically between Day 29 and Day 43, but with S1-binding antibody GMCs remaining well above that observed in a COVID-19 HCS panel at Day 85 (63 d after Dose 2; 10 to 30 µg dose level).

The frequency of participants with seroconversion (defined as at least a 4-fold increase of S1-binding IgG GMC response as compared to baseline) after dosing with BNT162b1 and BNT162b2 is summarized in Figure 33 and Figure 34.

Almost all BNT162b1- and BNT162b2-immunized participants seroconverted with regard to the S1-binding antibody response as early as 21 d after Dose 1 (Day 22). Similar observations were made using only the RBD domain as the target antigen.

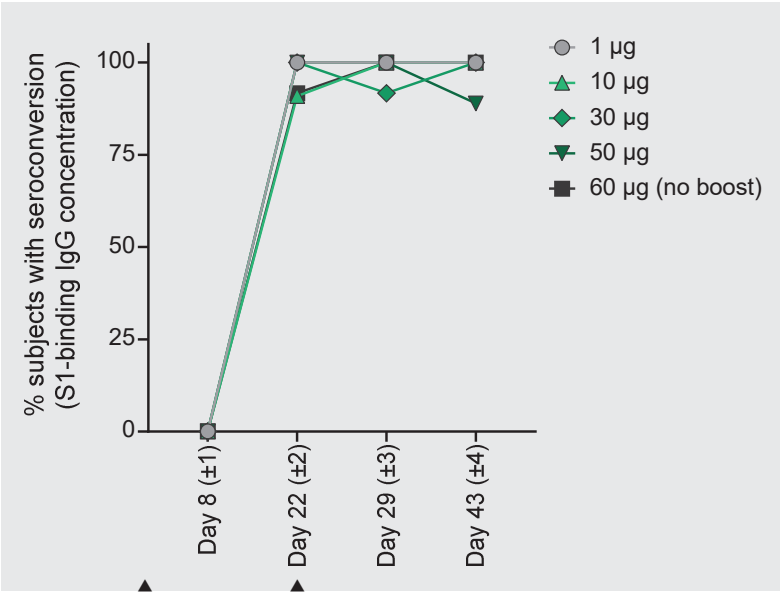


Figure 33: BNT162b1 – Frequency of participants with S1-binding IgG seroconversion – IMM

Seroconversion with regard to S1-binding antibody GMC is shown for younger participants (aged 18 to 55 yrs) immunized with 1, 10, 30, 50, or 60 µg BNT162b1. Seroconversion is defined as at least a 4-fold increase of S1-binding IgG GMC response as compared to baseline. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). Dose 2 was not performed in the 60 µg dose group.
GMC = geometric mean concentration; IMM = Immunogenicity set.
Source: Report R-20-0253.

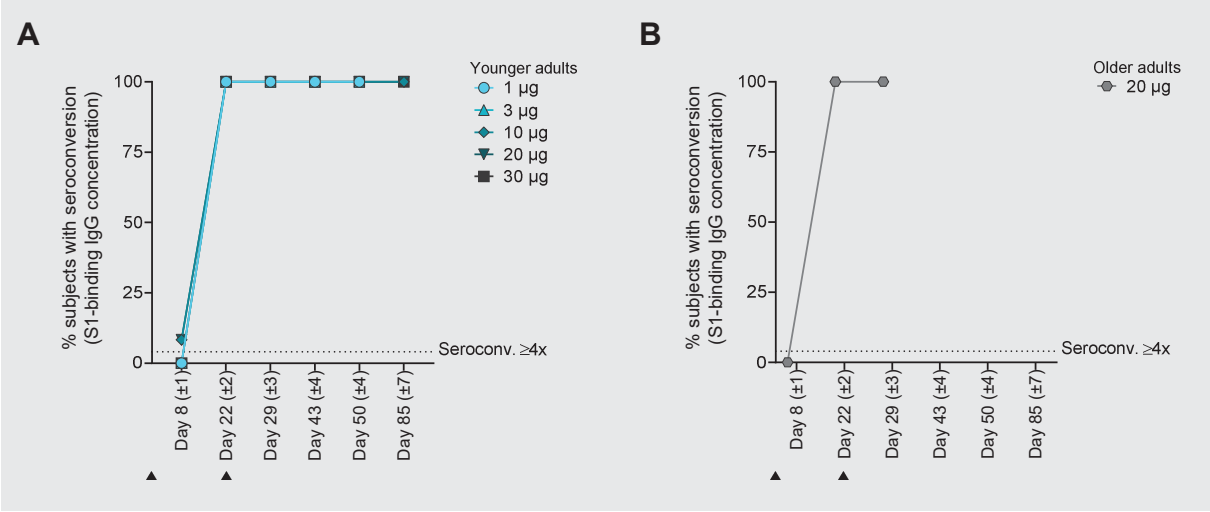


Figure 34: BNT162b2 – Frequency of participants with S1-binding IgG seroconversion – IMM

Seroconversion with regard to S1-binding antibody GMC is shown for (**A**) younger participants (aged 18 to 55 yrs) immunized with 1, 3, 10, 20, or 30 µg BNT162b2, and (**B**) older participants (aged 56 to 85 yrs) dosed with 20 µg BNT162b2. Seroconversion is defined as at least a 4-fold increase of S1-binding IgG GMC response as compared to baseline. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). GMC = geometric mean concentration; IMM = Immunogenicity set.

Source: Report R-20-0253.

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

CD4⁺ and CD8⁺ T-cell response data were available from 97 study participants receiving BNT162b1, 70 younger participants at dose levels of 1, 3, 10, 20, 30, 50, or 60 µg (note: Dose 2 was not given in the 60 µg dose group), and 27 older participants at dose levels of 10, 20, or 30 µg, as well as 76 participants receiving BNT162b2 at dose levels of 1, 3, 10, 20, or 30 µg (47 younger participants), or 10, 20, or 30 µg (29 older participants).

BNT162b1 induced strong RBD-specific CD4⁺ T-cell responses in the majority of participants given both Dose 1 and Dose 2 (86 of 88 [97.7%]), including all older participants (27 of 27 [100%]); CD8⁺ responses were induced in 47 of 61 (77.0%) younger participants and in 21 of 27 (77.7%) of older participants. In contrast, T-cell responses were detected less often and were lower in magnitude in nine younger participants who received only Dose 1 in the 60 µg dose group, indicating the importance of a booster dose.

BNT162b2 induced strong SARS-CoV-2 S protein-specific CD4⁺ T-cell responses in all of the dosed younger or older participants (76 of 76 [100%]); CD8⁺ T-cell responses were induced in 45/47 (95.7%) of younger participants and 24/29 (82.8%) older participants. Despite the slightly lower CD8⁺ immunogenicity rate in older participants, the magnitude of the BNT162b2-induced responses was comparable to those induced in younger participants receiving 30 µg of BNT162b2. These T-cell responses were directed against different parts of the antigen including non-RBD sequences, indicating the induction of multi-epitopic responses by BNT162b2 in both age groups.

For a summary of the frequency and magnitude of BNT162b1-induced CD4⁺ and CD8⁺ T-cell responses, see Figure 35. Dosing twice with BNT162b1 or BNT162b2, led to a substantial increase in incidence and magnitude of T-cell responses in both age groups,

and across all dose levels for BNT162b1. While the magnitude of CD4+ T-cell responses induced by BNT162b2 was also similar across different dose levels, the magnitude of CD8+ T-cell responses was highest at the 30 µg dose level. 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 in the same participants. The same participants also had strong CD8+ T-cell responses that were comparable to memory responses against the above mentioned viral antigens.

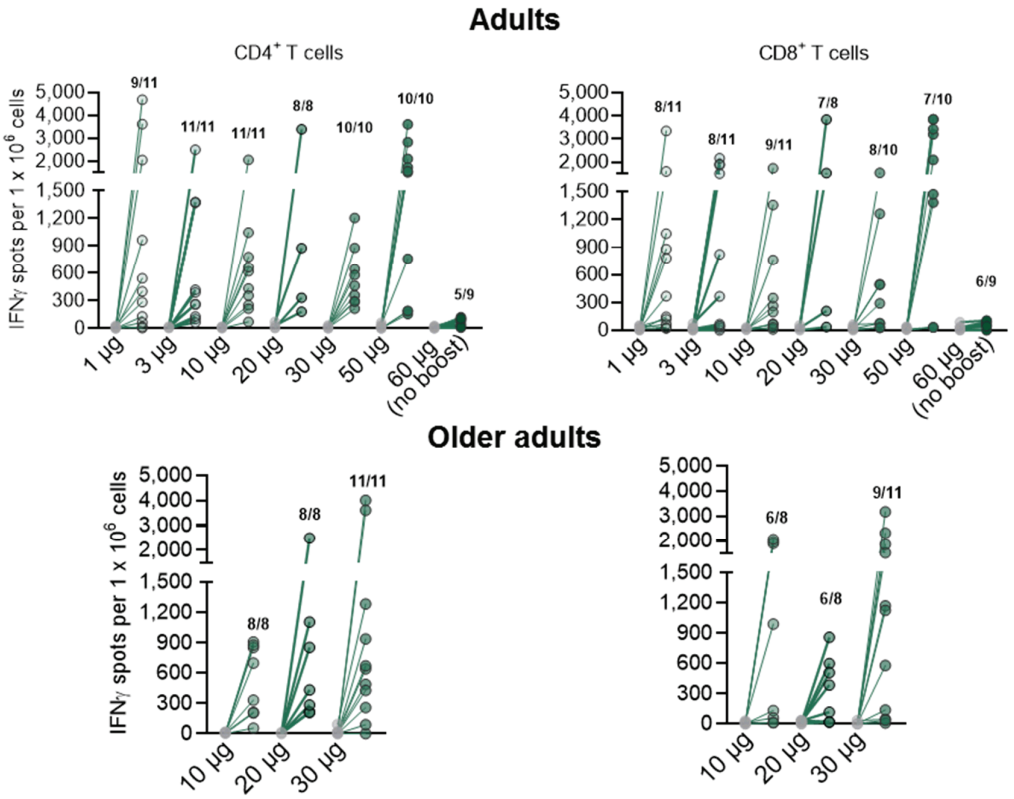


Figure 35: Frequency and magnitude of BNT162b1-induced CD4+ and CD8+ T-cell responses

PBMCs obtained on Day 1 (pre-Dose 1) and on Day 29 (7 d post-Dose 2 for cohorts with 1 to 50 µg, or 28 d after Dose 1 for the 60 µg cohort) were analyzed in *ex vivo* IFNγ ELISpot (see GA-RB-022-01A). Common pathogen T-cell epitope pools CEF (cytomegalovirus, Epstein-Barr virus, and influenza virus human leukocyte antigen (HLA) class I epitopes) and CEFT (cytomegalovirus, Epstein-Barr virus, 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 normalized mean spot count from duplicate wells for one participant, after subtraction of the medium-only control. Shown are ratios above post-vaccination data points are the number of participants with detectable CD4+ or CD8+ T-cell response within the total number of tested participants per dose cohort.

Note: CD4 and CD8 data from one adult from the 10 µg cohort, from one adult from the 30 µg cohort, and from four participants from the 20 µg cohort could not be normalized and hence have not been included in the plots. Horizontal lines represent the median of each group.

RBD- and S protein-specific CD4+ T-cell responses observed after vaccination were induced *de novo* by BNT162b1 in 97.5% of participants and by BNT162b2 in 100% of participants. RBD- and S protein-specific CD8+ T-cell responses observed after

vaccination were induced *de novo* by BNT162b1 in 95.5% of participants and by BNT162b2 in 96.6% of participants.

6.1.1.1.4 Functional and pro-inflammatory CD4⁺/CD8⁺ T-cell responses

BNT162b1

The functionality and polarization of vaccine induced SARS-CoV-2 RBD-specific T cells were assessed by intracellular accumulation of the cytokines IFNγ, IL-2, and IL-4 in response to stimulation with overlapping peptides representing the full length sequence of the vaccine-encoded RBD (aa 1-16 fused to aa 327-528 of the S protein) and the wild-type SARS-CoV-2 S protein by intracellular cytokine staining. For bench-marking, PBMCs from 15 COVID-19 convalescent virologically confirmed patients were used.

Two doses of BNT162b1 (dose range 1 to 50 µg) induced cluster of differentiation 4 (CD4) and CD8 vaccine-specific T-cell responses. RBD-specific $CD4^+$ T-cell responses have a Th1 cell cytokine profile secreting IFNγ, or IL-2, or both. For 81 of the 84 analyzed participants who received both BNT162b1 doses, no production of Th2 cytokine IL-4 in response to RBD peptide pool stimulation was detected. Similarly, RBD-specific $CD8^+$ T cells secreted IFNγ in 54 of the analyzed 84 participants who received both BNT162b1 doses, however, lower levels of IL-2-secreting $CD8^+$ T cells compared to $CD4^+$ T cells were detected. In the 30 µg dose groups, the fractions of RBD-specific $IFN\gamma^+$ $CD8^+$ T cells reached up to 0.49% (younger participants) and 1.58% (older participants) of total peripheral blood $CD8^+$ T cells. In the 50 µg dose group with younger participants, fractions of up to 3.87% were detected. The mean fraction of both $CD4^+$ and $CD8^+$ cytokine-producing T cells in the BNT162b1 dosed participants (1 to 50 µg) was substantially higher (e.g., for participants dosed at 30 µg, 11-fold higher) than that observed in 15 patients who recovered from COVID-19. In the 60 µg cohort, treated with Dose 1 only, mean fractions of cytokine-producing T cells were lower compared to the other cohorts, indicating the importance of the booster vaccination. Importantly, the cytokine responses elicited after dosing with BNT162b1 in older participants was similar in response pattern and intensity with that of the younger participants.

BNT162b1 induced poly-functional and pro-inflammatory $CD4^+/CD8^+$ T-cell responses in almost all participants, with a Th1 polarization of the helper response. The detection of IFNγ, IL-2 but not IL-4 indicates a favorable Th1 profile and the absence of a potentially deleterious Th2 immune response.

BNT162b2

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 IL-4 in response to stimulation with overlapping peptides representing the full length sequence of the vaccine-encoded RBD and the wild-type SARS-CoV-2 S protein, respectively. For bench-marking, PBMCs from 18 COVID-19 convalescent virologically confirmed patients were used.

Two doses of BNT162b2 (dose range 1 to 30 µg), induced vaccine-specific T-cell responses in both age groups analyzed (Figure 36 and Figure 37). Testing for SARS-CoV-2 S protein-specific T-cell responses was performed with two different peptide

pools – S pool 1 comprising overlapping peptides from the N-terminal region of the S protein (which is not equivalent to structural domains) and S pool 2 comprising C-terminal regions of the S protein. S-specific $CD4^+$ T-cell responses analyzed in 74 participants dosed with BNT162b2 are characterized by a Th1 cytokine profile secreting IFNγ, or IL-2, or both.

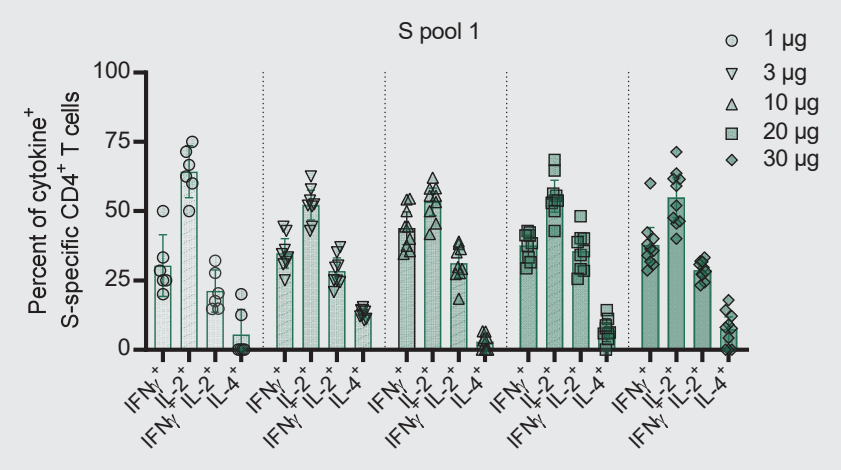


Figure 36: S-specific $CD4^+$ T cells producing the indicated cytokines in response to S protein pool 1 as a fraction of total cytokine-producing S-specific $CD4^+$ T cells (1 to 30 µg younger participant dose groups)

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

Source: Report R-20-0241.

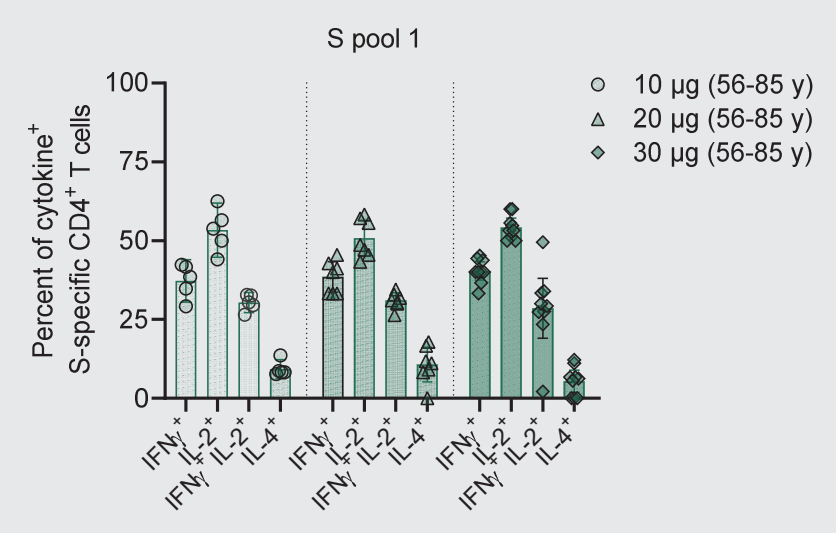


Figure 37: S-specific CD4⁺ T cells producing the indicated cytokines in response to S protein pool 1 as a fraction of total cytokine-producing S-specific CD4⁺ T cells (10 to 30 µg older participant dose groups)

Bar charts show arithmetic means with 95% CI. 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. Six participants from the 10 µg cohort and one participant from the 20 µg cohort were excluded from this analysis (frequency of total cytokine-producing CD4⁺ T cells < 0.03%). CI = confidence interval IFN = interferon; IL = interleukin; older participants = participants aged 56 to 85 yrs; S protein = SARS-CoV-2 sp ke protein.

Source: Report R-20-0241.

Almost no Th2 cytokine IL-4 secreting T cells were detectable in response to S peptide sub-pool stimulations (mean fractions: 0.01% and 0.02% of antigen-specific circulating CD4⁺ T cells in the 20 and 30 µg adult cohort, respectively; separate stimulation with S protein sub-pool 1 and sub-pool 2). S-specific CD8⁺ T cells secreted IFNγ in 61 of the 74 analyzed participants (adults: 40 of 46 participants and older adults: 21 of 28 participants) and also IL-2 secreting CD8⁺ T cells were detectable. Fractions of S-specific IFNγ⁺ CD8⁺ T cells targeting the N-terminal domain of the S protein reached up to 1% of total peripheral blood CD8⁺ T cells in the 20 and 30 µg younger participant dose groups and up to 2.4% in the 30 µg older participant dose group. Pre-existing CD8⁺ T-cell responses against the C-terminal region of the S protein were detected in 17 of 74 dosed participants (range: 0.07 to 5.59% IFNγ-producing CD8⁺ T cells). In 6 of 17 participants, these pre-existing responses were slightly amplified upon BNT162b2 dosing.

Overall, the mean fractions of S-specific CD4⁺ and CD8⁺ T cells were substantially higher (e.g., the S protein pool 1 IFNγ CD8⁺ response of 30 µg dosed participants was 12.5-fold higher) than that observed in 18 patients who recovered from COVID-19. Importantly, for the clinically targeted 30 µg dose group, the cytokine responses elicited after vaccination with BNT162b2 in older participants was mostly identical in response pattern and intensity with that of the younger participants.

BNT162b2-induced T-cell responses, especially for CD8⁺ T cells, were not limited to the RBD, and pronounced and strong T cell recognition of non-RBD regions of the S protein were observed.

BNT162b2 induced poly-functional and pro-inflammatory $CD4^+/CD8^+$ T-cell responses in almost all participants. The Th1 polarization of the helper 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.

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 dose regimens tested per vaccine in this study are summarized in Table 10.

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.
- BNT162b1 and BNT162b2 are well tolerated and have an acceptable safety profile in younger participants and older participants.
- 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.

For the current status of dosing with BNT162a1 by dose level in BNT162-01, see Table 8. 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 subjects 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 subjects reported only injection site reactions (pain and tenderness, almost exclusively of mild intensity) and no systemic reactions.

In the first six subjects 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 subjects 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 last IB.

For the current status of dosing with BNT162b1 by dose level in BNT162-01, see Table 8. 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.

Solicited local reactions – BNT162b1

For a summary of solicited local reactions in younger and older participants, see Table 11.

Table 11: Summary of solicited local reactions – BNT162b1 (SAF)

Time interval		Younger participants							
		1 µg (N=12)	3 µg (N=12)	10 µg (N=12)	20 µg (N=12)	30 µg (N=12)	50 µg (N=12)	60 µg (N=12)	Total (N=84)
Dose 1 up to Day 7 after Dose 1	nn	12	12	12	12	12	12	12	84
	Any local reaction n (%)	6 (50)	5 (42)	10 (83)	12 (100)	11 (92)	12 (100)	12 (100)	68 (81)
	Any grade ≥ 3 local reaction n (%)	0 (0)	0 (0)	1 (8)	2 (17)	4 (33)	2 (17)	1 (8)	10 (12)
Dose 2 up to Day 7 after Dose 2	nn	12	6	11	10	12	11	N/A	69
	Any local reaction n (%)	7 (58)	5 (42)	10 (91)	11 (100)	11 (92)	11 (100)	N/A	55 (80)
	Any grade ≥ 3 local reaction n (%)	2 (17)	0 (0)	0 (0)	0 (0)	2 (17)	3 (27)	N/A	7 (10)

Time interval		Older participants				All Total (N=120)
		10 µg (N=12)	20 µg (N=12)	30 µg (N=12)	Total (N=36)	
Dose 1 up to Day 7 after Dose 1	nn	12	12	12	36	120
	Any local reaction n (%)	7 (58)	11 (92)	11 (92)	29 (81)	97 (81)
	Any grade ≥ 3 local reaction n (%)	0 (0)	0 (0)	0 (0)	0 (0)	10 (8)
Dose 2 up to Day 7 after Dose 2	nn	12	11	12	35	104
	Any local reaction n (%)	8 (67)	9 (82)	9 (75)	26 (74)	81 (78)
	Any grade ≥ 3 local reaction n (%)	0 (0)	0 (0)	0 (0)	0 (0)	7 (7)

All = all is the sum of younger and older participants; N = number of participants in the analysis set; n = number of participants with the respective reactions; nn = number of participants with any information on reactions available; N/A = not available, SAF = Safety Set.
Source: BNT162-01 CSR v2.0.

Solicited local reactions – BNT162b1 – Younger participants

In the younger participants group, in the combined time interval, after both doses, the majority of the participants experienced mild (n=72, 86%) followed by moderate (n=45, 54%) solicited local reactions, while few participants experienced severe (n=15, 18%) solicited local reactions (data not shown).

- The most frequent severe solicited local reactions were reported in 30 µg (5 participants [42%]), 50 µg (4 participants [33%]), 20 µg (2 participants [17%]), 60 µg and 10 µg (1 participant each [8%], respectively) dose groups.

The most frequently reported solicited local reactions of any severity were tenderness (n=70, 83%) and pain (n=67, 80%). The remaining symptom terms were infrequently described.

- Only mild and moderate reactions were reported for erythema and induration.
- For pain and tenderness each symptom was assessed as severe in ≤ 14% of participants.
- No clear pattern of dose dependency was seen across the symptom terms for mild reactions in 10 µg and above dose groups. However, a possible dose dependency for moderate local reactions between the 10 µg group (5 participant) and the 20 µg and 30 µg groups (6 and 11 participants) was seen.

Solicited local reactions – BNT162b1 (SAF) – Older participants and all (younger and older) participants

In the older participants group, in the combined time interval, after both doses, the majority of the participants experienced mild (n=30, 83%) followed by moderate (n=15, 42%) solicited local reactions, while no older participants experienced severe solicited local reactions (data not shown).

The most frequently reported solicited local reactions of any severity were tenderness (n=28, 78%) and pain (n=27, 75%). The remaining symptom terms were infrequently described.

- Only mild reactions were reported for erythema and induration.
- For pain and tenderness each symptom was assessed as moderate in < 40% of participants.

Solicited systemic reactions – BNT162b1

For a summary of solicited systemic reactions in younger and older participants, see Table 12.

Table 12: Summary of solicited systemic reactions – BNT162b1 (SAF)

Time interval		Younger participants							
		1 µg (N=12)	3 µg (N=12)	10 µg (N=12)	20 µg (N=12)	30 µg (N=12)	50 µg (N=12)	60 µg (N=12)	Total (N=84)
Dose 1 up to Day 7 after Dose 1	nn	12	12	12	12	12	12	12	84
	Any systemic reaction n (%)	9 (75)	8 (67)	8 (67)	11 (92)	11 (92)	12 (100)	12 (100)	71 (85)
	Any grade ≥ 3 systemic reaction n (%)	0 (0)	0 (0)	1 (8)	2 (17)	3 (25)	5 (42)	8 (67)	19 (23)
Dose 2 up to Day 7 after Dose 2	nn	12	12	11	11	12	11	N/A	69
	Any systemic reaction n (%)	7 (58)	7 (58)	9 (82)	10 (91)	11 (92)	11 (100)	N/A	55 (80)
	Any grade ≥ 3 systemic reaction n (%)	3 (25)	1 (8)	5 (45)	5 (45)	6 (50)	5 (45)	N/A	25 (36)

Time interval		Older participants				All Total (N=120)
		10 µg (N=12)	20 µg (N=12)	30 µg (N=12)	Total (N=36)	
Dose 1 up to Day 7 after Dose 1	nn	12	12	12	36	120
	Any systemic reaction n (%)	9 (75)	11 (92)	11 (92)	31 (86)	102 (85)
	Any grade ≥ 3 systemic reaction n (%)	1 (8)	1 (8)	2 (17)	4 (11)	23 (19)
Dose 2 up to Day 7 after Dose 2	nn	12	11	12	35	104
	Any systemic reaction n (%)	8 (67)	10 (91)	12 (100)	30 (86)	85 (82)
	Any grade ≥ 3 systemic reaction n (%)	2 (17)	2 (18)	4 (33)	8 (23)	33 (32)

The denominator for the percentage calculation is nn. N = number of participants in the analysis set; n = number of participants with the respective systemic reactions; nn = number of participants with any information on systemic reactions available; N/A = not available; SAF = Safety Set.

Source: BNT162-01 CSR v2.0.

Solicited systemic reactions – BNT162b1 (SAF) – Younger participants

Overall, in the combined time interval, after both doses, the majority of the participants experienced mild (n=76, 90%) followed by moderate (n=62, 74%) solicited systemic reactions. A few participants experienced severe (n=37, 44%) solicited systemic reactions (data not shown).

- The most frequent severe systemic reactions were reported in 50 µg and 60 µg groups (8 participants each [67%]) followed by 10 µg and 30 µg (6 participants each [50%]) groups.
- The most frequently reported solicited systemic reactions of any severity were fatigue (n=68, 81%), headache (n=66, 79%), myalgia (n=51, 61%), malaise (n=50, 60%), and chills (n=47, 56%). The remaining symptom terms were infrequently described.

- For nausea, vomiting, diarrhoea, myalgia, arthralgia and fever each symptom was assessed as severe in ≤10% of participants.
- A possible dose dependency for both severe headache and chills was seen with two participants at 10 µg vs. 6 participants at 50 µg and three participants at 10 µg vs. 5 participants at 50 µg, respectively. A possible dose dependency for both severe fatigue and loss of appetite was seen with each one case at 10 µg vs. 4 participants at 50 µg, respectively.
- No clear pattern of dose dependency was seen across the symptom terms for mild or moderate reactions, with the exception of moderate intensity malaise which was reported for 25% of participants receiving 10 µg and 75% of participants with 30 µg dose.

Older participants and all (younger and older) participants

Overall, in the combined time interval, after both doses, the majority of the participants experienced mild (n=32, 89%) followed by moderate (n=22, 61%) solicited systemic reactions. A few participants experienced severe (n=10, 28%) solicited systemic reactions (data not shown).

- The most frequent severe systemic reactions were reported in the 30 µg group (5 participants, 42%) followed by 20 µg (3 participants, 25%) and 10 µg (2 participants, 17%) groups.
- The most frequently reported solicited systemic reactions of any severity were headache (n=29, 81%), fatigue (n=27, 75%), and myalgia (n=18, 50%). The remaining symptom terms were infrequently described.
- No clear pattern of dose dependency was seen across the symptom terms for mild, moderate, or severe reactions.

Unsolicited TEAEs after BNT162b1 dosing

For a summary of unsolicited TEAEs in younger see Table 13 and Table 14, and in older participants see Table 15.

Table 13: Summary of TEAEs without AEs based on solicited reporting via diaries – BNT162b1 – Younger participants (SAF)

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 (N=84) n (%) E
Dose 1 up to Dose 2 or Day 28 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 Day 28 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

The denominator for the percentage calculation is N. AE = adverse event; E = number of events; N = number of participants in the analysis set; n = number of participants with the specified characteristic; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; SAF = Safety Set.

Source: BNT162-01 CSR v2.0.

Table 14: Summary of TEAEs without AEs based on solicited reporting via diaries – BNT162b1 – Younger participants (SAFB)

Time interval		1 µg (N=12) n (%) E	3 µg (N=6) n (%) E	10 µg (N=11) n (%) E	20 µg (N=11) n (%) E	30 µg (N=12) n (%) E	50 µg (N=11) n (%) E	Total (N=63) n (%) E
Dose 2 up to Day 28 after Dose 2	Any TEAE	6 (50) 15	0 (0) 0	4 (36) 5	3 (27) 8	3 (25) 4	6 (55) 13	22 (32) 45
	Related TEAE	4 (33) 9	0 (0) 0	3 (27) 3	2 (18) 5	2 (17) 2	5 (45) 9	16 (23) 28
	Grade ≥ 3 TEAE	0 (0) 0	0 (0) 0	0 (0) 0	2 (18) 4	0 (0) 0	0 (0) 0	2 (3) 4
	Related grade ≥ 3 TEAE	0 (0) 0	0 (0) 0	0 (0) 0	1 (9) 3	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
	Related TESAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0

The denominator for the percentage calculation is N. AE = adverse event; E = number of events; N = number of participants in the analysis set; n = number of participants with the specified characteristic; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; SAFB = Safety Dose 2 set (Safety Boost Set).

Source: BNT162-01 CSR v2.0.

Table 15: Summary of TEAEs without AEs based on solicited reporting via diaries – BNT162b1 – Older participants and all participants (SAF)

Time interval		Dose ranging groups				All Total (N=120) n (%) E
		10 µg (N=12) n (%) E	20 µg (N=12) n (%) E	30 µg (N=12) n (%) E	Total (N=36) n (%) E	
Dose 1 up to Day 7 after Dose 1	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 1 up to Dose 2 or Day 28 after Dose 1 (whatever comes first)	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
Dose 1 up to Day 28 after Dose 2 or after Dose 1 (if no Dose 2)	Any TEAE	3 (25) 3	2 (17) 4	8 (67) 17	13 (36) 24	51 (43) 107
	Related TEAE	0 (0) 0	0 (0) 0	5 (42) 9	5 (14) 9	35 (29) 60
	Grade ≥ 3 TEAE	1 (8) 1	1 (8) 1	2 (17) 2	4 (11) 4	6 (5) 8
	Related grade ≥ 3 TEAE	0 (0) 0	0 (0) 0	1 (8) 1	1 (3) 1	2 (2) 4
	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

The denominator for the percentage calculation is N. All = all is the sum of younger and older participants; AE = adverse event; E = number of events; N = number of participants in the analysis set; n = number of participants with the specified characteristic; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; SAF = Safety Set.

Source: BNT162-01 CSR v2.0.

Clinical laboratory, vital signs, physical findings, and other observations related to safety

Transient changes from baseline in lymphocyte (low) count were reported in all dose groups 48 h after dosing with BNT162b1. RNA vaccines are known to induce type I IFN (Kranz et al. 2016), and type I IFNs regulate lymphocyte recirculation and are associated with transient migration and/or redistribution of lymphocytes (Kamphuis et al. 2006).

There were a few abnormal hematology parameters but none of them were clinically relevant abnormalities except for one younger participant in the BNT162b1 (1 µg) who had a high lymphocyte count (4.33 x 10^9/L; normal 1.22 to 3.56 x 10^9/L) on Day 29, 7 d after Dose 2, which was assessed as related TEAE and also as clinically significant event. The event resolved 8 d after the last dose without any medication.

A few abnormal chemistry parameters were reported but none of them were clinical relevant abnormalities, except for C-reactive protein reported on Day 2 by two participants (3%) (n=1 each in 30 µg and 50 µg groups) for BNT162b1. These values were normal without clinical consequence at the subsequent visit (Day 7).

There were a few abnormal urinalysis parameters but none of them were clinically relevant abnormalities.

Five participants (8%) experienced elevated body temperature on Day 2, which was assessed as related TEAE. These values were normal without clinical consequence at the subsequent visit (Day 7).

6.1.1.2.3 BNT162b2 - Summary of safety

At the time of preparation of this summary, 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.

For the current status of dosing with BNT162b2 by dose level in BNT162-01, see Table 8. 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 are clinically ongoing:

- Cohort 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. Cohort 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.
- Cohort 13 is investigating safety and long term immune responses in immunocompromised adults after two 30 µg BNT162b2 doses given ~21 d apart.

Given the availability of safety data from the Phase 2/3 part of the BNT162-02 / C4591001 study, 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 the BNT162-02 / C4591001 study 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.

For the current status of dosing with BNT162c2 by dose level in BNT162-01, see Table 8. 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 (two dose regimen) / ~184 d post-dose (one dose regimen). No further clinical investigation of BNT162c2 is currently planned.

In the study 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, there were no SAEs, AESIs, or subjects 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 BNT162-02/C4591001 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).

Study 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 was 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, BNT162b2, and is intended to support licensure globally.

For the current status of dosing with BNT162 vaccines candidates by dose level in BNT162-02, see Table 8.

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 two 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 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. Subjects 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. 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.

6.1.2.2 Summary of efficacy (Phase 3)

In pivotal Study C4591001, 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).

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 Final analysis of primary efficacy endpoints

Vaccine efficacy – At least 7 d after Dose 2 – Final Analysis

For the first primary efficacy endpoint, vaccine efficacy (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 and without prior evidence of SARS-CoV-2 infection at least 7 d after Dose 2.

A final analysis based on 170 evaluable cases showed VE against confirmed COVID-19 (> 7 d after Dose 2) in participants without prior evidence of SARS -CoV-2 infection was 95.0%, with 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group (Table 16). The 95% credible interval for the VE was 90.3% to 97.6%, indicating that the true VE is at least 90.3% with a 97.5% probability given the observed data.

For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 occurring at least 7 d after Dose 2 was 94.6% (with 9 and 169 cases in the BNT162b2 and placebo groups, respectively) among participants with and without evidence of prior SARS-CoV-2 infection. The posterior probability of > 99.99% for the true VE greater than 30% met the prespecified success criterion of > 98.6% for this endpoint. The 95% credible interval for the VE was 89.9% to 97.3%, indicating that the true VE is at least 89.9% with a 97.5% probability given the available data (Table 16). Note that with a posterior probability of 98.6%, the true VE is at least 89.2% with the available data.

Table 16: Vaccine efficacy – First COVID-19 occurrence from 7 d after Dose 2 – Subjects without and subjects with and 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 (Subjects Without Evidence of Infection)	18,198	8	2.214 (17,411)	18,325	162	2.222 (17,511)	95.0	(90.3, 97.6)	> 0.9999
First COVID-19 occurrence from 7 d after Dose 2 (Subjects With and Without Evidence of Infection)	19,965	9	2.332 (18,559)	20,172	169	2.345 (18,708)	94.6	(89.9, 97.3)	> 0.9999

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2; VE = vaccine efficacy.

Note: Subjects who had no serological or virological evidence (prior to 7 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 subjects in the specified group.

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

c. Total surveillance time in 1000 person-yrs for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 d after Dose 2 to the end of the surveillance period.

d. n2 = Number of subjects at risk for the endpoint.

e. Cred ble interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 17NOV2020 (16:46)

(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output Files:
./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_7pd2_wo_eval and :
./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_7pd2_eval

All confirmed cases of COVID-19 after Dose 1

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

All reports of COVID-19 with onset at any time after Dose 1 are accounted for in Table 17, which provides a summary of cases for all participants in the Dose 1 all-available efficacy (modified intention-to-treat) population, regardless of evidence of infection before or during the vaccination regimen. Among these participants, 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared to 275 cases in the placebo group.

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

Table 17: Vaccine efficacy – First COVID-19 occurrence after Dose 1 – Dose 1 All-Available Efficacy Population

	Vaccine group (as randomized)					
	BNT162b2 (30 µg) (N[a]=21,669)		Placebo (N[a]=21,686)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0	(75.6, 86.9)
After Dose 1 to before Dose 2	39		82		52.4	(29.5, 68.4)
Dose 2 to 7 d after Dose 2	2		21		90.5	(61.0, 98.9)
≥ 7 d after Dose 2	9		172		94.8	(89.8, 97.6)

Abbreviations: VE = vaccine efficacy.

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

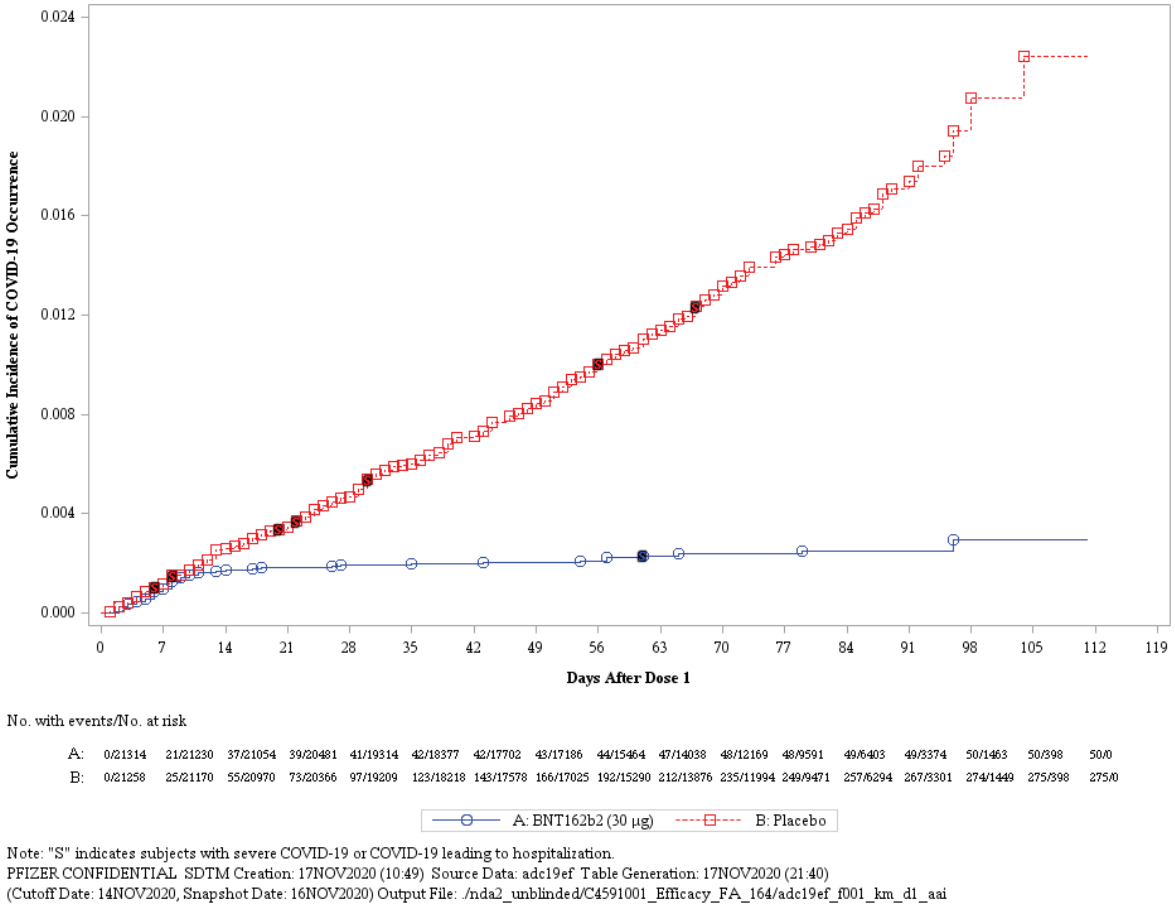
b. n1 = Number of subjects meeting the endpoint definition.

c. Total surveillance time in 1,000 person-yrs for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.

d. n2 = Number of subjects at risk for the endpoint.

e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method (adjusted for surveillance time for overall row).
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 18NOV2020 (17:06) (Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_pd1_aai

The early onset of protection is readily apparent in Figure 38, which displays cumulative incidence for the first COVID-19 occurrence after Dose 1 among all vaccinated participants based on Dose 1 all-available efficacy (modified intention-to-treat) population. Disease onset appears to track together for BNT162b2 and placebo until ~14 d after Dose 1, at which point the curves diverge, with cases steadily accumulating in the placebo group, while remaining virtually flat in the BNT162b2 group.



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

Figure 38: Cumulative incidence curves for the first COVID-19 occurrence after Dose 1 – Dose 1 All-Available Efficacy Population

6.1.2.2.2 Vaccine efficacy by subgroup – Final analysis

Observed VE was > 93% for the first primary efficacy endpoint across subgroups of age, sex, race/ethnicity, and country, with the exception of "all others" race group (89.3% VE)

and Brazil (87.7% VE) among participants without prior evidence of infection (Table 18). In participants with comorbidities, VE was > 91% for the first primary efficacy endpoint in all risk subgroups analyzed (at risk participants were defined as those meeting at least one Charlson Comorbidity Index condition or obesity [defined as BMI > 30 kg/m^2]) (Table 19).

Vaccine efficacy was 94.7% in participants ≥ 65 yrs of age.

Table 18: Vaccine efficacy – First COVID-19 occurrence from 7 d after Dose 2, by subgroup – Subjects 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]=18,198)		Placebo (N[a]=18,325)			
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	8	2.214 (17,411)	162	2.222 (17,511)	95.0	(90.0, 97.9)
Age group (years)						
16 to 55	5	1.234 (9,897)	114	1.239 (9,955)	95.6	(89.4, 98.6)
> 55	3	0.980 (7,500)	48	0.983 (7,543)	93.7	(80.6, 98.8)
≥65	1	0.508 (3,848)	19	0.511 (3,880)	94.7	(66.7, 99.9)
Sex						
Male	3	1.124 (8,875)	81	1.108 (8,762)	96.4	(88.9, 99.3)
Female	5	1.090 (8,536)	81	1.114 (8,749)	93.7	(84.7, 98.0)
Race						
White	7	1.889 (14,504)	146	1.903 (14,670)	95.2	(89.8, 98.1)
Black or African American	0	0.165 (1,502)	7	0.164 (1,486)	100.0	(31.2, 100.0)
All others[f]	1	0.160 (1,405)	9	0.155 (1,355)	89.3	(22.6, 99.8)
Ethnicity						
Hispanic/Latino	3	0.605 (4,764)	53	0.600 (4,746)	94.4	(82.7, 98.9)
Non-Hispanic/non-Latino	5	1.596 (12,548)	109	1.608 (12,661)	95.4	(88.9, 98.5)
Country						
Argentina	1	0.351 (2,545)	35	0.346 (2,521)	97.2	(83.3, 99.9)
Brazil	1	0.119 (1,129)	8	0.117 (1,121)	87.7	(8.1, 99.7)
USA	6	1.732 (13,359)	119	1.747 (13,506)	94.9	(88.6, 98.2)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2; VE = vaccine efficacy.

Note: Subjects who had no serological or virological evidence (prior to 7 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 subjects in the specified group.

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

c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 d after Dose 2 to the end of the surveillance period.

d. n2 = Number of subjects at risk for the endpoint.

e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

f. All others = American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

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Table 19: Vaccine Efficacy – First COVID-19 occurrence from 7 d after Dose 2, by risk status – subjects 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]=18,198)		Placebo (N[a]=18,325)			
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	8	2.214 (17,411)	162	2.222 (17,511)	95.0	(90.0, 97.9)
At risk[f]						
Yes	4	1.025 (8,030)	86	1.025 (8,029)	95.3	(87.7, 98.8)
No	4	1.189 (9,381)	76	1.197 (9,482)	94.7	(85.9, 98.6)
Age group (years) and at risk						
16-64 and not at risk	4	0.962 (7,671)	69	0.964 (7,701)	94.2	(84.4, 98.5)
16-64 and at risk	3	0.744 (5,878)	74	0.746 (5,917)	95.9	(87.6, 99.2)
≥ 65 and not at risk	0	0.227 (1,701)	7	0.233 (1,771)	100.0	(29.0, 100.0)
≥ 65 and at risk	1	0.281 (2,147)	12	0.279 (2,109)	91.7	(44.2, 99.8)
Obese[g]						
Yes	3	0.763 (6,000)	67	0.782 (6,103)	95.4	(86.0, 99.1)
No	5	1.451 (11,406)	95	1.439 (11,404)	94.8	(87.4, 98.3)
Age group (years) and obese						
16-64 and not obese	4	1.107 (8,811)	83	1.101 (8,825)	95.2	(87.3, 98.7)
16-64 and obese	3	0.598 (4,734)	60	0.609 (4,789)	94.9	(84.4, 99.0)
≥ 65 and not obese	1	0.343 (2,582)	12	0.338 (2,567)	91.8	(44.5, 99.8)
≥ 65 and obese	0	0.165 (1,265)	7	0.173 (1,313)	100.0	(27.1, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2; VE = vaccine efficacy.

Note: Subjects who had no serological or virological evidence (prior to 7 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 subjects in the specified group.

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

c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 d after Dose 2 to the end of the surveillance period.

d. n2 = Number of subjects at risk for the endpoint.

e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least one of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥ 30 kg/m^2).
g. Obese is defined as BMI ≥ 30 kg/m^2.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:54) Source Data: adc19ef Table Generation: 24NOV2020 (17:41) (Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_EUA_FAEF_RR/adc19ef_ve_cov_7pd2_wo_rg_eval

6.1.2.2.3 Final analysis of secondary efficacy endpoints

Vaccine efficacy – At least 14 d after Dose 2

Among participants without prior evidence of SARS-CoV-2 infection, VE was 94.2%, with 8 and 139 cases in the BNT162b2 and placebo groups, respectively, and met the prespecified success criterion (> 98.6%) for this endpoint. The 95% credible interval for the VE was 88.7% to 97.2%, indicating that the true VE is at least 88.7% with a 97.5% probability given the available data.

Among participants with and without prior evidence of SARS-CoV-2 infection, VE was 94.4%, with 8 and 144 cases in the BNT162b2 and placebo groups, respectively, and met the prespecified success criterion (> 98.6%) for this endpoint. The 95% credible interval for the VE was 89.1% to 97.3%, indicating that the true VE is at least 89.1% with a 97.5% probability given the available data.

Vaccine efficacy for severe COVID-19 Cases – Final Analysis

Efficacy against severe COVID-19 (≥ 7 d and ≥ 14 d after Dose 2)

Among participants without evidence of SARS-CoV-2 infection before and during vaccination, observed VE against severe COVID-19 (> 7 d after Dose 2) was 66.4% which did not meet prespecified success criterion of the posterior probability > 98.6%, due to the small number of severe cases (1 and 3 cases in the BNT162b2 and placebo groups, respectively) (Table 20).

Among participants with and without evidence of SARS-CoV-2 infection before and during vaccination, VE against severe COVID-19 (> 7 d after Dose 2) was 66.3%, with 1 and 3 cases in the BNT162b2 and placebo groups respectively. The posterior probability for the true VE greater than 30% is 74.19% (Table 20).

The VE against severe COVID-19 > 14 d after Dose 2 was similar to VE against severe COVID-19 > 7 d after Dose 2 (Table 20).

All confirmed cases of severe COVID-19 after Dose 1 – All-Available Population

Among participants in the Dose 1 all-available efficacy (modified intention-to-treat) population, one case of severe COVID-19 occurred after Dose 1 in the BNT162b2 group compared to 9 cases in the placebo group. The estimated VE against severe COVID-19 occurring after Dose 1 was 88.9% (2-sided 95% CI: 20.1%, 99.7%), with an estimated VE of 75.0% (1 case in BNT162b2 and 4 cases in placebo groups) against severe COVID-19 occurring at least 7 d after Dose 2 (Table 20).

Table 20: Vaccine efficacy for severe COVID-19 cases

	Vaccine group (as randomized)								
	BNT162b2 (30 µg)			Placebo					
Efficacy Endpoint	N[a]	n1[b]	Surveillance Time (n2)	N[a]	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI)	Pr (VE > 30% | data)[f]
First severe COVID-19 occurrence from 7 d after Dose 2 (Subjects without evidence of infection)	18198	1	2.215[c] (17,411[d])	18325	3	2.232[c] (17,511[d])	66.4	(-124.8, 96.3[e])	0.7429
First severe COVID-19 occurrence from 7 d after Dose 2 (Subjects with or without evidence of infection)	19965	1	2.333[c] (18,566[d])	20172	3	2.358[c] (18,733[d])	66.3	(-125.5, 96.3[e])	0.7419
First severe COVID-19 occurrence from 14 d after Dose 2 (Subjects without evidence of infection)	18175	1	1.888[g] (16,612[d])	18261	3	1.901[g] (16,663[d])	66.4	(-124.7, 96.3[e])	0.7432
First severe COVID-19 occurrence from 14 d after Dose 2 (Subjects with or without evidence of infection)	19965	1	1.985[g] (17,652[d])	20171	3	2.007[g] (17,792[d])	66.3	(-125.6, 96.3[e])	0.7418
First Severe COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population	21669	1	4.021[h] (21,314[d])	21686	9	4.006[h] (21,259[d])	88.9	(20.1, 99.7[i])	NA
After Dose 1 to before Dose 2		0	NA		4		100.0	(-51.5, 100.0[i])	NA
Dose 2 to 7 d after Dose 2		0	NA		1		100.0	(-3800.0, 100.0[i])	NA
≥ 7 d after Dose 2		1	NA		4		75.0	(-152.6, 99.5[i])	NA

Abbreviations: NA = not applicable; VE = vaccine efficacy

a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 d after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

g. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 14 d after Dose 2 to the end of the surveillance period.

h. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.

i. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method (adjusted for surveillance time for overall row).

PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 17NOV2020 (16:47) (Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
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./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_sev_cov_pd1_aai

6.1.2.2.4 Efficacy conclusions from study C4591001/BNT162-02

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

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

6.1.2.3 Summary of immunogenicity in C4591001 / BNT162-02

6.1.2.3.1 Phase 1 immunogenicity

BNT162b1 - Summary of immunogenicity

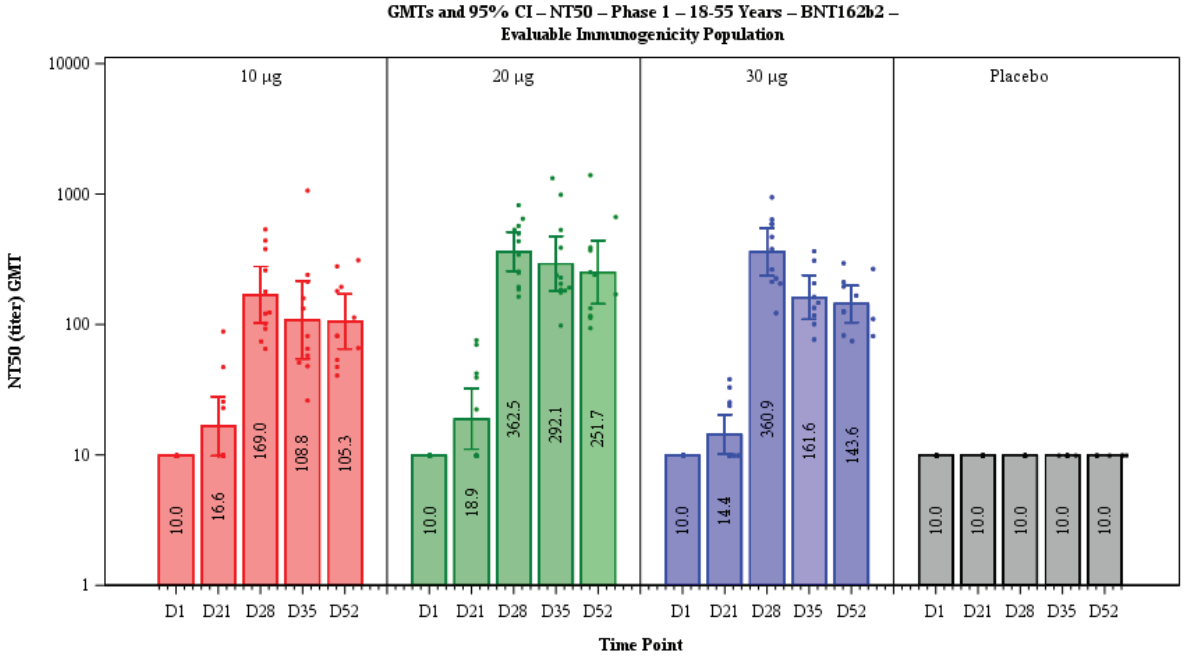
SARS-CoV-2 neutralizing titers and IgG responses (as measured by RBD-binding IgG levels) for BNT162b1 were similar to those observed in BNT162-01 (Sahin et al. 2020a; Walsh et al. 2020).

BNT162b2 - Summary of immunogenicity

SARS-CoV-2 50% Neutralizing Titers

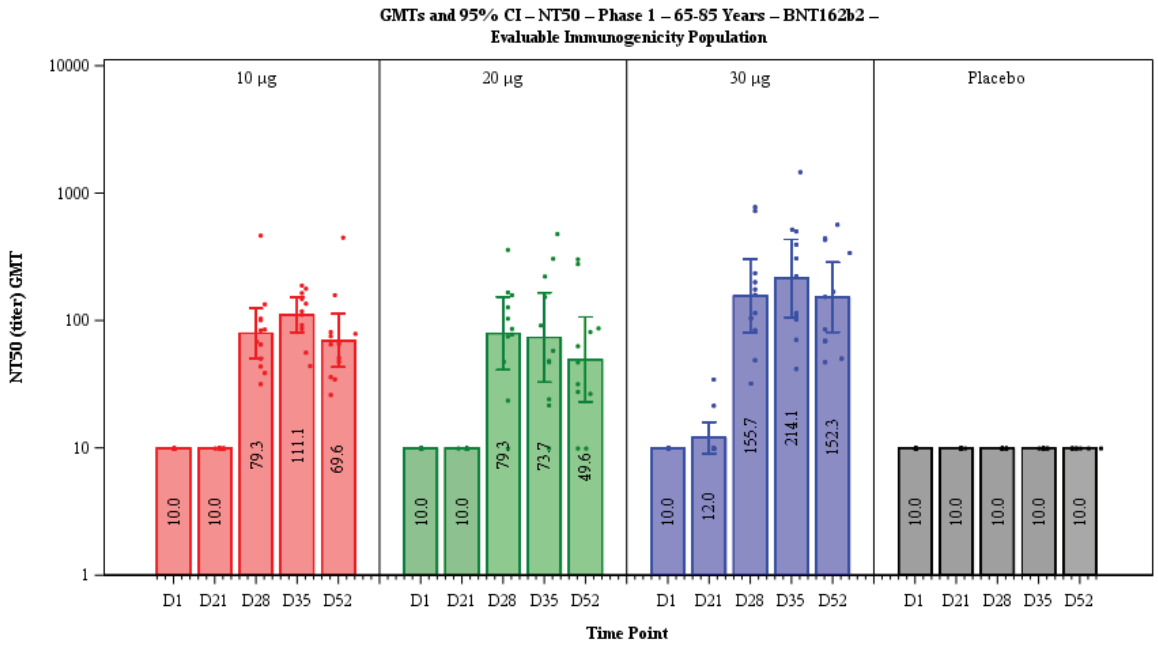
After administration of Dose 1 and prior to administration of Dose 2, BNT162b2 showed modest increases in SARS-CoV-2 neutralizing GMTs over baseline across dose levels and younger and older groups (Walsh et al. 2020). Overall, BNT162b2 elicited higher antigen-binding and neutralizing responses in younger participants (Figure 39) than in older participants (Figure 40). The boost effect after receiving Dose 2 was most pronounced at the 30 µg dose level for older participants.

GMTs measured at 7 d after Dose 2 for BNT162b2 at the 30 µg dose were 360.9 in the younger group and 155.7 in the older group. When compared to an HCS panel GMT of 94, the GMT for the younger group was ~3.8 times that of HCS and for the older group was ~1.7-times that of HCS (Walsh et al. 2020). By 1 month after Dose 2, GMTs were generally stable and remained ~1.6- to 1.9-times that of HCS.



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

Figure 39: GMTs and 95% CI: SARS-CoV-2 neutralization assay - NT50 – Phase 1, 2 Doses, 21 d apart – 18-55 yrs of age – BNT162b2 – Evaluable Immunogenicity Population

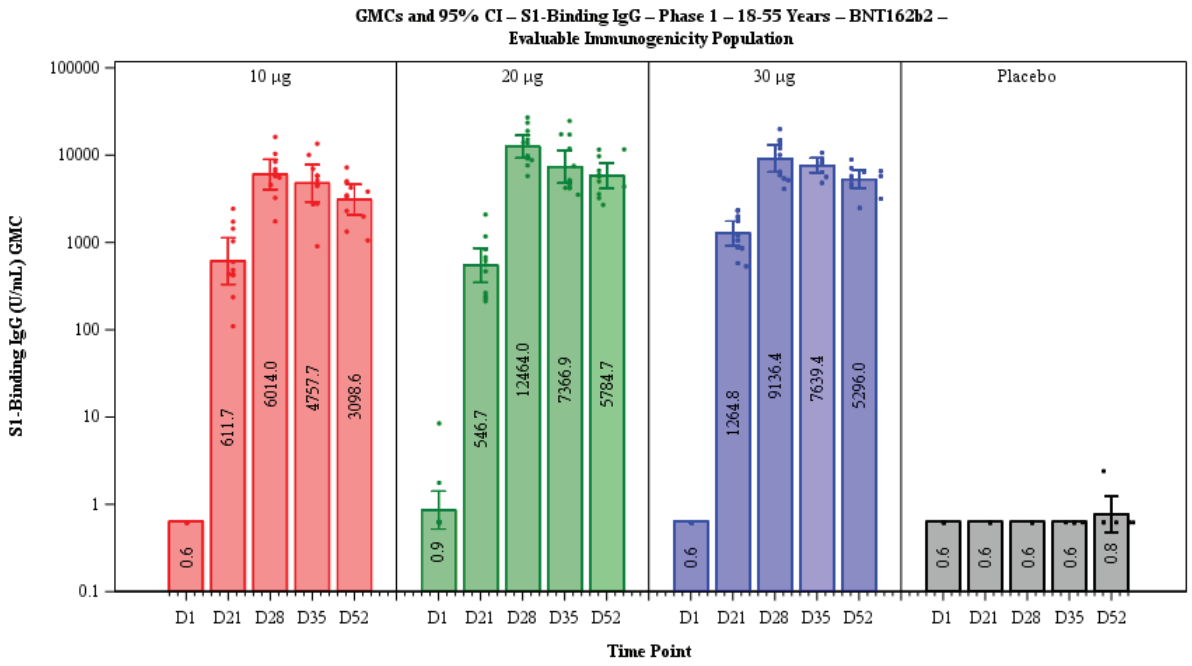


Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: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

Figure 40: GMTs and 95% CI: SARS-CoV-2 neutralization assay - NT50 – Phase 1, 2 doses, 21 d apart – 65-85 yrs of age – BNT162b2 – Evaluable Immunogenicity Population

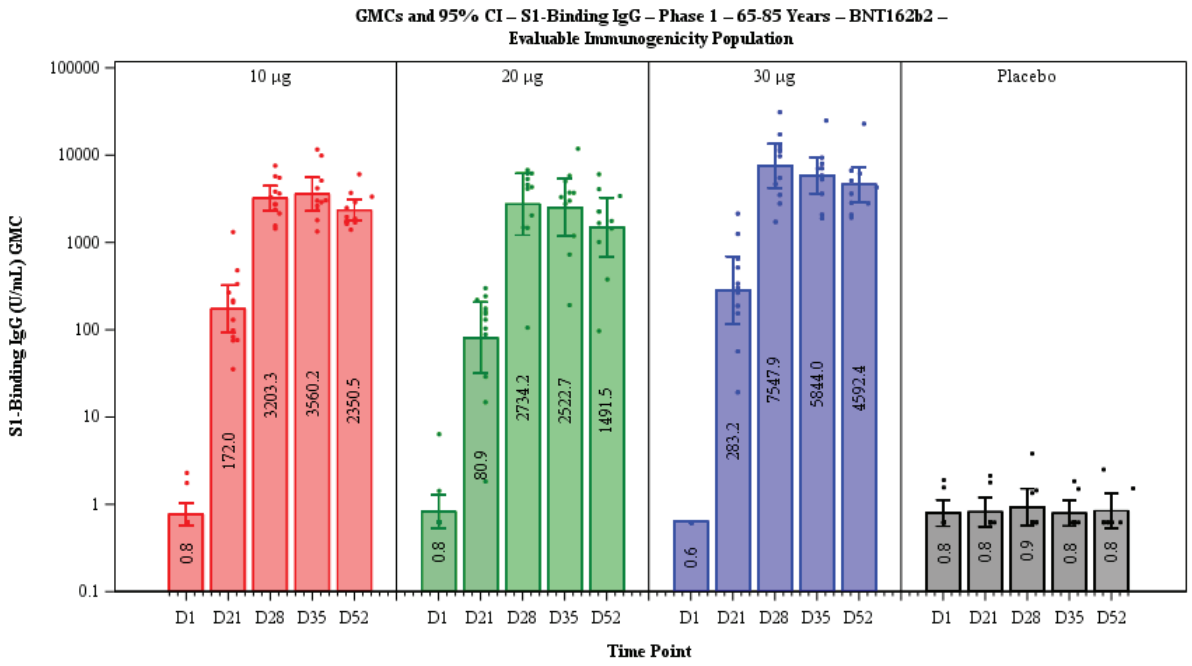
S1-binding IgG levels

There was generally a dose level response between 10 µg and 20 µg of BNT162b2, but a dose level response between 20 µg and 30 µg was not consistent across age groups (Figure 41 and Figure 42).



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

Figure 41: GMCs and 95% CI: SARS-CoV-2 S1-binding IgG level assay – Phase 1, 2 doses, 21 d apart – 18-55 yrs of age – BNT162b2 – Evaluable Immunogenicity Population



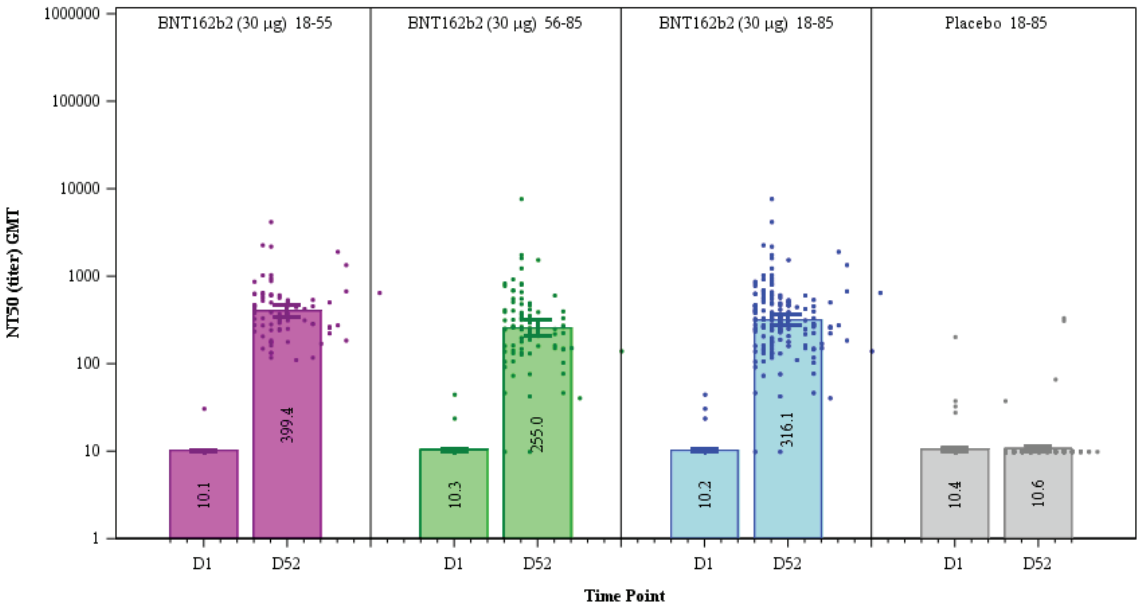
Abbreviations: GMC = geometric mean concentration; IgG = immunoglobulin G; S1 = spike protein S1 subunit.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020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

Figure 42: GMCs and 95% CI: SARS-CoV-2 S1-binding IgG level assay – Phase 1, 2 doses, 21 d apart – 65-85 yrs of age – BNT162b2 – Evaluable Immunogenicity Population

6.1.2.3.2 Phase 2 Immunogenicity

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 timepoint for the immunogenicity-evaluable population.

BNT162b2 elicited robust SARS-CoV-2 immune responses at 1 month after Dose 2 defined by both SARS-CoV-2 50% neutralizing titers (GMTs) (Figure 43). 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 HCS (GMT = 319) (Walsh et al. 2020; Sahin et al. 2020a).



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 43: 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.

6.1.2.4 Summary of safety in C4591001 / BNT162-02

6.1.2.4.1 Phase 1 Safety

Overall, the dose levels 10 µg, 20 µg, and 30 µg of BNT162b1 and BNT162b2 exhibited a tolerability and safety profile consistent with modRNA-based vaccines. 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.

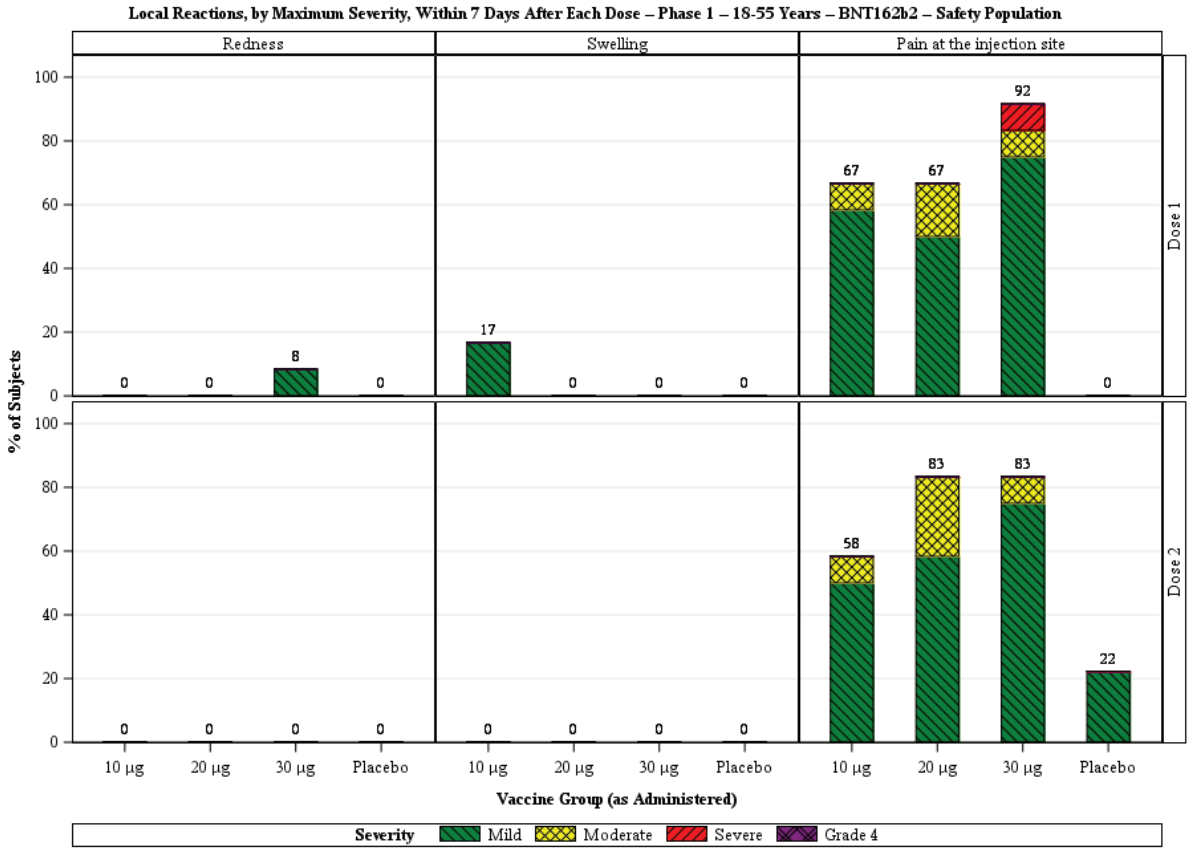
The available safety and tolerability data for younger and older adults dosed with BNT162b1 were broadly comparable to those in study BNT162-01.

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

Local reactions - BNT162b2

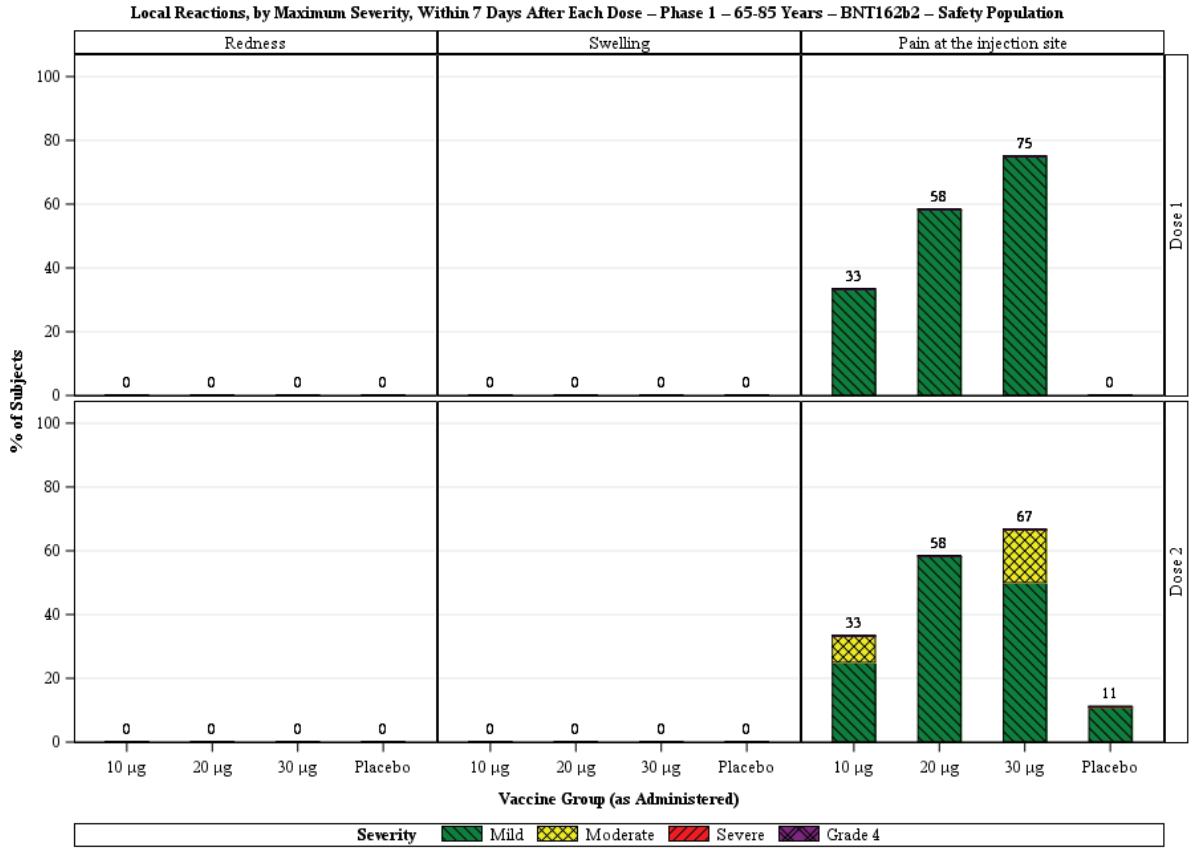
For BNT162b2 recipients, the frequency of local reactions was lower for the older group compared to the younger group (Figure 44 and Figure 45). Local reactions were generally infrequent in placebo recipients. The majority of local reactions in the BNT162b2 groups

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.
PFIZER CONFIDENTIAL SDTM Creation: 28AUG2020 (16:29) Source Data: adfacevd Table Generation: 29AUG2020 (00:51)
(Cutoff Date: 24AUG2020, Snapshot Date: 28AUG2020) Output File: (CDISC)/C4591001_IA_P1/adce_f001_lr_maxsev_18_b2_p1

Figure 44: Subjects reporting local reactions, by maximum severity, within 7 d after each dose – Phase 1, 2 Doses, 21 d apart – 18-55 yrs of age – BNT162b2 – Safety Population

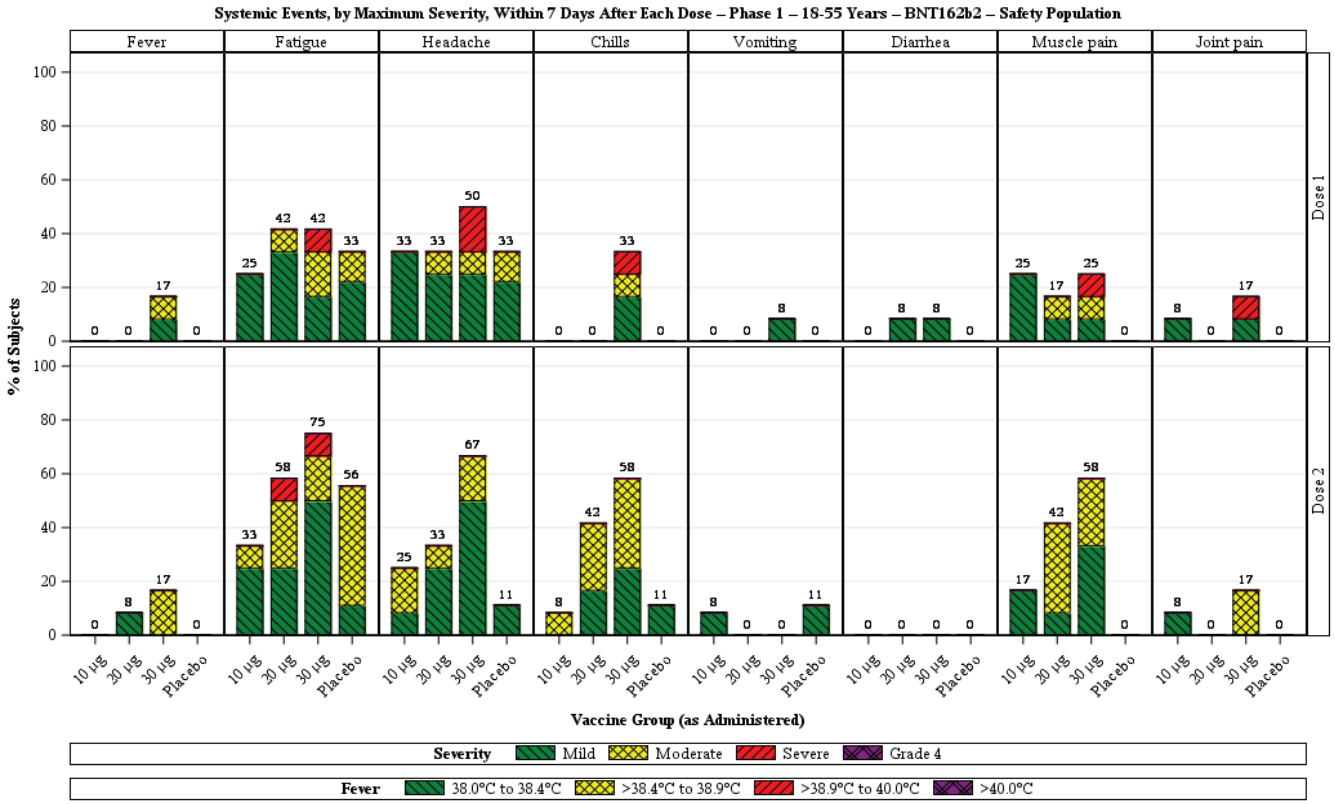


Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 28AUG2020 (16:29) Source Data: adfacevd Table Generation: 29AUG2020 (00:51)
(Cutoff Date: 24AUG2020, Snapshot Date: 28AUG2020) Output File: (CDISC)/C4591001_IA_P1/adce_f001_lr_maxsev_65_b2_p1

Figure 45: Subjects reporting local reactions, by maximum severity, within 7 d after each dose – Phase 1, 2 Doses, 21 d apart – 65-85 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 46 and Figure 47). 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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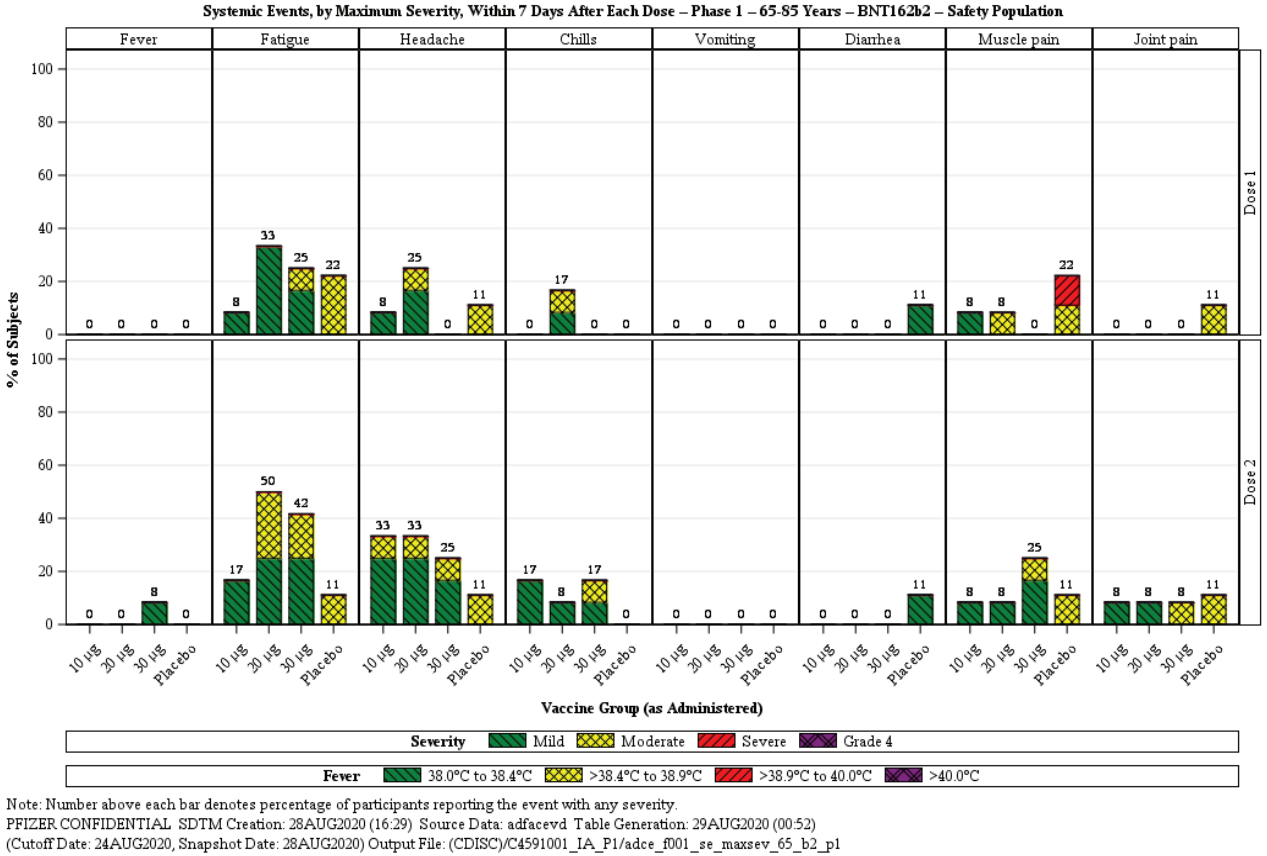
(Cutoff Date: 24AUG2020, Snapshot Date: 28AUG2020) Output File: (CDISC)/C4591001_IA_P1/adce_f001_se_maxsev_18_b2_p1

Figure 46: Subjects reporting systemic events, by maximum severity, within 7 d after each dose – Phase 1, 2 doses, 21 d apart – 18-55 yrs of age – BNT162b2 – Safety Population



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

Figure 47: Subjects reporting systemic events, by maximum severity, within 7 d after each dose – Phase 1, 2 doses, 21 d apart – 65-85 yrs of age – BNT162b2 – Safety Population

Adverse events - BNT162b2

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

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

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

Analysis of AEs

For BNT162b2 recipients, the most common AEs overall by standard organ class (SOC) and preferred term (PT) across dose levels in the younger group were general disorders and administration site conditions, which included injection site pain and injection site erythema. The most common AEs overall by SOC and PT across dose levels in the older group were nervous system disorders, which included sciatica and radiculopathy. No AEs were reported for > 1 participant in either age group for BNT162b2 or placebo recipients.

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

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

Additional follow-up from 1 to 4 months after Dose 2 to the data cutoff date (14 NOV 2020) included 1 severe SAE (neuritis) reported by 1 participant in the younger BNT162b2 30 µg group; per the participant's medical examination and history, this event was linked to a blood draw, and the investigator considered there was a reasonable possibility that the event neuritis was related to clinical study procedure (blood draw) but unrelated to

vaccination. The AE profile for remaining non-serious events was unchanged. No additional participants had related AEs.

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

Safety populations

A total of 43,252 participants (participants include BNT162b2 and placebo recipients) had some follow-up for safety from Dose 1 to the data cutoff date of 14 NOV 2020.

A total of 37,706 participants had a median follow-up time of 2 months after Dose 2; of these, 19,067 (50.6%) had at least 2 months of follow-up after Dose 2. There were 120 HIV positive participants included in demographic and disposition summaries but excluded from safety and efficacy endpoints. Therefore, 37,586 participants were included in the primary AE analyses.

The phase 2/3 reactogenicity subset was comprised of 8183 participants (≥ 12 yrs of age). The reactogenicity subset described here did not include adolescents 16 and 17 yrs of age. Reactogenicity in 100 adolescent participants aged 12 to 15 yrs is shown separately.

Reactogenicity

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

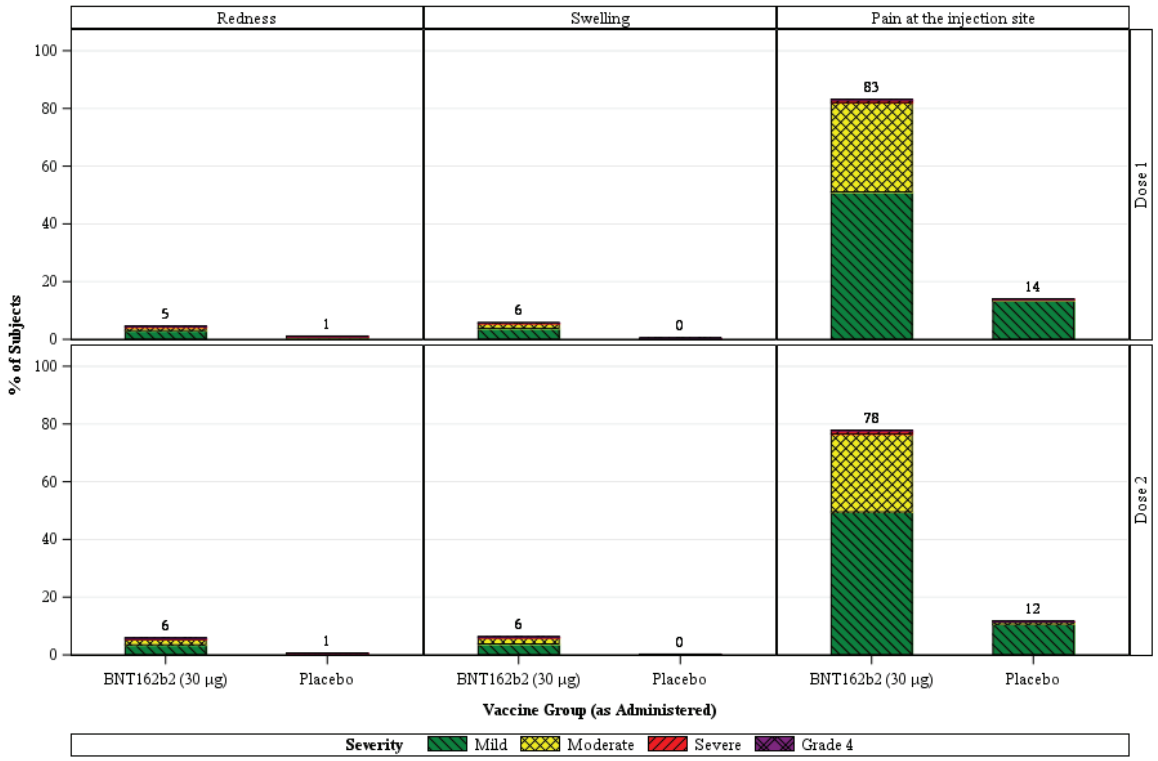
Local reactions

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

In the BNT162b2 group, frequencies of redness and swelling were similar in the younger and older age group and were generally similar in frequency after Dose 1 and Dose 2.

Most local reactions were mild or moderate in severity. Few severe local reactions were reported after either dose. The frequency of any severe local reactions after Dose 1 and after Dose 2 was ≤ 0.6%. No grade 4 (potentially life-threatening) reactions were reported.

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



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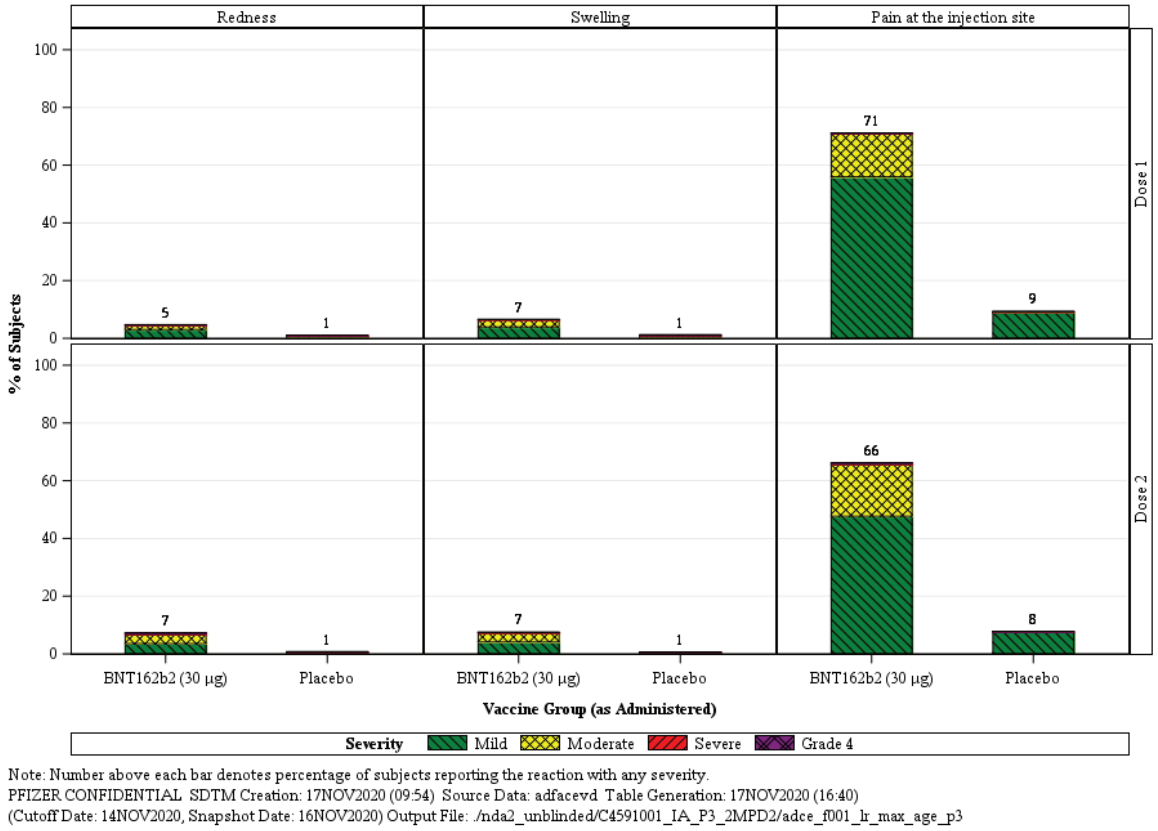
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adce_f001_lr_max_age_p3

Figure 48: 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: 16-55 yrs



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

Figure 49: 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

Local reactions in younger adolescents

In adolescents 12-15 yrs of age, pain at the injection site was the most frequent local reaction in the BNT162b2 group, reported in 71.4% of participants compared to 17.6% in the placebo group after Dose 1. The incidence of pain was reduced in the BNT162b2 group and placebo group after Dose 2 (down to 58.7% vs 8.7%,). Redness and swelling were infrequent. Most local reactions were mild to moderate in severity. Two severe reactions were reported, both in the BNT162b2 group: severe redness and severe pain at the injection site.

Systemic events

Systemic events were generally increased in frequency and severity in the younger age group (Figure 50) compared with the older age group (Figure 51), 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.

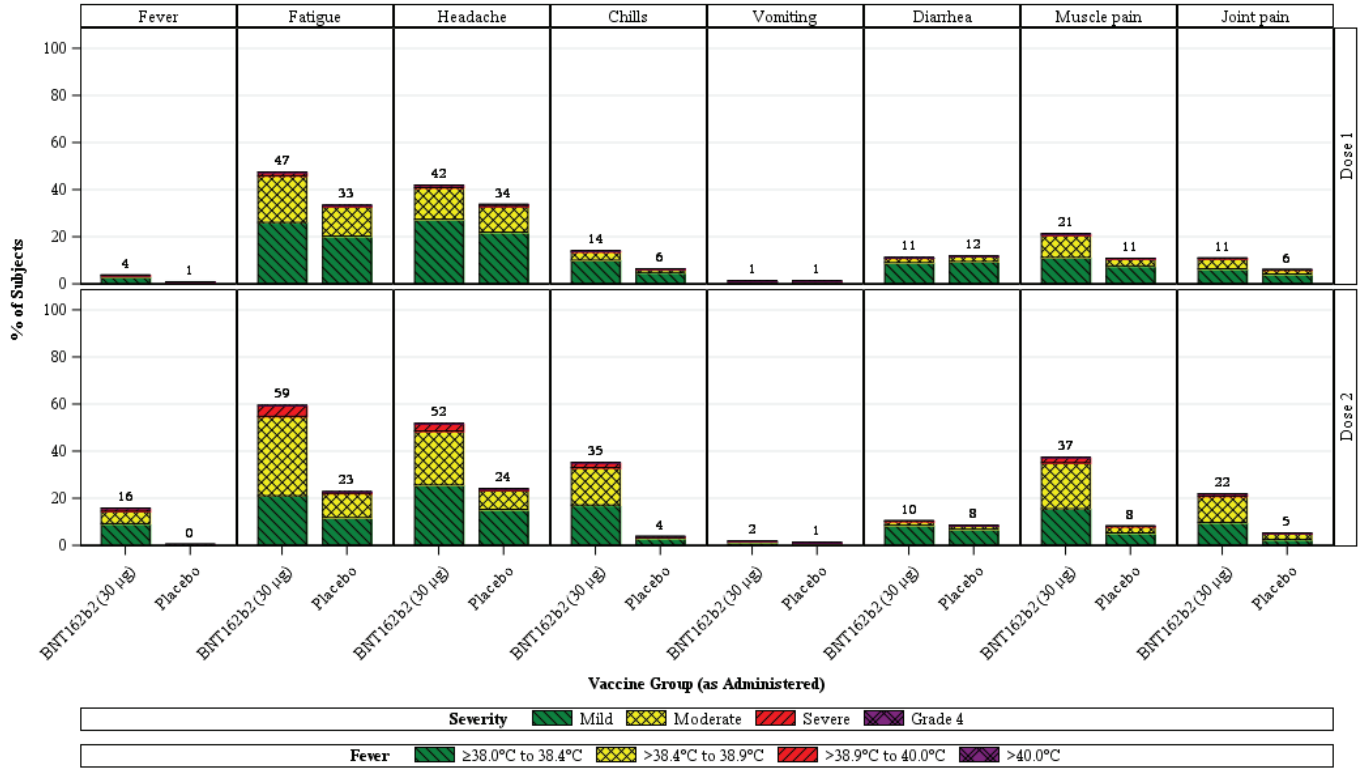
Systemic events were generally mild or moderate in intensity, more frequent in the BNT162b2 group than the placebo group, more frequent in the younger group compared with the older group, and more frequent after the second compared to the first dose. Fever was reported in 3.7% of younger adults after the first dose compared to 15.8% after the second dose compared to only 1.4% of older adults after the first dose and 10.9% after the second.

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 50). In the older age group, fever and joint pain (after Dose 1) and vomiting and diarrhea (after Dose 1 and Dose 2) were reported at similar frequencies in the placebo group and the BNT162b2 group (Figure 51).

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

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

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



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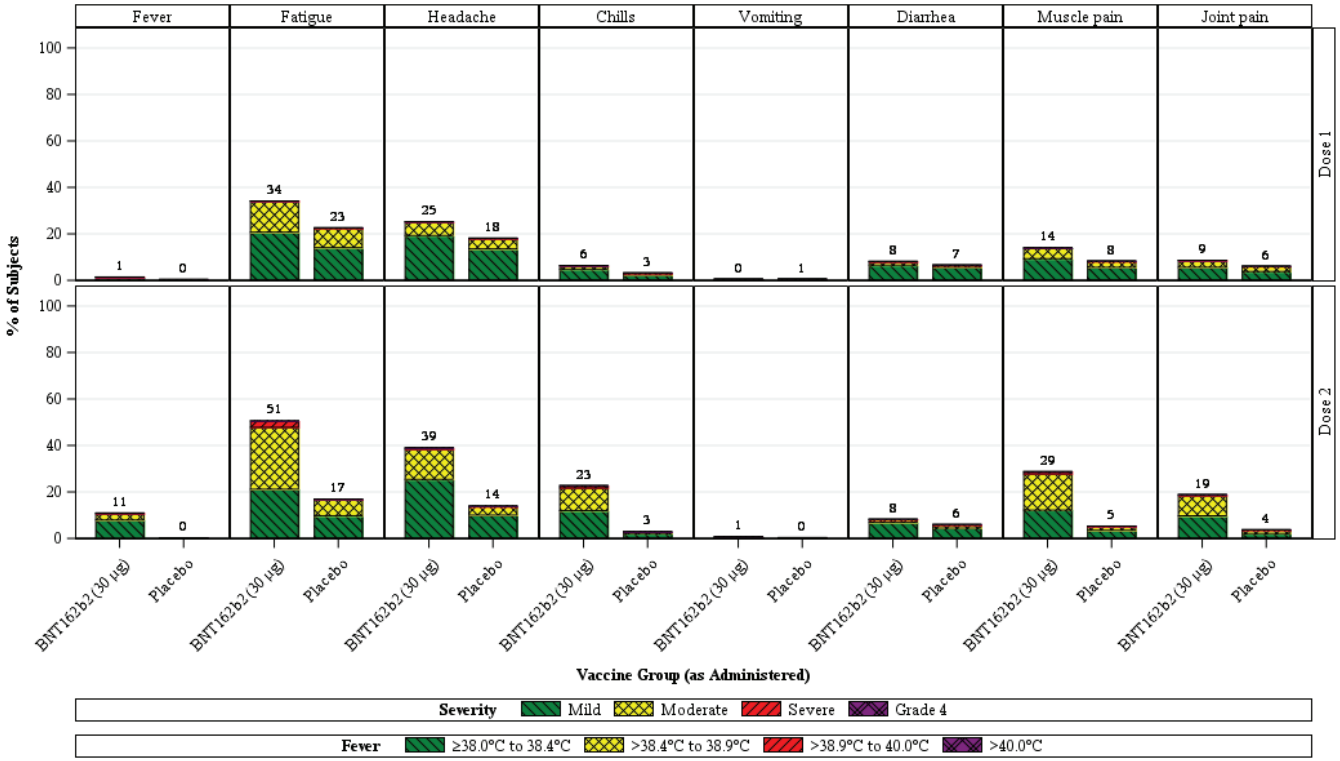
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adce_f001_se_max_age_p3

Figure 50: 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: 16-55 yrs



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

Figure 51: 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

Systemic events in younger adolescents

In younger adolescents 12 to 15 yrs of age most systemic events (other than vomiting and diarrhea, which had low incidences across groups) were reported at higher incidence in the BNT162b2 group than in the placebo group. However, there was no clear trend for increasing incidence or severity after Dose 1 compared to after Dose 2. In this age group, the most frequent prompted systemic events after Dose 1 compared to Dose 2 were (Dose 1 vs Dose 2):

- Fatigue: BNT162b2 (49.0% vs 50.0%) compared to placebo (25.5% vs 6.5%).
- Headache: BNT162b2 (42.9% vs 45.7%) compared to placebo (35.3% vs 21.7%).
- Muscle pain: BNT162b2 (22.4% vs 30.4%) compared to placebo (13.7% vs 4.3%).
- Chills: BNT162b2 (30.6% vs 28.3%) compared to placebo (7.8% vs 8.7%).
- Joint pain: BNT162b2 (12.2% vs 17.4%) compared to placebo (9.8% vs 6.5%).
- Fever: BNT162b2 (14.3% vs 19.6%) compared to placebo (0% vs 0%).
- Vomiting: reported at similar frequencies in both groups and similar after each dose.
- Diarrhea: reported at similar frequencies in both groups and similar after each dose.

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

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

Adverse events

The pattern of AEs in the 37,586 subjects with a median two month follow-up is shown in Table 21 and a similar pattern was observed in all 43,252 enrolled subjects as shown in Table 22. Among all enrolled participants, the imbalance of increased AEs in the BNT162b2 group compared to the placebo group is primarily accounted for by an increased frequency of AEs that were reactogenicity events: general disorders and administration site conditions (includes injection site pain, fatigue, pyrexia, chills), musculoskeletal and connective tissue disorders (includes myalgia and arthralgia), and nervous system disorders (includes headaches).

Table 21: Number (%) of subjects reporting at least one AE from Dose 1 to 1 month after Dose 2 – ~38,000 subjects for Phase 2/3 Analysis – Safety Population

	Vaccine group (as administered)	
Adverse Event	BNT162b2 (30 µg) (N[a]=18,801) n[b] (%)	Placebo (N[a]=18,785) n[b] (%)
Any event	5,071 (27.0)	2,356 (12.5)
Related[c]	3,915 (20.8)	953 (5.1)
Severe	220 (1.2)	109 (0.6)
Life-threatening	18 (0.1)	20 (0.1)
Any serious adverse event	103 (0.5)	81 (0.4)
Related[c]	3 (0.0)	0
Severe	57 (0.3)	48 (0.3)
Life-threatening	18 (0.1)	19 (0.1)
Any adverse event leading to withdrawal	34 (0.2)	25 (0.1)
Related[c]	14 (0.1)	7 (0.0)
Severe	13 (0.1)	7 (0.0)
Life-threatening	2 (0.0)	4 (0.0)
Death	1 (0.0)	2 (0.0)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.

b. n = Number of subjects reporting at least one occurrence of the specified event category. For "any event", n = the number of subjects reporting at least one occurrence of any event.

c. Assessed by the investigator as related to investigational product.

PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:21)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2_unblinded/C4591001_IA_P3_2MPD2/adae_s091_all_pd2_p3_saf

Table 22: Number (%) of subjects reporting at least 1 AE from Dose 1 to data cutoff date (14 NOV 2020) – Phase 2/3 (All Subjects) – Safety Population

	Vaccine group (as administered)	
Adverse event	BNT162b2 (30 µg) (N[a]=21,621) n[b] (%)	Placebo (N[a]=21,631) n[b] (%)
Any event	5,770 (26.7)	2,638 (12.2)
Related[c]	4,484 (20.7)	1,095 (5.1)
Severe	240 (1.1)	139 (0.6)
Life-threatening	21 (0.1)	24 (0.1)
Any serious adverse event	126 (0.6)	111 (0.5)
Related[c]	4 (0.0)	0
Severe	71 (0.3)	68 (0.3)
Life-threatening	21 (0.1)	23 (0.1)
Any adverse event leading to withdrawal	37 (0.2)	30 (0.1)
Related[c]	16 (0.1)	9 (0.0)
Severe	13 (0.1)	9 (0.0)
Life-threatening	3 (0.0)	6 (0.0)
Death	2 (0.0)	4 (0.0)

Note: Data for subjects randomized on or after 10 OCT 2020 are included to comprehensively show all data reported but are subject to change with additional follow-up.

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.

b. n = Number of subjects reporting at least one occurrence of the specified event category. For "any event", n = the number of subjects reporting at least one occurrence of any event.

c. Assessed by the investigator as related to investigational product.

PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:29)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2_unblinded/C4591001_IA_P3_2MPD2/adae_s091_all_p23_saf

AEs in participants with median 2 months of follow-up after Dose 2

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

- general disorders and administration site conditions (18.6% BNT162b2 vs 3.9% placebo)
- musculoskeletal and connective tissue disorders (7.3% BNT162b2 vs 2.0% placebo)
- nervous system disorders (6.1% BNT162b2 vs 2.4% placebo)
- infections and infestations (1.5% BNT162b2 vs 1.5% placebo)
- gastrointestinal disorders (2.9% BNT162b2 vs 1.9% placebo)

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

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

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

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

AEs of lymphadenopathy were reported in 64 participants (0.3%) in the BNT162b2 group and six participants (0.0%) in the placebo group. Among the AEs of lymphadenopathy in the BNT162b2 group, the majority (47 of 64) were assessed by the investigator as related to study intervention, occurred in the arm and neck region, and were reported within 2 to 4 d after vaccination.

AEs Reported in > 1% of participants in either treatment group

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

- Gastrointestinal disorders

  - Nausea (1.1% vs 0.3%)
- General disorders and administration site conditions
  - Injection site pain (11.2% vs 1.5%)
  - Pyrexia (6.1% vs 0.3%)
  - Fatigue (5.5% vs 1.4%)
  - Chills (5.3% vs 0.5%)
  - Pain (2.4% vs 0.2%)
- Musculoskeletal and connective tissue disorders
  - Myalgia (4.8% vs 0.7%)
  - Arthralgia (1.1% vs 0.4%)
- Nervous system disorders
  - Headache (5.1% vs 1.6%)

All enrolled participants

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

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

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

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

Severe or life-threatening AEs – Participants with median 2 months of follow-up after Dose 2

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

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

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

Related AEs - Participants with median 2 months of follow-up after Dose 2

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

Immediate AEs - Participants with median 2 months of follow-up after Dose 2

Among the 37,586 participants with a median of 2 months of follow-up after Dose 2 immediate AEs were low in frequency (0.4% after Dose 1; ≤ 0.3% after Dose 2). Most immediate AEs were in the SOC of general disorders and administration site conditions, primarily injection site reactions, in the BNT162b2 versus placebo groups with injection site pain (0.3% vs 0.2% after Dose 1; 0.2% vs 0.1% after Dose 2) most frequently reported.

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

Deaths in study C4591001 Phase 2/3

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

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

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

- One participant in the younger placebo group experienced an SAE of death (cause unknown; no additional information currently available at the time of this report) 34 d after Dose 2.
- One participant in the older placebo group experienced an SAE of myocardial infarction 16 d after Dose 1 and died the same day.

Serious adverse events in study C4591001 Phase 2/3

Participants with median 2 months of follow-up after Dose 2

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

The most frequently reported SAEs were in the cardiac disorders SOC (0.1% in each treatment group), nervous system disorders SOC (0.1% in each treatment group), and infections and infestations SOC (0.1% in each treatment group).

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

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

With 8,496.05 yrs of participant follow-up as of 16 NOV 2020, an observation of 12 appendicitis cases across both treatment groups is not greater than expected based on background rates estimated in a US Electronic Health Records database. The ratio of the observed number of cases compared with the expected number of cases was 1.19 (95% CI 0.62 - 2.09) overall, 0.98 (95% CI, 0.39 - 2.02) within the 18 to 54 yr age category and 1.73 (95% CI, 0.56 - 4.03) in the 55 yrs and older age category.

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

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

All enrolled participants

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

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

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

AEs leading to study withdrawal

Among all 43,448 enrolled participants included in the safety database up to the data cutoff date, few participants in the BNT162b2 group (0.2%) and in the placebo group (0.1%) were withdrawn because of AEs. Thirty-seven (37) participants in the BNT162b2 group and 30 participants in the placebo group had an AE leading to withdrawal.

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

AEs of clinical interest in study C4591001 Phase 2/3

No AESIs were prespecified in the Study C4591001 protocol.

Adverse events of clinical interest, such as the US Centers for Disease Control and Prevention (CDC) list of AESIs for COVID-19, which both includes terms potentially indicative of severe COVID-19 or serious autoimmune and neuroinflammatory disorders, were considered in the review of reported events.

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

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

Severe COVID-19 cases in study C4591001 Phase 2/3

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

Pregnancies in study C4591001

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

6.1.2.4.3 Safety conclusions from Study C4591001/BNT162-02

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

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

6.1.2.5 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. The vaccine appears to be safe and well tolerated across the safety population and within demographic subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status. The preponderance of severe cases of COVID-19 in the placebo group relative to the BNT162b2 group (9 of 10) suggests no evidence of VAED.

Vaccine efficacy was remarkably high in participants without evidence of prior SARS-CoV-2 infection, at ≥ 95% for participants without prior evidence of SARS-CoV-2 infection and

> 94% for those with and without prior infection, in the planned interim and final analyses. Observed VE was > 93% across subgroups identified by age, sex, race/ethnicity, and country with the exception of "all others" race group (89.3% VE) and Brazil (87.7% VE).

Severe cases evaluated for efficacy were confined predominantly to the placebo group; only one severe case was reported in the BNT162b2 group in the final analysis. The efficacy data suggest highly effective protection against COVID-19 in a broad population of individuals across demographic characteristics.

6.1.3 BNT162-03 for BNT162b1 in healthy Chinese younger and older adults

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

Clinical conduct of the study is ongoing. For an overview of the number of participants dosed per dose level and age group, see Table 8. All planned vaccine administration to trial participants has been completed and the dosed participants are now in follow-up.

Currently, only preliminary reactogenicity, safety, and tolerability data is available. BNT162b1 dosed twice at 10 µg and 30 µg was generally safe and well tolerated. There were two SAEs (both in one participant who was hospitalized due to joint dislocation and humeral fracture after a car accident; this SAE was considered not related to IMP by the investigator), no AESIs, and two participants were withdrawn due to related AEs. One participant was withdrawn due to AEs considered related to IMP by the investigator (after Dose 1, 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.

6.1.4 BNT162-04 for BNT162b3 in healthy younger and older adults

This is a multi-site, Phase 1/2, 2-part, 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. For an overview of the number of adults immunized per dose level and age group, see Table 8. Except for at the 30 µg dose level, all planned vaccine administration to trial participants has been completed and the dosed participants are now in follow-up.

Currently, only preliminary unaudited reactogenicity and tolerability data after dosing with BNT162b3 in younger adults aged 18 to 55 yrs and older adults aged 65 to 85 yrs is available. Younger and older adults dosed once or twice at dose levels up 30 µg, showed acceptable tolerability, there were no SAEs, AESIs, or subjects withdrawn due to related AEs after dosing with BNT162b3.

6.1.5 C4591005/BNT162-05 (Japan)

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

This study is ongoing clinically. For an overview of the number of adults immunized per dose level and age group, see Table 8.

6.1.6 BNT162-06 for BNT162b2 in healthy Chinese younger and older 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. For an overview of the number of adults immunized per dose level and age group, see Table 8. 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 SAEs, no AESIs, and no subjects were withdrawn due to related AEs

6.2 Marketing experience

BNT162b2 has been authorized for emergency use or been given conditional marketing authorization in numerous countries worldwide.

The safety profile of BNT162b2 based on available data in the ongoing Phase 2/3 BNT162-02/C4591001 study is favorable. Following authorization, BNT162b2 has been administered to millions of individuals worldwide. Anaphylactic reactions have been reported in the post-authorization setting; they were not observed in association with the vaccine in the clinical study. The benefit-risk profile of BNT162b2 remains positive. It is estimated that ~26,079,300 doses of BNT162b2 were shipped worldwide during the reporting interval from 01 DEC 2020 through 31 DEC 2020.

The BNT162 vaccine candidates BNT162a1, BNT162b1, BNT162b3, and BNT162c2 have neither been approved for use nor been marketed in any country.

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). A fifth vaccine candidate (BNT162b3) was later added to the program.

BNT162b2 was selected for further development and has been authorized for emergency use or been given conditional marketing authorization in numerous countries worldwide. Since then, BNT162b2 has been administered to millions of individuals worldwide. Further clinical investigation of BNT162b2 is ongoing to expand the studied populations.

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

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 16 yrs of age and older.

7.2 Posology and method of administration

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. BNT162c2 is also under clinical investigation for single dose administration.

BNT162b2

Individuals 16 years of age and older

BNT162b2 is administered intramuscularly after dilution as a series of 2 doses (0.3 mL each) 3 weeks apart. The approved dose is 30 µg.

There are no data available on the interchangeability of BNT162b2 with other COVID-19 vaccines to complete the vaccination series. Individuals who have received 1 dose of BNT162b2 should receive a second dose of BNT162b2 to complete the vaccination course.

Pediatric population

The safety and efficacy of BNT162b2 in children and adolescents aged < 16 yrs of age have not yet been established. Limited data are available.

Elderly population

No dosage adjustment is required in elderly individuals ≥ 65 yrs of age.

Method of administration

BNT162 vaccines should be administered IM. The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccines intravenously, intradermally, subcutaneously, orally or by any route other than intramuscular.

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, BNT162b3, and BNT162c2, which are vaccine candidates under development.

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 trial participants has been completed and all dosed participants are now in follow-up.

BNT162b2

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported for BNT162b2 during post-marketing surveillance. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of vaccine.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic

response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination with BNT162b2 should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other IM injections, BNT162b2 should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy, safety and immunogenicity of BNT162b2 has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy in powered clinical studies. The efficacy of BNT162b2 may be lower in immunosuppressed individuals.

Duration of protection

The duration of protection afforded by BNT162b2 is unknown as it is still being determined in ongoing clinical studies.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with BNT162b2 may not protect all vaccine recipients. For BNT162b2 requiring two immunizations, individuals may not be fully protected until 7 d after their second immunization.

Excipients

BNT162b2 contains less than 1 mmol potassium (39 mg) per dose, i.e., is essentially 'potassium-free'.

BNT162b2 contains less than 1 mmol sodium (23 mg) per dose, i.e., is essentially 'sodium-free'.

For study-specific special warnings and precautions, see the respective study protocol.

7.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed for any of the BNT162 vaccines.

Concomitant administration of BNT162 vaccines with other vaccines has not been studied.

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

No macroscopic or microscopic changes in male and female reproductive tissues were reported in repeat-dose toxicity study testing of BNT162a1, BNT162b1, BNT162b2, and BNT162c1 performed in rats.

Pregnancy

There is limited experience with use of BNT162b2 in pregnant women. There is no experience with use of the other BNT162 candidate vaccines in pregnant women.

For BNT162b1, BNT162b2, and BNT162b3, animal studies indicate no direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or postnatal development (see Section 5.3.4).

For BNT162a1 and BNT162c2, no studies with pregnant animals have been performed.

Administration of BNT162b2 in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Breast-feeding

It is unknown whether BNT162 vaccines are excreted in human milk.

Fertility

For BNT162b1, BNT162b2, and BNT162b3, animal studies indicate no direct or indirect harmful effects with respect to reproductive toxicity (see Section 5.3.4).

For BNT162a1 and BNT162c2, no fertility studies have been performed.

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 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-marketing 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

The safety of BNT162b2 was evaluated in participants 16 yrs of age and older in the clinical study C4591001/BNT162-02 that included 21,744 participants that have received at least one dose of BNT162b2.

In study C4591001/BNT162-02 as of the cutoff date of 14 NOV 2020, a total of 21,720 participants 16 yrs of age or older received at least one dose of BNT162b2, and a total of 21,728 participants 16 yrs of age or older received placebo (including 138 and 145 adolescents 16 and 17 yrs of age in the vaccine and placebo groups, respectively). A total of 20,519 participants 16 yrs of age or older received two doses of BNT162b2.

At the time of the analysis of study C4591001/BNT162-02, a total of 19,067 (9,531 BNT162b2 and 9,536 placebo) participants 16 yrs of age or older were evaluated for safety for at least 2 months after the second dose of BNT162b2. This included a total of 10,727 (5,350 BNT162b2 and 5,377 placebo) participants 16 to 55 yrs of age and a total of 8,340 (4,181 BNT162b2 and 4,159 placebo) participants 56 yrs and older.

The most frequent ARs in participants 16 yrs of age and older were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia and 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 slightly lower frequency of reactogenicity events was associated with greater age.

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 23: 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		
Immune system disorders			Hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema) *		Anaphylaxis*
Psychiatric disorders					
Nervous system disorders	Headache				
Gastrointestinal disorders		Nausea			
Musculoskeletal and connective tissue disorders	Arthralgia; myalgia		Pain in extremity*		
General disorders and administration site conditions	Injection site pain; fatigue; chills; pyrexia;† injection site swelling	Injection site redness	Malaise		

* These were identified as adverse reactions in the post-authorization/approval setting; Urticaria and Angioedema frequency is rare.
† A higher frequency of pyrexia was observed after the 2nd dose.

The safety profile in 545 subjects receiving BNT162b2, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

In Study C4591001 / BNT162-02 (cutoff date of 14 NOV 2020), Bell's palsy (facial paralysis) was reported by four participants in the BNT162b2 group. Onset of facial paralysis was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of Bell's palsy were reported in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine.

7.8.2 Reference safety information for assessment of expectedness of serious adverse drug reactions

The RSI is used for the assessment of expectedness for regulatory reporting of serious adverse drug reactions (SARs) that are reported in clinical studies.

BNT162b2

The RSI for BNT162b2 is in Section 7.8.1. Based on post-authorization experience with BNT162b2, anaphylaxis has been identified as an SAR that is considered expected by the sponsor for regulatory reporting purposes.

BNT162a1, BNT162b1, BNT162b3, and BNT162c2

For BNT162a1, BNT162b1, BNT162b3, and BNT162c2, no SARs are considered `expected´ at this time. All SARs and ARs will therefore be considered as unexpected.

7.9 Overdose

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, or BNT162c2 vaccine candidates.

For BNT162b2, overdose data is available from 52 study participants included in the clinical study that due to an error in dilution received 58 µg of BNT162b2. The vaccine recipients did not report an increase in reactogenicity or ARs.

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 participant exposure to BNT162 vaccines in ongoing clinical studies, see Table 8. 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

See Section 7.8.1.

7.11.3 Known drug class effects and other human experience

Vaccine-associated enhanced disease (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 are too limited to fully exclude that BNT162 vaccines may cause enhanced disease in vaccinated subjects. 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 et al. 2020); that immune profile is elicited by BNT162b2 in clinical and preclinical studies of BNT162b2 (Sahin et al. 2020b; Vogel et al. 2020). 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.

7.11.4 Use of BNT162b2 in individuals 12 to 15 yrs of age

In Study C4591001, individuals 12 to 15 yrs of age were included in the Phase 2/3 reactogenicity subset. Pain at the injection site was the most frequent local reaction in the BNT162b2 group. Most local reactions were mild to moderate in severity. The most frequent prompted systemic events were fatigue, headache, muscle pain, chills, joint pain, fever, vomiting, and diarrhea. Most systemic events were mild to moderate in severity. Refer to Section 6.1.2.4.2 for additional details.

7.11.5 Overall conclusions

BNT162a1, BNT162b1, BNT162b3, BNT162c2

The AEs observed after administration of BNT162a1, BNT162b1, BNT162b3, or BNT162c2 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 intramuscularly. Reactogenicity was mostly mild to moderate and short-lived after dosing, and the AE profile did not suggest any serious safety concerns.

BNT162b2

The ARs determined for BNT162b2 from the available unblinded clinical study data are mostly reflective of mild to moderate local and systemic reactogenicity events. Additional ARs determined from the clinical study data are lymphadenopathy, nausea and malaise. Since authorization of BNT162b2, anaphylaxis has been reported and determined to be an AR.

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 16 yrs of age and older and supports the continued study of BNT162b2.

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9 APPENDICES

Table 24: Tabular summaries of non-clinical studies - primary pharmacodynamic effects

Study number	Study type	Species / Test system	Product code, (RNA type, sequence variant)		Dose [µg]	Results	Cross reference
BNT162 vaccine studies (clinical candidates)							
R-20-0074	*In vitro* antigen expression and localization	HEK293T cells	BNT162a1 BNT162b1 BNT162b2 BNT162c2	(uRNA, V5) (modRNA, V5) (modRNA, V9) (saRNA, V9)	1, 2, 5 1, 2, 5	All tested items expressed the encoded S protein derived antigen.	Section 5.1.1.1
R-20-0040 and R-20-0140	*In vivo* immunogenicity	Mice BALB/c	BNT162a1	(uRNA, V5)	1, 5, 10	Immunogenicity was shown in all tested doses.	Section 5.1.1.2.4
R-20-0042 and R-20-0084	*In vivo* immunogenicity	Mice BALB/c	BNT162b1	(modRNA, V5)	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 5.1.1.2.1
R-20-0085	*In vivo* immunogenicity	Mice BALB/c	BNT162b2	(modRNA, V9)	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 5.1.1.2.2
R-20-0145	*In vivo* immunogenicity	Mice BALB/c	BNT162b3	(modRNA, V5TM)	0.2, 1	Immunogenicity was shown in all tested doses.	Section 5.1.1.2.3
R-20-0053	*In vivo* immunogenicity	Mice BALB/c	BNT162c2	(saRNA, V9)	0.2, 1, 5	Immunogenicity was shown in all tested doses.	Section 5.1.1.2.4
Study 38166	*In vivo* immunogenicity	Wistar Han rats	BNT162a1 BNT162b1	(uRNA, V5) (modRNA, V5)	10, 30 30, 100	Immunogenicity was shown in all tested doses.	Section 5.1.1.3.1
VAC-2020-NIRC-COVID-1681	*In vivo* immunogenicity	NHP rhesus macaques (*Maccaca mulatta)*	BNT162b1	(modRNA, V5)	30, 100	Immunogenicity was shown in all tested doses.	Section 5.1.1.4.1
COVID-Rh-2020-01	*In vivo* immunogenicity	NHP rhesus macaques (*Maccaca mulatta)*	BNT162b3	(modRNA, V5TM)	30	Immunogenicity was shown.	Section 5.1.1.4.1

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 BNT162b2 BNT162c1 BNT162c2	(uRNA, V8) (modRNA, V8) (saRNA, V5) (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 38166	*In vivo* immunogenicity	Wistar Han rats	BNT162b2 BNT162c1	(modRNA, V8) (saRNA, V5)	100 30	Immunogenicity was shown in all tested doses.	Section 5.1.1.3.1
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 5.1.1.4.1

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 25: Overview planned clinical studies with BNT162b2

Study number (if assigned)	Population	Study objective	Approx. start
BNT162-06	Aged 18 to 55 yrs and aged > 55 yrs	Use of BNT162b2 in healthy Chinese adults.	Q1-2021
BNT162-07 / C4591007	Aged 5 to 11 yrs	Use of BNT162b2 in pediatric aged 5 to 11 yrs and older.	Q2-2021
BNT162-09 / C4591017	Aged 12 to 50 yrs	Lot consistency and immunogenicity study.	Q1-2021
BNT162-10 / C4591015	Women between 24 and 34 weeks gestation	Use of BNT162b2 in pregnancy.	Q1-2021
C4591018	Aged ≥ 18 yrs with rheumatoid arthritis	Use of BNT162b2 in adults with rheumatoid arthritis receiving immunomodulators.	Q2-2021
(tbd) / C4591020	Aged 18 to 55 yrs	Bridging study for thermostable lyophilized formulations.	Q2-2021
PIP study 3	Aged 0 to 4 yrs	Use of BNT162b2in pediatrics aged 0 to 4 yrs.	Q3-2021
PIP study 4	Aged < 18 yrs	Use of BNT162b2 in immunocompromised subjects aged < 18 yrs.	Q3-2021

PIP = pediatric investigation plan; tbd = to be decided.

10 SUMMARY OF CHANGES TO THE LAST IB VERSION

This tabulation summarizes the key changes introduced when preparing version 6.0. This summary does not include editorial or formatting changes.

IB Section updated	Summary of the updates
Title page and all headers	Change of sponsor from BioNTech RNA Pharmaceuticals GmbH to BioNTech SE.
2 Summary	There were substantial changes. This section was updated to reflect changes in Sections 4 to 6.
3 Introduction	No substantial changes. This section was shortened and updated to reflect clinical development status.
4 Physical, chemical, and pharmaceutical properties and formulation	No substantial changes.
5.1 Non-clinical studies - Non-clinical pharmacology	There were substantial changes. Additional data from ongoing studies was added. Figure 7 is updated to include flow cytometry analysis of transfected HEK293T cells (Figure 7B). Figure 8 was added depicting flow cytometry analysis to assess BNT162b2 surface expression. Section 5.1.4 was updated to include additional data from rhesus macaques. Data for BNT162b3 was added to Figures 14 and 15.
5.2 Non-clinical studies - Non-clinical pharmacokinetics and metabolism	There were substantial changes. Addition of new data from excipient pharmacokinetic studies in Section 5.2.2. Addition of new data from excipient metabolism studies was added in Section 5.2.4.
5.3 Non-clinical studies - Toxicology	There were substantial changes. Section 5.3.4 is expanded to include additional data from DART studies.
6 Effects in humans	There were substantial changes. For the ongoing studies BNT162-01 and BNT162-02/C4591001, preliminary data was replaced with reported data in Section 6.1. Marketing experience data was added for BNT162b2 in Section 6.2.
7 Summary of data and guidance for the investigator	There were substantial changes. This section was updated to reflect the approved product label for BNT162b2, the new non-clinical and clinical data described in Sections 5 and 6 ongoing studies BNT162-01 and BNT162-02/C4591001, preliminary data was replaced with reported data. Marketing experience data was added for BNT162b2.
8 References	No substantial changes. This section was updated according to the citations added/deleted in Sections 3 to 6.
9 Appendices	No substantial changes. Addition of a tabular overview of the planned clinical studies with BNT162b2.

Appendix 3.2
Status of Ongoing Clinical Trials (Started, or Concluded with No Final Clinical Study Reports) During the Reporting Period (S5.2)
Report Name - PF-07302048::ALL
Reporting Period: 22-Apr-2020 Through 21-Apr-2021

Protocol Id: C4591001 EudraCT Number: 2020-002641-42 Phase: III Planned Enrollment: 43998

Study Design Blinding: DOUBLE-BLIND Statistical Design: PARALLEL

Minimum Age: 12 YR Maximum Age: 999 YR Gender: BOTH (MALES AND FEMALES)

IND Number Filed To: 019736

Protocol Title: 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

Country: ARGENTINA; BRAZIL; GERMANY; SOUTH AFRICA; TURKEY; UNITED STATES

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim -Final Report Date
ONGOING	BNT162B1	STUDY DRUG	INTRAMUSCULAR-INJECTION VIAL-100UG	COVID-19 INFECTION	29-Apr-2020/ N/A	INTERIM	14-Apr-2021
	BNT162B2	STUDY DRUG	INTRAMUSCULAR-INJECTION VIAL-30UG				
	BNT162B2SA	STUDY DRUG	INTRAMUSCULAR-INJECTION VIAL-30UG				
	PLACEBO	PLACEBO	INTRAMUSCULAR-INJECTION VIAL-0UG				

Appendix 3.2
Status of Ongoing Clinical Trials (Started, or Concluded with No Final Clinical Study Reports) During the Reporting Period (S5.2)
Report Name - PF-07302048::ALL
Reporting Period: 22-Apr-2020 Through 21-Apr-2021

Protocol Id: C4591005 EudraCT Number: Phase: II Planned Enrollment: 160

Study Design Blinding: DOUBLE-BLIND Statistical Design: PARALLEL

Minimum Age: 20 YR Maximum Age: 85 YR Gender: BOTH (MALES AND FEMALES)

IND Number Filed To: NONE

Protocol Title: 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

Country: JAPAN

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim -Final Report Date
ONGOING	BNT162B2	STUDY DRUG	INTRAMUSCULAR-INJECTION VIAL-30UG	COVID-19 INFECTION	21-Oct-2020/ N/A		
	PLACEBO	PLACEBO	INTRAMUSCULAR-INJECTION VIAL-0UG				

Appendix 3.2
Status of Ongoing Clinical Trials (Started, or Concluded with No Final Clinical Study Reports) During the Reporting Period (S5.2)
Report Name - PF-07302048::ALL
Reporting Period: 22-Apr-2020 Through 21-Apr-2021

Protocol Id: C4591007 EudraCT Number: 2020-005442-42 Phase: I Planned Enrollment: 4644

Study Design Blinding: OPEN Statistical Design: PARALLEL

Minimum Age: 6 MTH Maximum Age: 11 YR Gender: BOTH (MALES AND FEMALES)

IND Number Filed To: 019736

Protocol Title: 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 <12 YEARS OF AGE

Country: UNITED STATES

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim -Final Report Date
ONGOING	BNT162B2	STUDY DRUG	INTRAMUSCULAR-INJECTION VIAL-30UG	COVID-19 INFECTION	24-Mar-2021/ N/A		

Appendix 3.2
Status of Ongoing Clinical Trials (Started, or Concluded with No Final Clinical Study Reports) During the Reporting Period (S5.2)
Report Name - PF-07302048::ALL
Reporting Period: 22-Apr-2020 Through 21-Apr-2021

Protocol Id: C4591015 EudraCT Number: 2020-005444-35 Phase: III Planned Enrollment: 4000

Study Design Blinding: DOUBLE-BLIND Statistical Design: PARALLEL

Minimum Age: 0 YR Maximum Age: 999 YR Gender: BOTH (MALES AND FEMALES)

IND Number Filed To: 019736

Protocol Title: 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 YEARS OF AGE AND OLDER

Country: UNITED STATES

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim -Final Report Date
ONGOING	BNT162B2	STUDY DRUG	INTRAMUSCULAR-INJECTION VIAL-30UG	MATERNAL IMMUNISATION	16-Feb-2021/ N/A		
	PLACEBO	PLACEBO	INTRAMUSCULAR-INJECTION VIAL-0NO UNITS				

Appendix 3.2
Status of Ongoing Clinical Trials (Started, or Concluded with No Final Clinical Study Reports) During the Reporting Period (S5.2)
Report Name - PF-07302048::ALL
Reporting Period: 22-Apr-2020 Through 21-Apr-2021

Protocol Id: C4591017 EudraCT Number: Phase: III Planned Enrollment: 1530

Study Design Blinding: THIRD-PARTY BLIND Statistical Design: PARALLEL

Minimum Age: 12 YR Maximum Age: 50 YR Gender: BOTH (MALES AND FEMALES)

IND Number Filed To: 019736

Protocol Title: 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 YEARS OF AGE

Country: UNITED STATES

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim -Final Report Date
ONGOING	BNT162B2	STUDY DRUG	INTRAMUSCULAR-INJECTION VIAL-30UG	COVID-19 INFECTION	15-Feb-2021/ N/A		

Appendix 3.2
Status of Ongoing Clinical Trials (Started, or Concluded with No Final Clinical Study Reports) During the Reporting Period (S5.2)
Report Name - PF-07302048::ALL
Reporting Period: 22-Apr-2020 Through 21-Apr-2021

Protocol Id: C4591020 EudraCT Number: Phase: III Planned Enrollment: 550

Study Design Blinding: DOUBLE-BLIND Statistical Design: PARALLEL

Minimum Age: 18 YR Maximum Age: 55 YR Gender: BOTH (MALES AND FEMALES)

IND Number Filed To: 019736

Protocol Title: A PHASE 3, RANDOMIZED, OBSERVER-BLIND STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A LYOPHILIZED FORMULATION OF THE VACCINE CANDIDATE BNT162b2 AGAINST COVID-19 IN HEALTHY ADULTS 18 THROUGH 55 YEARS OF AGE

Country: UNITED STATES

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim -Final Report Date
ONGOING	BNT162B2	STUDY DRUG	INTRAMUSCULAR-INJECTION VIAL-30UG	COVID-19 INFECTION	01-Apr-2021/ N/A		

Appendix 3.2.1
Status of Ongoing Clinical Trials (Started, or Concluded with no Final Clinical Study Reports) During the Reporting Period from the License Partner
Reporting Period: 22-Apr-2020 Through 21-Apr-2021

Protocol Id: BNT162-01 EudraCT Number: 2020-001038-36 Phase: I Planned Enrollment: 618

Study Design Blinding: OPEN LABEL Statistical Design: DOSE ESCALATION AND EXPANSION

Minimum Age: 18 YR Maximum Age: 85 YR Gender: BOTH (MALES AND FEMALES)

IND Number Filed To: N/A (German trial)

Protocol Title: 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

Country: GERMANY

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim-Final Report Date
ONGOING	BNT162b1	STUDY DRUG	INTRAMUSCULAR-INJECTION 1 - 60 µg	COVID-19 INFECTION	23-Apr-2020/ N/A	INTERIM	v. 1 23-Sep-2020, v. 2 28-Nov-2020, v. 3 22-Mar-2021
	BNT162b2	STUDY DRUG	INTRAMUSCULAR-INJECTION 1 - 30 µg				
	BNT162c2	STUDY DRUG	INTRAMUSCULAR-INJECTION 0.1 - 3 µg				
	BNT162a1	STUDY DRUG	INTRAMUSCULAR-INJECTION 0.1 – 3 µg				

Appendix 3.2.1
Status of Ongoing Clinical Trials (Started, or Concluded with no Final Clinical Study Reports) During the Reporting Period from the License Partner
Reporting Period: 22-Apr-2020 Through 21-Apr-2021

Protocol Id: BNT162-04 EudraCT Number: 2020-003267-26 Phase: I/II Planned Enrollment: 144

Study Design Blinding: OPEN-LABEL Statistical Design: DOSE ESCALATION AND EXPANSION

Minimum Age: 18 YR Maximum Age: 85 YR Gender: BOTH (MALES AND FEMALES)

IND Number Filed To: N/A

Protocol Title: 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

Country: GERMANY

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim-Final Report Date
ONGOING	BNT162b3	STUDY DRUG	INTRAMUSCULAR-INJECTION 3 - 30 µg	COVID-19 INFECTION	09-Sep-2020/ N/A	N/A	

Appendix 3.2.1
Status of Ongoing Clinical Trials (Started, or Concluded with no Final Clinical Study Reports) During the Reporting Period from the License Partner
Reporting Period: 22-Apr-2020 Through 21-Apr-2021

Protocol Id: BNT162-03[1] Chinese CT Number: ChiCTR2000034825 [Clinical Trial NCT: 04523571] Phase: I Planned Enrollment: 144

Study Design Blinding: SINGLE-BLIND Statistical Design: PARALLEL

Minimum Age: 18 YR Maximum Age: 85 YR Gender: BOTH (MALES AND FEMALES)

IND Number (China) Filed To: 2020L00033

Protocol Title: SAFETY AND IMMUNOGENICITY OF SARS-COV-2 mRNA VACCINE (BNT162B1) IN CHINESE HEALTHY SUBJECTS: A PHASE I, RANDOMIZED, PLACEBO-CONTROLLED, OBSERVER-BLIND STUDY

Country: CHINA

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim-Final Report Date
ONGOING	BNT162b1	STUDY DRUG	INTRAMUSCULAR-INJECTION VIAL– 10 µg	COVID-19 INFECTION	29-Jul-2020/ N/A	INTERIM	08-Feb-2021
	BNT162b1	STUDY DRUG	INTRAMUSCULAR-INJECTION 30 µg				
	PLACEBO	PLACEBO	INTRAMUSCULAR-INJECTION 0 µg				

[1] This study is conducted by Shanghai Fosun Pharmaceutical Development, Inc. and sponsored by BioNTech SE.

Appendix 3.2.1
Status of Ongoing Clinical Trials (Started, or Concluded with no Final Clinical Study Reports) During the Reporting Period from the License Partner
Reporting Period: 22-Apr-2020 Through 21-Apr-2021

Protocol Id: BNT162-06[2] Chinese CT Number: ChiCTR2000040044 [Clinical Trial NCT: 04649021] Phase: II Planned Enrollment: 960

Study Design Blinding: SINGLE-BLIND Statistical Design: PARALLEL

Minimum Age: 18 YR Maximum Age: 85 YR Gender: BOTH (MALES AND FEMALES)

IND Number (China) Filed To: 2020L00046

Protocol Title: SAFETY AND IMMUNOGENICITY OF SARS-COV-2 mRNA VACCINE (BNT162B2) IN CHINESE HEALTHY POPULATION: A PHASE II, RANDOMIZED, PLACEBO-CONTROLLED, OBSERVER-BLIND STUDY

Country: CHINA

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim-Final Report Date
ONGOING	BNT162b2	STUDY DRUG	INTRAMUSCULAR-INJECTION VIAL – 30 µg	COVID-19 INFECTION	05-Dec-2020/ N/A		
	PLACEBO	PLACEBO	INTRAMUSCULAR-INJECTION 0 µg				

[2] This study is conducted by Shanghai Fosun Pharmaceutical Development, Inc. and sponsored by BioNTech SE.

APPENDIX 3.3 Subjects Exposure Per Protocol by Treatment Arm (S5.3)
BNT162/PF-07302048, DSUR
Subject exposure entered into the database through 21-APR-2021

	BNT162b1	BNT162b2	BNT162b2 & Blinded boost	Placebo to BNT162b2
Protocol Number	**Number of Subjects (N)**	**Number of Subjects (N)**	**Number of Subjects (N)**	**Number of Subjects (N)**
C4591001	195	20088	758	20291
C4591005	0	119	0	0
C4591007	0	112	0	0
C4591015	0	0	0	0
C4591017	0	0	0	0
C4591020	0	0	0	0
Total	195	20319	758	20291

	BNT162b2SA	Blinded Therapy	Placebo	Total
Protocol Number	**Number of Subjects (N)**	**Number of Subjects (N)**	**Number of Subjects (N)**	**Number of Subjects (N)**
C4591001	329	4186	1012	46859
C4591005	0	0	41	160
C4591007	0	0	0	112
C4591015	0	52	0	52
C4591017	0	1573	0	1573
C4591020	0	559	0	559
Total	329	6370	1053	49315

Includes Protocols: C4591001,C4591005,C4591007,C4591015,C4591017,C4591020
PFIZER CONFIDENTIAL Date of Generation: 25MAY2021 (09:31)

	BNT162b1 (N=195)	BNT162b2 (N=20319)	BNT162b2 & Blinded boost (N=758)
Age (years)			
<=17	0	510 (2.5)	0
18-30	39 (20.0)	2483 (12.2)	127 (16.8)
31-50	48 (24.6)	6720 (33.1)	424 (55.9)
51-64	18 (9.2)	6175 (30.4)	179 (23.6)
65-74	81 (41.5)	3540 (17.4)	21 (2.8)
>=75	9 (4.6)	891 (4.4)	7 (0.9)
UNSPECIFIED	0	0	0
Mean	51.90	49.95	43.15
Median (range)	53.00 (19- 82)	52.00 (0- 89)	44.00 (18- 82)
Race, n (%)			
WHITE	177 (90.8)	16717 (82.3)	615 (81.1)
BLACK	6 (3.1)	1787 (8.8)	69 (9.1)
ASIAN	12 (6.2)	985 (4.8)	51 (6.7)
HISPANIC	0	132 (0.6)	8 (1.1)
OTHER	0	668 (3.3)	12 (1.6)
UNSPECIFIED	0	30 (0.1)	3 (0.4)
Gender, n (%)			
MALE	83 (42.6)	10389 (51.1)	369 (48.7)
FEMALE	112 (57.4)	9930 (48.9)	389 (51.3)

	Placebo to BNT162b2 (N=20291)	BNT162b2SA (N=329)	Blinded Therapy (N=6370)
Age (years)			
<=17	430 (2.1)	0	2610 (41.0)
18-30	2522 (12.4)	119 (36.2)	1249 (19.6)
31-50	6929 (34.1)	177 (53.8)	1686 (26.5)
51-64	6140 (30.3)	33 (10.0)	614 (9.6)
65-74	3441 (17.0)	0	165 (2.6)
>=75	829 (4.1)	0	46 (0.7)
UNSPECIFIED	0	0	0
Mean	49.76	35.78	28.97
Median (range)	51.00 (15- 91)	36.00 (18- 55)	24.00 (12- 86)
Race, n (%)			
WHITE	16828 (82.9)	257 (78.1)	5012 (78.7)
BLACK	1748 (8.6)	40 (12.2)	685 (10.8)
ASIAN	875 (4.3)	26 (7.9)	439 (6.9)
HISPANIC	150 (0.7)	3 (0.9)	54 (0.8)
OTHER	655 (3.2)	3 (0.9)	171 (2.7)
UNSPECIFIED	35 (0.2)	0	9 (0.1)
Gender, n (%)			
MALE	10185 (50.2)	170 (51.7)	3367 (52.9)
FEMALE	10106 (49.8)	159 (48.3)	3003 (47.1)

	Placebo (N=1053)	Total (N=49315)
Age (years)		
<=17	20 (1.9)	3570 (7.2)
18-30	187 (17.8)	6726 (13.6)
31-50	375 (35.6)	16359 (33.2)
51-64	275 (26.1)	13434 (27.2)
65-74	147 (14.0)	7395 (15.0)
>=75	49 (4.7)	1831 (3.7)
UNSPECIFIED	0	0
Mean	47.45	46.92
Median (range)	47.00 (15- 85)	48.00 (0- 91)
Race, n (%)		
WHITE	759 (72.1)	40365 (81.9)
BLACK	171 (16.2)	4506 (9.1)
ASIAN	92 (8.7)	2480 (5.0)
HISPANIC	10 (0.9)	357 (0.7)
OTHER	21 (2.0)	1530 (3.1)
UNSPECIFIED	0	77 (0.2)
Gender, n (%)		
MALE	522 (49.6)	25085 (50.9)
FEMALE	531 (50.4)	24230 (49.1)

APPENDIX 4.2 Cumulative Summary Tabulations of Demographic Data (BNT Studies BNT162-01 and BNT162-04)
BNT162, PF-07302048 DSUR

	BNT162a1 (N=30)	BNT162b1 (N=120)	BNT162b2 (N=246)	BNT162c2 P/B (N=48)	BNT162c2 SD (N=48)	BNT162b3 (N=96)	TOTAL* (N = 588)
Age [years]							
≥18 to <30 years	4 (13)	23 (19)	27 (11)	16 (33)	20 (42)	19 (20)	109 (19%)
≥30 to <50 years	10 (33)	43 (36)	70 (28)	24 (50)	15 (31)	26 (27)	188 (32%)
≥50 to <65 years	16 (53)	32 (27)	95 (39)	8 (17)	13 (27)	25 (26)	189 (32%)
≥65 to <75 years	0 (0)	20 (17)	48 (20)	0 (0)	0 (0)	20 (21)	88 (15%)
≥75 years	0 (0)	2 (2)	6 (2)	0 (0)	0 (0)	6 (6)	14 (2%)
Mean (SD)	47.3 (9.4)	46.5 (15.9)	51.92 (15.0)	36.4 (10.5)	37. 6 (12.7)	50.8 (18.3)	45.7 (ND)
Median	50.5	47.6	55.46	33.5	37.8	56.0	37.8
Min	22.4	19.9	19	21	20.4	19.8	19
Max	55.6	76.8	84	54.9	55.9	83.2	84
Race, n (%)							
Asian	0 (0)	2 (2)	1 (0)	1 (2)	1 (2)	1 (1)	6 (1%)
Black or African American	0 (0)	1 (1)	1 (0)	0 (0)	0 (0)	0 (0)	2 (0%)
White	29 (97)	117 (98)	244 (99)	46 (96)	47 (98)	95 (99)	578 (98%)
Other/multiple	1 (3)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	2 (0%)
Hispanic or Latino	0 (0)	2 (2)	1 (0)	2 (4)	1 (2)	0 (0)	6 (1%)
Not Hispanic or Latino	30 (100)	118 (98)	245 (100)	46 (96)	47 (98)	96 (100)	582 (99%)
Gender, n (%)							
Male	18 (60)	57 (48)	124 (50)	24 (50)	18 (38)	42 (44)	283 (48%)
Female	12 (40)	63 (53)	122 (50)	24 (50)	30 (63)	54 (56)	305 (52%)

ND = not determined
*Calculated by adding total exposures by mRNA constructs: BNT162a1 includes 0.1, 0.3, and 3 µg younger dose ranging cohorts; BNT162b1 includes 1, 3, 10, 20, 30, 50, 60 µg younger dose ranging cohorts and 10, 20, 30 µg older dose ranging cohorts; BNT162b2 include 1, 3, 10, 20, 30 µg younger dose ranging cohorts, 10, 20, 30 µg older dose ranging cohorts, and 3-30 µg expansion cohorts (including immunocompromised); BNT162c2 P/B includes 0.1, 0.3, 1, 3 µg younger dose ranging cohorts; BNT162c2 SD includes 0.1, 0.3, 0.6, 1 µg younger dose ranging cohorts; BNT162b3 include 3, 10, 20, 30 µg younger dose ranging cohorts and 3, 10, 20, 30 µg older dose ranging cohorts.

Dates of generation: 30APR2021 (Study BNT162-01); 28APR2021 (Study BNT162-04)
CONFIDENTIAL

Study BNT162-01 - BNT162a1

Table of content

14.1 Disposition and baseline characteristics

14.1-3 Demographic characteristics

Table 14.1-3.1-1: Demographic characteristics, continuous - BNT162a1

Safety set

Younger dose ranging cohorts					
		0.1 µg (N=12)	**0.3 µg (N=12)**	**3 µg (N=6)**	**Total (N=30)**
Age [years]	n	12	12	6	30
	Mean (SD)	50.80 (2.58)	48.31 (9.04)	38.22 (13.87)	47.29 (9.44)
	Min	47.3	27.1	22.4	22.4
	Median	50.08	51.54	36.63	50.46
	Max	55.3	55.6	54.5	55.6
Height [cm]	n	12	12	6	30
	Mean (SD)	178.1 (7.1)	172.8 (7.9)	177.5 (11.2)	175.9 (8.4)
	Min	165	160	156	156
	Median	178.0	171.5	180.0	177.0
	Max	187	188	187	188
Weight [kg]	n	12	12	6	30
	Mean (SD)	77.68 (7.59)	72.54 (10.85)	78.58 (14.93)	75.81 (10.60)
	Min	66.3	56.6	54.6	54.6
	Median	78.75	76.25	80.55	78.95
	Max	91.4	84.5	95.0	95.0

Table 14.1-3.1-1: Demographic characteristics, continuous - BNT162a1

Safety set

		Younger dose ranging cohorts			
		0.1 µg (N=12)	**0.3 µg (N=12)**	**3 µg (N=6)**	**Total (N=30)**
BMI [kg/m2]	n	12	12	6	30
	Mean (SD)	24.61 (3.14)	24.23 (2.78)	24.73 (2.63)	24.48 (2.81)
	Min	20.5	19.4	22.1	19.4
	Median	25.20	24.60	24.35	24.95
	Max	30.1	28.7	29.0	30.1

SD is only calculated if values of at least 3 subjects are available.
N = number of subjects in the analysis set; n = number of subjects with data available; SD = standard deviation.

Program: Tbase_Demo_4_1_DSUR.sas (Page 1 of 3)

Table 14.1-3.1-2: Demographic characteristics, categorical - BNT162a1

Safety set

		Younger dose ranging cohorts			
		0.1 µg (N=12) n (%)	**0.3 µg (N=12) n (%)**	**3 µg (N=6) n (%)**	**Total (N=30) n (%)**
Sex	Male	7 (58)	6 (50)	5 (83)	18 (60)
	Female	5 (42)	6 (50)	1 (17)	12 (40)
Ethnicity	Not Hispanic or Latino	12 (100)	12 (100)	6 (100)	30 (100)
Race	White	12 (100)	12 (100)	5 (83)	29 (97)
	Other	0 (0)	0 (0)	1 (17)	1 (3)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tbase_Demo_4_2_DSUR.sas (Page 2 of 3)

Table 14.1-3.1-3: Age group by gender, continuous - BNT162a1

Safety set

		Younger dose ranging cohorts			
Sex	**Age category**	**0.1 µg (N=12) n (%)**	**0.3 µg (N=12) n (%)**	**3 µg (N=6) n (%)**	**Total (N=30) n (%)**
Female	≥30 to <50 years	0 (0)	2 (17)	1 (17)	3 (10)
	≥50 to <65 years	5 (42)	4 (33)	0 (0)	9 (30)
Male	≥18 to <30 years	0 (0)	1 (8)	3 (50)	4 (13)
	≥30 to <50 years	6 (50)	1 (8)	0 (0)	7 (23)
	≥50 to <65 years	1 (8)	4 (33)	2 (33)	7 (23)
All	≥18 to <30 years	0 (0)	1 (8)	3 (50)	4 (13)
	≥30 to <50 years	6 (50)	3 (25)	1 (17)	10 (33)
	≥50 to <65 years	6 (50)	8 (67)	2 (33)	16 (53)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tbase_Demo_4_3_DSUR.sas (Page 3 of 3)

14.3 Safety

14.3.2 Further safety endpoints

14.3.2-1 Compliance

Table 14.3.2-1.1: IMP compliance - BNT162a1

Safety set

	Younger dose ranging cohorts			
	0.1 µg (N=12) n (%)	**0.3 µg (N=12) n (%)**	**3 µg (N=6) n (%)**	**Total (N=30) n (%)**
Subjects receiving first immunization	12 (100)	12 (100)	6 (100)	30 (100)
Subjects receiving boost immunization	12 (100)	12 (100)	0 (0)	24 (80)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tfsaf_IMP_1_1_DSUR.sas (Page 1 of 1)

Study BNT162-01 – BNT162b1

Table of content

14.1 Disposition and baseline characteristics

14.1-3 Demographic characteristics

Table 14.1-3.1-1: Demographic characteristics, continuous - BNT162b1 (Younger)

Safety set

		Younger dose ranging cohorts							
		1 µg (N=12)	3 µg (N=12)	10 µg (N=12)	20 µg (N=12)	30 µg (N=12)	50 µg (N=12)	60 µg (N=12)	Total (N=84)
Age [years]	n	12	12	12	12	12	12	12	84
	Mean (SD)	38.21 (10.48)	41.44 (11.27)	43.62 (11.03)	39.42 (11.41)	35.74 (8.60)	33.88 (10.72)	35.81 (12.50)	38.30 (10.99)
	Min	21.4	23.8	25.1	20.9	23.9	19.9	20.9	19.9
	Median	39.83	45.00	46.58	37.50	35.17	30.79	30.13	36.29
	Max	55.8	55.2	55.0	55.8	54.0	47.8	53.2	55.8
Height [cm]	n	12	12	12	12	12	12	12	84
	Mean (SD)	169.5 (8.8)	175.2 (7.9)	171.1 (9.7)	173.5 (10.0)	176.1 (9.0)	173.1 (7.8)	176.4 (9.6)	173.5 (9.0)
	Min	152	164	155	159	162	159	162	152
	Median	169.0	174.0	171.0	171.0	176.5	173.5	178.0	172.0
	Max	183	194	193	192	189	185	192	194
Weight [kg]	n	12	12	12	12	12	12	12	84
	Mean (SD)	72.99 (14.79)	77.11 (14.07)	71.57 (14.09)	73.58 (11.88)	79.84 (13.81)	76.73 (13.32)	78.70 (13.85)	75.79 (13.52)
	Min	50.1	57.6	54.5	55.1	59.0	57.4	62.2	50.1
	Median	70.25	77.65	71.50	72.55	79.40	79.40	77.15	75.45
	Max	97.0	110.2	100.5	103.7	97.0	97.0	105.6	110.2

Table 14.1-3.1-1: Demographic characteristics, continuous - BNT162b1 (Younger)

Safety set

		Younger dose ranging cohorts							
		1 µg (N=12)	**3 µg (N=12)**	**10 µg (N=12)**	**20 µg (N=12)**	**30 µg (N=12)**	**50 µg (N=12)**	**60 µg (N=12)**	**Total (N=84)**
BMI [kg/m2]	n	12	12	12	12	12	12	12	84
	Mean (SD)	25.17 (2.89)	24.94 (2.68)	24.20 (2.32)	24.34 (2.33)	25.68 (3.44)	25.52 (3.50)	25.19 (3.09)	25.00 (2.87)
	Min	21.2	20.9	21.0	20.6	20.2	19.6	19.8	19.6
	Median	25.35	25.05	23.95	24.05	26.15	25.20	25.15	25.00
	Max	29.6	29.3	28.7	28.1	29.8	29.9	29.8	29.9

SD is only calculated if values of at least 3 subjects are available.
N = number of subjects in the analysis set; n = number of subjects with data available; SD = standard deviation.

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Table 14.1-3.1-2: Demographic characteristics, categorical - BNT162b1 (Younger)

Safety set

		Younger dose ranging cohorts							
		1 µg (N=12) n (%)	3 µg (N=12) n (%)	10 µg (N=12) n (%)	20 µg (N=12) n (%)	30 µg (N=12) n (%)	50 µg (N=12) n (%)	60 µg (N=12) n (%)	Total (N=84) n (%)
Sex	Male	5 (42)	6 (50)	4 (33)	8 (67)	8 (67)	6 (50)	7 (58)	44 (52)
	Female	7 (58)	6 (50)	8 (67)	4 (33)	4 (33)	6 (50)	5 (42)	40 (48)
Ethnicity	Hispanic or Latino	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)	2 (2)
	Not Hispanic or Latino	11 (92)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	11 (92)	82 (98)
Race	Asian	0 (0)	0 (0)	0 (0)	1 (8)	0 (0)	0 (0)	1 (8)	2 (2)
	Black or African American	0 (0)	0 (0)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
	White	12 (100)	12 (100)	11 (92)	11 (92)	12 (100)	12 (100)	11 (92)	81 (96)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

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Table 14.1-3.1-3: Age group by gender, continuous - BNT162b1 (Younger)

Safety set

		Younger dose ranging cohorts							
Sex	**Age category**	**1 µg (N=12) n (%)**	**3 µg (N=12) n (%)**	**10 µg (N=12) n (%)**	**20 µg (N=12) n (%)**	**30 µg (N=12) n (%)**	**50 µg (N=12) n (%)**	**60 µg (N=12) n (%)**	**Total (N=84) n (%)**
Female	≥18 to <30 years	2 (17)	2 (17)	1 (8)	1 (8)	1 (8)	4 (33)	2 (17)	13 (15)
	≥30 to <50 years	4 (33)	3 (25)	3 (25)	2 (17)	3 (25)	2 (17)	1 (8)	18 (21)
	≥50 to <65 years	1 (8)	1 (8)	4 (33)	1 (8)	0 (0)	0 (0)	2 (17)	9 (11)
	≥65 to <75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	≥75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Male	≥18 to <30 years	1 (8)	0 (0)	1 (8)	1 (8)	2 (17)	1 (8)	4 (33)	10 (12)
	≥30 to <50 years	3 (25)	4 (33)	1 (8)	5 (42)	5 (42)	5 (42)	2 (17)	25 (30)
	≥50 to <65 years	1 (8)	2 (17)	2 (17)	2 (17)	1 (8)	0 (0)	1 (8)	9 (11)
	≥65 to <75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	≥75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
All	≥18 to <30 years	3 (25)	2 (17)	2 (17)	2 (17)	3 (25)	5 (42)	6 (50)	23 (27)
	≥30 to <50 years	7 (58)	7 (58)	4 (33)	7 (58)	8 (67)	7 (58)	3 (25)	43 (51)
	≥50 to <65 years	2 (17)	3 (25)	6 (50)	3 (25)	1 (8)	0 (0)	3 (25)	18 (21)
	≥65 to <75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	≥75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

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Table 14.1-3.2-1: Demographic characteristics, continuous - BNT162b1 (Older)

Safety set

		Older dose ranging cohorts				
		10 µg (N=12)	**20 µg (N=12)**	**30 µg (N=12)**	**Total (N=36)**	**Total (N=120)**
Age [years]	n	12	12	12	36	120
	Mean (SD)	64.31 (5.89)	65.66 (5.95)	67.16 (6.47)	65.71 (6.05)	46.53 (15.94)
	Min	56.1	57.0	57.3	56.1	19.9
	Median	64.17	67.38	67.96	67.21	47.63
	Max	73.9	75.8	76.8	76.8	76.8
Height [cm]	n	12	12	12	36	120
	Mean (SD)	170.2 (9.1)	165.7 (7.5)	165.3 (8.6)	167.0 (8.5)	171.6 (9.3)
	Min	156	153	155	153	152
	Median	169.5	165.5	162.0	166.5	171.0
	Max	190	178	179	190	194
Weight [kg]	n	12	12	12	36	120
	Mean (SD)	71.90 (10.98)	70.38 (9.14)	69.98 (8.06)	70.75 (9.23)	74.28 (12.57)
	Min	55.6	57.6	60.3	55.6	50.1
	Median	74.90	68.85	68.10	69.00	72.55
	Max	91.7	87.2	87.1	91.7	110.2

Table 14.1-3.2-1: Demographic characteristics, continuous - BNT162b1 (Older)

Safety set

		Older dose ranging cohorts				
		10 µg (N=12)	**20 µg (N=12)**	**30 µg (N=12)**	**Total (N=36)**	**Total (N=120)**
BMI [kg/m2]	n	12	12	12	36	120
	Mean (SD)	24.73 (2.46)	25.59 (2.22)	25.63 (2.22)	25.32 (2.28)	25.10 (2.70)
	Min	20.7	22.8	22.5	20.7	19.6
	Median	25.50	24.95	25.65	25.40	25.00
	Max	27.4	28.5	28.6	28.6	29.9

SD is only calculated if values of at least 3 subjects are available.
N = number of subjects in the analysis set; n = number of subjects with data available; SD = standard deviation.

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Table 14.1-3.2-2: Demographic characteristics, categorical - BNT162b1 (Older)

Safety set

		Older dose ranging cohorts				
		10 µg (N=12) n (%)	**20 µg (N=12) n (%)**	**30 µg (N=12) n (%)**	**Total (N=36) n (%)**	**Total (N=120) n (%)**
Sex	Male	7 (58)	2 (17)	4 (33)	13 (36)	57 (48)
	Female	5 (42)	10 (83)	8 (67)	23 (64)	63 (53)
Ethnicity	Hispanic or Latino	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)
	Not Hispanic or Latino	12 (100)	12 (100)	12 (100)	36 (100)	118 (98)
Race	Asian	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)
	Black or African American	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
	White	12 (100)	12 (100)	12 (100)	36 (100)	117 (98)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

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Table 14.1-3.2-3: Age group by gender, continuous - BNT162b1 (Older)

Safety set

		Older dose ranging cohorts				
Sex	**Age category**	**10 µg (N=12) n (%)**	**20 µg (N=12) n (%)**	**30 µg (N=12) n (%)**	**Total (N=36) n (%)**	**Total (N=120) n (%)**
Female	≥18 to <30 years	0 (0)	0 (0)	0 (0)	0 (0)	13 (11)
	≥30 to <50 years	0 (0)	0 (0)	0 (0)	0 (0)	18 (15)
	≥50 to <65 years	2 (17)	2 (17)	3 (25)	7 (19)	16 (13)
	≥65 to <75 years	3 (25)	7 (58)	5 (42)	15 (42)	15 (13)
	≥75 years	0 (0)	1 (8)	0 (0)	1 (3)	1 (1)
Male	≥18 to <30 years	0 (0)	0 (0)	0 (0)	0 (0)	10 (8)
	≥30 to <50 years	0 (0)	0 (0)	0 (0)	0 (0)	25 (21)
	≥50 to <65 years	4 (33)	2 (17)	1 (8)	7 (19)	16 (13)
	≥65 to <75 years	3 (25)	0 (0)	2 (17)	5 (14)	5 (4)
	≥75 years	0 (0)	0 (0)	1 (8)	1 (3)	1 (1)
All	≥18 to <30 years	0 (0)	0 (0)	0 (0)	0 (0)	23 (19)
	≥30 to <50 years	0 (0)	0 (0)	0 (0)	0 (0)	43 (36)
	≥50 to <65 years	6 (50)	4 (33)	4 (33)	14 (39)	32 (27)
	≥65 to <75 years	6 (50)	7 (58)	7 (58)	20 (56)	20 (17)
	≥75 years	0 (0)	1 (8)	1 (8)	2 (6)	2 (2)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

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14.3 Safety

14.3.2 Further safety endpoints

14.3.2-1 Compliance

Table 14.3.2-1.1-1: IMP compliance - BNT162b1 (Younger)

Safety set

	Younger dose ranging cohorts							
	1 µg (N=12) n (%)	3 µg (N=12) n (%)	10 µg (N=12) n (%)	20 µg (N=12) n (%)	30 µg (N=12) n (%)	50 µg (N=12) n (%)	60 µg (N=12) n (%)	Total (N=84) n (%)
Subjects receiving first immunization	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	84 (100)
Subjects receiving boost immunization	12 (100)	12 (100)	11 (92)	11 (92)	12 (100)	11 (92)	0 (0)	69 (82)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tfsaf_IMP_1_1_DSUR.sas (Page 1 of 2)

Table 14.3.2-1.1-2: IMP compliance - BNT162b1 (Older)

Safety set

	Older dose ranging cohorts				
	10 µg (N=12) n (%)	20 µg (N=12) n (%)	30 µg (N=12) n (%)	Total (N=36) n (%)	Total (N=120) n (%)
Subjects receiving first immunization	12 (100)	12 (100)	12 (100)	36 (100)	120 (100)
Subjects receiving boost immunization	12 (100)	11 (92)	12 (100)	35 (97)	104 (87)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tfsaf_IMP_1_1_DSUR.sas (Page 2 of 2)

Study BNT162-01 BNT162b2

Table of content

14.1 Disposition and baseline characteristics

14.1-3 Demographic characteristics

Table 14.1-3.1-1: Demographic characteristics, continuous - BNT162b2 (Younger)

Safety set

		Younger dose ranging cohorts					
		1 µg (N=12)	**3 µg (N=12)**	**10 µg (N=12)**	**20 µg (N=12)**	**30 µg (N=12)**	**Total (N=60)**
Age [years]	n	12	12	12	12	12	60
	Mean (SD)	36.65 (10.14)	39.64 (10.14)	35.07 (10.46)	42.75 (9.89)	47.21 (6.43)	40.26 (10.20)
	Min	21.6	24.6	19.0	29.4	35.8	19.0
	Median	37.54	40.83	36.00	42.04	47.42	41.50
	Max	53.4	55.8	51.5	55.8	55.7	55.8
Height [cm]	n	12	12	12	12	12	60
	Mean (SD)	177.8 (9.3)	173.8 (11.5)	173.6 (9.0)	168.3 (6.8)	176.3 (10.1)	174.0 (9.7)
	Min	169	155	165	157	157	155
	Median	174.5	174.0	171.0	168.0	179.0	173.0
	Max	204	195	191	181	189	204
Weight [kg]	n	12	12	12	12	12	60
	Mean (SD)	80.18 (14.13)	77.08 (10.84)	76.11 (11.67)	72.45 (10.97)	77.78 (8.43)	76.72 (11.26)
	Min	55.7	57.2	60.6	56.9	60.6	55.7
	Median	81.50	76.35	74.65	71.40	81.40	77.30
	Max	99.1	98.0	97.1	90.2	86.0	99.1

Table 14.1-3.1-1: Demographic characteristics, continuous - BNT162b2 (Younger)

Safety set

		Younger dose ranging cohorts					
		1 µg (N=12)	**3 µg (N=12)**	**10 µg (N=12)**	**20 µg (N=12)**	**30 µg (N=12)**	**Total (N=60)**
BMI [kg/m2]	n	12	12	12	12	12	60
	Mean (SD)	25.25 (3.26)	25.50 (2.79)	25.13 (2.07)	25.43 (2.34)	25.01 (1.38)	25.27 (2.37)
	Min	19.5	22.0	22.0	21.2	22.8	19.5
	Median	24.90	24.60	24.95	25.65	25.35	25.05
	Max	29.8	29.8	29.0	29.0	27.4	29.8

SD is only calculated if values of at least 3 subjects are available.
N = number of subjects in the analysis set; n = number of subjects with data available; SD = standard deviation.

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Table 14.1-3.1-2: Demographic characteristics, categorical - BNT162b2 (Younger)

Safety set

		Younger dose ranging cohorts					
		1 µg (N=12) n (%)	**3 µg (N=12) n (%)**	**10 µg (N=12) n (%)**	**20 µg (N=12) n (%)**	**30 µg (N=12) n (%)**	**Total (N=60) n (%)**
Sex	Male	7 (58)	5 (42)	4 (33)	2 (17)	8 (67)	26 (43)
	Female	5 (42)	7 (58)	8 (67)	10 (83)	4 (33)	34 (57)
Ethnicity	Hispanic or Latino	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Not Hispanic or Latino	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	60 (100)
Race	Asian	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Black or African American	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	White	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	60 (100)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

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Table 14.1-3.1-3: Age group by gender, continuous - BNT162b2 (Younger)

Safety set

		Younger dose ranging cohorts					
Sex	**Age category**	**1 µg (N=12) n (%)**	**3 µg (N=12) n (%)**	**10 µg (N=12) n (%)**	**20 µg (N=12) n (%)**	**30 µg (N=12) n (%)**	**Total (N=60) n (%)**
Female	≥18 to <30 years	1 (8)	2 (17)	3 (25)	1 (8)	0 (0)	7 (12)
	≥30 to <50 years	4 (33)	4 (33)	5 (42)	6 (50)	2 (17)	21 (35)
	≥50 to <65 years	0 (0)	1 (8)	0 (0)	3 (25)	2 (17)	6 (10)
	≥65 to <75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	≥75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Male	≥18 to <30 years	2 (17)	1 (8)	1 (8)	0 (0)	0 (0)	4 (7)
	≥30 to <50 years	4 (33)	3 (25)	2 (17)	1 (8)	6 (50)	16 (27)
	≥50 to <65 years	1 (8)	1 (8)	1 (8)	1 (8)	2 (17)	6 (10)
	≥65 to <75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	≥75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
All	≥18 to <30 years	3 (25)	3 (25)	4 (33)	1 (8)	0 (0)	11 (18)
	≥30 to <50 years	8 (67)	7 (58)	7 (58)	7 (58)	8 (67)	37 (62)
	≥50 to <65 years	1 (8)	2 (17)	1 (8)	4 (33)	4 (33)	12 (20)
	≥65 to <75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	≥75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

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Table 14.1-3.2-1: Demographic characteristics, continuous - BNT162b2 (Older)

Safety set

		Older dose ranging cohorts			
		10 µg (N=12)	**20 µg (N=12)**	**30 µg (N=12)**	**Total (N=36)**
Age [years]	n	12	12	12	36
	Mean (SD)	65.44 (7.42)	65.88 (6.56)	63.87 (5.42)	65.06 (6.39)
	Min	56.9	56.8	57.0	56.8
	Median	64.58	65.79	63.96	65.29
	Max	84.0	80.6	73.4	84.0
Height [cm]	n	12	12	12	36
	Mean (SD)	174.8 (7.9)	172.8 (9.9)	170.8 (8.1)	172.8 (8.6)
	Min	154	153	158	153
	Median	178.0	171.5	170.5	175.5
	Max	182	185	183	185
Weight [kg]	n	12	12	12	36
	Mean (SD)	77.87 (9.78)	76.91 (12.38)	75.80 (11.98)	76.86 (11.14)
	Min	55.5	57.7	60.4	55.5
	Median	78.55	77.90	78.50	78.20
	Max	91.0	101.8	94.6	101.8

Table 14.1-3.2-1: Demographic characteristics, continuous - BNT162b2 (Older)

Safety set

		Older dose ranging cohorts			
		10 µg (N=12)	**20 µg (N=12)**	**30 µg (N=12)**	**Total (N=36)**
BMI [kg/m2]	n	12	12	12	36
	Mean (SD)	25.43 (2.15)	25.62 (2.47)	25.85 (2.75)	25.63 (2.40)
	Min	21.8	22.6	21.9	21.8
	Median	25.50	25.00	25.55	25.30
	Max	28.4	29.7	29.4	29.7

SD is only calculated if values of at least 3 subjects are available.
N = number of subjects in the analysis set; n = number of subjects with data available; SD = standard deviation.

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Table 14.1-3.2-2: Demographic characteristics, categorical - BNT162b2 (Older)

Safety set

		Older dose ranging cohorts			
		10 µg (N=12) n (%)	**20 µg (N=12) n (%)**	**30 µg (N=12) n (%)**	**Total (N=36) n (%)**
Sex	Male	8 (67)	6 (50)	4 (33)	18 (50)
	Female	4 (33)	6 (50)	8 (67)	18 (50)
Ethnicity	Hispanic or Latino	0 (0)	0 (0)	0 (0)	0 (0)
	Not Hispanic or Latino	12 (100)	12 (100)	12 (100)	36 (100)
Race	Asian	0 (0)	0 (0)	0 (0)	0 (0)
	Black or African American	0 (0)	0 (0)	0 (0)	0 (0)
	White	12 (100)	12 (100)	12 (100)	36 (100)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

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Table 14.1-3.2-3: Age group by gender, continuous - BNT162b2 (Older)

Safety set

		Older dose ranging cohorts			
Sex	**Age category**	**10 µg (N=12) n (%)**	**20 µg (N=12) n (%)**	**30 µg (N=12) n (%)**	**Total (N=36) n (%)**
Female	≥18 to <30 years	0 (0)	0 (0)	0 (0)	0 (0)
	≥30 to <50 years	0 (0)	0 (0)	0 (0)	0 (0)
	≥50 to <65 years	2 (17)	0 (0)	4 (33)	6 (17)
	≥65 to <75 years	2 (17)	5 (42)	4 (33)	11 (31)
	≥75 years	0 (0)	1 (8)	0 (0)	1 (3)
Male	≥18 to <30 years	0 (0)	0 (0)	0 (0)	0 (0)
	≥30 to <50 years	0 (0)	0 (0)	0 (0)	0 (0)
	≥50 to <65 years	4 (33)	5 (42)	2 (17)	11 (31)
	≥65 to <75 years	3 (25)	1 (8)	2 (17)	6 (17)
	≥75 years	1 (8)	0 (0)	0 (0)	1 (3)
All	≥18 to <30 years	0 (0)	0 (0)	0 (0)	0 (0)
	≥30 to <50 years	0 (0)	0 (0)	0 (0)	0 (0)
	≥50 to <65 years	6 (50)	5 (42)	6 (50)	17 (47)
	≥65 to <75 years	5 (42)	6 (50)	6 (50)	17 (47)
	≥75 years	1 (8)	1 (8)	0 (0)	2 (6)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

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Table 14.1-3.3-1: Demographic characteristics, continuous - BNT162b2 (Expansion)

Safety set

		Expansion cohorts				
		3-30 µg (N=30)	**30 µg (N=90)**	**30 µg Immunocompromised (N=30)**	**Total (N=150)**	**Total (N=246)**
Age [years]	n	30	90	30	150	246
	Mean (SD)	51.92 (13.57)	55.59 (16.07)	48.49 (10.95)	53.44 (14.89)	51.92 (15.03)
	Min	23.7	20.3	26.4	20.3	19.0
	Median	55.17	60.42	51.04	57.67	55.46
	Max	73.7	80.8	70.1	80.8	84.0
Height [cm]	n	30	90	30	150	246
	Mean (SD)	174.0 (8.7)	173.0 (10.0)	172.8 (7.4)	173.1 (9.2)	173.3 (9.2)
	Min	158	155	159	155	153
	Median	174.5	172.0	172.0	172.0	173.0
	Max	188	202	186	202	204
Weight [kg]	n	30	90	30	150	246
	Mean (SD)	77.79 (12.92)	75.44 (13.02)	73.67 (9.70)	75.56 (12.40)	76.03 (11.92)
	Min	52.1	52.0	57.1	52.0	52.0
	Median	78.45	74.50	75.00	75.00	76.00
	Max	99.0	107.5	96.5	107.5	107.5

Table 14.1-3.3-1: Demographic characteristics, continuous - BNT162b2 (Expansion)

Safety set

		Expansion cohorts				
		3-30 µg (N=30)	**30 µg (N=90)**	**30 µg Immunocompromised (N=30)**	**Total (N=150)**	**Total (N=246)**
BMI [kg/m2]	n	30	90	30	150	246
	Mean (SD)	25.53 (2.72)	25.08 (2.73)	24.62 (2.57)	25.08 (2.70)	25.21 (2.58)
	Min	19.6	19.1	20.7	19.1	19.1
	Median	25.30	25.20	24.55	24.90	25.00
	Max	29.9	29.7	29.8	29.9	29.9

SD is only calculated if values of at least 3 subjects are available.
N = number of subjects in the analysis set; n = number of subjects with data available; SD = standard deviation.

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Table 14.1-3.3-2: Demographic characteristics, categorical - BNT162b2 (Expansion)

Safety set

		Expansion cohorts				
		3-30 µg (N=30) n (%)	**30 µg (N=90) n (%)**	**30 µg Immunocompromised (N=30) n (%)**	**Total (N=150) n (%)**	**Total (N=246) n (%)**
Sex	Male	17 (57)	45 (50)	18 (60)	80 (53)	124 (50)
	Female	13 (43)	45 (50)	12 (40)	70 (47)	122 (50)
Ethnicity	Hispanic or Latino	0 (0)	1 (1)	0 (0)	1 (1)	1 (0)
	Not Hispanic or Latino	30 (100)	89 (99)	30 (100)	149 (99)	245 (100)
Race	Asian	0 (0)	0 (0)	1 (3)	1 (1)	1 (0)
	Black or African American	0 (0)	1 (1)	0 (0)	1 (1)	1 (0)
	White	30 (100)	89 (99)	29 (97)	148 (99)	244 (99)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tbase_Demo_4_2_DSUR.sas (Page 8 of 9)

Table 14.1-3.3-3: Age group by gender, continuous - BNT162b2 (Expansion)

Safety set

		Expansion cohorts				
Sex	**Age category**	**3-30 µg (N=30) n (%)**	**30 µg (N=90) n (%)**	**30 µg Immunocompromised (N=30) n (%)**	**Total (N=150) n (%)**	**Total (N=246) n (%)**
Female	≥18 to <30 years	2 (7)	8 (9)	1 (3)	11 (7)	18 (7)
	≥30 to <50 years	1 (3)	4 (4)	5 (17)	10 (7)	31 (13)
	≥50 to <65 years	7 (23)	17 (19)	6 (20)	30 (20)	42 (17)
	≥65 to <75 years	3 (10)	13 (14)	0 (0)	16 (11)	27 (11)
	≥75 years	0 (0)	3 (3)	0 (0)	3 (2)	4 (2)
Male	≥18 to <30 years	0 (0)	4 (4)	1 (3)	5 (3)	9 (4)
	≥30 to <50 years	7 (23)	9 (10)	7 (23)	23 (15)	39 (16)
	≥50 to <65 years	9 (30)	18 (20)	9 (30)	36 (24)	53 (22)
	≥65 to <75 years	1 (3)	13 (14)	1 (3)	15 (10)	21 (9)
	≥75 years	0 (0)	1 (1)	0 (0)	1 (1)	2 (1)
All	≥18 to <30 years	2 (7)	12 (13)	2 (7)	16 (11)	27 (11)
	≥30 to <50 years	8 (27)	13 (14)	12 (40)	33 (22)	70 (28)
	≥50 to <65 years	16 (53)	35 (39)	15 (50)	66 (44)	95 (39)
	≥65 to <75 years	4 (13)	26 (29)	1 (3)	31 (21)	48 (20)
	≥75 years	0 (0)	4 (4)	0 (0)	4 (3)	6 (2)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tbase_Demo_4_3_DSUR.sas (Page 9 of 9)

14.3 Safety

14.3.2 Further safety endpoints

14.3.2-1 Compliance

Table 14.3.2-1.1-1: IMP compliance - BNT162b2 (Younger)

Safety set

	Younger dose ranging cohorts					
	1 µg (N=12) n (%)	3 µg (N=12) n (%)	10 µg (N=12) n (%)	20 µg (N=12) n (%)	30 µg (N=12) n (%)	Total (N=60) n (%)
Subjects receiving first immunization	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	60 (100)
Subjects receiving boost immunization	11 (92)	12 (100)	11 (92)	12 (100)	12 (100)	58 (97)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tfsaf_IMP_1_1_DSUR.sas (Page 1 of 3)

Table 14.3.2-1.1-2: IMP compliance - BNT162b2 (Older)

Safety set

	Older dose ranging cohorts			
	10 µg (N=12) n (%)	20 µg (N=12) n (%)	30 µg (N=12) n (%)	Total (N=36) n (%)
Subjects receiving first immunization	12 (100)	12 (100)	12 (100)	36 (100)
Subjects receiving boost immunization	12 (100)	12 (100)	12 (100)	36 (100)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tfsaf_IMP_1_1_DSUR.sas (Page 2 of 3)

Table 14.3.2-1.1-3: IMP compliance - BNT162b2 (Expansion)

Safety set

	Expansion cohorts				
	3-30 µg (N=30) n (%)	**30 µg (N=90) n (%)**	**30 µg Immunocompromised (N=30) n (%)**	**Total (N=150) n (%)**	**Total (N=246) n (%)**
Subjects receiving first immunization	30 (100)	90 (100)	30 (100)	150 (100)	246 (100)
Subjects receiving boost immunization	30 (100)	89 (99)	30 (100)	149 (99)	243 (99)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tfsaf_IMP_1_1_DSUR.sas (Page 3 of 3)

Study BNT162 - BNT162c2 P/B

Table of content

14.1 Disposition and baseline characteristics

14.1-3 Demographic characteristics

Table 14.1-3.1-1: Demographic characteristics, continuous - BNT162c2 P/B

Safety set

		Younger dose ranging cohorts				
		0.1 µg (N=12)	**0.3 µg (N=12)**	**1 µg (N=12)**	**3 µg (N=12)**	**Total (N=48)**
Age [years]	n	12	12	12	12	48
	Mean (SD)	36.42 (10.33)	39.41 (12.34)	34.47 (10.24)	35.42 (9.68)	36.43 (10.52)
	Min	22.6	21.0	22.4	23.2	21.0
	Median	33.38	39.04	31.54	34.00	33.50
	Max	52.7	54.9	52.3	53.2	54.9
Height [cm]	n	12	12	12	12	48
	Mean (SD)	169.3 (10.6)	173.8 (10.0)	174.6 (6.6)	168.2 (5.5)	171.5 (8.6)
	Min	157	161	163	160	157
	Median	166.5	174.0	175.0	168.0	171.0
	Max	192	189	186	177	192
Weight [kg]	n	12	12	12	12	48
	Mean (SD)	67.45 (13.53)	76.41 (15.66)	72.44 (6.86)	70.94 (11.43)	71.81 (12.35)
	Min	52.1	53.6	63.8	51.6	51.6
	Median	63.60	79.55	71.80	73.10	71.55
	Max	91.2	97.5	83.5	85.6	97.5

Table 14.1-3.1-1: Demographic characteristics, continuous - BNT162c2 P/B

Safety set

		Younger dose ranging cohorts				
		0.1 µg (N=12)	**0.3 µg (N=12)**	**1 µg (N=12)**	**3 µg (N=12)**	**Total (N=48)**
BMI [kg/m2]	n	12	12	12	12	48
	Mean (SD)	23.31 (2.38)	25.02 (2.85)	23.83 (2.39)	25.06 (3.73)	24.30 (2.90)
	Min	19.1	20.2	20.7	19.7	19.1
	Median	23.65	25.45	22.85	25.15	23.95
	Max	26.9	29.5	27.4	29.8	29.8

SD is only calculated if values of at least 3 subjects are available.
N = number of subjects in the analysis set; n = number of subjects with data available; SD = standard deviation.

Program: Tbase_Demo_4_1_DSUR.sas (Page 1 of 3)

Table 14.1-3.1-2: Demographic characteristics, categorical - BNT162c2 P/B

Safety set

		Younger dose ranging cohorts				
		0.1 µg (N=12) n (%)	**0.3 µg (N=12) n (%)**	**1 µg (N=12) n (%)**	**3 µg (N=12) n (%)**	**Total (N=48) n (%)**
Sex	Male	4 (33)	7 (58)	9 (75)	4 (33)	24 (50)
	Female	8 (67)	5 (42)	3 (25)	8 (67)	24 (50)
Ethnicity	Hispanic or Latino	0 (0)	0 (0)	2 (17)	0 (0)	2 (4)
	Not Hispanic or Latino	12 (100)	12 (100)	10 (83)	12 (100)	46 (96)
Race	Asian	1 (8)	0 (0)	0 (0)	0 (0)	1 (2)
	White	11 (92)	11 (92)	12 (100)	12 (100)	46 (96)
	Multiple	0 (0)	1 (8)	0 (0)	0 (0)	1 (2)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tbase_Demo_4_2_DSUR.sas (Page 2 of 3)

Table 14.1-3.2-3: Age group by gender, continuous - BNT162c2 P/B

Safety set

		Younger dose ranging cohorts				
Sex	**Age category**	**0.1 µg (N=12) n (%)**	**0.3 µg (N=12) n (%)**	**1 µg (N=12) n (%)**	**3 µg (N=12) n (%)**	**Total (N=48) n (%)**
Female	≥18 to <30 years	2 (17)	1 (8)	1 (8)	2 (17)	6 (13)
	≥30 to <50 years	4 (33)	3 (25)	2 (17)	4 (33)	13 (27)
	≥50 to <65 years	2 (17)	1 (8)	0 (0)	2 (17)	5 (10)
Male	≥18 to <30 years	1 (8)	2 (17)	5 (42)	2 (17)	10 (21)
	≥30 to <50 years	3 (25)	3 (25)	3 (25)	2 (17)	11 (23)
	≥50 to <65 years	0 (0)	2 (17)	1 (8)	0 (0)	3 (6)
All	≥18 to <30 years	3 (25)	3 (25)	6 (50)	4 (33)	16 (33)
	≥30 to <50 years	7 (58)	6 (50)	5 (42)	6 (50)	24 (50)
	≥50 to <65 years	2 (17)	3 (25)	1 (8)	2 (17)	8 (17)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tbase_Demo_4_3_DSUR.sas (Page 3 of 3)

14.3 Safety

14.3.2 Further safety endpoints

14.3.2-1 Compliance

Table 14.3.2-1.1-1: IMP compliance - BNT162c2 P/B

Safety set

	Younger dose ranging cohorts				
	0.1 µg (N=12) n (%)	**0.3 µg (N=12) n (%)**	**1 µg (N=12) n (%)**	**3 µg (N=12) n (%)**	**Total (N=48) n (%)**
Subjects receiving first immunization	12 (100)	12 (100)	12 (100)	12 (100)	48 (100)
Subjects receiving boost immunization	12 (100)	12 (100)	12 (100)	11 (92)	47 (98)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tfsaf_IMP_1_1_DSUR.sas (Page 1 of 1)

Study BNT162-01 – BNT162c2 SD

Table of content

14.1 Disposition and baseline characteristics

14.1-3 Demographic characteristics

Table 14.1-3.1-1: Demographic characteristics, continuous - BNT162c2 SD

Safety set

		Younger dose ranging cohorts				
		0.1 µg (N=12)	**0.3 µg (N=12)**	**0.6 µg (N=12)**	**1 µg (N=12)**	**Total (N=48)**
Age [years]	n	12	12	12	12	48
	Mean (SD)	40.03 (14.67)	35.23 (11.88)	42.40 (12.04)	32.60 (10.87)	37.56 (12.66)
	Min	20.4	22.3	22.5	21.3	20.4
	Median	41.42	32.25	41.54	27.42	37.83
	Max	55.9	53.3	55.8	53.3	55.9
Height [cm]	n	12	12	12	12	48
	Mean (SD)	167.0 (4.1)	170.4 (10.2)	174.1 (7.7)	168.8 (9.5)	170.1 (8.4)
	Min	160	157	164	155	155
	Median	167.0	166.5	174.5	167.5	168.0
	Max	173	186	189	188	189
Weight [kg]	n	12	12	12	12	48
	Mean (SD)	63.75 (6.14)	73.26 (15.39)	73.48 (9.51)	68.90 (11.56)	69.85 (11.52)
	Min	54.4	53.1	64.5	51.0	51.0
	Median	62.85	72.60	69.90	69.40	67.60
	Max	73.9	100.3	93.5	88.9	100.3

Table 14.1-3.1-1: Demographic characteristics, continuous - BNT162c2 SD

Safety set

		Younger dose ranging cohorts				
		0.1 µg (N=12)	**0.3 µg (N=12)**	**0.6 µg (N=12)**	**1 µg (N=12)**	**Total (N=48)**
BMI [kg/m2]	n	12	12	12	12	48
	Mean (SD)	22.82 (1.54)	24.97 (3.17)	24.19 (2.04)	24.04 (2.59)	24.00 (2.46)
	Min	20.2	20.4	21.1	21.1	20.2
	Median	23.00	25.15	24.05	23.60	23.90
	Max	24.7	29.7	27.7	29.9	29.9

SD is only calculated if values of at least 3 subjects are available.
N = number of subjects in the analysis set; n = number of subjects with data available; SD = standard deviation.

Program: Tbase_Demo_4_1_DSUR.sas (Page 1 of 3)

Table 14.1-3.1-2: Demographic characteristics, categorical - BNT162c2 SD

Safety set

		Younger dose ranging cohorts				
		0.1 µg (N=12) n (%)	**0.3 µg (N=12) n (%)**	**0.6 µg (N=12) n (%)**	**1 µg (N=12) n (%)**	**Total (N=48) n (%)**
Sex	Male	2 (17)	4 (33)	7 (58)	5 (42)	18 (38)
	Female	10 (83)	8 (67)	5 (42)	7 (58)	30 (63)
Ethnicity	Hispanic or Latino	0 (0)	1 (8)	0 (0)	0 (0)	1 (2)
	Not Hispanic or Latino	12 (100)	11 (92)	12 (100)	12 (100)	47 (98)
Race	Asian	0 (0)	1 (8)	0 (0)	0 (0)	1 (2)
	White	12 (100)	11 (92)	12 (100)	12 (100)	47 (98)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tbase_Demo_4_2_DSUR.sas (Page 2 of 3)

Table 14.1-3.1-3: Age group by gender, continuous - BNT162c2 SD

Safety set

		Younger dose ranging cohorts				
Sex	**Age category**	**0.1 µg (N=12) n (%)**	**0.3 µg (N=12) n (%)**	**0.6 µg (N=12) n (%)**	**1 µg (N=12) n (%)**	**Total (N=48) n (%)**
Female	≥18 to <30 years	4 (33)	6 (50)	1 (8)	6 (50)	17 (35)
	≥30 to <50 years	2 (17)	1 (8)	3 (25)	1 (8)	7 (15)
	≥50 to <65 years	4 (33)	1 (8)	1 (8)	0 (0)	6 (13)
Male	≥18 to <30 years	1 (8)	0 (0)	1 (8)	1 (8)	3 (6)
	≥30 to <50 years	0 (0)	3 (25)	2 (17)	3 (25)	8 (17)
	≥50 to <65 years	1 (8)	1 (8)	4 (33)	1 (8)	7 (15)
All	≥18 to <30 years	5 (42)	6 (50)	2 (17)	7 (58)	20 (42)
	≥30 to <50 years	2 (17)	4 (33)	5 (42)	4 (33)	15 (31)
	≥50 to <65 years	5 (42)	2 (17)	5 (42)	1 (8)	13 (27)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tbase_Demo_4_3_DSUR.sas (Page 3 of 3)

14.3 Safety

14.3.2 Further safety endpoints

14.3.2-1 Compliance

Table 14.3.2-1.1-1: IMP compliance - BNT162c2 SD

Safety set

	Younger dose ranging cohorts				
	0.1 µg (N=12) n (%)	**0.3 µg (N=12) n (%)**	**0.6 µg (N=12) n (%)**	**1 µg (N=12) n (%)**	**Total (N=48) n (%)**
Subjects receiving first immunization	12 (100)	12 (100)	12 (100)	12 (100)	48 (100)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tfsaf_IMP_1_1_DSUR.sas (Page 1 of 1)

Study BNT162-04 – BNT162b3

Table of content

14.1 Disposition and baseline characteristics

14.1-3 Demographic characteristics

Table 14.1-3.1-1: Demographic characteristics, continuous - BNT162b3 (Younger)

Safety set

		Younger dose ranging cohorts				
		3 µg (N=12)	**10 µg (N=12)**	**20 µg (N=12)**	**30 µg (N=12)**	**Total (N=48)**
Age [years]	n	12	12	12	12	48
	Mean (SD)	39.32 (9.79)	31.20 (9.11)	31.89 (13.51)	37.28 (6.40)	34.92 (10.32)
	Min	21.3	22.1	19.8	28.2	19.8
	Median	41.79	27.67	24.08	37.79	33.83
	Max	54.7	47.3	55.6	47.8	55.6
Height [cm]	n	12	12	12	12	48
	Mean (SD)	174.2 (6.4)	172.1 (9.8)	172.4 (11.4)	172.3 (11.4)	172.8 (9.7)
	Min	162	163	150	159	150
	Median	174.5	167.5	173.5	169.5	173.0
	Max	185	195	188	192	195
Weight [kg]	n	12	12	12	12	48
	Mean (SD)	72.74 (11.43)	71.68 (11.67)	71.40 (14.40)	71.02 (13.80)	71.71 (12.49)
	Min	54.9	53.0	50.0	57.2	50.0
	Median	74.05	74.45	71.65	65.90	72.05
	Max	91.4	92.0	96.3	99.5	99.5

Table 14.1-3.1-1: Demographic characteristics, continuous - BNT162b3 (Younger)

Safety set

		Younger dose ranging cohorts				
		3 µg (N=12)	**10 µg (N=12)**	**20 µg (N=12)**	**30 µg (N=12)**	**Total (N=48)**
BMI [kg/m2]	n	12	12	12	12	48
	Mean (SD)	23.89 (2.92)	24.23 (3.68)	23.80 (2.74)	23.69 (2.03)	23.90 (2.81)
	Min	19.9	19.9	20.4	21.0	19.9
	Median	23.35	22.80	22.95	23.15	23.30
	Max	29.3	29.8	28.6	27.9	29.8

SD is only calculated if values of at least 3 subjects are available.
N = number of subjects in the analysis set; n = number of subjects with data available; SD = standard deviation.

Program: Tbase_Demo_4_1.sas (Page 1 of 4)

Table 14.1-3.1-2: Demographic characteristics, categorical - BNT162b3 (Younger)

Safety set

		Younger dose ranging cohorts				
		3 µg (N=12) n (%)	**10 µg (N=12) n (%)**	**20 µg (N=12) n (%)**	**30 µg (N=12) n (%)**	**Total (N=48) n (%)**
Sex	Male	9 (75)	8 (67)	5 (42)	4 (33)	26 (54)
	Female	3 (25)	4 (33)	7 (58)	8 (67)	22 (46)
Ethnicity	Hispanic or Latino	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Not Hispanic or Latino	12 (100)	12 (100)	12 (100)	12 (100)	48 (100)
Race	Asian	0 (0)	0 (0)	1 (8)	0 (0)	1 (2)
	Black or African American	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	White	12 (100)	12 (100)	11 (92)	12 (100)	47 (98)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tbase_Demo_4_2_DSUR.sas (Page 2 of 3)

Table 14.1-3.1-3: Age group by gender, continuous - BNT162b3 (Younger)

Safety set

		Younger dose ranging cohorts				
Sex	**Age category**	**3 µg (N=12) n (%)**	**10 µg (N=12) n (%)**	**20 µg (N=12) n (%)**	**30 µg (N=12) n (%)**	**Total (N=48) n (%)**
Female	≥18 to <30 years	0 (0)	3 (25)	5 (42)	2 (17)	10 (21)
	≥30 to <50 years	3 (25)	1 (8)	1 (8)	6 (50)	11 (23)
	≥50 to <65 years	0 (0)	0 (0)	1 (8)	0 (0)	1 (2)
	≥65 to <75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	≥75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Male	≥18 to <30 years	2 (17)	5 (42)	2 (17)	0 (0)	9 (19)
	≥30 to <50 years	6 (50)	3 (25)	2 (17)	4 (33)	15 (31)
	≥50 to <65 years	1 (8)	0 (0)	1 (8)	0 (0)	2 (4)
	≥65 to <75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	≥75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
All	≥18 to <30 years	2 (17)	8 (67)	7 (58)	2 (17)	19 (40)
	≥30 to <50 years	9 (75)	4 (33)	3 (25)	10 (83)	26 (54)
	≥50 to <65 years	1 (8)	0 (0)	2 (17)	0 (0)	3 (6)
	≥65 to <75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	≥75 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tbase_Demo_4_3_DSUR.sas (Page 3 of 3)

Table 14.1-3.2-1: Demographic characteristics, continuous - BNT162b3 (Older)

Safety set

		Older dose ranging cohorts					
		3 µg (N=12)	**10 µg (N=12)**	**20 µg (N=12)**	**30 µg (N=12)**	**Total (N=48)**	**Total (N=96)**
Age [years]	n	12	12	12	12	48	96
	Mean (SD)	66.08 (7.16)	69.32 (8.74)	64.93 (6.63)	66.42 (6.82)	66.69 (7.33)	50.80 (18.28)
	Min	56.3	58.6	57.3	56.4	56.3	19.8
	Median	65.29	66.71	64.58	66.75	66.00	55.96
	Max	79.3	83.2	73.8	81.6	83.2	83.2
Height [cm]	n	12	12	12	12	48	96
	Mean (SD)	170.8 (10.4)	169.6 (12.3)	169.0 (12.3)	176.9 (13.9)	171.6 (12.3)	172.2 (11.0)
	Min	159	155	152	151	151	150
	Median	167.5	172.5	166.0	175.5	169.5	171.5
	Max	190	189	200	199	200	200
Weight [kg]	n	12	12	12	12	48	96
	Mean (SD)	76.05 (11.88)	70.90 (10.69)	69.06 (14.25)	84.43 (17.53)	75.11 (14.68)	73.41 (13.66)
	Min	58.9	51.0	52.9	60.3	51.0	50.0
	Median	74.00	71.60	65.45	80.35	72.00	72.00
	Max	101.5	85.7	98.4	106.4	106.4	106.4

Table 14.1-3.2-1: Demographic characteristics, continuous - BNT162b3 (Older)

Safety set

		Older dose ranging cohorts					
		3 µg (N=12)	**10 µg (N=12)**	**20 µg (N=12)**	**30 µg (N=12)**	**Total (N=48)**	**Total (N=96)**
BMI [kg/m2]	n	12	12	12	12	48	96
	Mean (SD)	25.92 (1.66)	24.69 (3.09)	24.03 (3.17)	26.73 (2.75)	25.34 (2.85)	24.62 (2.91)
	Min	23.3	20.0	19.4	20.9	19.4	19.4
	Median	25.65	24.50	24.35	26.70	25.45	24.60
	Max	28.8	29.8	29.5	29.8	29.8	29.8

SD is only calculated if values of at least 3 subjects are available.
N = number of subjects in the analysis set; n = number of subjects with data available; SD = standard deviation.

Program: Tbase_Demo_4_1_DSUR.sas (Page 1 of 3)

Table 14.1-3.2-2: Demographic characteristics, categorical - BNT162b3 (Older)

Safety set

		Older dose ranging cohorts					
		3 µg (N=12) n (%)	**10 µg (N=12) n (%)**	**20 µg (N=12) n (%)**	**30 µg (N=12) n (%)**	**Total (N=48) n (%)**	**Total (N=96) n (%)**
Sex	Male	3 (25)	4 (33)	3 (25)	6 (50)	16 (33)	42 (44)
	Female	9 (75)	8 (67)	9 (75)	6 (50)	32 (67)	54 (56)
Ethnicity	Not Hispanic or Latino	12 (100)	12 (100)	12 (100)	12 (100)	48 (100)	96 (100)
Race	Asian	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
	White	12 (100)	12 (100)	12 (100)	12 (100)	48 (100)	95 (99)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tbase_Demo_4_2_DSUR.sas (Page 2 of 3)

Table 14.1-3.2-3: Age group by gender, continuous - BNT162b3 (Older)

Safety set

		Older dose ranging cohorts					
Sex	**Age category**	**3 µg (N=12) n (%)**	**10 µg (N=12) n (%)**	**20 µg (N=12) n (%)**	**30 µg (N=12) n (%)**	**Total (N=48) n (%)**	**Total (N=96) n (%)**
Female	≥18 to <30 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	10 (10)
	≥30 to <50 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	11 (11)
	≥50 to <65 years	3 (25)	2 (17)	3 (25)	1 (8)	9 (19)	10 (10)
	≥65 to <75 years	5 (42)	3 (25)	6 (50)	4 (33)	18 (38)	18 (19)
	≥75 years	1 (8)	3 (25)	0 (0)	1 (8)	5 (10)	5 (5)
Male	≥18 to <30 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (9)
	≥30 to <50 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	15 (16)
	≥50 to <65 years	3 (25)	2 (17)	3 (25)	5 (42)	13 (27)	15 (16)
	≥65 to <75 years	0 (0)	1 (8)	0 (0)	1 (8)	2 (4)	2 (2)
	≥75 years	0 (0)	1 (8)	0 (0)	0 (0)	1 (2)	1 (1)
All	≥18 to <30 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	19 (20)
	≥30 to <50 years	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	26 (27)
	≥50 to <65 years	6 (50)	4 (33)	6 (50)	6 (50)	22 (46)	25 (26)
	≥65 to <75 years	5 (42)	4 (33)	6 (50)	5 (42)	20 (42)	20 (21)
	≥75 years	1 (8)	4 (33)	0 (0)	1 (8)	6 (13)	6 (6)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tbase_Demo_4_3_DSUR.sas (Page 3 of 3)

14.3 Safety

14.3.2 Further safety endpoints

14.3.2.1 Compliance

Table 14.3.2.1-1: IMP compliance - BNT162b3 (Younger)

Safety set

	Younger dose ranging cohorts				
	3 µg (N=12) n (%)	10 µg (N=12) n (%)	20 µg (N=12) n (%)	30 µg (N=12) n (%)	Total (N=48) n (%)
Subjects receiving first immunization	12 (100)	12 (100)	12 (100)	12 (100)	48 (100)
Subjects receiving boost immunization	12 (100)	12 (100)	12 (100)	0 (0)	36 (75)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tfsaf_IMP_1_1_DSUR.sas (Page 1 of 2)

Table 14.3.2.1-2: IMP compliance - BNT162b3 (Older)

Safety set

	Older dose ranging cohorts					
	3 µg (N=12) n (%)	10 µg (N=12) n (%)	20 µg (N=12) n (%)	30 µg (N=12) n (%)	Total (N=48) n (%)	Total (N=96) n (%)
Subjects receiving first immunization	12 (100)	12 (100)	12 (100)	12 (100)	48 (100)	96 (100)
Subjects receiving boost immunization	12 (100)	12 (100)	12 (100)	12 (100)	48 (97)	84 (88)

The denominator for the percentage calculation is N.
N = number of subjects in the analysis set; n = number of subjects with the specified characteristic.

Program: Tfsaf_IMP_1_1_DSUR.sas (Page 2 of 2)

APPENDIX 4.3 Cumulative Summary Tabulations of Demographic Data (BNT STUDIES BNT162-03, BNT162-06) (Fosun)
BNT162, PF-07302048 DSUR

	BNT162b1 10µg (N=48)	BNT162b1 30µg (N=48)	Placebo (N=48)	BNT162b2/ Placebo (959)	TOTAL* (N = 1103)
Age [years]					
≥18 to <30 years	7 (14.6)	6 (12.5)	5 (10.4)	49 (5.1)	67 (6.1%)
≥30 to <50 years	14 (29.2)	16 (33.3)	15 (31.3)	338 (35.3)	383 (34.7%)
≥50 to <65 years	3 (6.3)	2 (4.2)	4 (8.3)	412 (43.0)	421 (38.2%)
≥65 to <75 years	19 (39.6)	22 (45.8)	19 (39.6)	149 (15.5)	209 (18.9%)
≥75 years	5 (10.4)	2 (4.2)	5 (10.4)	11 (1.2)	23 (2.1%)
Mean (SD)	54 (18.1)	54 (16.0)	56 (16.0)	53 (11.9)	54.3 (ND)
Median	60	59	60	54	59.5
Min	22	24	28	18	18
Max	82	75	82	84	84
Race, n (%)					
Asian	48 (100.0)	48 (100.0)	48 (100.0)	959 (100.0)	1103 (100.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chinese Nationality					
Han Nationality n (%)	48 (100.0)	48 (100.0)	48 (100.0)	959 (100.0)	1103 (100.0)
Other n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gender, n (%)					
Male	24 (50.0)	24 (50.0)	24 (50.0)	491 (51.2)	563 (51.0%)
Female	24 (50.0)	24 (50.0)	24 (50.0)	468 (48.8)	540 (41.0%)
*Calculated; Includes BNT162-03 (b1 study) and BNT62-06 (B2 study)					

APPENDIX 5 Line-Listing of Serious Adverse Reactions During the Reporting Period (S7.2)

PF-07302048

Reporting Period: 22-APR-2020 Through 21-APR-2021

Total Number of Cases: 9

Total Number of Adverse Events (PT): 9

MedDRA Version: v.23.1J

Clinical Trial No: C4591001

SOC: Blood and lymphatic system disorders

AER Number: (b) (6) * **Subject ID: 11781107** **Country: UNITED STATES** **EUDRACT No: 2020-002641-42**

Patient Age / Sex / Patient Outcome	Suspect Drug(s)	Indication	Total Daily Dose / Dosage Form / Rt of Admin	Therapy Dates From / To	Onset Date / Latency	MedDRA Preferred Term [Verbatim Term]	Suspect Drug(s)	Causality (Investigator/ Sponsor)
48 YEARS FEMALE RECOVERED/RESOLVED	BNT162B2	Immunisation	SOLUTION FOR INJECTION INTRAMUSCULAR	04-SEP-2020 - 04-SEP-2020	16-SEP-2020 11 DAY(S)	Lymphadenopathy [right axilla lymphadenopathy]**^	BNT162B2	RELATED/ UNRELATED

Comments

Absence of any information in any of the fields indicates that information was not reported.
* Indicates an expedited case involving SUSAR(s) sent to European Medicines Agency
**Indicates a SUSAR
^ Indicates an adverse event that is considered related
~ Indicates an adverse event that is considered related to the clinical trial procedure

Reporting Period: 22-APR-2020 Through 21-APR-2021

Total Number of Cases: 9

Total Number of Adverse Events (PT): 9

Clinical Trial No: C4591001

SOC: Cardiac disorders

AER Number: (b) (6)	Subject ID: 11421247	Country: UNITED STATES	EUDRACT No: 2020-002641-42

Patient Age Sex Patient Outcome	Suspect Drug(s)	Indication	Total Daily Dose Dosage Form Rt of Admin	Therapy Dates From To	Onset Date Latency	MedDRA Preferred Term [Verbatim Term]	Suspect Drug(s)	Causality (Investigator/ Sponsor)
71 YEARS FEMALE RECOVERED/RESOLVED	BNT162B2	Immunisation	SOLUTION FOR INJECTION INTRAMUSCULAR	14-OCT-2020 - 14-OCT-2020	14-OCT-2020	Ventricular arrhythmia [paroxysmal ventricular arrhythmias]**^	BNT162B2	RELATED/ UNRELATED

Comments

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**Indicates a SUSAR
^ Indicates an adverse event that is considered related
~ Indicates an adverse event that is considered related to the clinical trial procedure

APPENDIX 5 Line-Listing of Serious Adverse Reactions During the Reporting Period (S7.2)

PF-07302048

Reporting Period: 22-APR-2020 Through 21-APR-2021

Total Number of Cases: 9

Total Number of Adverse Events (PT): 9

Clinical Trial No: C4591001

SOC: Cardiac disorders

AER Number: (b) (6) *	Subject ID: 12121024	Country: TURKEY	EUDRACT No: 2020-002641-42

Patient Age Sex Patient Outcome	Suspect Drug(s)	Indication	Total Daily Dose Dosage Form Rt of Admin	Therapy Dates From To	Onset Date Latency	MedDRA Preferred Term [Verbatim Term]	Suspect Drug(s)	Causality (Investigator/ Sponsor)
41 YEARS MALE RECOVERED/RESOLVED	BNT162B2	COVID-19 immunisation	SOLUTION FOR INJECTION INTRAMUSCULAR	04-NOV-2020 - 04-NOV-2020 25-NOV-2020 - 25-NOV-2020	03-FEB-2021 91 DAY(S)	Myocardial infarction [probable heart attack]**^	BNT162B2	RELATED/ UNRELATED

Comments

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**Indicates a SUSAR
^ Indicates an adverse event that is considered related
~ Indicates an adverse event that is considered related to the clinical trial procedure

Reporting Period: 22-APR-2020 Through 21-APR-2021

Total Number of Cases: 9

Total Number of Adverse Events (PT): 9

Clinical Trial No: C4591001

SOC: General disorders and administration site conditions

AER Number (b) (6) *	Subject ID: 10151047	Country: UNITED STATES	EUDRACT No: 2020-002641-42

Patient Age Sex Patient Outcome	Suspect Drug(s)	Indication	Total Daily Dose Dosage Form Rt of Admin	Therapy Dates From To	Onset Date Latency	MedDRA Preferred Term [Verbatim Term]	Suspect Drug(s)	Causality (Investigator/ Sponsor)
30 YEARS FEMALE RECOVERED/RESOLVED	BNT162B2	COVID-19 immunisation	SOLUTION FOR INJECTION INTRAMUSCULAR	09-SEP-2020 - 09-SEP-2020	09-SEP-2020 0 DAY(S)	Shoulder injury related to vaccine administration [SIRVA]**^	BNT162B2	RELATED/ RELATED

Comments

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**Indicates a SUSAR
^ Indicates an adverse event that is considered related
~ Indicates an adverse event that is considered related to the clinical trial procedure

Reporting Period: 22-APR-2020 Through 21-APR-2021

Total Number of Cases: 9

Total Number of Adverse Events (PT): 9

Clinical Trial No: C4591001

SOC: Musculoskeletal and connective tissue disorders

AER Number (b) (6)	Subject ID: 10031111	Country: UNITED STATES	EUDRACT No: 2020-002641-42

Patient Age Sex Patient Outcome	Suspect Drug(s)	Indication	Total Daily Dose Dosage Form Rt of Admin	Therapy Dates From To	Onset Date Latency	MedDRA Preferred Term [Verbatim Term]	Suspect Drug(s)	Causality (Investigator/ Sponsor)
26 YEARS MALE NOT RECOVERED/NOT RESOLVED	PLACEBO	COVID-19 immunisation	SOLUTION FOR INJECTION INTRAMUSCULAR	20-AUG-2020 - 20-AUG-2020	26-SEP-2020 73 DAY(S)	Psoriatic arthropathy [psoriatic arthritis]^	PLACEBO	RELATED/ UNRELATED

Comments

Absence of any information in any of the fields indicates that information was not reported.
* Indicates an expedited case involving SUSAR(s) sent to European Medicines Agency
**Indicates a SUSAR
^ Indicates an adverse event that is considered related
~ Indicates an adverse event that is considered related to the clinical trial procedure

Reporting Period: 22-APR-2020 Through 21-APR-2021

Total Number of Cases: 9

Total Number of Adverse Events (PT): 9

Clinical Trial No: C4591001

SOC: Nervous system disorders

AER Number: (b) (6) *	Subject ID: 10181159	Country: UNITED STATES	EUDRACT No: 2020-002641-42

Patient Age / Sex / Patient Outcome	Suspect Drug(s)	Indication	Total Daily Dose / Dosage Form / Rt of Admin	Therapy Dates From / To	Onset Date / Latency	MedDRA Preferred Term [Verbatim Term]	Suspect Drug(s)	Causality (Investigator/ Sponsor)
53 YEARS FEMALE RECOVERING/RESOLVING	BNT162B2	Immunisation	SOLUTION FOR INJECTION INTRAMUSCULAR	04-SEP-2020 - 04-SEP-2020	20-OCT-2020 45 DAY(S)	Paraesthesia [right leg paresthesia]**^	BNT162B2	RELATED/ UNRELATED

Comments

AER Number: (b) (6)	Subject ID: 10031065	Country: UNITED STATES	EUDRACT No: 2020-002641-42

Patient Age / Sex / Patient Outcome	Suspect Drug(s)	Indication	Total Daily Dose / Dosage Form / Rt of Admin	Therapy Dates From / To	Onset Date / Latency	MedDRA Preferred Term [Verbatim Term]	Suspect Drug(s)	Causality (Investigator/ Sponsor)
52 YEARS FEMALE RECOVERED/RESOLVED	BLINDED THERAPY	COVID-19 immunisation	SOLUTION FOR INJECTION INTRAMUSCULAR	15-JUL-2020 - 15-JUL-2020	29-JUL-2020 14 DAY(S)	Neuritis [Neuritis]~	BLINDED THERAPY	UNRELATED/ UNRELATED

Comments

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* Indicates an expedited case involving SUSAR(s) sent to European Medicines Agency
**Indicates a SUSAR
^ Indicates an adverse event that is considered related
~ Indicates an adverse event that is considered related to the clinical trial procedure

APPENDIX 5 Line-Listing of Serious Adverse Reactions During the Reporting Period (S7.2)

PF-07302048

Reporting Period: 22-APR-2020 Through 21-APR-2021

Total Number of Cases: 9

Total Number of Adverse Events (PT): 9

Clinical Trial No: C4591001-OPENLABEL

SOC: Immune system disorders

AER Number (b) (6) *	Subject ID: 11291260	Country: UNITED STATES	EUDRACT No: 2020-002641-42

Patient Age Sex Patient Outcome	Suspect Drug(s)	Indication	Total Daily Dose Dosage Form Rt of Admin	Therapy Dates From To	Onset Date Latency	MedDRA Preferred Term [Verbatim Term]	Suspect Drug(s)	Causality (Investigator/ Sponsor)
17 YEARS FEMALE RECOVERED/RESOLVED	BNT162B2	COVID-19 immunisation	SOLUTION FOR INJECTION INTRAMUSCULAR	25-JAN-2021 - 25-JAN-2021	27-JAN-2021 2 DAY(S)	Anaphylactoid reaction [Anaphylactoid reaction]**^	BNT162B2	RELATED/ RELATED

Comments

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**Indicates a SUSAR
^ Indicates an adverse event that is considered related
~ Indicates an adverse event that is considered related to the clinical trial procedure

Reporting Period: 22-APR-2020 Through 21-APR-2021

Total Number of Cases: 9

Total Number of Adverse Events (PT): 9

Clinical Trial No: C4591001-OPENLABEL

SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

AER Number (b) (6) *	Subject ID: 10961181	Country: UNITED STATES	EUDRACT No: 2020-002641-42

Patient Age Sex Patient Outcome	Suspect Drug(s)	Indication	Total Daily Dose Dosage Form Rt of Admin	Therapy Dates From To	Onset Date Latency	MedDRA Preferred Term [Verbatim Term]	Suspect Drug(s)	Causality (Investigator/ Sponsor)
63 YEARS MALE NOT RECOVERED/NOT RESOLVED	BNT162B2	COVID-19 immunisation	SOLUTION FOR INJECTION INTRAMUSCULAR	01-FEB-2021 - 01-FEB-2021	11-MAR-2021 37 DAY(S)	Acute myeloid leukaemia [acute myeloblastic leukemia]**^	BNT162B2	RELATED/ UNRELATED

Comments

This case is cross-referenced to case (b) (6) and (b) (6) : same patient, same drug, different event.

Absence of any information in any of the fields indicates that information was not reported.
* Indicates an expedited case involving SUSAR(s) sent to European Medicines Agency
**Indicates a SUSAR
^ Indicates an adverse event that is considered related
~ Indicates an adverse event that is considered related to the clinical trial procedure

APPENDIX 5.1 Line-Listing of Serious Adverse Reactions During the Reporting Period (S7.2)

PF-07302048

Reporting Period: 22-APR-2020 Through 21-APR-2021

Total Number of Cases: 1

Total Number of Adverse Events (PT): 1

MedDRA Version: v.23.1J

Clinical Trial No: BNT162-01 - RN9391R00

SOC: Infections and infestations

AER Number: (b) (6) **Subject ID: 01|276-01-0403** **Country: GERMANY** **EUDRACT No:**

Patient Age Sex Patient Outcome	Suspect Drug(s)	Indication	Total Daily Dose Dosage Form Rt of Admin	Therapy Dates From To	Onset Date Latency	MedDRA Preferred Term [Verbatim Term]	Suspect Drug(s)	Causality (Investigator/ Sponsor)
24 YEARS FEMALE RECOVERED/RESOLVED	BNT162B2	COVID-19 immunisation	30 ug SOLUTION FOR INJECTION INTRAMUSCULAR	09-DEC-2020 - 09-DEC-2020 29-DEC-2020 - 29-DEC-2020	31-DEC-2020 22 DAY(S)	Cystitis [Cystitis]^	BNT162B2	UNRELATED/ RELATED

Comments

Absence of any information in any of the fields indicates that information was not reported.
* Indicates an expedited case involving SUSAR(s) sent to European Medicines Agency
**Indicates a SUSAR
^ Indicates an adverse event that is considered related
~ Indicates an adverse event that is considered related to the clinical trial procedure

APPENDIX 6 - Cumulative Summary Tabulation of Serious Adverse Events from Clinical Trials (S7.3)

PF-07302048

Reporting Period: Through 21-APR-2021
Total Number of Cases: 865
Total Number of Adverse Events (PT): 1,053
MedDRA Version: v.23.1J

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
Blood and lymphatic system disorders	Anaemia	1	1		
	Anaemia macrocytic			1	
	Blood loss anaemia	1			
	Febrile neutropenia	1			
	Lymphadenopathy	1			
	Microcytic anaemia		1		
	Neutropenia		1		
	Pancytopenia	1			
	Red blood cell abnormality		1		
	Thrombocytopenia		2		
Sub Total:		**5**	**6**	**1**	
Cardiac disorders	Accelerated idioventricular rhythm	1			
	Acute coronary syndrome	1	5		
	Acute left ventricular failure		1		
	Acute myocardial infarction	1	15		
	Angina pectoris	1	2		

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Angina unstable		3		
	Aortic valve incompetence			2	
	Arrhythmia supraventricular		1		
	Arteriosclerosis coronary artery		1		
	Arteriospasm coronary	1	1		
	Atrial fibrillation	5	17	1	
	Atrial flutter	1			
	Atrioventricular block complete		1		
	Bradycardia		2		
	Cardiac arrest		8		
	Cardiac failure acute			1	
	Cardiac failure chronic			1	
	Cardiac failure congestive	1	5		
	Cardio-respiratory arrest	1	2		
	Cardiovascular disorder	1			
	Coronary artery disease		5	2	
	Coronary artery dissection		1		
	Coronary artery occlusion		3		
	Hypertensive heart disease		1		

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Ischaemic cardiomyopathy	1			
	Junctional ectopic tachycardia		1		
	Myocardial infarction	6	12	1	
	Myocardial ischaemia		1		
	Palpitations	1			
	Pericarditis	1			
	Supraventricular extrasystoles	1			
	Supraventricular tachycardia	2			
	Tachyarrhythmia		1		
	Tachycardia		1		
	Ventricular arrhythmia	1			
	Ventricular extrasystoles	1			
	Ventricular fibrillation		1		
	Ventricular tachycardia	2	1		
	Wolff-Parkinson-White syndrome	1			
Sub Total:		**31**	**92**	**8**	
Congenital, familial and genetic disorders	Congenital bladder neck obstruction			1	
	Congenital ureteropelvic junction obstruction			1	
	Heart disease congenital		1		

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Hypertrophic cardiomyopathy	1			
	Sickle cell disease		1		
Sub Total:		**1**	**2**	**2**	
Ear and labyrinth disorders	Vertigo	2	3		
Sub Total:		**2**	**3**		
Endocrine disorders	Goitre	1			
Sub Total:		**1**			
Eye disorders	Blindness unilateral		1		
	Choroidal neovascularisation		1		
	Diplopia	2	1		
	Eye haemorrhage			1	
	Eyelid ptosis	1			
	Retinal artery occlusion		1		
	Retinal tear	1			
	Retinal vein thrombosis		1		
	Visual impairment		2		
Sub Total:		**4**	**7**	**1**	
Gastrointestinal disorders	Abdominal adhesions		1		
	Abdominal hernia		1		
	Abdominal pain		2		
	Abdominal pain upper		2		
	Acute abdomen			1	
	Anal fistula			1	
	Anal prolapse	1			

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Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Colitis		2		
	Colitis ischaemic		1		
	Constipation		3		
	Diarrhoea		1		
	Diverticular perforation		2		
	Diverticulum intestinal			1	
	Duodenal obstruction		1		
	Enterocolitis		1		
	Food poisoning	1			
	Gastritis		2		
	Gastrointestinal haemorrhage	2	4		
	Gastrointestinal mucosa hyperaemia		1		
	Gastrointestinal necrosis		1		
	Gastrooesophageal reflux disease	1			
	Haemorrhoidal haemorrhage		1		
	Haemorrhoids		1		
	Hiatus hernia		1		
	Ileus		1		
	Impaired gastric emptying		1		
	Incarcerated inguinal hernia		1		
	Inguinal hernia	2		1	
	Intestinal mass			1	

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Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Intestinal obstruction	2	2		
	Intestinal perforation		1		
	Intestinal strangulation		1		
	Intestinal ulcer perforation	1			
	Large intestine perforation		1		
	Lower gastrointestinal haemorrhage	1	1		
	Obstructive pancreatitis		1		
	Oesophageal food impaction		1		
	Oesophageal varices haemorrhage		1		
	Pancreatic cyst		1		
	Pancreatitis		4		
	Pancreatitis acute	1	5	1	
	Rectal haemorrhage		1		
	Retroperitoneal haematoma		1		
	Salivary gland calculus			1	
	Small intestinal obstruction		9		
	Umbilical hernia		1		
	Volvulus		1		
Sub Total:		**12**	**63**	**7**	
General disorders and administration site conditions	Asthenia	1	1		

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Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Chest pain	1	4		
	Condition aggravated	6	19	3	
	Death	1		1	
	Disease progression		1		
	Disease recurrence	1			
	Drug ineffective	1			
	Drug withdrawal syndrome	1	1		
	Electrocution	1			
	Fatigue	2			
	Impaired healing		1		
	Influenza like illness		1		
	Multiple organ dysfunction syndrome			1	
	Non-cardiac chest pain		3		
	Pain		1		
	Shoulder injury related to vaccine administration	1			
	Sudden cardiac death		1		
	Vascular stent occlusion		1		
Sub Total:		**16**	**34**	**5**	
Hepatobiliary disorders	Acute hepatic failure		1		
	Bile duct stone	1	1		
	Biliary colic	1	1		
	Cholecystitis	1	2	1	
	Cholecystitis acute	1	8		

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Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Cholecystitis chronic		1		
	Cholelithiasis	1	7		
	Cholelithiasis obstructive	1			
	Hepatitis acute	1			
	Hepatocellular injury		1		
	Portosplenomesenteric venous thrombosis	1			
Sub Total:		**8**	**22**	**1**	
Immune system disorders	Anaphylactic reaction		1		
	Anaphylactic shock	1	1		
	Anaphylactoid reaction	1			
	Drug hypersensitivity		1		
	Hypersensitivity		1		
Sub Total:		**2**	**4**		
Infections and infestations	Abdominal abscess		1		
	Abdominal infection	1			
	Abscess		1		
	Anal abscess		2		
	Appendicitis	1	24	3	
	Appendicitis perforated	1	2		
	Arthritis bacterial		1		
	Bacteraemia		1		
	Bacterial sepsis		1		
	Brain abscess		1		
	Cellulitis		5		

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Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Clostridium difficile colitis		1		
	Clostridium difficile infection	1			
	Colonic abscess		1		
	Complicated appendicitis		2		
	COVID-19		12	2	
	COVID-19 pneumonia	1	3		
	Device related infection		1		
	Diabetic foot infection		1		
	Diverticulitis	1	2	1	
	Emphysematous cholecystitis		1		
	Empyema		1		
	Encephalitis	1			
	Endocarditis		1		
	Escherichia urinary tract infection		1		
	Extradural abscess		1		
	Focal peritonitis	1	1		
	Gangrene		1		
	Gastroenteritis	2	1	1	
	Gastroenteritis bacterial				1
	Herpes zoster oticus		1		
	Localised infection		1		
	Meningitis bacterial	1	2		

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Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Osteomyelitis		1		
	Pelvic abscess	1			
	Pelvic inflammatory disease	1			
	Penile infection	1			
	Peritoneal abscess		1		
	Peritonitis		3		
	Peritonsillar abscess		2		
	Pharyngitis streptococcal			1	
	Pneumonia	5	13	1	
	Pneumonia bacterial			1	
	Postoperative abscess		1		
	Postoperative wound infection		3		
	Post procedural infection		1	1	
	Pyelonephritis		4		
	Pyelonephritis acute		2		
	Renal abscess		1		
	Respiratory tract infection viral		1		
	Sepsis	2	3		
	Septic shock		2		
	Shigella sepsis		1		
	Staphylococcal infection		1		
	Staphylococcal sepsis		1		

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Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Subacute endocarditis			1	
	Subcutaneous abscess		2		
	Suspected COVID-19		1		
	Tooth infection		1		
	Upper respiratory tract infection		2		
	Urinary tract infection	1	8		
	Urosepsis	1	1		
Sub Total:		**23**	**130**	**12**	**1**
Injury, poisoning and procedural complications	Alcohol poisoning		1		
	Ankle fracture	2	3		
	Brain contusion		1		
	Burns second degree	1			
	Burns third degree	1			
	Cervical vertebral fracture		1		
	Clavicle fracture		1		
	Colon injury		1		
	Concussion		1		
	Craniocerebral injury		3		
	Delayed recovery from anaesthesia			1	
	Facial bones fracture		2		
	Fall	1	2		
	Femur fracture		2		
	Flail chest		1		

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Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Foot fracture		1	1	
	Forearm fracture		1		
	Fractured sacrum		1		
	Hand fracture		1		
	Head injury	1	1		
	Hip fracture		2	1	
	Humerus fracture		1	1	
	Injury		1		
	Jaw fracture	1			
	Ligament rupture	1	1		
	Limb injury	1			
	Lower limb fracture		2	1	
	Lumbar vertebral fracture		1		
	Maternal exposure during pregnancy	1	3		
	Meniscus injury		1		
	Multiple injuries		1		
	Overdose		3		
	Patella fracture		1		
	Pelvic fracture		1		
	Postoperative ileus		1		
	Post procedural haematoma		1		
	Post-traumatic pain		1		
	Procedural dizziness	1			
	Procedural haemorrhage		1		
	Procedural pain	1			
	Radius fracture			1	

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Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	R b fracture	2	2		
	Road traffic accident		8		
	Scapula fracture	1			
	Spinal column injury		1		
	Spinal cord injury cervical		1		
	Spinal fracture	1			
	Subdural haematoma		3		
	Tibia fracture		1		
	Toxicity to various agents		3		
	Traumatic haemothorax		1		
	Traumatic intracranial haemorrhage		1		
	Ulna fracture		1		
	Upper limb fracture	1	1		
	Wrist fracture		2		
Sub Total:		**17**	**71**	**6**	
Investigations	Blood glucose abnormal		1		
	Blood lactic acid	1			
	Blood pressure increased		1		
	Cardiac stress test abnormal		1		
	Hepatic enzyme increased		1		
Sub Total:		**1**	**4**		

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Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
Metabolism and nutrition disorders	Dehydration	1			
	Diabetes mellitus inadequate control		1		
	Diabetic ketoacidosis	1	2		
	Fluid retention		1		
	Hyperglycaemia	1	1	1	
	Hypoglycaemia		3		
	Hypokalaemia	1	2		
	Hyponatraemia		1		
	Ketoacidosis		1		
	Type 2 diabetes mellitus	1	3		
Sub Total:		**5**	**15**	**1**	
Musculoskeletal and connective tissue disorders	Arthralgia		2		
	Arthritis	1	1		
	Back pain	2			
	Intervertebral disc compression		1		
	Intervertebral disc degeneration		1	1	
	Intervertebral disc protrusion		4		1
	Muscular weakness		2		
	Musculoskeletal chest pain		1		
	Osteoarthritis	5	6	2	
	Osteochondritis		1		
	Pain in extremity		1		

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Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Psoriatic arthropathy			1	
	Spondylolisthesis		2	1	
Sub Total:		**8**	**22**	**5**	**1**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukaemia	1	1		
	Adenocarcinoma gastric		1		
	Adenocarcinoma of colon	1			
	Adenocarcinoma pancreas	1	2		
	Adrenal gland cancer		1		
	Basal cell carcinoma			1	
	B-cell lymphoma		1		
	Benign hydatidiform mole		1		
	Biliary cancer metastatic		1		
	Bladder cancer		2		
	Borderline serous tumour of ovary	1			
	Brain neoplasm	1			
	Breast cancer	3	6	3	
	Breast cancer in situ		1		
	Breast cancer metastatic	1			
	Breast cancer stage I	1	1		
	Carcinoid tumour of the stomach	1			

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Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Chronic myeloid leukaemia		1		
	Clear cell renal cell carcinoma			1	
	Colon adenoma		1		
	Colon cancer metastatic		1		
	Endometrial cancer stage I	1			
	Gallbladder cancer stage II		1		
	Gastric cancer	1			
	Hepatic cancer	1			
	Hormone receptor positive breast cancer	1	1		
	Hypergammaglobulinaemia benign monoclonal	1			
	Intraductal proliferative breast lesion	1	2		
	Invasive ductal breast carcinoma	3	2		
	Invasive lobular breast carcinoma	1			
	Leydig cell tumour of the testis		1		
	Lipoma		1		
	Lung adenocarcinoma			2	
	Lung cancer metastatic		1		
	Lymphoma		1		

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Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Malignant melanoma	1	5	1	
	Meningioma		1		
	Metastases to central nervous system	1	1		
	Metastases to liver		1		
	Metastases to lung		1		
	Metastases to lymph nodes		1	1	
	Metastatic squamous cell carcinoma		1		
	Neoplasm recurrence	1			
	Non-Hodgkin's lymphoma recurrent			1	
	Non-small cell lung cancer stage III	1			
	Non-small cell lung cancer stage IV		1		
	Oropharyngeal cancer recurrent		1		
	Oropharyngeal squamous cell carcinoma		1		
	Ovarian cancer	1			
	Ovarian neoplasm	1			
	Pancreatic carcinoma		3		
	Pancreatic carcinoma metastatic		1		
	Papillary serous endometrial carcinoma			1	

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Papillary thyroid cancer			1	
	Penile neoplasm		1		
	Plasma cell myeloma		1		
	Polycythaemia vera		1		
	Prostate cancer		5		
	Prostate cancer metastatic	1			
	Sebaceous carcinoma		1		
	Seminoma		1		
	Squamous cell carcinoma	1			
	Teratoma			1	
	Thyroid cancer		1		
	Tonsil cancer		1		
	Transitional cell carcinoma	2	1		
	Uterine cancer		1		
	Uterine leiomyoma		3	1	
Sub Total:		**31**	**66**	**14**	
Nervous system disorders	Amnesia		1		
	Amyotrophic lateral sclerosis		1		
	Aphasia	1			
	Brachial plexopathy	1			
	Carotid artery stenosis	1			
	Carpal tunnel syndrome		1		
	Cerebral infarction		1		

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Cerebrovascular accident	6	4	1	
	Cervicogenic headache		1		
	Dementia Alzheimer's type		1	1	
	Dizziness		3		
	Encephalopathy	1			
	Guillain-Barre syndrome			1	
	Haemorrhagic stroke		1		
	Hemiplegic migraine		1		
	Idiopathic intracranial hypertension	1	1		
	Intracranial aneurysm		1		
	Intraventricular haemorrhage		1		
	Ischaemic stroke		4		
	Neuritis		1		
	Optic neuritis	1	1		
	Paraesthesia	1	1		
	Peripheral nerve lesion	1			
	Seizure	2	2		
	Spinal cord compression		1		
	Status migrainosus		1		
	Subarachnoid haemorrhage	1	4	1	
	Syncope	3	6	1	

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Toxic encephalopathy		1		
	Transient global amnesia		1		
	Transient ischaemic attack	2	5		
	Tremor	1			
	Uraemic encephalopathy		1		
Sub Total:		**23**	**47**	**5**	
Pregnancy, puerperium and perinatal conditions	Abortion incomplete			1	
	Abortion spontaneous	1	9	3	
	Abortion spontaneous incomplete		1		
	Foetal hypokinesia		1		
	Retained products of conception		1		
Sub Total:		**1**	**12**	**4**	
Psychiatric disorders	Affective disorder		1		
	Alcohol abuse		1		
	Alcohol withdrawal syndrome		1		
	Anxiety	1	1		
	Bipolar disorder	1	3		
	Bipolar I disorder	1			
	Completed suicide	1	1		
	Conversion disorder		2		
	Depression	1	8		
	Depression suicidal		1	1	

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Disorientation	1			
	Drug dependence		1		
	Major depression	5	3		
	Mental disorder		1		
	Panic attack		1		
	Psychotic behaviour		1		
	Psychotic disorder		1		
	Substance-induced mood disorder		1		
	Suicidal ideation	1	4		
	Suicide attempt	2	2		
Sub Total:		**14**	**34**	**1**	
Renal and urinary disorders	Acute kidney injury	1	2		
	Hydronephrosis			1	
	Nephrolithiasis	2	14		
	Renal colic		1		
	Subcapsular renal haematoma		1		
	Ureterolithiasis		2		
	Urinary tract obstruction	1			
Sub Total:		**4**	**20**	**1**	
Reproductive system and breast disorders	Adenomyosis		1		
	Adnexal torsion		1	1	
	Breast hyperplasia		1		
	Endometrial thickening		1		
	Endometriosis		2		
	Ovarian cyst		2		

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Ovarian mass		1		
	Rectocele			1	
	Uterine prolapse		1		
	Vaginal haemorrhage		1		
	Vaginal prolapse			1	
Sub Total:			**11**	**3**	
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	3	5		
	Asphyxia		1		
	Asthma		3		
	Asthmatic crisis		1		
	Chronic obstructive pulmonary disease	1	6		
	Dyspnoea		2		
	Dyspnoea exertional		2		
	Hypoxia		1		
	Interstitial lung disease		2		
	Nasal septum deviation		1		
	Pneumonia aspiration	1	3		
	Pneumonitis		1		
	Pneumothorax	1	1		
	Pulmonary embolism	9	11	1	
	Pulmonary mass		1		
	Respiratory arrest		1		
	Respiratory failure		2		
Sub Total:		**15**	**44**	**1**	

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
Skin and subcutaneous tissue disorders	Diabetic foot	1			
	Pruritus		1		
Sub Total:		**1**	**1**		
Vascular disorders	Accelerated hypertension		1		
	Aortic aneurysm		3		
	Aortic rupture		2		
	Aortic stenosis	1		2	
	Arterial occlusive disease		1		
	Arteriosclerosis		2		
	Deep vein thrombosis	3	7	1	
	Hypertension	1	3		
	Hypertensive crisis		1		
	Hypertensive emergency	1	1		
	Hypertensive urgency	1	2		
	Hypovolaemic shock	1			
	Orthostatic hypotension		2		
	Peripheral artery stenosis		1		
	Thrombosis	1			
Sub Total:		**9**	**26**	**3**	
Total Number of Cases:		**195**	**598**	**70**	**2**
Total Number of Events:		**234**	**736**	**81**	**2**

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect

APPENDIX 6.1 - Cumulative Summary Tabulation of Serious Adverse Events from Clinical Trials (S7.3)

PF-07302048

Reporting Period: Through 21-APR-2021
Total Number of Cases: 17
Total Number of Adverse Events (PT): 19
MedDRA Version: v.23.1J

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY
Congenital, familial and genetic disorders	Thyroglossal cyst		1
Sub Total:			**1**
Gastrointestinal disorders	Diverticulum intestinal haemorrhagic	1	
	Inguinal hernia	1	
Sub Total:		**2**	
General disorders and administration site conditions	Disease progression		1
	Pelvic mass	1	
Sub Total:		**1**	**1**
Hepatobiliary disorders	Cholecystitis acute		1
Sub Total:			**1**
Infections and infestations	COVID-19	2	
	Cystitis	1	
Sub Total:		**3**	
Injury, poisoning and procedural complications	Ankle fracture	1	
	Humerus fracture		1

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY
	Joint dislocation		1
	Lower limb fracture		1
Sub Total:		**1**	**3**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung carcinoma cell type unspecified stage 0		1
	Oesophageal carcinoma	1	
Sub Total:		**1**	**1**
Nervous system disorders	Cerebral infarction		2
	Diabetic neuropathy		1
	Syncope	1	
Sub Total:		**1**	**3**
Total Number of Cases:		**9**	**8**
Total Number of Events:		**9**	**10**

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

APPENDIX 8. CUMULATIVE APPROVAL/AUTHORISATION STATUS

Product Detail Set Name	Marketing Authorization Holder	Country	Approval Date	Authorization Type
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer/BioNTech	United Kingdom	1-Dec-20	Temporary authorization under regulation 174
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer/BioNTech	United Kingdom	22-Apr-21	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Bahrain	3-Dec-20	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Israel	6-Dec-20	Special import approval Clause 29
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Canada	9-Dec-20	Interim Order
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Qatar	10-Dec-20	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Saudi Arabia	10-Dec-20	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Mexico	11-Dec-20	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	United States	11-Dec-20	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Kuwait	13-Dec-20	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Oman	13-Dec-20	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Lebanon	14-Dec-20	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Singapore	14-Dec-20	Pandemic Special Access Route
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Costa Rica	15-Dec-20	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Ecuador	15-Dec-20	Importation Authorization
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	United Arab Emirates	15-Dec-20	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Chile	16-Dec-20	Special import for emergency use article 99
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Panama	16-Dec-20	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Jordan	17-Dec-20	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Serbia	17-Dec-20	Import License
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Switzerland	19-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Austria	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Belgium	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Bulgaria	21-Dec-20	Conditional marketing authorization approval

Product Detail Set Name	Marketing Authorization Holder	Country	Approval Date	Authorization Type
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Croatia	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Cyprus	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Czech Republic	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Denmark	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Estonia	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Finland	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	France	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Germany	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Greece	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Hungary	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Iceland	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Ireland	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Italy	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Latvia	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Liechtenstein	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Lithuania	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Luxembourg	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Malta	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Netherlands	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Norway	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Poland	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Portugal	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Romania	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Slovakia	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Slovenia	21-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Spain	21-Dec-20	Conditional marketing authorization approval

Product Detail Set Name	Marketing Authorization Holder	Country	Approval Date	Authorization Type
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Sweden	21-**Dec**-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Argentina	22-Dec-20	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Iraq	27-Dec-20	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Colombia	6-Jan-21	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Malaysia	8-Jan-21	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Tunisia	11-Jan-21	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Philippines	14-Jan-21	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Uruguay	21-Jan-21	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Australia	24-Jan-21	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Hong Kong[a]	25-Jan-21	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Peru	1-Feb-21	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	New Zealand	3-Feb-21	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Dominican Republic	8-Feb-21	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Japan	14-Feb-21	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Ukraine	22-Feb-21	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Brazil	23-Feb-21	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Macau[a]	23-Feb-21	Special import permit
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Albania	24-Feb-21	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Rwanda	1-Mar-21	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Turkey	1-Mar-21	Supply from Abroad Import permit
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	South Korea	5-Mar-21	Conditional marketing authorization approval
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	South Africa	11-Mar-21	Special Import Permit - Section 21
Pfizer-BioNTech COVID-19 mRNA vaccine	Pfizer	Palestine	25-Mar-21	EUA
Pfizer-BioNTech COVID-19 mRNA vaccine	BioNTech	Algeria	12-Apr-21	EUA

a. Distributed through Shanghai Fosun Pharmaceutical in this territory.

APPENDIX 16.1 - Cumulative Summary Tabulation of Serious Adverse Reactions from Clinical Trials

PF-07302048

Reporting Period: Through 21-APR-2021
Total Number of Cases: 9
Total Number of Adverse Events (PT): 9
MedDRA Version: v.23.1J

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO
Blood and lymphatic system disorders	Lymphadenopathy**	1		
Sub Total:		**1**		
Cardiac disorders	Myocardial infarction**	1		
	Ventricular arrhythmia**	1		
Sub Total:		**2**		
General disorders and administration site conditions	Shoulder injury related to vaccine administration**	1		
Sub Total:		**1**		
Immune system disorders	Anaphylactoid reaction**	1		
Sub Total:		**1**		
Musculoskeletal and connective tissue disorders	Psoriatic arthropathy			1
Sub Total:				**1**

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
**Indicates an unexpected event for at least one case
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug and the event is related to at least one of the suspect products for this case, the related event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the related event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the related event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the related event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the related events will fall under Comparator.
Other Suspects: If none of the above categories are met, the related event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2	BLINDED THERAPY	PLACEBO
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukaemia**	1		
Sub Total:		**1**		
Nervous system disorders	Neuritis**		1	
	Paraesthesia**	1		
Sub Total:		**1**	**1**	
Total Number of Cases:		**7**	**1**	**1**
Total Number of Events:		**7**	**1**	**1**

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
**Indicates an unexpected event for at least one case
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug and the event is related to at least one of the suspect products for this case, the related event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the related event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the related event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the related event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the related events will fall under Comparator.
Other Suspects: If none of the above categories are met, the related event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect

APPENDIX 16.1.1 - Cumulative Summary Tabulation of Serious Adverse Reactions from Clinical Trials

PF-07302048

Reporting Period: Through 21-APR-2021
Total Number of Cases: 1
Total Number of Adverse Events (PT): 1
MedDRA Version: v.23.1J

SOC	PT	BNT162A1;BNT162B1;BNT162B2;BNT162B3;BNT162C2
Infections and infestations	Cystitis**	1
Sub Total:		**1**
Total Number of Cases:		**1**
Total Number of Events:		**1**

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
**Indicates an unexpected event for at least one case
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug and the event is related to at least one of the suspect products for this case, the related event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the related event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the related event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the related event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the related events will fall under Comparator.
Other Suspects: If none of the above categories are met, the related event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect

APPENDIX R16.1.2 Line Listings of SUSARs During the Reporting Period

PF-07302048

Total Number of Cases: 7

Reporting Period: 22-APR-2020 Through 21-APR-2021

MedDRA Version: v.23.1J

Protocol #	AER Number	Suspect Product	Preferred Term [Verbatim Term]	Event Seriousness	IB Labelled	Causality per Reporter	Causality per Company
C4591001	(b) (6)	BNT162B2	Shoulder injury related to vaccine administration [SIRVA]	SERIOUS	N	RELATED	RELATED
	(b) (6)	BNT162B2	Lymphadenopathy [right axilla lymphadenopathy]	SERIOUS	N	RELATED	UNRELATED
	(b) (6)	BNT162B2	Ventricular arrhythmia [paroxysmal ventricular arrhythmias]	SERIOUS	N	RELATED	UNRELATED
	(b) (6)	BNT162B2	Paraesthesia [right leg paresthesia]	SERIOUS	N	RELATED	UNRELATED
	(b) (6)	BNT162B2	Myocardial infarction [probable heart attack]	SERIOUS	N	RELATED	UNRELATED
C4591001-OPENLABEL	(b) (6)	BNT162B2	Anaphylactoid reaction [Anaphylactoid reaction]	SERIOUS	N	RELATED	RELATED
	(b) (6)	BNT162B2	Acute myeloid leukaemia [acute myeloblastic leukemia]	SERIOUS	N	RELATED	UNRELATED

APPENDIX R16.2 Listing of Subjects Who Died During the Reporting Period

Reporting Period: 22-APR-2020 Through 21-APR-2021
Total Number of Cases: 51
Total Number of Adverse Events (PT): 70

MedDRA Version: v.23.1J

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Cardiac disorders

AER Number: (b) (6)	Subject ID: 10071101	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
56 YEARS	BLINDED THERAPY	COVID-19 immunisation		20-AUG-2020 - 20-AUG-2020	Cardiac arrest [Cardiac Arrest]
FEMALE			SOLUTION FOR INJECTION		
FATAL			INTRAMUSCULAR		

AER Number (b) (6)	Subject ID: 10661350	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
58 YEARS	BLINDED THERAPY	COVID-19 immunisation		19-OCT-2020 - 19-OCT-2020	Disease progression [Disease progression]
MALE			SOLUTION FOR INJECTION		Myocardial infarction [myocardial infarction]
FATAL			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

APPENDIX R16.2 Listing of Subjects Who Died During the Reporting Period

Reporting Period: 22-APR-2020 Through 21-APR-2021
Total Number of Cases: 51
Total Number of Adverse Events (PT): 70

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Cardiac disorders

AER Number: (b) (6)	Subject ID: 10811194	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
51 YEARS	BLINDED THERAPY	COVID-19 immunisation		29-SEP-2020 - 29-SEP-2020	Disease progression [disease progression]
FEMALE			SOLUTION FOR INJECTION		Myocardial infarction [myocardial infarction]
FATAL			INTRAMUSCULAR		

AER Number: (b) (6)	Subject ID: 11201050	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
58 YEARS	BLINDED THERAPY	COVID-19 immunisation		27-AUG-2020 - 27-AUG-2020	Cardio-respiratory arrest [Cardio Pulmonary Arrest Immediate]
FEMALE			SOLUTION FOR INJECTION		
FATAL			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

APPENDIX R16.2 Listing of Subjects Who Died During the Reporting Period

Reporting Period: 22-APR-2020 Through 21-APR-2021
Total Number of Cases: 51
Total Number of Adverse Events (PT): 70

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Cardiac disorders

AER Number: (b) (6)	Subject ID: 11271112	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
53 YEARS	BLINDED THERAPY	COVID-19 immunisation		10-SEP-2020 - 10-SEP-2020	Cardio-respiratory arrest [Cardiopulmonary arrest]
MALE					
FATAL			SOLUTION FOR INJECTION		
			INTRAMUSCULAR		

AER Number: (b) (6)	Subject ID: 12314987	Country: ARGENTINA	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
47 YEARS	BLINDED THERAPY	Immunisation		16-SEP-2020 - 16-SEP-2020	Cardiac arrest [non-traumatic cardiac arrest]
MALE					
FATAL			SOLUTION FOR INJECTION		
			NO DATA		
				28-AUG-2020 - 28-AUG-2020	

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Cardiac disorders

AER Number: (b) (6)	Subject ID: 11401117	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
59 YEARS	BLINDED THERAPY	COVID-19 immunisation		04-SEP-2020 - 04-SEP-2020	Cardiac arrest [Cardiac Arrest]
MALE			SOLUTION FOR INJECTION		
FATAL			INTRAMUSCULAR		

AER Number: (b) (6)	Subject ID: 10211127	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
54 YEARS	BLINDED THERAPY	COVID-19 immunisation		23-SEP-2020 - 23-SEP-2020	Cardiac failure congestive [acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure]
MALE			SOLUTION FOR INJECTION		Disease progression [Disease progression]
FATAL			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

APPENDIX R16.2 Listing of Subjects Who Died During the Reporting Period

Reporting Period: 22-APR-2020 Through 21-APR-2021
Total Number of Cases: 51
Total Number of Adverse Events (PT): 70

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Cardiac disorders

AER Number (b) (6)	Subject ID: 10211127	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
54 YEARS	BLINDED THERAPY	COVID-19 immunisation		23-SEP-2020 - 23-SEP-2020	Cardiac failure congestive [stage IV congestive heart failure]
MALE					
RECOVERED/RESOLVED			SOLUTION FOR INJECTION		Disease progression [disease progression]
			INTRAMUSCULAR		

AER Number: (b) (6)	Subject ID: 10971064	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
78 YEARS	BLINDED THERAPY	COVID-19 immunisation		24-SEP-2020 - 24-SEP-2020	Atrial fibrillation [Persistent Atrial fib]
MALE					
FATAL			SOLUTION FOR INJECTION		Disease progression [Disease Progression]
			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Cardiac disorders

AER Number (b) (6)	Subject ID: 10881126	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
66 YEARS	BLINDED THERAPY	COVID-19 immunisation		23-SEP-2020 - 23-SEP-2020	Cardiac arrest [cardiac arrest due to coronary artery disease]
MALE			SOLUTION FOR INJECTION		Coronary artery disease [cardiac arrest due to coronary artery disease]
FATAL			INTRAMUSCULAR		COVID-19 [COVID-19]

AER Number: (b) (6)	Subject ID: 11291166	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
79 YEARS	BNT162B2	COVID-19 immunisation		28-SEP-2020 - 28-SEP-2020	Disease progression [Disease progression]
FEMALE			SOLUTION FOR INJECTION		Myocardial infarction [Myocardial infarction]
FATAL			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

APPENDIX R16.2 Listing of Subjects Who Died During the Reporting Period

Reporting Period: 22-APR-2020 Through 21-APR-2021
Total Number of Cases: 51
Total Number of Adverse Events (PT): 70

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Cardiac disorders

AER Number: (b) (6)	Subject ID: 11361102	Country: UNITED STATES	EUDRACT No: 2020-002641-42

Patient Age / Sex / Patient Outcome	Suspect Drug(s)	Indication	Total Daily Dose / Dosage Form / Rt of Admin	Therapy Dates From / To	Cause of Death MedDRA Preferred Term [Cause of Death Verbatim Term]
76 YEARS MALE FATAL	BLINDED THERAPY	COVID-19 immunisation	 SOLUTION FOR INJECTION INTRAMUSCULAR	19-NOV-2020 - 19-NOV-2020	Cardiac arrest [Cardiac arrest/Sudden onset]

AER Number: (b) (6)	Subject ID: 10161055	Country: UNITED STATES	EUDRACT No: 2020-002641-42

Patient Age / Sex / Patient Outcome	Suspect Drug(s)	Indication	Total Daily Dose / Dosage Form / Rt of Admin	Therapy Dates From / To	Cause of Death MedDRA Preferred Term [Cause of Death Verbatim Term]
61 YEARS MALE FATAL	BNT162B2	COVID-19 immunisation	 SOLUTION FOR INJECTION INTRAMUSCULAR	28-AUG-2020 - 28-AUG-2020	Myocardial infarction [heart attack/MI]

Absence of any information in any of the fields indicates that information was not reported.

Reporting Period: 22-APR-2020 Through 21-APR-2021
Total Number of Cases: 51
Total Number of Adverse Events (PT): 70

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Cardiac disorders

AER Number (b) (6)	Subject ID: 10461090	Country: UNITED STATES		EUDRACT No: 2020-002641-42	
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
71 YEARS	BLINDED THERAPY	COVID-19 immunisation		14-SEP-2020 - 14-SEP-2020	Myocardial infarction [Myocardial Infarction]
MALE			SOLUTION FOR INJECTION		
FATAL			INTRAMUSCULAR		

SOC: Gastrointestinal disorders

AER Number (b) (6)	Subject ID: 10831050	Country: UNITED STATES		EUDRACT No: 2020-002641-42	
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
79 YEARS	PLACEBO	COVID-19 immunisation		03-SEP-2020 - 03-SEP-2020	Acute abdomen [acute abdomen]
FEMALE			SOLUTION FOR INJECTION		
FATAL			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: General disorders and administration site conditions

AER Number: (b) (6)	Subject ID: 11521085	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
42 YEARS	PLACEBO	COVID-19 immunisation		19-AUG-2020 - 19-AUG-2020	Death [undetermined]
FEMALE					
FATAL			SOLUTION FOR INJECTION		
			INTRAMUSCULAR		
	ESSURE	Contraception		-------2017 -	
			NO DATA		
			NO DATA		

AER Number: (b) (6)	Subject ID: 11141050	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
64 YEARS	BLINDED THERAPY	Immunisation		08-SEP-2020 - 08-SEP-2020	Sudden cardiac death [Sudden cardiac death]
FEMALE					
FATAL			SOLUTION FOR INJECTION		
			INTRAMUSCULAR		
				18-AUG-2020 - 18-AUG-2020	

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: General disorders and administration site conditions

AER Number: (b) (6)	Subject ID: 10941025	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
56 YEARS	BLINDED THERAPY	COVID-19 immunisation		10-SEP-2020 - 10-SEP-2020	Death [passed away]
MALE			SOLUTION FOR INJECTION		
FATAL			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Infections and infestations

AER Number: (b) (6)	Subject ID: 11521497	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
72 YEARS	BLINDED THERAPY	COVID-19 immunisation		07-OCT-2020 - 07-OCT-2020	Disease progression [disease progression]
MALE					
FATAL			SOLUTION FOR INJECTION		Shigella sepsis [sepsis related to a Shigella infection (Shigellosis)]
			INTRAMUSCULAR		

AER Number (b) (6)	Subject ID: 10841266	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
77 YEARS	BLINDED THERAPY	COVID-19 immunisation		14-SEP-2020 - 14-SEP-2020	Disease progression [disease progression]
MALE					
FATAL			SOLUTION FOR INJECTION		Emphysematous cholecystitis [acute emphysematous cholecystitis]
			INTRAMUSCULAR		Sepsis [Sepsis]

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Infections and infestations

AER Number: (b) (6)	Subject ID: 11281009	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
66 YEARS	BLINDED THERAPY	Immunisation		19-AUG-2020 - 19-AUG-2020	Pneumonia [Pneumonia]
MALE			SOLUTION FOR INJECTION		
FATAL			INTRAMUSCULAR		
				31-JUL-2020 - 31-JUL-2020	

AER Number (b) (6)	Subject ID: 10941112	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
57 YEARS	BLINDED THERAPY	COVID-19 immunisation		29-SEP-2020 - 29-SEP-2020	Acute respiratory failure [acute hypoxemic respiratory failure]
FEMALE			SOLUTION FOR INJECTION		COVID-19 [COVID-19]
FATAL			SUBCUTANEOUS		Pneumonia [Pneumonia]

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Infections and infestations

AER Number (b) (6)	Subject ID: 10971023	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
87 YEARS	BLINDED THERAPY	COVID-19 immunisation		15-SEP-2020 - 15-SEP-2020	Septic shock [septic shock]
FEMALE					
FATAL			SOLUTION FOR INJECTION		
			INTRAMUSCULAR		

AER Number: (b) (6)	Subject ID: 12521010	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
81 YEARS	BLINDED THERAPY	COVID-19 immunisation		08-SEP-2020 - 08-SEP-2020	COVID-19 pneumonia [Pneumonia Due to COVID-19]
MALE					
FATAL			SOLUTION FOR INJECTION		
			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Infections and infestations

AER Number (b) (6)	Subject ID: 12291083	Country: SOUTH AFRICA	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
55 YEARS	BLINDED THERAPY	COVID-19 immunisation		22-OCT-2020 - 22-OCT-2020	COVID-19 pneumonia [Covid pneumonia]
FEMALE			SOLUTION FOR INJECTION		Disease progression [disease progression]
FATAL			INTRAMUSCULAR		

AER Number: (b) (6)	Subject ID: 10841470	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
65 YEARS	PLACEBO	COVID-19 immunisation		21-OCT-2020 - 21-OCT-2020	COVID-19 [COVID-19 infection]
MALE			SOLUTION FOR INJECTION		Disease progression [disease progression]
FATAL			INTRAMUSCULAR		Multiple organ dysfunction syndrome [multi-system organ failure]

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Infections and infestations

AER Number (b) (6)	Subject ID: 12071055	Country: TURKEY	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
65 YEARS	PLACEBO	COVID-19 immunisation		26-NOV-2020 - 26-NOV-2020	Cardiac arrest [cardiac arrest]
MALE					
FATAL			SOLUTION FOR INJECTION		Pneumonia bacterial [Bacterial pneumonia, unspecified]
			INTRAMUSCULAR		

AER Number: (b) (6)	Subject ID: 12315324	Country: ARGENTINA	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
59 YEARS	BLINDED THERAPY	COVID-19 immunisation		18-SEP-2020 - 18-SEP-2020	Acute respiratory failure [Acute Respiratory Failure; Multiorganic Failure; Multilobar Pneumonia]
FEMALE					
FATAL			SOLUTION FOR INJECTION		COVID-19 [Severe COVID-19 illness]
			INTRAMUSCULAR		Multiple organ dysfunction syndrome [Acute Respiratory Failure; Multiorganic Failure; Multilobar Pneumonia]
					Pneumonia [Acute Respiratory Failure; Multiorganic Failure; Multilobar Pneumonia]

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Injury, poisoning and procedural complications

AER Number: (b) (6)	Subject ID: 11561160	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
62 YEARS	BLINDED THERAPY	COVID-19 immunisation		12-OCT-2020 - 12-OCT-2020	Road traffic accident [MVA]
FEMALE					
FATAL			SOLUTION FOR INJECTION		
			INTRAMUSCULAR		

AER Number: (b) (6)	Subject ID: 10361140	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
64 YEARS	BLINDED THERAPY	COVID-19 immunisation		12-NOV-2020 - 12-NOV-2020	Injury [traumatic injuries from a motor vehicle collision]
MALE					
FATAL			SOLUTION FOR INJECTION		Road traffic accident [motor vehicle collision]
			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

AER Number (b) (6)	Subject ID: 10191146	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
67 YEARS	BLINDED THERAPY	COVID-19 immunisation		22-SEP-2020 - 22-SEP-2020	Biliary cancer metastatic [biliary carcinoma metastatic to liver]
MALE					
FATAL			SOLUTION FOR INJECTION		Disease progression [disease progression]
			INTRAMUSCULAR		Metastases to liver [biliary carcinoma metastatic to liver]

AER Number: (b) (6)	Subject ID: 11201266	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
51 YEARS	BLINDED THERAPY	COVID-19 immunisation		29-SEP-2020 - 29-SEP-2020	Lung cancer metastatic [Metastatic Lung cancer]
MALE					
FATAL			SOLUTION FOR INJECTION		
			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

AER Number: (b) (6)	Subject ID: 10881139	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
83 YEARS	BLINDED THERAPY	COVID-19 immunisation		15-OCT-2020 - 15-OCT-2020	Metastases to lung [death due to metastatic pancreatic cancer due to metastases to the lungs]
MALE			SOLUTION FOR INJECTION		Pancreatic carcinoma metastatic [death due to metastatic pancreatic cancer due to metastases to the lungs]
FATAL			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Nervous system disorders

AER Number: (b) (6)	Subject ID: 12313972	Country: ARGENTINA	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
61 YEARS	BLINDED THERAPY	COVID-19 immunisation		13-SEP-2020 - 13-SEP-2020	Disease progression [disease progression]
FEMALE			SOLUTION FOR INJECTION		Haemorrhagic stroke [HEMORRHAGIC STROKE]
FATAL			INTRAMUSCULAR		

AER Number: (b) (6)	Subject ID: 10891088	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
82 YEARS	BLINDED THERAPY	COVID-19 immunisation		28-AUG-2020 - 28-AUG-2020	Dementia Alzheimer's type [Worsening of dementia (Alzheimer's)]
FEMALE			SOLUTION FOR INJECTION		Disease progression [disease progression]
FATAL			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Nervous system disorders

AER Number: (b) (6)	Subject ID: 11161048	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
75 YEARS	PLACEBO	COVID-19 immunisation		18-SEP-2020 - 18-SEP-2020	Dementia Alzheimer's type [Progression of dementia and Alzheimer's resulting in death]
FEMALE			SOLUTION FOR INJECTION		
FATAL			INTRAMUSCULAR		

SOC: Psychiatric disorders

AER Number: (b) (6)	Subject ID: 12211068	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
31 YEARS	BLINDED THERAPY	COVID-19 immunisation		21-DEC-2020 - 21-DEC-2020	Completed suicide [murder or suicide]
MALE			SOLUTION FOR INJECTION		
FATAL			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Respiratory, thoracic and mediastinal disorders

AER Number: (b) (6)	Subject ID: 11561124	Country: UNITED STATES	EUDRACT No: 2020-002641-42

Patient Age / Sex / Patient Outcome	Suspect Drug(s)	Indication	Total Daily Dose / Dosage Form / Rt of Admin	Therapy Dates From / To	Cause of Death MedDRA Preferred Term [Cause of Death Verbatim Term]
53 YEARS MALE FATAL	BLINDED THERAPY	Immunisation	SOLUTION FOR INJECTION INTRAMUSCULAR	02-OCT-2020 - 02-OCT-2020 10-SEP-2020 - 10-SEP-2020	Accidental death [accidental death by fentanyl, "despropionyl fentanyl (4-ANPP)", ethanol and alprazolam intoxication] Toxicity to various agents [fentanyl, despropionyl fentanyl (4-ANPP), Ethanol and Alprazolam intoxication]
	FENTANYL CITRATE	Substance use	UNKNOWN NO DATA	-	
	ALPRAZOLAM	Substance use	UNKNOWN NO DATA	-	
	ETHANOL	Substance use	NO DATA NO DATA	-	

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Respiratory, thoracic and mediastinal disorders

AER Number: (b) (6)	Subject ID: 10891073	Country: UNITED STATES		EUDRACT No: 2020-002641-42	
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
63 YEARS	BLINDED THERAPY	COVID-19 immunisation		04-SEP-2020 - 04-SEP-2020	Chronic obstructive pulmonary disease [Worsening of COPD]
FEMALE			SOLUTION FOR INJECTION		Disease progression [Disease progression]
FATAL			INTRAMUSCULAR		

AER Number: (b) (6)	Subject ID: 10271191	Country: UNITED STATES		EUDRACT No: 2020-002641-42	
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
68 YEARS	BLINDED THERAPY	COVID-19 immunisation		02-OCT-2020 - 02-OCT-2020	Acute respiratory failure [Acute Hypoxic Respiratory Failure caused by COVID-19]
FEMALE			SOLUTION FOR INJECTION		COVID-19 [Acute Hypoxic Respiratory Failure caused by COVID-19]
FATAL			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Respiratory, thoracic and mediastinal disorders

AER Number: (b) (6)	Subject ID: 10561380	Country: UNITED STATES		EUDRACT No: 2020-002641-42	
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
67 YEARS	BLINDED THERAPY	COVID-19 immunisation		21-OCT-2020 - 21-OCT-2020	Pneumonia aspiration [aspiration pneumonia]
MALE			SOLUTION FOR INJECTION		
FATAL			INTRAMUSCULAR		

AER Number: (b) (6)	Subject ID: 12211082	Country: UNITED STATES		EUDRACT No: 2020-002641-42	
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
45 YEARS	BLINDED THERAPY	COVID-19 immunisation		22-DEC-2020 - 22-DEC-2020	Asphyxia [asphyxiation unknown cause]
FEMALE			SOLUTION FOR INJECTION		
FATAL			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Vascular disorders

AER Number (b) (6)	Subject ID: 11621327	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
60 YEARS	BLINDED THERAPY	Immunisation		10-SEP-2020 - 10-SEP-2020	Arteriosclerosis [Atherosclerotic Disease]
MALE					
FATAL			SOLUTION FOR INJECTION		Disease progression [Disease Progression]
			INTRAMUSCULAR		

AER Number: (b) (6)	Subject ID: 11681083	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
65 YEARS	BLINDED THERAPY	Immunisation		15-SEP-2020 - 15-SEP-2020	Aortic rupture [Aortic rupture]
MALE					
FATAL			SOLUTION FOR INJECTION		
			INTRAMUSCULAR		
				25-AUG-2020 - 25-AUG-2020	

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001

SOC: Vascular disorders

AER Number: (b) (6)	Subject ID: 10391010	Country: UNITED STATES	EUDRACT No: 2020-002641-42

Patient Age / Sex / Patient Outcome	Suspect Drug(s)	Indication	Total Daily Dose / Dosage Form / Rt of Admin	Therapy Dates From / To	Cause of Death MedDRA Preferred Term [Cause of Death Verbatim Term]
85 YEARS MALE FATAL	BLINDED THERAPY	Immunisation	SOLUTION FOR INJECTION INTRAMUSCULAR	09-SEP-2020 - 09-SEP-2020	Arteriosclerosis [atherosclerotic and hypertensive cardiovascular disease] Disease progression [Disease Progression]
				21-AUG-2020 - 21-AUG-2020	Hypertensive heart disease [atherosclerotic and hypertensive cardiovascular disease]

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001-OPENLABEL

SOC: Cardiac disorders

AER Number (b) (6)	Subject ID: 11311204	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
84 YEARS	BNT162B2	COVID-19 immunisation		21-JAN-2021 - 21-JAN-2021	Cardio-respiratory arrest [Cardiopulmonary arrest]
MALE			SOLUTION FOR INJECTION		
FATAL			INTRAMUSCULAR		

SOC: Gastrointestinal disorders

AER Number: (b) (6)	Subject ID: 12411829	Country: BRAZIL	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
64 YEARS	BNT162B2	COVID-19 immunisation		19-FEB-2021 - 19-FEB-2021	Gastrointestinal haemorrhage [high digestive bleeding]
FEMALE			SOLUTION FOR INJECTION		Hypovolaemic shock [hypovolemic shock]
FATAL			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

Drug Project Name: PF-07302048

Clinical Trial No: C4591001-OPENLABEL

SOC: General disorders and administration site conditions

AER Number (b) (6)	Subject ID: 12313105	Country: ARGENTINA	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
33 YEARS	BNT162B2	COVID-19 immunisation		14-SEP-2020 - 14-SEP-2020	Death [death]
MALE			SOLUTION FOR INJECTION		
FATAL			NO DATA		
				22-AUG-2020 - 22-AUG-2020	

SOC: Psychiatric disorders

AER Number (b) (6)	Subject ID: 11351033	Country: UNITED STATES	EUDRACT No: 2020-002641-42		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
67 YEARS	BNT162B2	COVID-19 immunisation		25-JAN-2021 - 25-JAN-2021	Completed suicide [Suicide]
MALE			SOLUTION FOR INJECTION		
FATAL			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

Reporting Period: 22-APR-2020 Through 21-APR-2021
Total Number of Cases: 51
Total Number of Adverse Events (PT): 70

Drug Project Name: PF-07302048

Clinical Trial No: C4591001-OPENLABEL

SOC: Vascular disorders

AER Number: (b) (6)	**Subject ID: 11311204**	**Country: UNITED STATES**	**EUDRACT No: 2020-002641-42**		
Patient Age	**Suspect Drug(s)**	**Indication**	**Total Daily Dose**	**Therapy Dates**	**Cause of Death MedDRA Preferred Term**
Sex			**Dosage Form**	**From**	**[Cause of Death Verbatim Term]**
Patient Outcome			**Rt of Admin**	**To**	
84 YEARS	BNT162B2	COVID-19 immunisation		21-JAN-2021 - 21-JAN-2021	Cardio-respiratory arrest [cardiopulmonary arrest]
MALE			SOLUTION FOR INJECTION		
RECOVERED/RESOLVED			INTRAMUSCULAR		

Absence of any information in any of the fields indicates that information was not reported.

APPENDIX R16.3
List of Subjects Discontinued from a Clinical Trial Due to Adverse Events (a)
BNT162/PF-07302048, DSUR
Discontinuations Entered into the Database from 22-APR-2020 to 21-APR-2021

Treatment	Protocol Number	Subject ID	Adverse Event MedDRA v23.1 Preferred Term
BNT162b2	C4591001	C4591001 1005 10051214	Facial pain
			Swelling face
		C4591001 1006 10061272	Anxiety
			Depression
		C4591001 1007 10071101	Cardiac arrest
		C4591001 1011 10111181	Paraesthesia oral
		C4591001 1012 10121103	Product administration error
		C4591001 1012 10121163	Injection site dermatitis
		C4591001 1016 10161055	Myocardial infarction
		C4591001 1016 10161087	Injection site swelling
		C4591001 1021 10211127	Cardiac failure congestive
		C4591001 1036 10361140	Injury
			Road traffic accident
		C4591001 1039 10391010	Arteriosclerosis
			Hypertensive heart disease
		C4591001 1046 10461090	Myocardial infarction
		C4591001 1047 10471114	Adverse Event-Unspecified
		C4591001 1056 10561380	Pneumonia aspiration
		C4591001 1071 10711023	Coronary artery disease
		C4591001 1071 10711169	Alcohol poisoning
		C4591001 1079 10791004	Adenocarcinoma gastric
		C4591001 1084 10841266	Emphysematous cholecystitis
			Sepsis
		C4591001 1087 10871121	Gastrointestinal haemorrhage
		C4591001 1087 10871557	Exposure during pregnancy
		C4591001 1088 10881139	Metastases to lung
		C4591001 1089 10891073	Chronic obstructive pulmonary disease

(a) Excludes Discontinuations as a Result of Death
The Treatment column represents the Actual Treatment Group Subjects Received. For Crossover Studies, the Actual Treatment Sequence will be displayed instead.
Includes Protocols: C4591001,C4591005,C4591017,C4591020
PFIZER CONFIDENTIAL Output File: ./dsur2021/OCS/adds_l003_ocs Date of Generation: 25MAY2021 (09:32)

List of Subjects Discontinued from a Clinical Trial Due to Adverse Events (a)
BNT162/PF-07302048, DSUR
Discontinuations Entered into the Database from 22-APR-2020 to 21-APR-2021

Treatment	Protocol Number	Subject ID	Adverse Event MedDRA v23.1 Preferred Term
BNT162b2	C4591001	C4591001 1089 10891289	Acute hepatic failure
		C4591001 1093 10931058	Exposure during pregnancy
		C4591001 1095 10951141	Diabetic foot
		C4591001 1097 10971023	Septic shock
		C4591001 1097 10971064	Atrial fibrillation
		C4591001 1109 11091503	Abdominal pain upper
		C4591001 1112 11121118	Tachycardia
		C4591001 1112 11121255	Chills
			Headache
			Pyrexia
		C4591001 1120 11201050	Cardiac arrest
		C4591001 1120 11201266	Lung cancer metastatic
		C4591001 1125 11251243	Headache
			Injection site pain
		C4591001 1127 11271112	Cardio-respiratory arrest
		C4591001 1129 11291166	Myocardial infarction
		C4591001 1134 11341153	Eye pain
		C4591001 1134 11341174	Headache
		C4591001 1136 11361102	Cardiac arrest
		C4591001 1140 11401117	Cardiac arrest
		C4591001 1147 11471327	Pyrexia
		C4591001 1152 11521476	Deafness unilateral
		C4591001 1152 11521497	Shigella sepsis
		C4591001 1156 11561160	Road traffic accident
		C4591001 1162 11621327	Arteriosclerosis
		C4591001 1163 11631005	Product administration error
		C4591001 1163 11631006	Product administration error

(a) Excludes Discontinuations as a Result of Death
The Treatment column represents the Actual Treatment Group Subjects Received. For Crossover Studies, the Actual Treatment Sequence will be displayed instead.
Includes Protocols: C4591001,C4591005,C4591017,C4591020
PFIZER CONFIDENTIAL Output File: ./dsur2021/OCS/adds_l003_ocs Date of Generation: 25MAY2021 (09:32)

List of Subjects Discontinued from a Clinical Trial Due to Adverse Events (a)
BNT162/PF-07302048, DSUR
Discontinuations Entered into the Database from 22-APR-2020 to 21-APR-2021

Treatment	Protocol Number	Subject ID	Adverse Event MedDRA v23.1 Preferred Term
BNT162b2	C4591001	C4591001 1178 11781107	Lymphadenopathy
		C4591001 1221 12211082	Asphyxia
		C4591001 1226 12261072	Myalgia
		C4591001 1230 12301045	Exposure during pregnancy
		C4591001 1231 12311815	Lymphoproliferative disorder
		C4591001 1231 12315429	Injection site pain
		C4591001 1231 12315441	Depression
		C4591001 1232 12321175	Hypertension
		C4591001 1232 12321293	Exposure during pregnancy
		C4591001 1241 12411766	Maternal exposure during pregnancy
		C4591001 1246 12461025	Urticaria
		C4591001 1252 12521010	COVID-19 pneumonia
		C4591001 1254 12541142	Maternal exposure during pregnancy
		C4591001 4444 44442319	Panic attack
	C4591005	C4591005 1002 10021069	Arthralgia
			Chills
			Fatigue
			Headache
			Injection site pain
Placebo to BNT162b2	C4591001	C4591001 1007 10071347	Atrial fibrillation
		C4591001 1008 10081667	Hepatic cancer
		C4591001 1015 10151134	Vertigo
		C4591001 1022 10221053	Chills
			Diarrhoea
			Headache
			Injection site pain
			Myalgia

(a) Excludes Discontinuations as a Result of Death
The Treatment column represents the Actual Treatment Group Subjects Received. For Crossover Studies, the Actual Treatment Sequence will be displayed instead.
Includes Protocols: C4591001,C4591005,C4591017,C4591020
PFIZER CONFIDENTIAL Output File: ./dsur2021/OCS/adds_l003_ocs Date of Generation: 25MAY2021 (09:32)

APPENDIX R16.3
List of Subjects Discontinued from a Clinical Trial Due to Adverse Events (a)
BNT162/PF-07302048, DSUR
Discontinuations Entered into the Database from 22-APR-2020 to 21-APR-2021

Treatment	Protocol Number	Subject ID	Adverse Event MedDRA v23.1 Preferred Term
Placebo to BNT162b2	C4591001	C4591001 1054 10541186	Dizziness
			Nausea
		C4591001 1083 10831060	Diverticular perforation
		C4591001 1090 10901415	Hypertension
		C4591001 1090 10901507	Urticaria
		C4591001 1093 10931128	Hypertension
		C4591001 1096 10961031	Exposure during pregnancy
		C4591001 1096 10961068	Product storage error
		C4591001 1123 11231235	Hypertension
		C4591001 1126 11261017	Allergy to vaccine
		C4591001 1129 11291260	Anaphylactoid reaction
		C4591001 1131 11311204	Cardio-respiratory arrest
		C4591001 1134 11341019	Angina pectoris
		C4591001 1145 11451076	Parkinsonism
		C4591001 1163 11631008	Product administration error
		C4591001 1163 11631059	Drug hypersensitivity
		C4591001 1163 11631062	Drug therapy
		C4591001 1166 11661047	Dizziness
		C4591001 1171 11711023	Angioedema
			Urticaria
		C4591001 1224 12241065	Heart rate irregular
		C4591001 1241 12411208	Maternal exposure during pregnancy
		C4591001 1241 12411279	Exposure during pregnancy
		C4591001 1241 12411514	Maternal exposure during pregnancy

(a) Excludes Discontinuations as a Result of Death
The Treatment column represents the Actual Treatment Group Subjects Received. For Crossover Studies, the Actual Treatment Sequence will be displayed instead.
Includes Protocols: C4591001,C4591005,C4591017,C4591020
PFIZER CONFIDENTIAL Output File: ./dsur2021/OCS/adds_l003_ocs Date of Generation: 25MAY2021 (09:32)

APPENDIX R16.3
List of Subjects Discontinued from a Clinical Trial Due to Adverse Events (a)
BNT162/PF-07302048, DSUR
Discontinuations Entered into the Database from 22-APR-2020 to 21-APR-2021

Treatment	Protocol Number	Subject ID	Adverse Event MedDRA v23.1 Preferred Term
Placebo to BNT162b2	C4591001	C4591001 1241 12411829	Gastrointestinal haemorrhage
			Hypovolaemic shock
		C4591001 1241 12412369	Maternal exposure during pregnancy
		C4591001 1241 12412411	Abortion spontaneous
			Maternal exposure during pregnancy
		C4591001 1247 12471135	Cerebral infarction
		C4591001 1247 12471244	Facial paralysis
		C4591001 1264 12641195	Dry mouth
			Eczema
			Pruritus
			Rash maculo-papular
Blinded Therapy	C4591017	C4591017 1014 10141004	Exposure during pregnancy
		C4591017 1017 10171064	Angioedema
			Antinuclear antibody positive
			Dermatitis
			White blood cell count increased
	C4591020	C4591020 1021 10211013	Hyponatraemia
			SARS-CoV-2 test positive
Placebo	C4591001	C4591001 1006 10061020	Coronary artery occlusion
		C4591001 1019 10191146	Biliary cancer metastatic
			Metastases to liver
		C4591001 1019 10191229	Adverse Event-Unspecified
		C4591001 1027 10271105	Drug hypersensitivity

(a) Excludes Discontinuations as a Result of Death
The Treatment column represents the Actual Treatment Group Subjects Received. For Crossover Studies, the Actual Treatment Sequence will be displayed instead.
Includes Protocols: C4591001,C4591005,C4591017,C4591020
PFIZER CONFIDENTIAL Output File: ./dsur2021/OCS/adds_l003_ocs Date of Generation: 25MAY2021 (09:32)

List of Subjects Discontinued from a Clinical Trial Due to Adverse Events (a)
BNT162/PF-07302048, DSUR
Discontinuations Entered into the Database from 22-APR-2020 to 21-APR-2021

Treatment	Protocol Number	Subject ID	Adverse Event MedDRA v23.1 Preferred Term
Placebo	C4591001	C4591001 1027 10271191	Acute respiratory failure
			COVID-19
		C4591001 1028 10281003	Exposure during pregnancy
		C4591001 1054 10541173	Adverse Event-Unspecified
		C4591001 1055 10551145	Dysphagia
		C4591001 1066 10661350	Myocardial infarction
		C4591001 1079 10791130	Wrong product administered
		C4591001 1081 10811194	Myocardial infarction
		C4591001 1082 10821149	Malignant melanoma
		C4591001 1083 10831029	Atrial fibrillation
		C4591001 1083 10831050	Acute abdomen
		C4591001 1084 10841470	COVID-19
			Multiple organ dysfunction syndrome
		C4591001 1085 10851129	Exposure during pregnancy
		C4591001 1087 10871228	Cardiac failure congestive
		C4591001 1087 10871354	Myalgia
		C4591001 1088 10881126	Cardiac arrest
		C4591001 1089 10891088	Dementia Alzheimer's type
		C4591001 1094 10941112	Acute respiratory failure
			COVID-19
			Pneumonia
		C4591001 1112 11121337	Diarrhoea
			Fatigue
		C4591001 1117 11171186	Suicide attempt
		C4591001 1120 11201127	Diarrhoea
		C4591001 1128 11281009	Pneumonia
		C4591001 1128 11281241	Breast cancer

(a) Excludes Discontinuations as a Result of Death
The Treatment column represents the Actual Treatment Group Subjects Received. For Crossover Studies, the Actual Treatment Sequence will be displayed instead.
Includes Protocols: C4591001,C4591005,C4591017,C4591020
PFIZER CONFIDENTIAL Output File: ./dsur2021/OCS/adds_l003_ocs Date of Generation: 25MAY2021 (09:32)

APPENDIX R16.3
List of Subjects Discontinued from a Clinical Trial Due to Adverse Events (a)
BNT162/PF-07302048, DSUR
Discontinuations Entered into the Database from 22-APR-2020 to 21-APR-2021

Treatment	Protocol Number	Subject ID	Adverse Event MedDRA v23.1 Preferred Term
Placebo	C4591001	C4591001 1135 11351368	Guillain-Barre syndrome
		C4591001 1140 11401035	Urticaria
		C4591001 1140 11401306	Amnesia
			Paraparesis
			Visual impairment
		C4591001 1156 11561015	Exposure during pregnancy
		C4591001 1156 11561124	Overdose
			Respiratory arrest
		C4591001 1163 11631030	Drug therapy
		C4591001 1168 11681083	Aortic rupture
		C4591001 1168 11681147	Respiratory failure
		C4591001 1170 11701013	Exposure during pregnancy
		C4591001 1207 12071055	Pneumonia bacterial
		C4591001 1217 12171031	Exposure during pregnancy
		C4591001 1229 12291083	COVID-19 pneumonia
		C4591001 1231 12313972	Haemorrhagic stroke
		C4591001 1231 12314987	Cardio-respiratory arrest
		C4591001 1231 12315324	COVID-19
			Septic shock
		C4591001 1232 12321213	Exposure during pregnancy
		C4591001 1251 12511228	Suicide attempt
		C4591001 1270 12701057	Pulmonary embolism
		C4591001 4444 44441979	Exposure during pregnancy

(a) Excludes Discontinuations as a Result of Death
The Treatment column represents the Actual Treatment Group Subjects Received. For Crossover Studies, the Actual Treatment Sequence will be displayed instead.
Includes Protocols: C4591001,C4591005,C4591017,C4591020
PFIZER CONFIDENTIAL Output File: ./dsur2021/OCS/adds_l003_ocs Date of Generation: 25MAY2021 (09:32)

Listing 16.3.1: Listing of subjects with premature discontinuation from BioNTech studies (BNT162-01 and BNT162-04)

Listing 16.3.1.1: Listing of subjects with premature discontinuation - Study BNT162-01

Listing 16.3.1.1-1: Listing of subjects with premature discontinuation - BNT162a1

Safety set

No subjects with premature discontinuation.

Staburo GmbH. Based on unclean SDTM data received on 22APR2021.

Listing 16.3.1.1-2: Listing of subjects with premature discontinuation - BNT162b1

Safety set

Dose group	Subject number	Date of last visit/contact	Date of premature termination	Main reason for premature termination	Epi/ Pandemic related
10 µg Younger	10010	22MAY2020	19MAY2020	Adverse Event	No
20 µg Younger	10178	03MAR2021	09SEP2020	Other (private reason)	No
	10182	06OCT2020	23JUL2020	Withdrawal By Subject	No
30 µg Younger	10031	27JUN2020	27JUN2020	Withdrawal By Subject	No
50 µg Younger	10050	03JUN2020	03JUN2020	Other (due to private reason.)	No
60 µg Younger	10103	14AUG2020	14AUG2020	Other (private reason)	No
20 µg Older	20241	15MAR2021	15MAR2021	Withdrawal By Subject	No

Program: Lbase_Disp_3.sas (Page 1 of 1)

Staburo GmbH. Based on unclean SDTM data received on 22APR2021.

Listing 16.3.1.1-3: Listing of subjects with premature discontinuation - BNT162b2

Safety set

Dose group	Subject number	Date of last visit/contact	Date of premature termination	Main reason for premature termination	Epi/ Pandemic related
1 µg Younger	20160	31JUL2020	30JUL2020	Withdrawal By Subject	No
10 µg Younger	20116	04AUG2020	16JUL2020	Adverse Event	No
20 µg Younger	20183	05OCT2020	05OCT2020	Withdrawal By Subject	No
20 µg Older	20226	15MAR2021	16NOV2020	Adverse Event	No
3-30 µg	20297	08FEB2021	08FEB2021	Withdrawal By Subject	No
30 µg	10379	17DEC2020	17DEC2020	Withdrawal By Subject	No

Program: Lbase_Disp_3.sas (Page 1 of 1)

Staburo GmbH. Based on unclean SDTM data received on 22APR2021.

Listing 16.3.1.1-4: Listing of subjects with premature discontinuation - BNT162c2 SD

Safety set

Dose group	Subject number	Date of last visit/contact	Date of premature termination	Main reason for premature termination	Epi/ Pandemic related
0.6 µg Younger	10158	07AUG2020	07AUG2020	Pregnancy	No
1 µg Younger	10153	26FEB2021	26FEB2021	Lost To Follow-Up	Yes

Program: Lbase_Disp_3.sas (Page 1 of 1)

Listing 16.3.1.1-5: Listing of subjects with premature discontinuation - BNT162c2 P/B

Safety set

Dose group	Subject number	Date of last visit/contact	Date of premature termination	Main reason for premature termination	Epi/ Pandemic related
3 µg Younger	10338	28DEC2020	28DEC2020	Lost To Follow-Up	No
	10340	23OCT2020	23OCT2020	Other (could not manage the schedule of the visits acc. to protocol (boost injection first postponed due to ae, but later volunteer skipped visits due to private reasons))	No

Program: Lbase_Disp_3.sas (Page 1 of 1)

Staburo GmbH. Based on unclean SDTM data received on 22APR2021.

Listing 16.3.1.2: Listing of subjects with premature discontinuation from Study BNT162-04

Listing 16.3.1.2-1: Listing of subjects with premature discontinuation - BNT162b3

Safety set

Dose group	Subject number	Date of last visit/contact	Date of premature termination	Main reason for premature termination	Epi/ Pandemic related
3 µg Younger	24008	28NOV2020	28NOV2020	Other (lack of time, new job in another town)	No
3 µg Older	24032	15APR2021	15APR2021	Withdrawal By Subject	No

Program: Lbase_Disp_3.sas (Page 1 of 1)

Staburo GmbH. Based on unclean SDTM data received on 22APR2021.

APPENDIX R16.3.2 List of Subjects Who Dropped Out of Clinical Trial Due to Any Adverse Event in China Within the Reporting Period

Table 1. BNT162-03– b1 Study (Safety Population)

AE Term	SOC// PT	Type Of Adverse Event	Severity (NMPA //FDA)	Start Date //End Date	Day from Inoculation //Duration	Relat.	Other Relat.	Action Taken	Outcome	AESI	DLT	SAE	Disc.
A2153, Elder group, BNT162b1 10ug, 71 Years, Female													
Greater tuberosity fracture of the left humerus; dislocation of left shoulder joint; dislocation of left acromioclavicular joint	Injury, poisoning and procedural complications// Humerus fracture	Unsolicited adverse events	Level III //	2020-08-27 //	13d //	Definitely unrelated	No //No //No	Hospitalization	Recovering/ resolving	No	No	Yes	Yes
Greater tuberosity fracture of the left humerus; dislocation of left shoulder joint; dislocation of left acromioclavicular joint	Injury, poisoning and procedural complications// Joint dislocation	Unsolicited adverse events	Level III //	2020-08-27 //	13d //	Definitely unrelated	No //No //No	Hospitalization	Recovering/ resolving	No	No	Yes	Yes
Greater tuberosity fracture of the left humerus; dislocation of left shoulder joint; dislocation of left acromioclavicular joint	Injury, poisoning and procedural complications// Joint dislocation	Unsolicited adverse events	Level III //	2020-08-27 //	13d //	Definitely unrelated	No //No //No	Hospitalization	Recovering/ resolving	No	No	Yes	Yes

Table 1. BNT162-03– b1 Study (Safety Population) *(Cont'd)*

A2001, Elder group, BNT162b1 30ug, 69 Years, Male													
Induration 4.0 cm	General disorders and administration site conditions// Vaccination site induration	Solicited adverse events //Solicited local reaction	Level I //Level I	2020-08-16 //2020-08-30	3d //15d	Definitely related	No //No //No	Drug / Non-drug medication	Recovered/ resolved	No	No	No	Yes
Pain	General disorders and administration site conditions// Vaccination site pain	Solicited adverse events //Solicited local reaction	Level I //Level I	2020-08-13 //2020-08-30	0d //18d	Definitely related	No //No //No	No action	Recovered/ resolved	No	No	No	Yes
Redness 8.0 cm	General disorders and administration site conditions// Vaccination site erythema	Solicited adverse events //Solicited local reaction	Level II //Level II	2020-08-16 //2020-08-30	3d //15d	Definitely related	No //No //No	Drug / Non-drug medication	Recovered/ resolved	No	No	No	Yes
Fever, Temperature 38.5 ℃	General disorders and administration site conditions// Pyrexia	Unsolicited adverse events	Level III //Level II	2020-08-27 //2020-09-01	14d //6d	Possibly related	No //No //No	Drug / Non-drug medication	Recovered/ resolved	No	No	No	Yes
Vaccination site pruritus	General disorders and administration site conditions// Vaccination site pruritus	Unsolicited adverse events	Level I //Level I	2020-08-16 //2020-08-30	3d //15d	Probably related	No //No //No	Drug / Non-drug medication	Recovered/ resolved	No	No	No	Yes
Vaccination site rash	General disorders and administration site conditions// Vaccination site rash	Unsolicited adverse events	Level I //Level I	2020-08-16 //2020-08-30	3d //15d	Probably related	No //No //No	Drug / Non-drug medication	Recovered/ resolved	No	No	No	Yes

AE=Adverse Event; AESI= Adverse event of special interest; d=day; Disc.=Discontinuation; DLT = dose limit toxicity ; FDA=Food and Drug Administration; h=hour; m=minute; NMPA= National Medical Products Administration; PT= Preferred Term; Relat. = Relationship; SAE= Serious Adverse Event; SOC= System Organ Class.

Table 2. BNT162-06- b2 Study (Safety Population)

AE Term	SOC// PT	Type Of Adverse Event	Severity (NMPA //FDA)	Start Date //End Date	Day from Inoculation //Duration	Relat.	Other Relat.	Action Taken	Outcome	AESI	SAE	Disc.
R10517, Adult Group, 50 Years, Male												
Fracture of left tibia and fibula	Injury, poisoning and procedural complications// Lower limb fracture	Unsolicited Event	Level III //	2021-01-03T17:00 //	15.0d //	Definitely unrelated	No //No //No	Drug /Non-drug medication	Recovering/ resolving	No	Yes	Yes
R20031, Elder Group, 58 Years, Male												
Right upper lobe lung carcinoma in situ	Neoplasms benign, malignant and unspecified (incl cysts and polyps)// Lung carcinoma cell type unspecified stage 0	Unsolicited Event	Level III //	2020-12-14 //	9d //	Definitely unrelated	No //No //No	Drug /Non-drug medication	Recovering/ resolving	No	Yes	Yes
R20369, Elder Group, 67 Years, Female												
Dizziness	Nervous system disorders// Dizziness	Unsolicited Event	Level II //	2020-12-27 //2021-01-15	8d //20d	Possibly unrelated	No //No //No	No action	Recovered/resolved	No	No	Yes
R20411, Elder Group, 63 Years, Female												
Type 2 diabetic peripheral neuropathy(painful) worsen	Nervous system disorders// Diabetic neuropathy	Unsolicited Event	Level III //	2020-12-19 //2021-01-14	0d //27d	Possibly unrelated	No //No //No	Drug /Non-drug medication	Recovered/resolved	No	Yes	Yes
R10420, Adult Group, 54 Years, Female												
Chronic cholecystitis acute attack	Hepatobiliary disorders// Cholecystitis acute	Unsolicited Event	Level III //	2020-12-26 //2021-01-12	8d //18d	Possibly unrelated	No //No //No	Drug /Non-drug medication	Recovered/resolved	No	Yes	Yes
R10447, Adult Group, 48 Years, Male												
Brain infarction	Nervous system disorders// Cerebral infarction	Unsolicited Event	Level III //	2020-12-24T14:35 //	5.3d //	Possibly unrelated	No //No //No	Drug /Non-drug medication	Recovering/ resolving	No	Yes	Yes

AE=Adverse Event; AESI= Adverse event of special interest; d=day; Disc.=Discontinuation; FDA=Food and Drug Administration; h=hour; m=minute; NMPA= National Medical Products Administration; PT= Preferred Term; Relat. = Relationship; SAE= Serious Adverse Event; SOC= System Organ Class.

APPENDIX R16.5.1 SIGNIFICANT MANUFACTURING CHANGES (US)

This is a region-specific section that applies to the US only and summarizes IND amendments that have occurred during the reporting period as required by US regulations and as applicable to the investigational supplies used in the US.

Significant manufacturing or microbiological changes have occurred during this reporting period and are summarized below.

Listing of Significant Changes

Serial Number	Submission Date	Summary of Changes
SN 0000	22 April 2020	Initial Investigational New Drug Application – SN0000
SN 0001	24 April 2020	IND Amendment – • (b) (4) • PACL for Study C4591001

(b) (4)

Serial Number	Submission Date	Summary of Changes
(b) (4)		

Serial Number	Submission Date	Summary of Changes
(b) (4)		

Serial Number	Submission Date	Summary of Changes
(b) (4)		

Changes that occurred during the reporting period have been submitted to Module 3.

APPENDIX R16.5.2 SIGNIFICANT MANUFACTURING CHANGES (CHINA)

This is a region-specific section that applies to China only and summarizes any significant manufacturing or microbiological changes that have occurred during the reporting period as applicable to the investigational supplies used in China.

Significant manufacturing changes have occurred during this reporting period and are summarized below.

Listing of Significant Changes

Date	Summary of Changes
(b) (4)	

Changes to the product used in clinical studies will be filed to China NMPA per the relevant regulation.

APPENDIX R16.6.1 DESCRIPTION OF THE GENERAL INVESTIGATIONAL PLAN FOR THE UPCOMING YEAR WITH RESPECT TO A US IND

Pfizer and BioNTech are developing investigational vaccines intended to prevent coronavirus disease 2019 (COVID-19) caused by the virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The goal of the development program is to rapidly develop and license a vaccine for use in adults ≥16 years of age, followed by a pediatric indication and an indication for use in pregnancy. The vaccine is based on SARS-CoV-2 S antigens encoded in ribonucleic acid (RNA) and formulated in lipid nanoparticles (LNPs), referred to as COVID-19 vaccine (BioNTech code number BNT162, Pfizer code number PF-07302048).

An investigational new drug (IND) application for the COVID-19 vaccine was submitted to the US food and drug administration (FDA) on 22 April 2020. On 29 April 2020 Pfizer was notified by the Center for Biologics Evaluation and Research (CBER) that there were no clinical hold issues identified, and the evaluation of this vaccine in the US could proceed. A Request for Fast Track Designation was submitted on 15 May 2020 (Serial Number 0005) and was granted on 07 July 2020.

Current efforts are being directed towards characterizing the safety and efficacy of the vaccine for the prevention of COVID-19. The clinical development program[1] for the upcoming reporting period is summarized below.

BB-IND #19736 (COVID-19 vaccine BNT162)

Phase 1 Studies

Protocol C4591001 is an ongoing, Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SAR-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals. A total of approximately 46,000 participants have been enrolled. Pfizer and BioNTech are conducting this study to evaluate the safety and immunogenicity of the prophylactic COVID-19 vaccine candidates using a range of dosage levels. Pfizer evaluated 2 vaccine candidates in Phase 1, both based on a platform of nucleoside-modified messenger ribonucleic acid (modRNA), BNT162b, and expressing either the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (BNT162b2) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (BNT162b1). Data from the Phase 1 portion of the study supported the advancement of the BNT162b2 candidate with two 30-µg doses administered at a 21-day interval in the pivotal Phase 2/3 safety, immunogenicity, and efficacy evaluation[i]. Some participants in the Phase 1 portion of the study have received a 30-µg booster dose and immunogenicity and safety will be assessed (protocol amendment 13).

Protocol C4591005 is an ongoing, Phase 1/2 placebo-controlled, randomized and observer-blind study to evaluate the safety, tolerability, and immunogenicity of SAR-CoV-2

[1] Please note that all studies (C459) are sponsored by BioNTech and conducted by Pfizer in the US, except to the 20-valent pneumococcal conjugate vaccine Study B7471026.

RNA vaccine candidates against COVID-19 in healthy Japanese adults. In this safety and immunogenicity study of the SARS-CoV-2 messenger RNA (mRNA) vaccine candidate BNT162b2, 160 Japanese participants (including 130 participants 20 to 64 years of age [younger age group] and 30 participants 65 to 85 years of age [older age group]) were randomized in an approximate 3:1 ratio of BNT162b2 (30-µg dose) to placebo. Results at 1 month after Dose 2 show BNT162b2 was well tolerated and had an acceptable safety profile and the immune responses elicited were robust. These encouraging results led to the marketing authorization of BNT162b2 in Japan. This study has since been converted to a postmarketing study.

Protocol C4591007 is an ongoing, 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 <12 years of age. In Phase 1, escalating doses will be assessed in an open, uncontrolled fashion for safety and immunogenicity, in age-de-escalating groups of 16 children ≥5 to <12 years of age, ≥2 to <5 years of age, and ≥6 months to <2 years of age.

Phase 2/3/4 Studies

Protocol C4591001 has an ongoing Phase 2/3 component. The majority of participants in the placebo group have now chosen to receive active vaccine. Follow-up of all participants continues for safety and cases of COVID-19. In protocol amendment 14 approximately 600 participants 18 to 55 years of age who had previously received 2 doses of BNT162b2 will be randomized to receive a 30-µg booster doses of BNT162b2 or BNT162b2s01 and another 30 participants will receive a third and fourth dose of BNT162b2s01. Safety and immunogenicity, including neutralization titers to reference SARS-CoV-2 and B.1.351 strains will be assessed. Approximately 300 new vaccine-naïve participants will receive 2 doses of 30-µg BNT162b2s01 at a 21-day interval. Safety and immunogenicity, including neutralization titers to reference SARS-CoV-2 and B.1.351 strains, will be compared to sera from matched participants who previously received 2 doses of BNT162b2 within Study C4591001. In protocol amendment 15 a further group of approximately 144 existing Phase 3 participants 18 years of age and older will be enrolled to receive a third, lower, dose of BNT162b2 of either 5 µg or 10 µg. Approximately 24 participants 18 to 55 years of age and 48 participants >55 years of age will be enrolled in each dose group. Safety and immunogenicity will be assessed.

Protocol C4591007 has a Phase 2/3 component conducted with dose levels selected in the Phase 1 portion of the study. This is a placebo-controlled, 2:1 randomized study in the same 3 age groups as the Phase 1 component. Assessments will include safety and immunogenicity noninferiority for each age group compared to the population 16 to 25 years of age in Study C4591001. A total of 4500 participants are planned (3000 active, 1500 placebo), of which 2250 are ≥5 to <12 years of age, 1125 are ≥2 to <5 years of age, and 1125 are ≥6 months to <2 years of age. Extension of the trial to infants <6 months of age is under consideration.

Protocol C4591015 is an ongoing, Phase 2/3, placebo-controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of a SAR-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older. This study will describe the safety of BNT162b2 in pregnant women and their infants, assess the immunogenicity in pregnant women, the transfer of antibody to their infants, and the kinetics of antibody transfer in the infant. A total of approximately 4000 participants are planned, and will be randomized in a 1:1 ratio of BNT162b2 (30-µg dose) to placebo.

Protocol C4591017 is an ongoing 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 years of age. To support distribution of this vaccine on a wider scale, the study will evaluate the immune response across 4 different BNT162b2 lots manufactured at a commercial scale: 3 lots of drug substance manufactured in the United States and 1 lot of drug substance manufactured in Europe (Arms 1-4) and a 20-µg dose from 1 of the US lots compared with the standard 30-µg dose. A total of approximately 1530 participants have been enrolled and have received their second dose of BNT162b2. An amendment may add assessment of safety and immunogenicity of a third dose of BNT162b2 or BNT162b2s01 in a small number of participants as early as 3 months after the second dose of BNT162b2.

Protocol C4591020 is an ongoing, Phase 3, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of a lyophilized formulation of the vaccine candidate BNT162b2 against COVID-19 in healthy adults 18 through 55 years of age. To optimize storage and distribution of this vaccine on a wide scale, a lyophilized formulation that will be stable at standard refrigerator temperatures is required. Therefore, this study will compare the safety and tolerability of lyophilized BNT162b2 presented in single-dose vials (SDVs) to those of frozen-liquid BNT162b2 in multidose vials (MDVs) and investigate noninferiority of the immune response. A total of approximately 560 participants are planned to be enrolled.

Protocol C4591024 is a planned, open, uncontrolled study of 2 doses BNT162b2 at a 21-day interval followed by a third dose 6 months after Dose 2 in immunocompromised adults and children. It is planned that 180 adults, with non-small cell lung cancer, chronic lymphocytic leukemia, or who are on maintenance haemodialysis for secondary to end stage renal disease, will receive a 30-µg dose level. The study calls for enrollment of 180 children in 3 age groups, ≥12 to 17 years of age, ≥5 to <12 years of age, and ≥2 to <5 years of age. Within these age groups, children will be enrolled who are receiving immunomodulators for autoimmune inflammatory conditions, who are on immunosuppressant treatments for solid organ transplants, or who received heterologous stem cell or bone marrow transplant at least 6 months previously. The ≥12 to 17 years age group will receive a 30-µg dose level and younger children will receive a dose level determined from the Phase 1 component of Study C4591007.

Protocol C4591028 is a planned, Phase 2, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of SAR-CoV-2 RNA vaccine candidates against COVID-19 when administered after prior receipt of the Janssen adenovirus-based COVID-19 vaccine in healthy individuals. This study is designed to demonstrate that the homologous immune response to BNT162 after a single dose of adenovirus-based vaccine is statistically

greater than a single dose of adenovirus-based vaccine alone. A total of approximately 400 participants are planned for enrollment.

BB-IND #s 19736 and 17039

Protocol B7471026 is a Phase 3, multicenter, randomized, double-blind study planned to start in May 2021. The study will be conducted in adults 65 years of age and older recruited from C4591001 study sites in the US. The purpose of this study is to describe the safety and immunogenicity after administration of 20-valent pneumococcal conjugate vaccine (20vPnC) and a booster dose of BNT162b2 together at the same visit. Control participants will receive either vaccine (20vPnC or BNT162b2) given with saline to maintain blinding. Approximately 600 participants, 65 years of age and older who received 2 doses of 30 µg BNT162b2 in Study C4591001, will be stratified by prior pneumococcal vaccine status (no pneumococcal vaccination or prior receipt of a pneumococcal vaccine) and randomized at a 1:1:1 ratio to 1 of 3 vaccine groups, 20vPnC and BNT162b2 coadministration, 20vPnC with saline placebo, or BNT162b2 with saline placebo. The injections will be given by an unblinded third-party administrator. A follow-up visit will take place approximately 28 days (21 to 35 days) after immunization for collection of safety data and a blood draw to assess pneumococcal OPA (opsonophagocytic activity) responses to 20vPnC serotypes and S1-binding immunoglobulin G (IgG) responses to the BNT62b2 booster dose.

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[i] Walsh EE, Frenck RW, Falsey AR, et al. Safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. N Engl J Med 2020; 383:2439-50, DOI: 10.1056/NEJMoa2027906

APPENDIX R16.6.2 DESCRIPTION OF THE GENERAL INVESTIGATIONAL PLAN FOR THE UPCOMING YEAR IN CHINA

Current efforts are being directed towards characterizing the safety and efficacy of the drug for the prevention of COVID-19. The clinical development program for the upcoming reporting period is summarized below.

Phase 1 Studies

Study BNT162-03 is an ongoing, Phase 1, dose confirmation study, which adopts a parallel two-dose cohort and placebo design in adult healthy subjects (adult group) and elderly healthy subjects (elderly group). The study is intended to confirm that the response (safety/immunogenicity) seen in foreign subjects is comparable to that observed in Chinese subjects. The design of this study, including the selection of two optimal dose levels are informed by safety and immunogenicity data from global clinical trials of BNT162b1. A total of 144 participants were enrolled in this study. All planned vaccine administration to trial participants have been completed and 142 participants (2 withdrew) are in 12-month follow-up period.

Phase 2 Studies

Study BNT162-06 is an ongoing, Phase 2, randomized, placebo-controlled, observer-blinded study of the safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b2) in Chinese healthy population. A total of 960 participants were enrolled in this study. 959 participants received at least one dose of investigational vaccine/placebo (1 participant was withdrawn before Dose 1 due to difficulty in blood collection) and 950 participants are now in follow-up period (10 participants were withdrawn).

Except for the two clinical studies described above, no other clinical trials for COVID-19 vaccine are planned in China for the next reporting period.