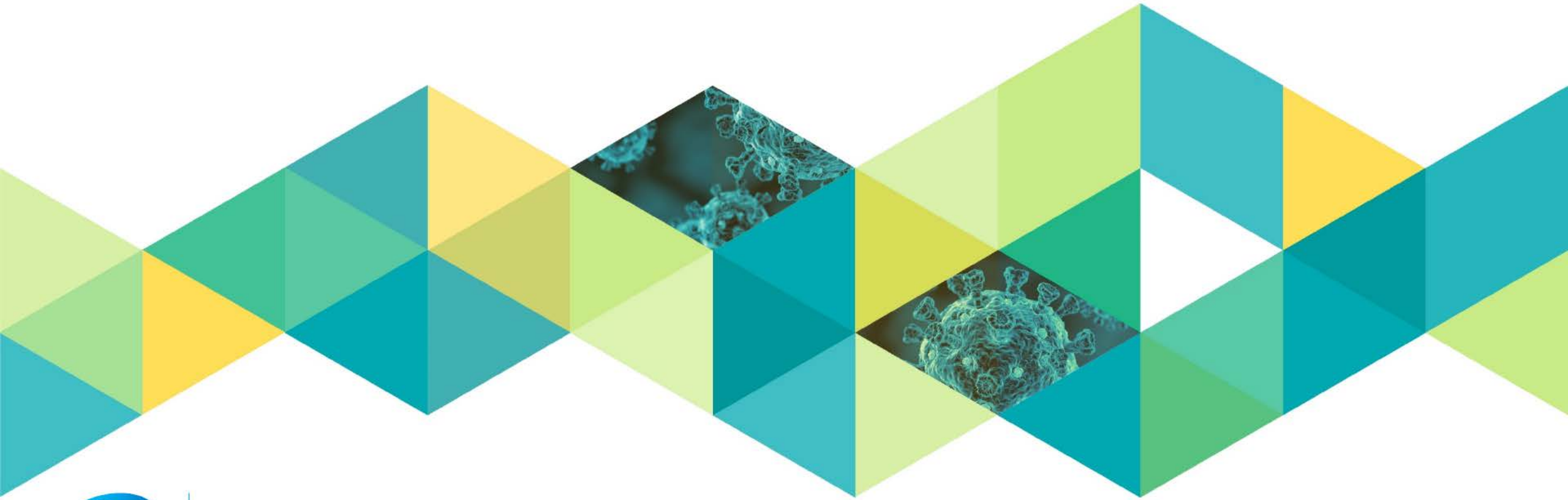
Pfizer/BioNTech COVID-19 mRNA vaccine (BNT162, PF-07302048)

TGA Pre-Submission Meeting

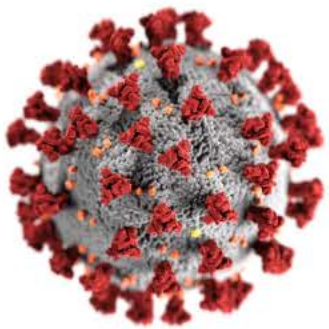
September 18, 2020

Clinical Overview

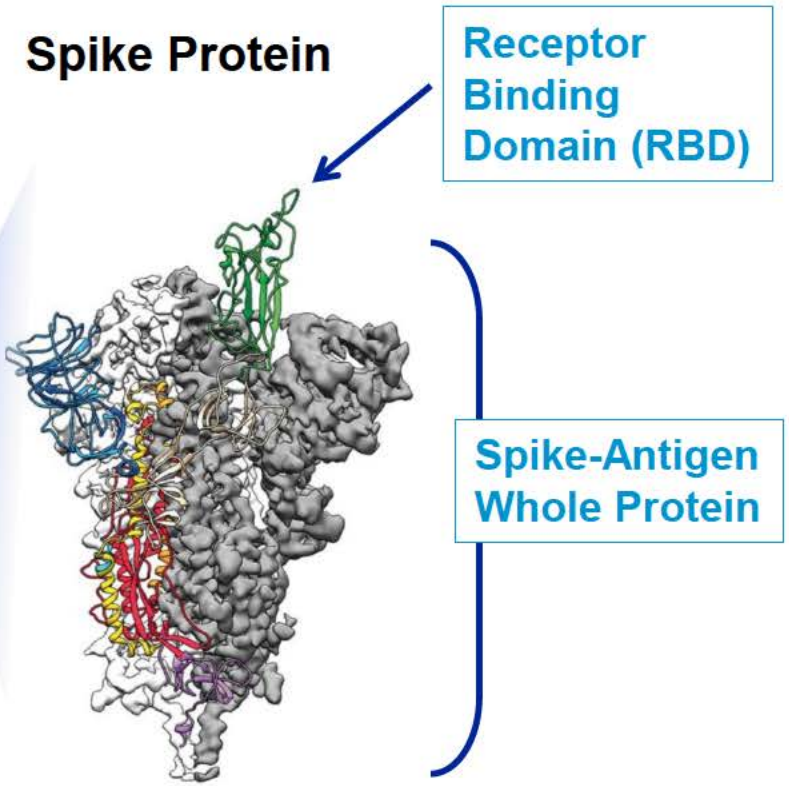


Pfizer/BioNTech COVID-19 mRNA vaccine program overview

Two Vaccine Antigens



SARS-COV-2
(3D Model)



SARS-COV-2
Spike Protein 3D Structure
(Wrapp et al., 2020, Science)

Four Vaccine Candidates

Variant	Target	RNA construct	Immunization
162a1	RBD subunit	uRNA	prime / boost
162b1	RBD subunit	modRNA	prime / boost
162b2	P2-mutated full spike protein	modRNA	prime / boost
162c2	P2-mutated full spike protein	saRNA	single injection

Focus of large-scale development

US Phase 1/2/3 study overview (C4591001 / NCT04368728)

Phase 1 (N=195)				
BNT162b1	N=15/group (4:1 randomization active:placebo)			
18-55 yrs	10 µg	20 µg	30 µg	100 µg
65-85 yrs	10 µg	20 µg	30 µg	

BNT162b2	N=15/group (4:1 randomization active:placebo)		
18-55 yrs	10 µg	20 µg	30 µg
65-85 yrs	10 µg	20 µg	30 µg

To describe the safety and tolerability profiles of prophylactic BNT162 vaccines:
- E-diary (local reactions, systemic events incl. fever, use of analgesics/antipyretics)
- Adverse events
  - All up to 1 month after last dose
  - Serious AEs up to 6 months after last dose
- Hematology & chemistry

To describe the immune responses elicited by prophylactic BNT162 vaccines:
- SARS-CoV-2 neutralizing titers
- S1-binding IgG levels
- RBD-binding IgG levels

Phase 2/3 (N=360/29,286)		
BNT162b2	N=180/14,643 group (1:1 randomization active:placebo)	
18-55 yrs	~60%	30 µg
56-85 yrs	~40%	30 µg

To define the safety profile of, and immune responses to, prophylactic BNT162b2 vaccine in Phase 2 participants

To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in Phase 2/3 participants:
- Without evidence of infection before vaccination
- With and without evidence of infection before vaccination

To define the safety profile of prophylactic BNT162b2 vaccine in Phase 2/3 participants
- E-diary (local reactions, systemic events incl. fever, use of analgesics/antipyretics) – in a subset of at least 6000 participants
- Adverse events
  - All up to 1 month after last dose
  - Serious AEs up to 6 months after last dose

Additional secondary & exploratory objectives

Two clinical studies assessed the safety, tolerability, and immunogenicity of ascending dose levels of BNT162 modRNA vaccine candidates

US Phase 1/2/3 Study* (C4591001 / NCT04368728)

- 15 healthy participants (18-55 or 65-85 years of age) per dose level [12 active vaccine recipients and 3 placebo recipients]
  - 10 µg, 20 µg, 30 µg, 100 µg
- Immunized on Day 1 and a boost dose on Day 21 [No boost for 100µg cohort]

Germany Phase 1/2 Study** (BNT162-01 / NCT04380701)

- 12 healthy participants (18-55 or 56-85 years of age) per dose level
  - 1 µg, 10 µg, 30 µg, 50 µg, 60 µg
- Immunized on Day 1 and a boost dose on Day 22 ± 2 [No boost for 60 µg cohort]

Human COVID-19 convalescent sera (HCS)

- 38 human SARS-CoV-2 infection/COVID-19 convalescent sera from subjects 18-83 years of age
  - N=29, 18-55 years of age
  - N=9, 56-83 years of age
- Collected at least 14 days after PCR-confirmed diagnosis, and at a time when subjects were asymptomatic
- Serum donors predominantly had symptomatic infections (35/38), and one had been hospitalized

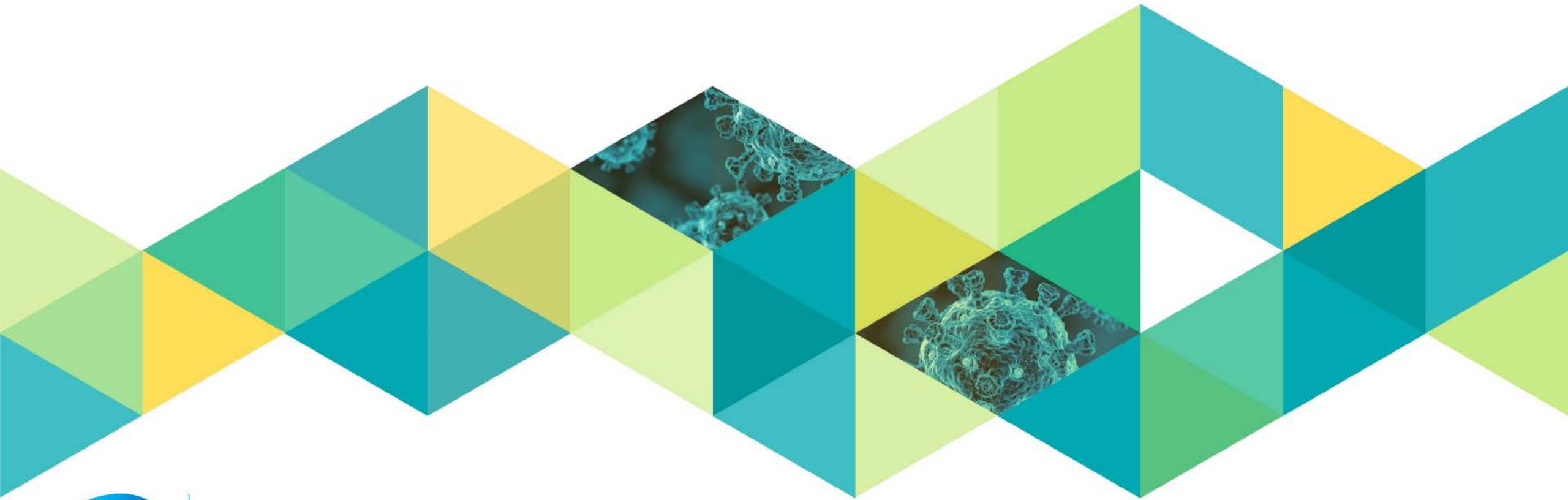
* Mulligan, M.J. et al. Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults. Nature https://doi.org/10.1038/s41586-020-2639-4 (2020)
* Walsh EW, Frenck R, Falsey AR, et al. medRxiv 2020.08.17.20176651; doi: https://doi.org/10.1101/2020.08.17.20176651 [preprint].
** Sahin U, Muik A, Derhovanessian E, et al. medRxiv 2020.07.17.20140533; doi: https://doi.org/10.1101/2020.07.17.20140533 [preprint].

Phase 1 culminated in selection of BNT162b2 30 µg for late stage development

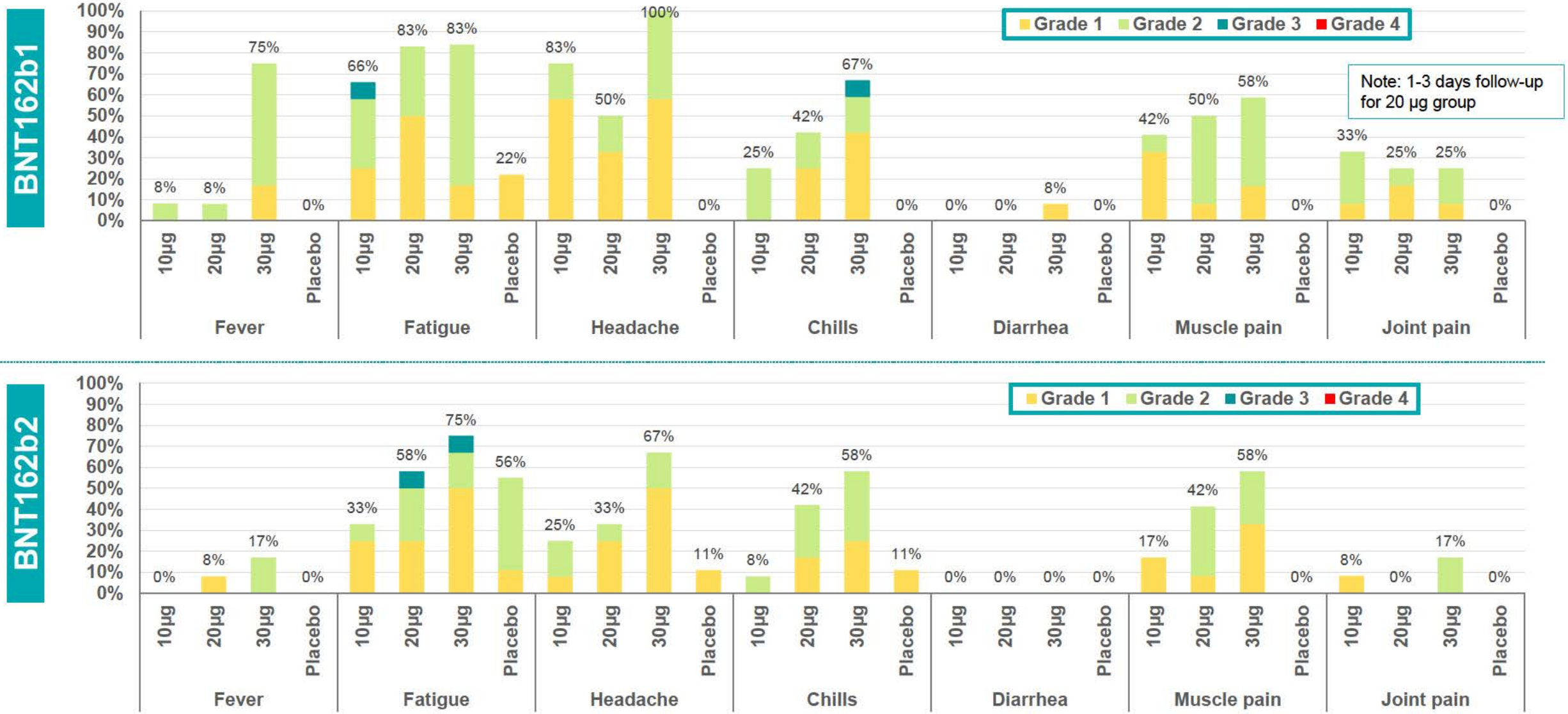
- To maximize a vaccine's potential to prevent COVID-19, the following key criteria were evaluated in the selection of the final vaccine candidate and dose level:
  - Acceptable safety and reactogenicity
  - SARS-CoV-2 neutralizing titers at or above a human convalescent serum panel (HCS)
  - Strong T_H1-type $CD4^+$ and $CD8^+$ T cell responses
- **Both BNT162b1 and BNT162b2 looked strong as vaccine candidates**
- However, the totality of data favored the selection of BNT162b2 based on the following findings:
  - A reactogenicity profile that is more favorable than BNT162b1 in both younger and older adults
  - A trend towards stronger $CD8^+$ T cell responses
  - Earlier clearance of SARS-CoV-2 RNA in the nose of BNT162b2 immunized and challenged rhesus

- Based on the totality of data, **we chose to advance BNT162b2 at the 30µg dose level**

Reactogenicity data from C4591001 Phase 1



BNT162b2 shows favorable systemic reactogenicity profile in Phase 1 (18-55 years after dose 2)



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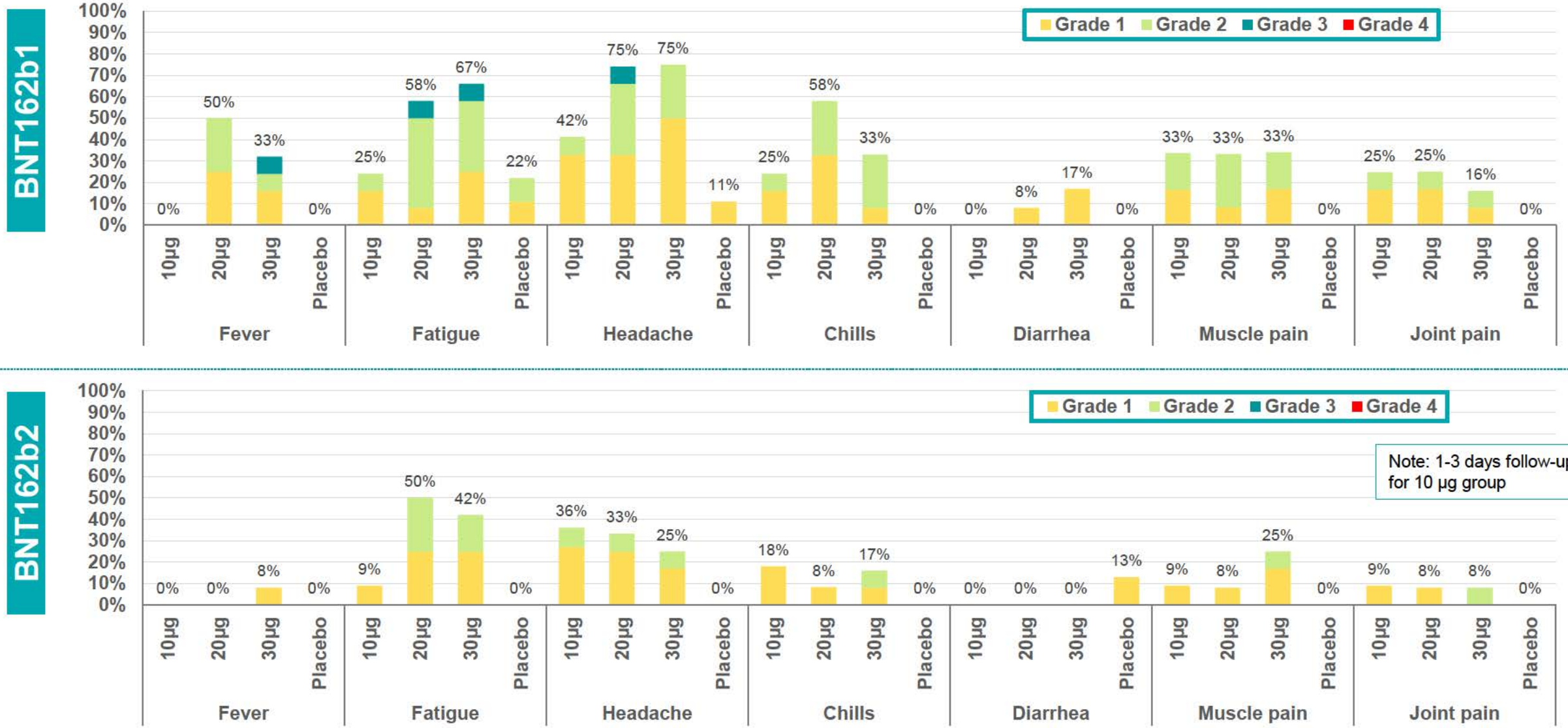
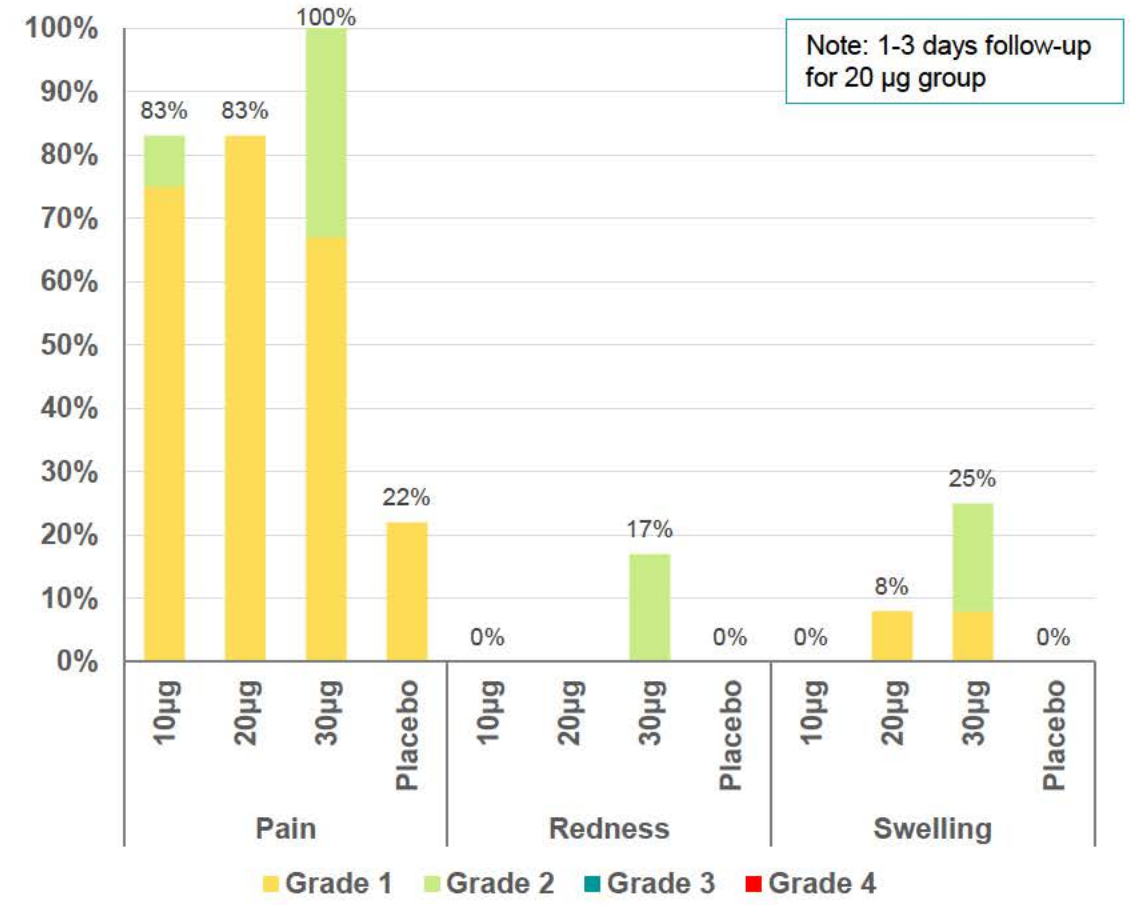
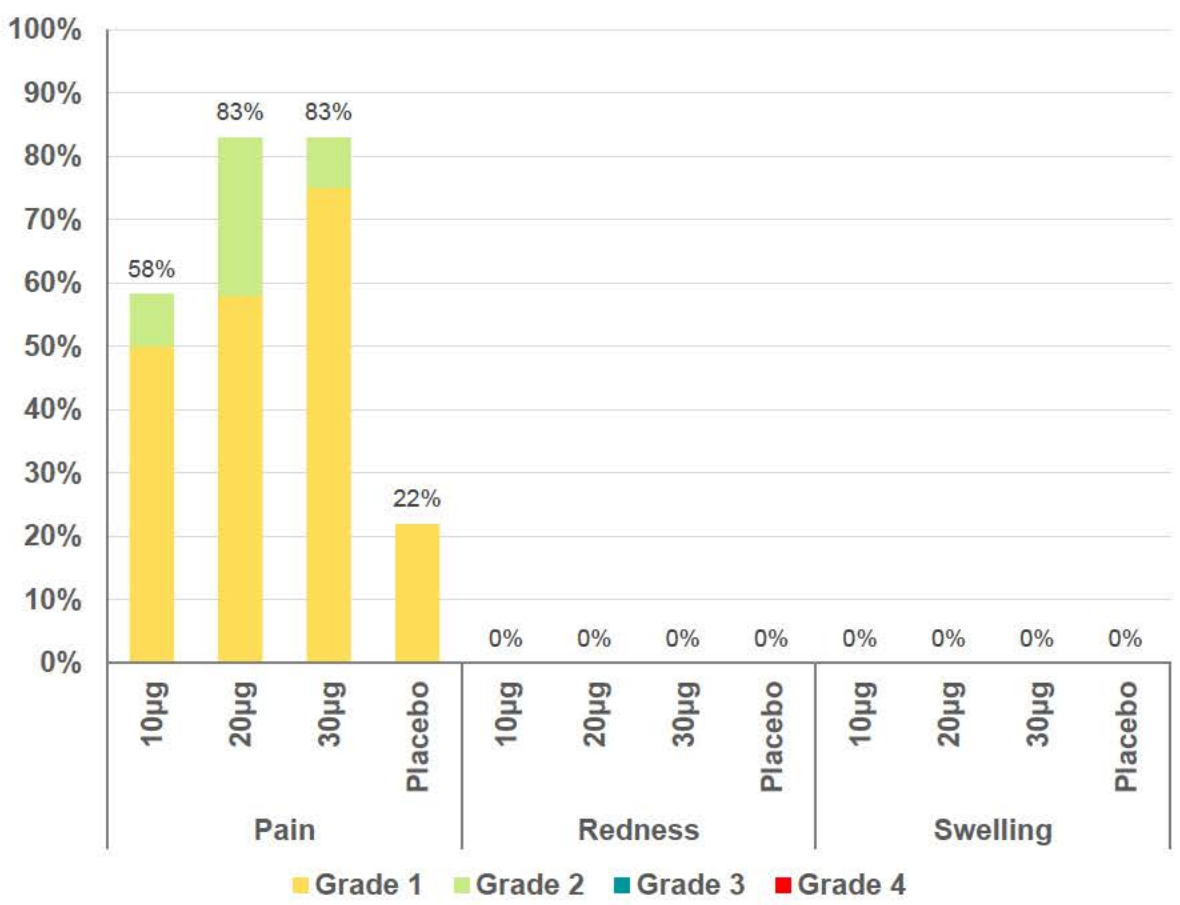


BNT162b2 shows a favorable local tolerability profile in Phase 1 (18-55 years after dose 2)

BNT162b1



BNT162b2



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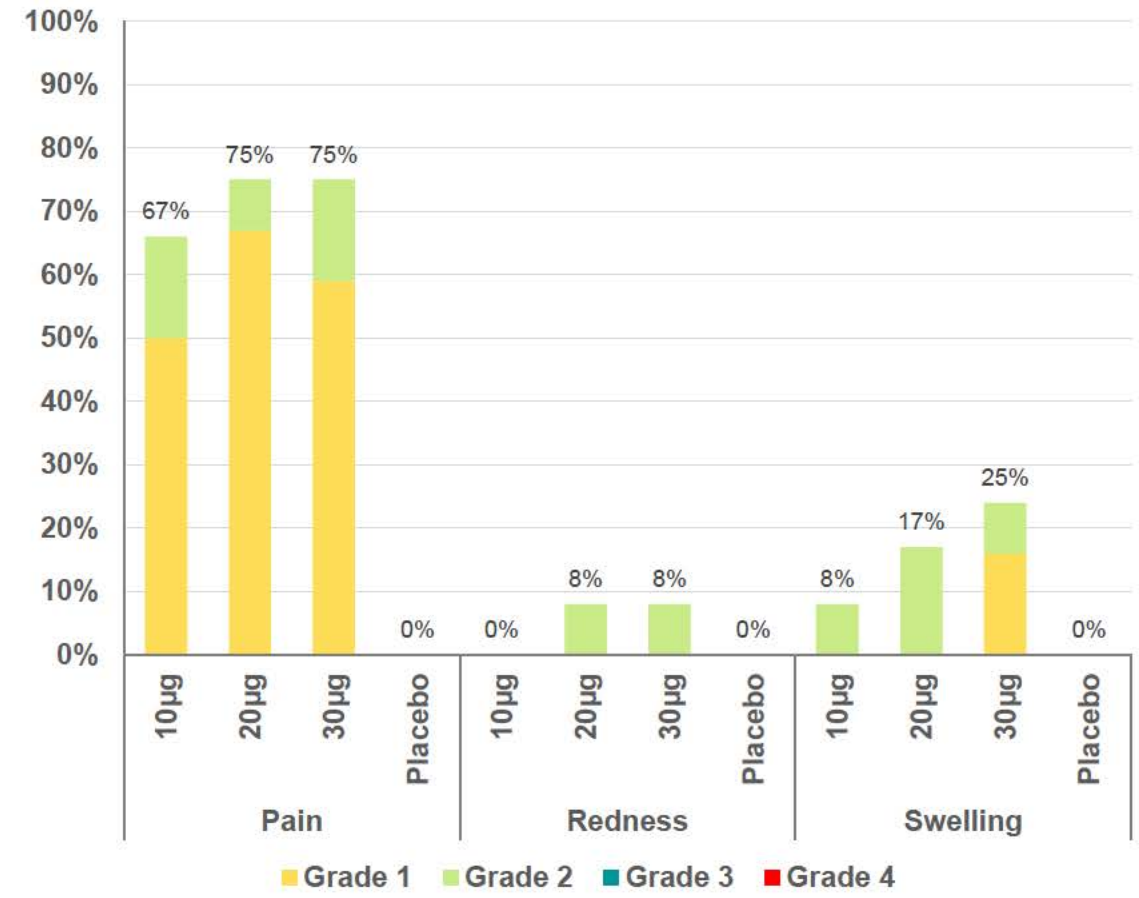
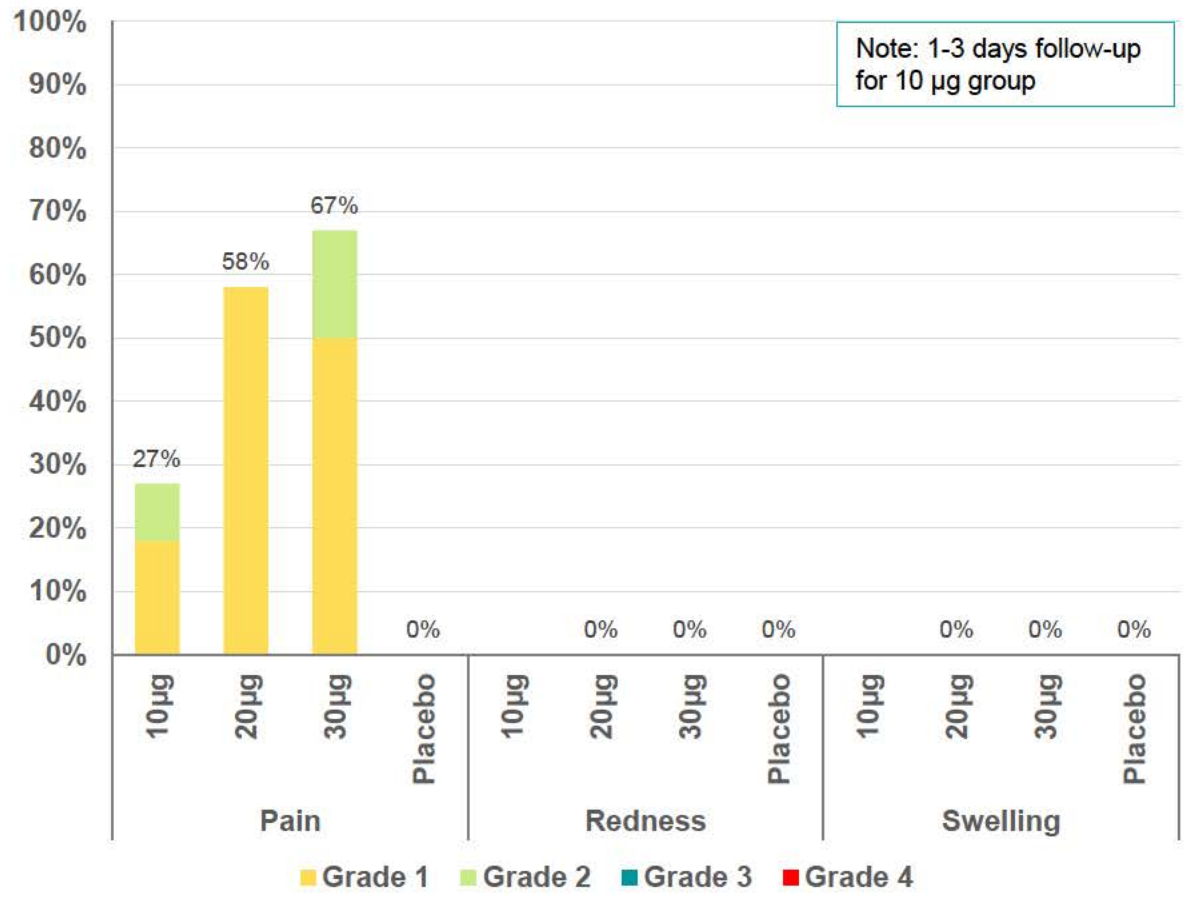
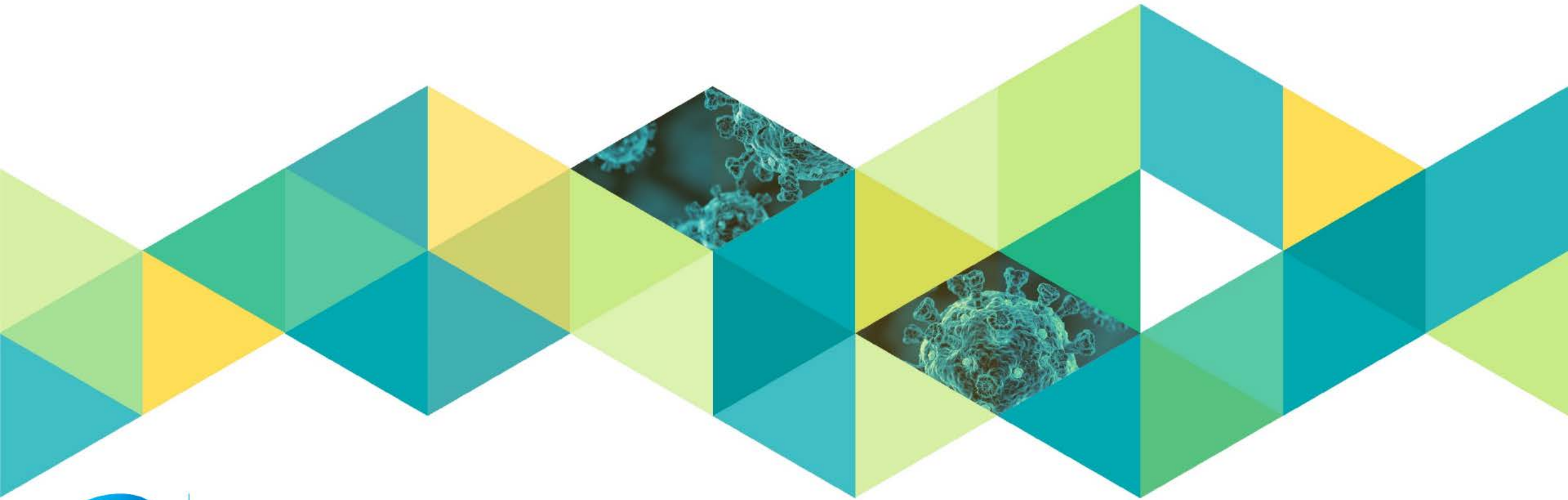
BNT162b1



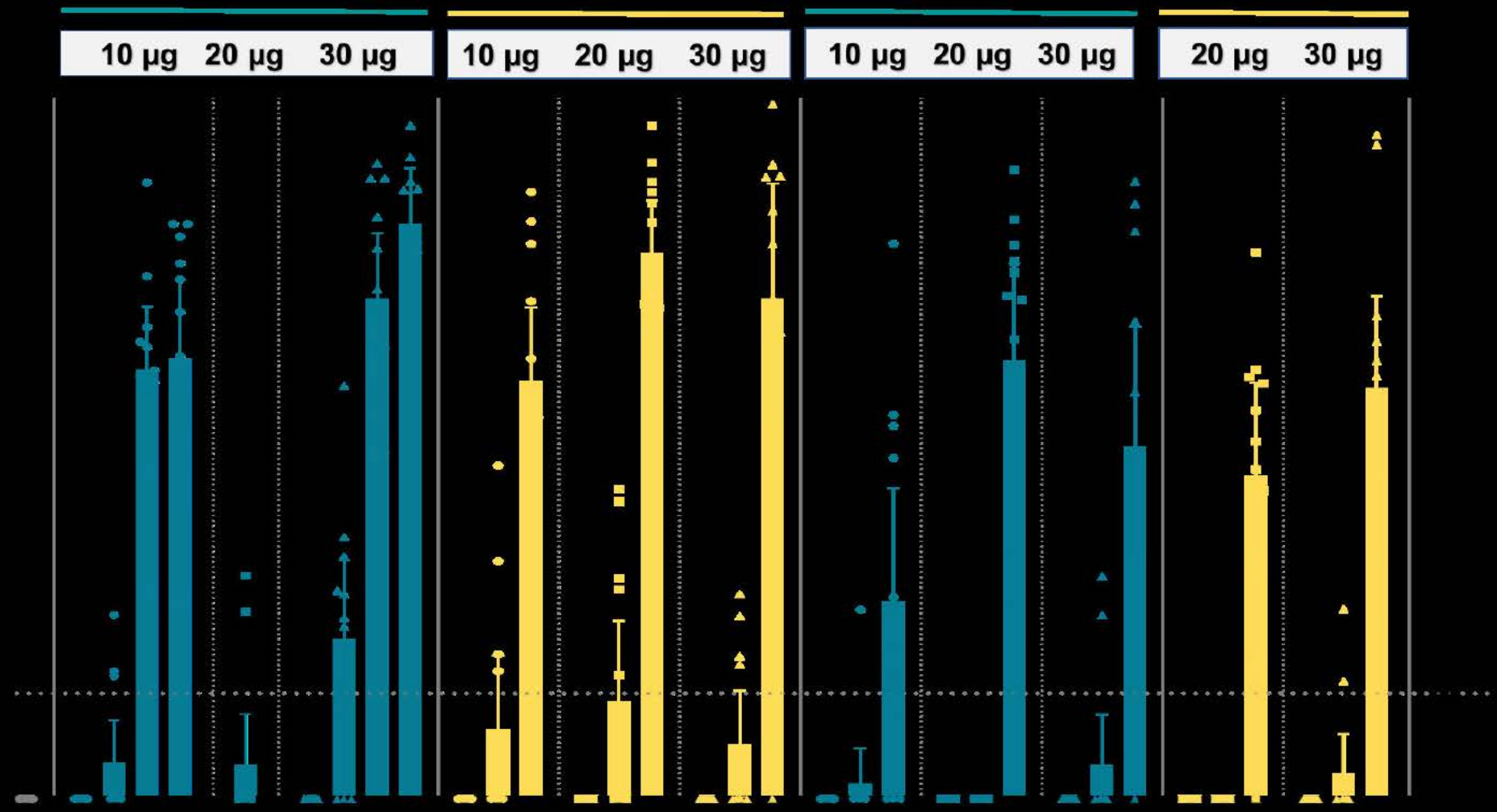
BNT162b2



Immunogenicity data from C4591001 Phase 1



Robust SARS-CoV-2 50% neutralization titers after 2 doses of BNT162b1 or BNT162b2 in Phase 1 exceed those in a human convalescent panel (HCS*)

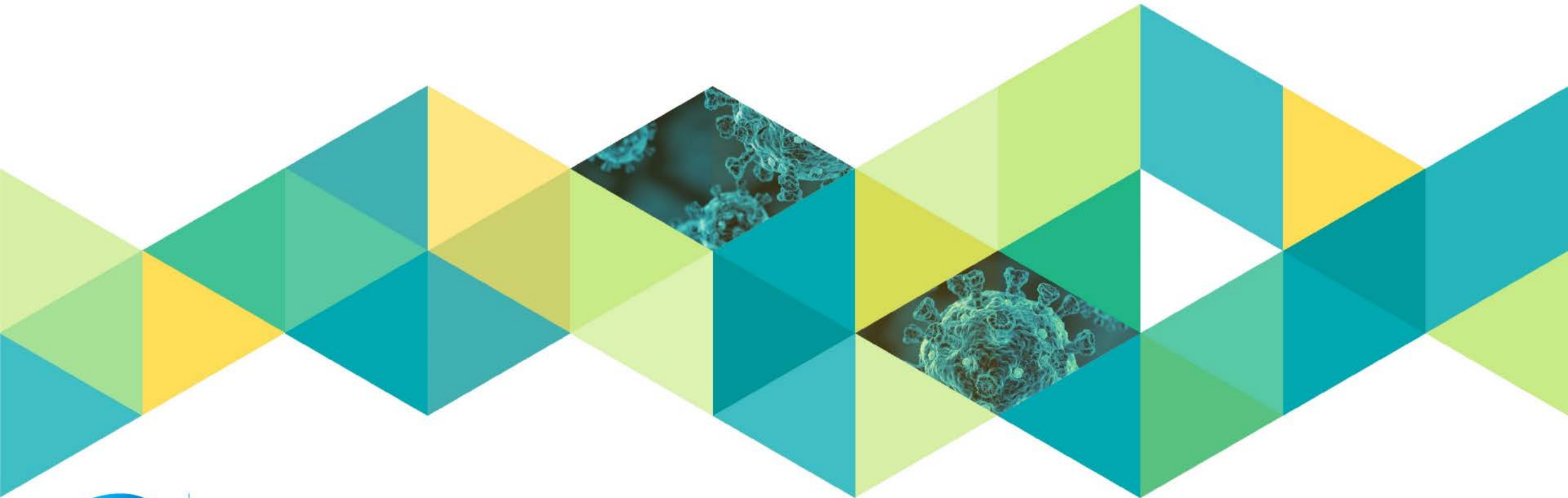


*38 human SARS-CoV-2 infection/COVID-19 convalescent sera

Phase 1 demonstrated encouraging safety & immunogenicity for BNT162b2, supporting advancement to Phase 2/3

- Reactogenicity:
  - Lower after first vaccination compared to second
  - Lower in older than younger participants
  - Profile appears at least as good as approved adult vaccines
- Immunogenicity:
  - Neutralizing antibody responses 7 days after second dose are robust and exceed those observed in a panel of human convalescent sera (38 human SARS-CoV-2 infection/COVID-19 convalescent sera)
  - Strong $CD4^+$ and $CD8^+$ T cell responses with T_H1 dominance

Overview of Phase 2/3



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- Adverse events
  - All up to 1 month after last dose
  - Serious AEs up to 6 months after last dose

Additional secondary & exploratory objectives

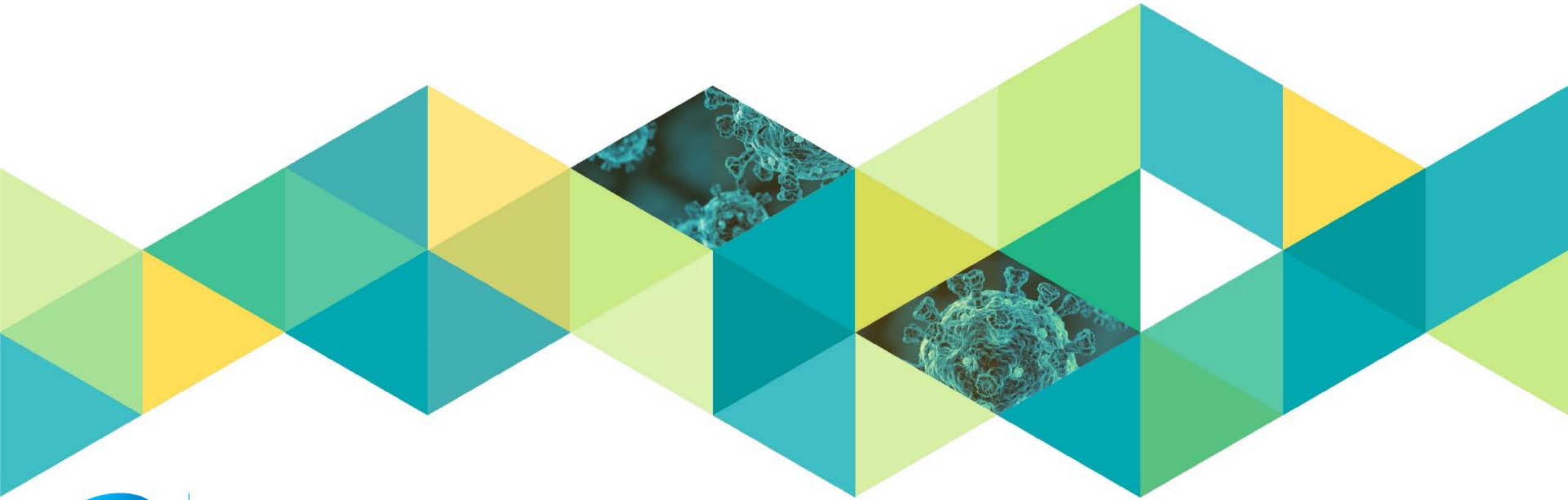
Phase 2/3 efficacy schema – started 27 July, 2020

Vaccination period | **Follow-up period**

Active surveillance for potential COVID-19 symptoms – triggering telehealth or in-person visit and nasal swab

- Cases defined based on:
  - Presence of symptom(s); and
  - Positive SARS-CoV-2 nasal swab
- Efficacy analyses in participants:
  - Without evidence of infection before vaccination; and
  - With and without evidence of infection before vaccination

Quality Overview



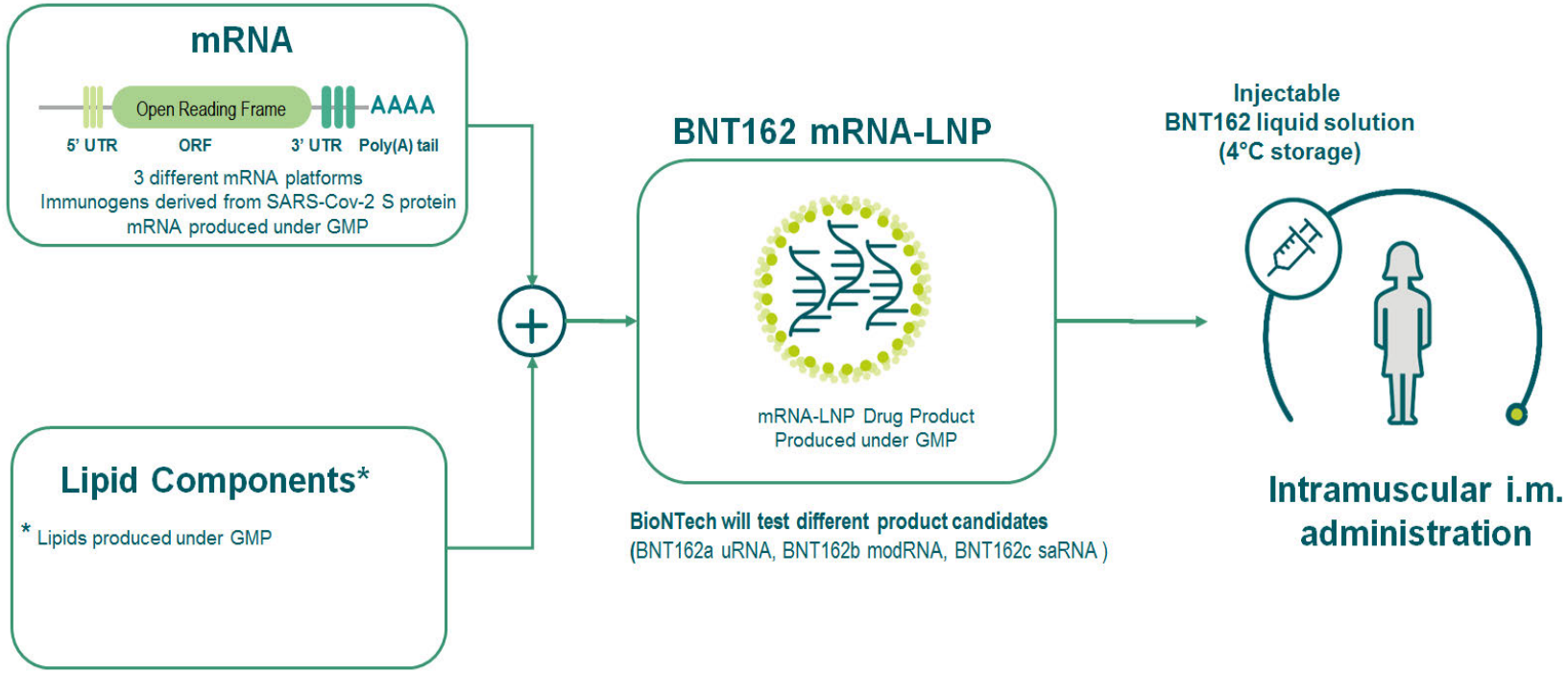


Figure 1: RNA-LNP-based BNT162 vaccines

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

BNT-162 LNP

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 1).

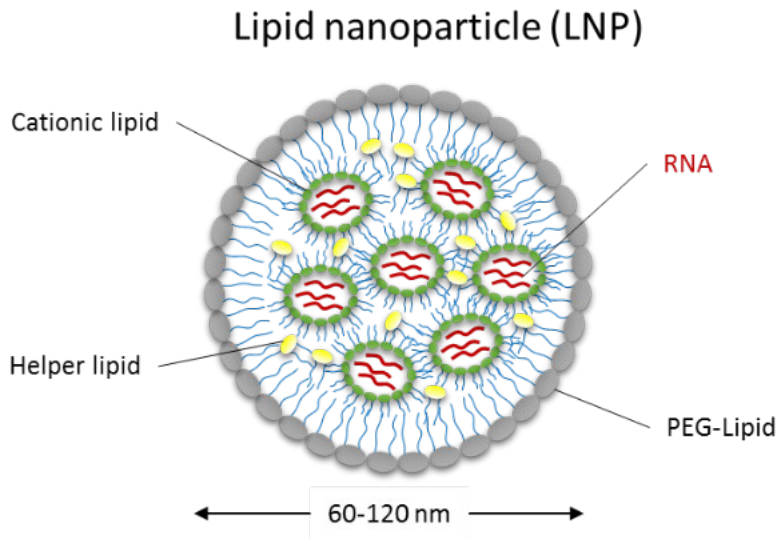
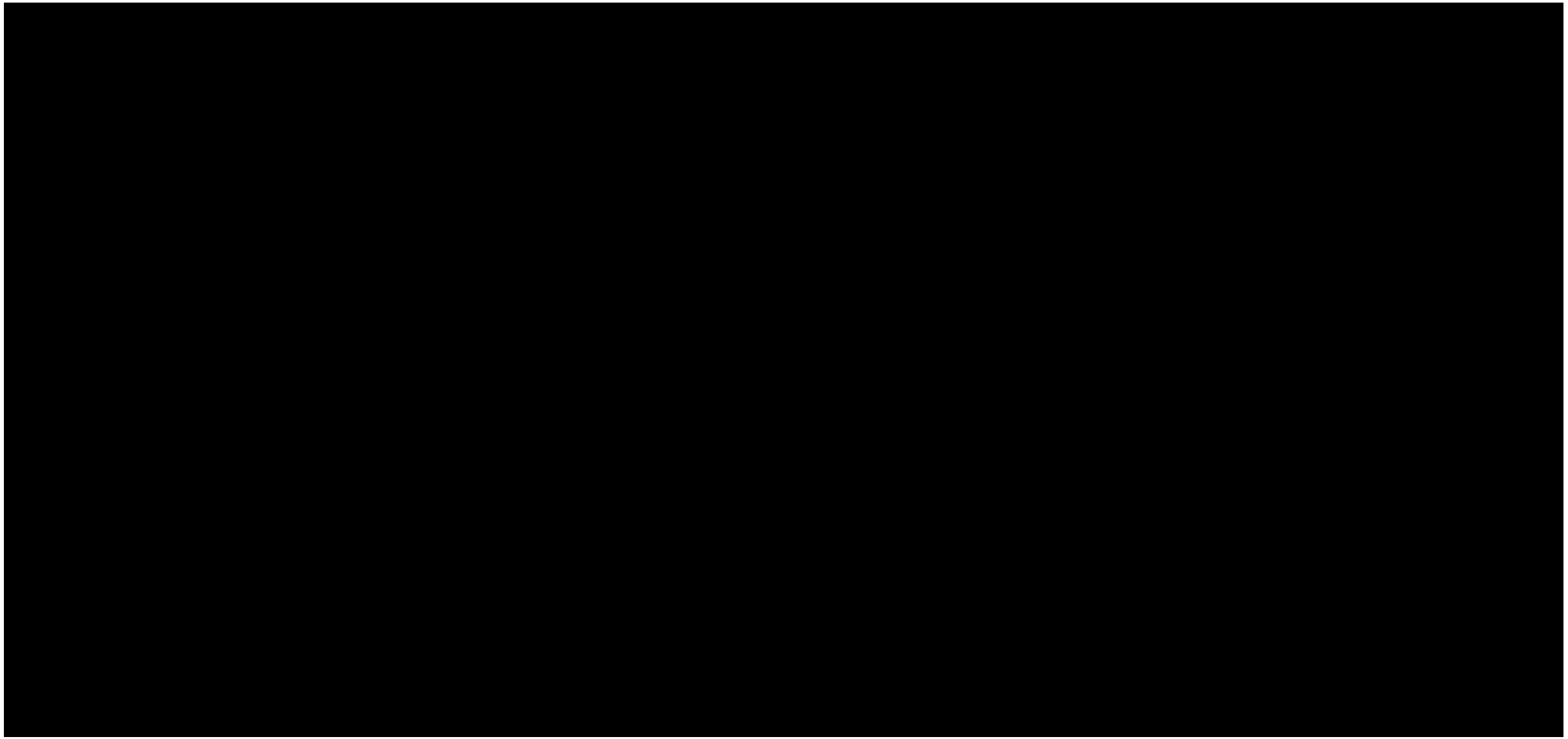
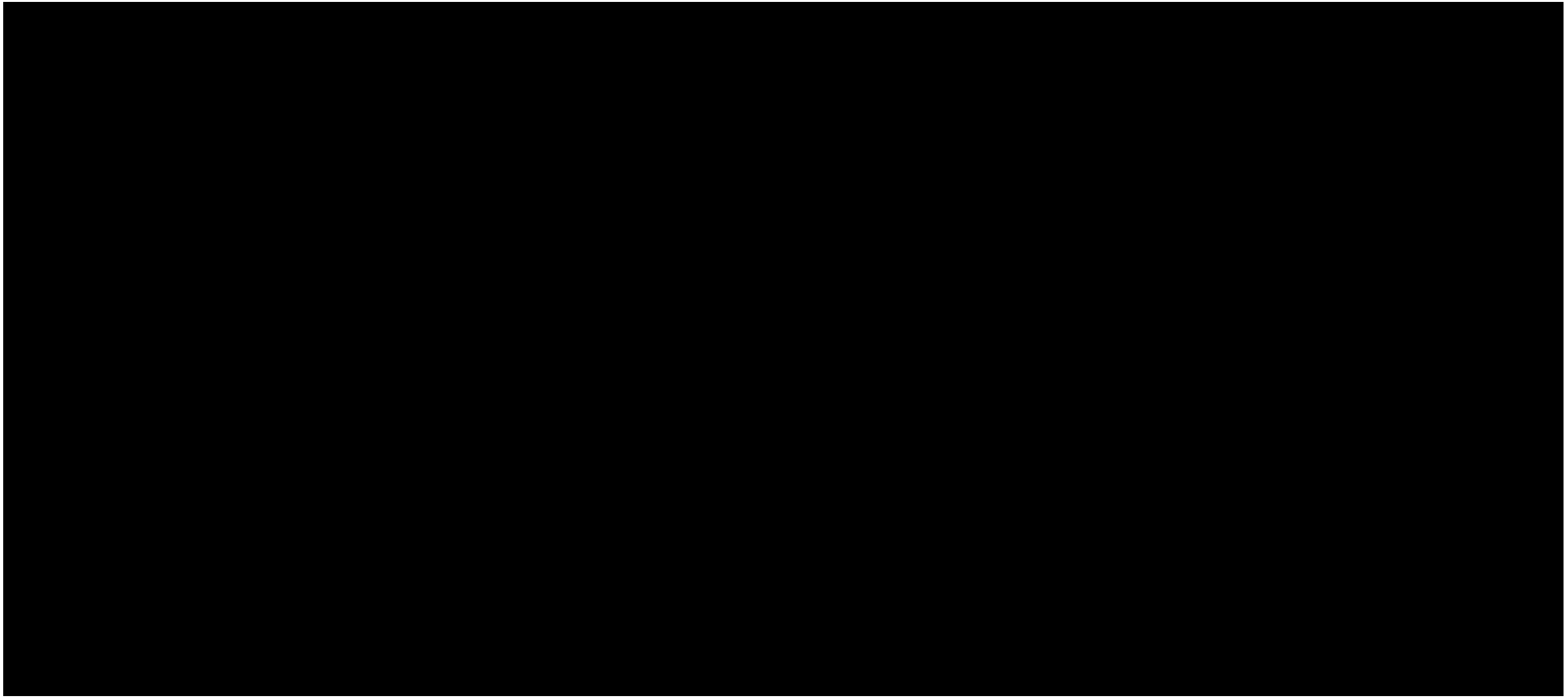


Figure 1: Schematic overview of a LNP

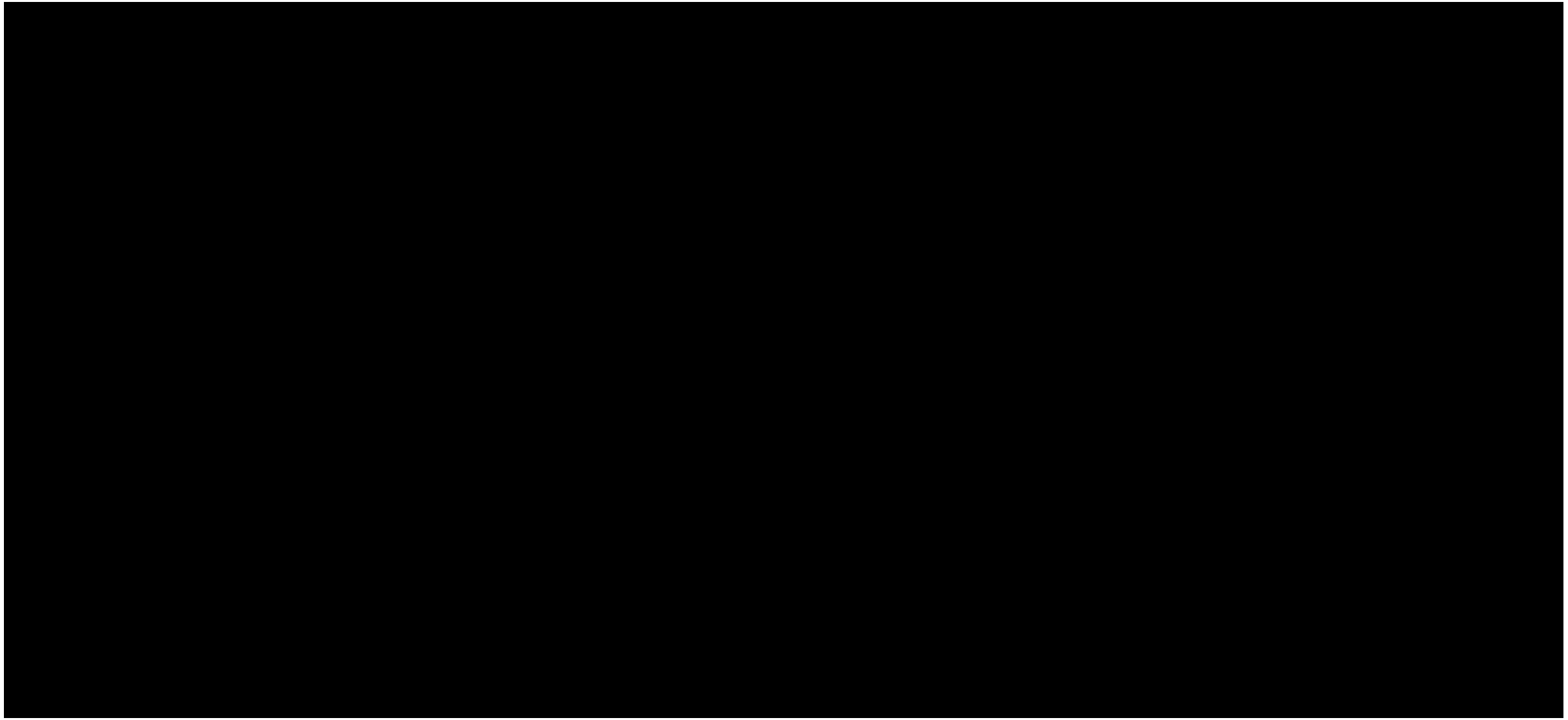
COVID-19 Vaccine Drug Substance Process Evolution



COVID-19 Vaccine Drug Product Process Evolution

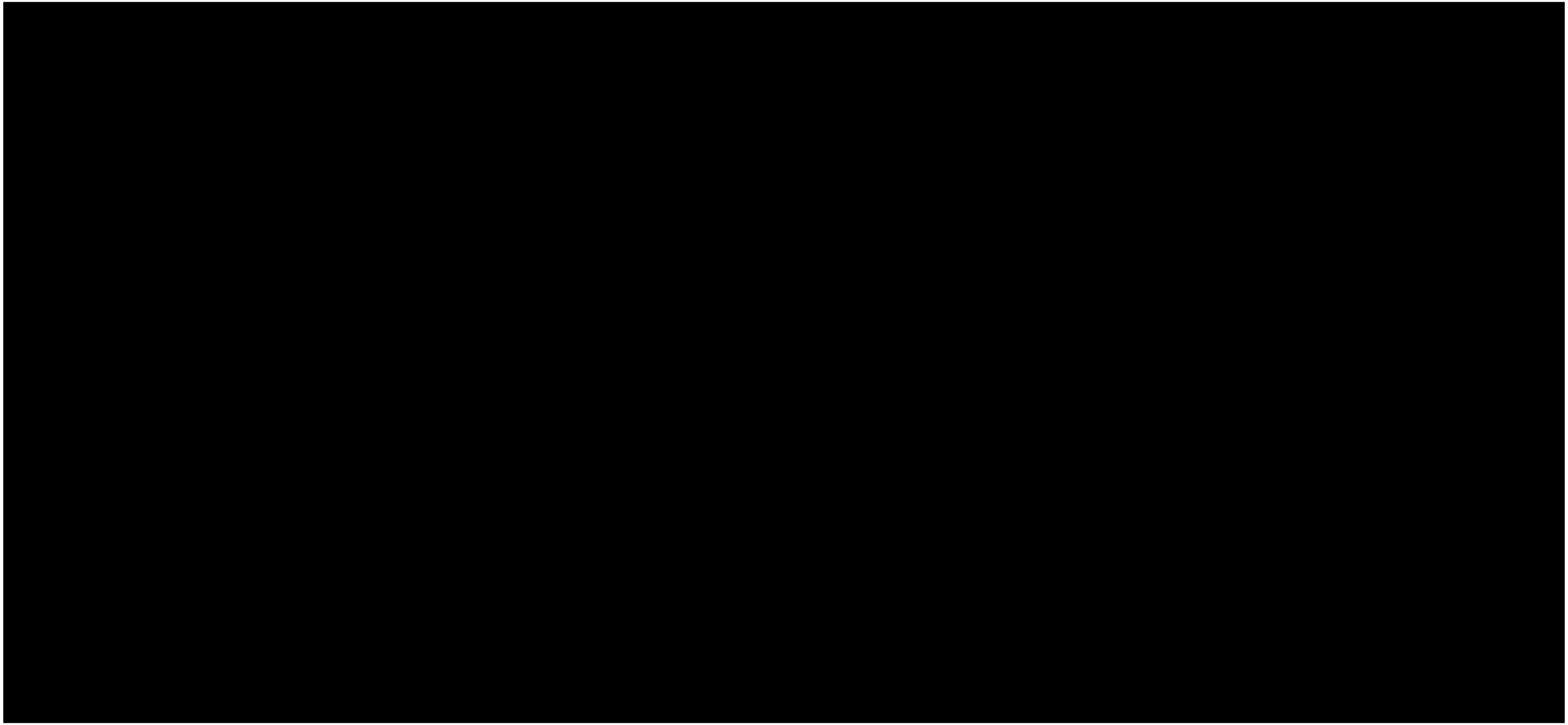


Comparison of Representative Messenger RNA Vaccine Drug Substance Manufacturing Process (Process 1 vs Process 2)

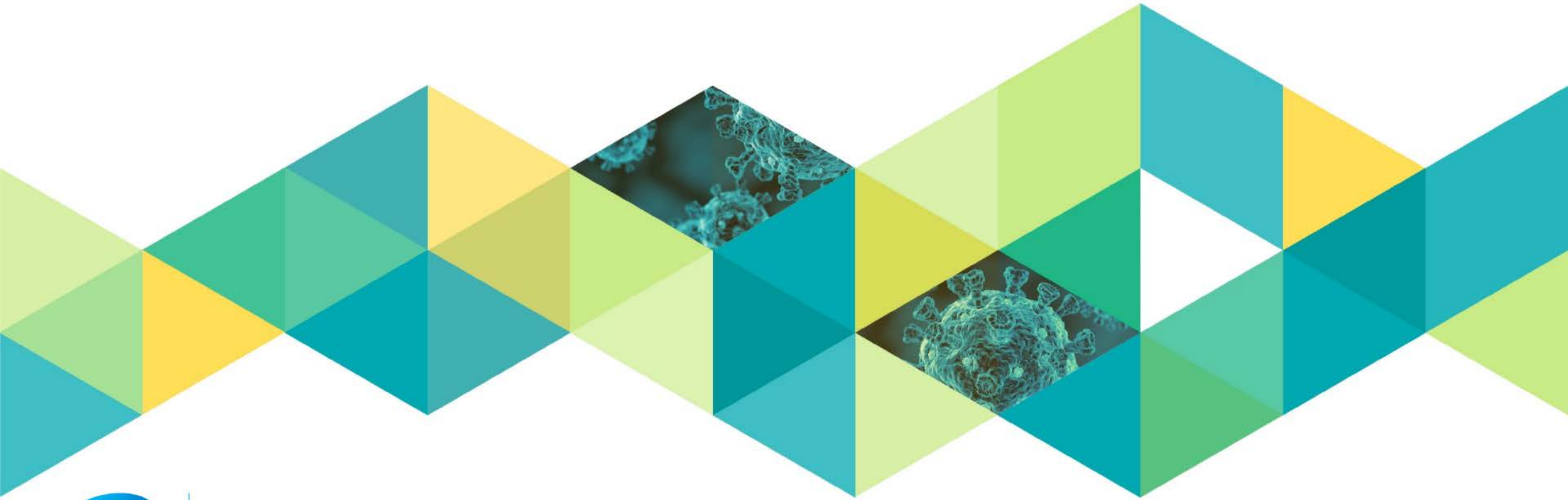


Comparison of Representative mRNA Vaccine Drug Product Manufacturing Process Diagram

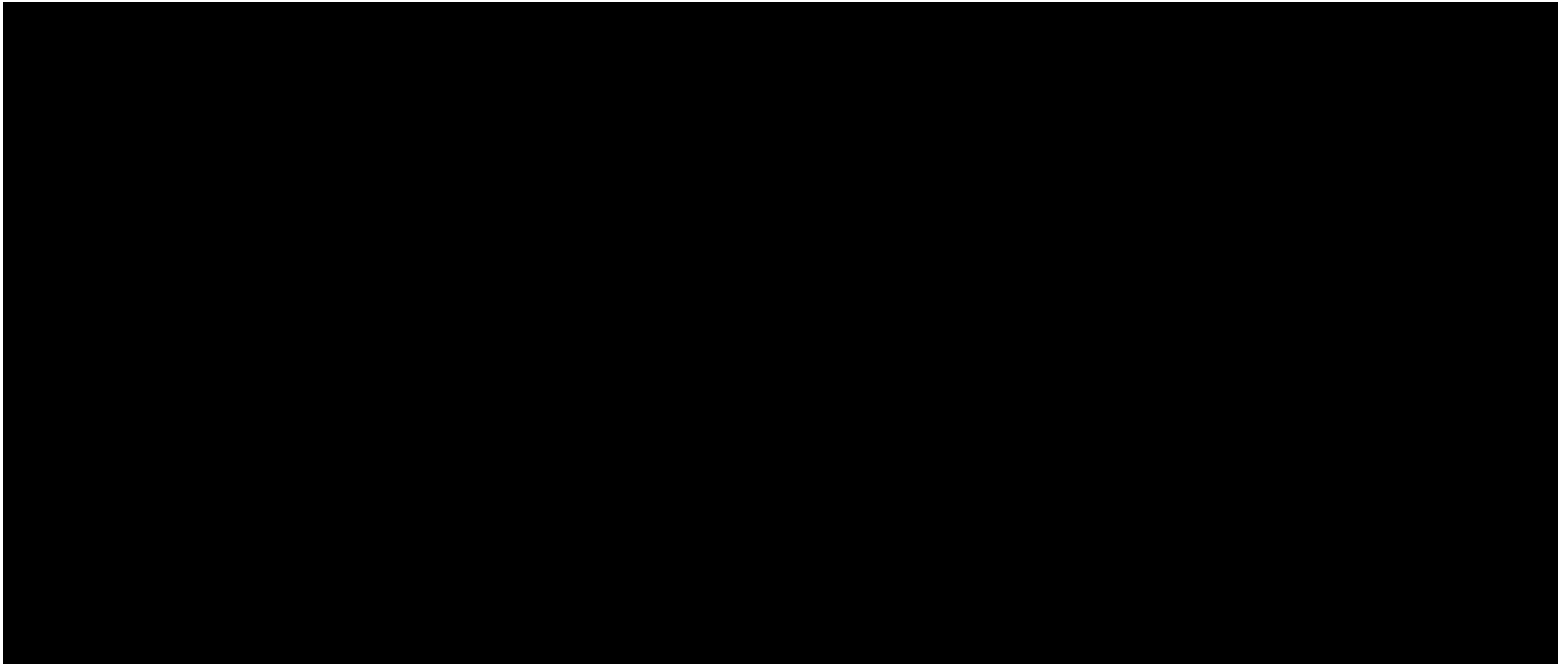
Components and Composition（modRNA）



QUESTIONS FOR DISCUSSION



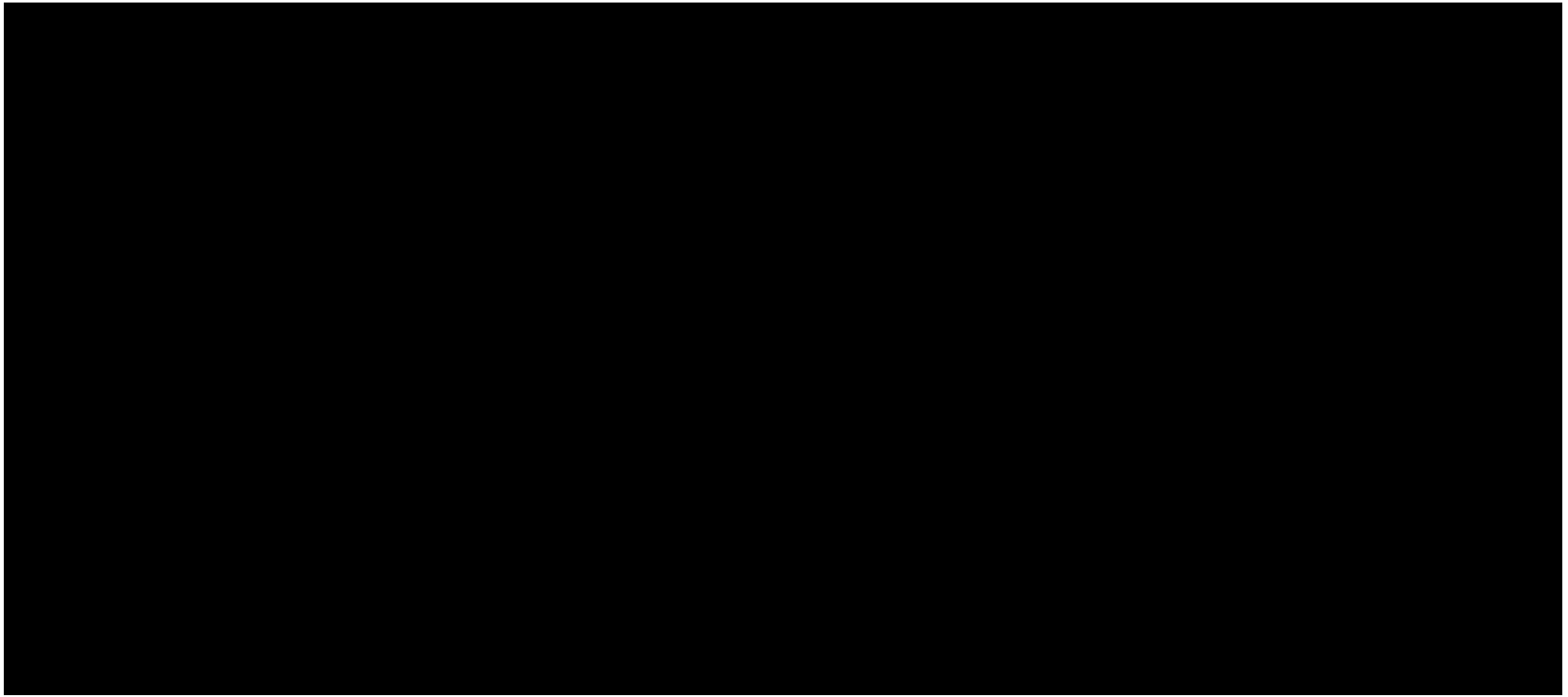
Question 1: Safety and Efficacy Data



Question 2: Australia-Specific Annex to the EU-RMP

Question 3: CMC Data Availability

Question 4: Shipping and Batch Release

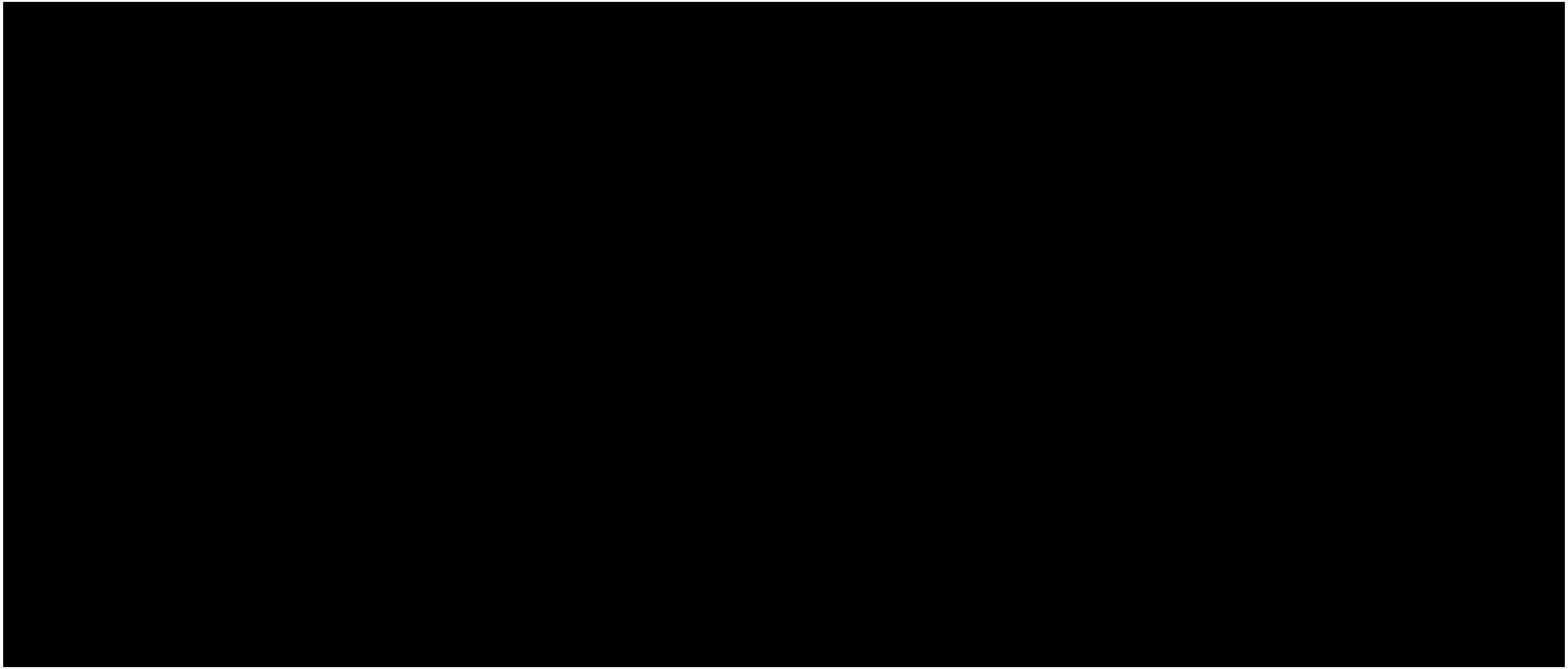


Question 5: Commercial Presentation

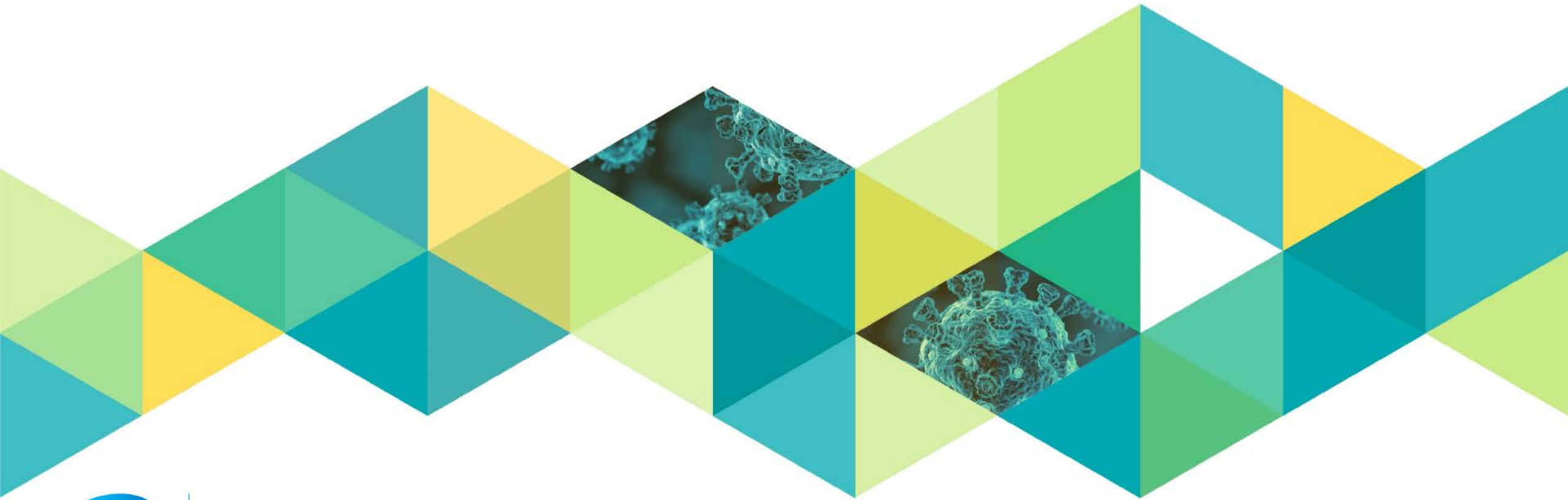
Question 6: Compliance with Applicable Standards

Question 7: Product Name

Question 8: Format of Application



Thank You



PRE-SUBMISSION MEETING BRIEFING DOCUMENT

COVID-19 VACCINE (BNT162, PF-07302048)

Prepared September 2020

For Pre-submission Meeting 18 September 2020

With the Therapeutic Goods Administration

Australia

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ABBREVIATIONS

Abbreviation	Definition
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)
ASA	Australia-Specific Annex
BNT	BioNTech
CBER	(US Food and Drug Administration) Center for Biologics Evaluation and Research
CMC	chemistry, manufacturing, and controls
CMO	Contract Manufacturing Organisation
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CTM	Clinical Trial Materials
D	Days
DART	developmental and reproductive toxicology (study)
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DP	drug product
DS	drug substance
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
EU	European Union
FDA	Food and Drug Administration
FIH	first-in-human
GGT	Gamma (γ)-glutamyl transpeptidase

Abbreviation	Definition
GLP	Good Laboratory Practice
HCT	haematocrit
HGB	haemoglobin
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IM	intramuscular(ly)
LNP	lipid nanoparticle
modRNA	nucleoside modified messenger RNA
mRNA	messenger RNA
NHP	non-human primate
P/B	prime/boost: dosing regimen of a priming immunisation and a booster immunisation
PCR	polymerase chain reaction
PPQ	process performance qualification
RBC	red blood cells
RMP	Risk Management Plan
RNA	ribonucleic acid
RNA-LNP	RNA lipid nanoparticle
RR	respiratory rate
RT-PCR	reverse transcription polymerase chain reaction
S glycoprotein	Spike glycoprotein
SAE	serious adverse event
saRNA	self-amplifying messenger RNA
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19

Abbreviation	Definition
TdaP	Tetanus toxoid, low dose diphtheria toxoid, acellular pertussis (vaccine)
TFF	tangential flow filtration
TGA	Therapeutic Goods Administration
TGO	Therapeutic Goods Order
uRNA	non-modified uridine containing mRNA
US	United States
VAED	vaccine-associated enhanced disease
VAERD	vaccine-enhanced respiratory disease
WHO	World Health Organization

1. OVERVIEW

SARS-CoV-2 infections and the resulting Coronavirus Disease 2019 (COVID-19) disease have spread globally. On 11 March 2020, the World Health Organization (WHO) characterised the COVID-19 outbreak as a pandemic. As of 1 September 2020, the WHO has confirmed >25 million cases, with cases numbers and mortality continuing to rise globally.[1]

There are currently no vaccines to prevent SARS-CoV-2 infections or the disease it causes, COVID-19.[2]

A prophylactic, RNA-based SARS-CoV-2 vaccine provides a flexible and fast approach to immunise against the emerging and fast-spreading virus.[3,4]

Development of RNA-based vaccines encoding a viral antigen which is expressed by the vaccine recipient and can elicit protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry risks associated with infection. RNA-based vaccines are manufactured by 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 could be traditionally achieved with conventional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

Pfizer and BioNTech are developing an RNA-based vaccine intended to prevent COVID-19 caused by the virus, SARS-CoV-2. The vaccine is based on SARS-CoV-2 spike (S) glycoprotein antigens encoded in RNA and formulated in lipid nanoparticles (LNPs), referred to as COVID-19 Vaccine (BioNTech code number BNT162, Pfizer code number PF-07302048). The core innovation is based on in vivo delivery of a pharmacologically optimised, antigen-encoding RNA to induce robust neutralising antibodies and a concomitant T cell response to achieve protective immunisation with minimal vaccine doses.[5-7]

The goal of the global development program is to rapidly develop and register a vaccine for use in individuals ≥16 years of age, followed by a paediatric indication.

1.1. Product Identification and Application

1.1.1. Chemical Name and Structure

One of BioNTech's two nucleoside-modified RNA (modRNA) vaccine candidates was selected as the final vaccine candidate to evaluate in Phase 3 and license. The nucleoside-modified mRNA (modRNA) candidate platform has blunted innate immune sensor activating capacity and thus augmented antigen expression. These RNA-based vaccines are formulated in the same LNPs. Each platform RNA encodes either a full-length SARS-CoV-2 S glycoprotein, the P2 mutant S glycoprotein (P2 S), and/or the receptor binding domain (RBD) of the S glycoprotein. Each candidate is also given a V number that indicates the

specific version of the optimised insert genomic sequence. The two modRNA candidates were:

BNT162b1 (RBP020.3) modRNA encoding RBD (V5):

[redacted]

BNT162b2 (RBP020.2) modRNA encoding P2 S (V9):

German study (1, 3, 10, 20, 30 µg) and Study C4591001 (10, 20, 30 µg)

The following are the details of the differences between the two expressed antigens.

- Nucleoside modified messenger RNA (modRNA), called BNT162b1, expresses the receptor binding domain of the SARS-CoV-2 S-glycoprotein.
- Nucleoside modified messenger RNA (modRNA), called BNT162b2, expresses a prefusion stabilised full-length variant of the SARS-CoV-2 S-glycoprotein.

Based on the totality of the clinical and preclinical data, summarised below, BNT162b2 was selected as the lead candidate to advance into pivotal trials BNT162b2:

- BNT162b2-vaccinated human participants displayed a favorable breadth of epitopes recognised in T cell responses specific to the SARS-CoV-2 spike antigen, and that BNT162b2 demonstrated concurrent induction of high magnitude CD4+ and CD8+ T cell responses against the receptor binding domain (RBD) and against the remainder of the spike glycoprotein
- Across all populations, BNT162b2 administration was well tolerated with mild to moderate fever in fewer than 20% of the participants
- These results informed the selection of the BNT162b2 candidate for the pivotal Phase 2/3 global study in up to 30,000 participants that started in July 2020, which has to date enrolled more than 11,000 participants, including in areas with significant SARS-CoV-2 transmission

1.2. Vaccine Composition

1.2.1. Vaccine Platforms

BioNTech has developed RNA-LNP platforms including nucleoside-modified RNA (modRNA), which has blunted innate immune sensor activating capacity and thus augmented

antigen expression. Each modRNA candidate encodes either a P2 mutant S (P2 S) or the trimerised receptor binding domain (RBD) of the S glycoprotein.

BNT162 modRNA vaccine candidates were tested at multiple dose levels in the German Study BNT162-01 and/or Study C4591001:

BNT162b1 (RBP020.3) modRNA encoding RBD (V5)

German study (1, 3, 10, 20, 30, 50, 60 µg) and Study C4591001 (10, 20, 30, 100 µg)

[redacted]

BNT162b2 (RBP020.2) modRNA encoding P2 S (V9)

German study (1, 3, 10, 20, 30 µg) and Study C4591001 (10, 20, 30 µg)

Based on review of safety and immunogenicity data from Phase 1, BNT162b2 at the 30 µg dose level was selected as the final vaccine candidate and proceeded into Phase 2/3 of Study C4591001.

2. OBJECTIVES OF THE MEETING

This Briefing Document presents background information on the COVID-19 Vaccine intended to prevent COVID-19 caused by the virus, SARS-CoV-2, for the pre-submission meeting with the Therapeutic Goods Administration (TGA).

The purpose and objectives of this meeting are as follows.

- To present the proposed content and format of the planned nonclinical, clinical, safety, pharmacovigilance, labelling and CMC sections of the dossier.
- To seek TGA's feedback and agreement on the proposed filing strategy and evaluation process.

This Briefing Document presents the proposed Clinical Development Program, including the ongoing Phase 1/2/3 Study C4591001, designed to evaluate the safety, efficacy and immunogenicity of candidate BNT162b2, which is the subject of the proposed Application and describes the strategy for provision of currently available and emerging Chemistry, Manufacturing and Controls (CMC) data.

Please note, the information provided in this document is based on data as of the date of preparation of this Briefing Document. Given the rapidly evolving nature of the development of this vaccine in the context of the current COVID-19 pandemic, any updates to information provided will be shared with the TGA, and additional data expected to

become available following submission of the proposed Application can be provided on a rolling basis during TGA's evaluation of the proposed Application.

3. PROPOSED INDICATION

The initial proposed indication, discussed herein, is:

> *Active immunisation against COVID-19 disease caused by SARS-CoV-2 virus in individuals aged 16 years and over.*

4. NONCLINICAL DEVELOPMENT

The primary pharmacology of a number of 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 immunised 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 neutralisation assay (pVNT). Cellular analysis included the T-cell specific response against the antigen.

4.1. Nonclinical Pharmacology

All tested non-clinical and clinical vaccine candidates, including those not the subject of the proposed Application, were immunogenic to highly immunogenic in non-clinical models including mice, rats, and NHPs. The available data demonstrate that [redacted], BNT162b2, [redacted] are capable of inducing robust immune responses in mice, ([redacted]) rats and NHPs.

In mice, the antibody response was detected at a very early time point by IgG analysis on 7 d post-immunisation.

The observed induction of an antibody response in mice by a very low immunisation dose (0.2 µg) with B[redacted], BNT162b2, and [redacted], indicates a high vaccine potency. Also, (pseudovirus) neutralising antibody responses are detectable 14 d post-immunisation in mice immunised with intermediate doses.

The neutralisation titers in mice after 1 µg immunisation with the vaccine candidates were as follows (Table 1):

Table 1. Neutralisation Titers in Mice After 1 µg Immunisation

pVN50 titer [reciprocal dilution] Day 28	1 µg dose
[redacted]	

The virus neutralisation titers in NHPs after 30 µg immunisation with the vaccine candidates were as follows (Table 2):

Table 2. Virus Neutralisation Titers in NHPs After 30 µg Immunisation

pVN50 titer [reciprocal dilution] Day 28	30 µg dose
[redacted]	

For further detail, please refer to Section 5.1 of the Investigator's Brochure in Appendix 1. Investigator's Brochure: BNT162/PF-07302048, Version 5.0 (12 Aug 2020).

4.2. Non-clinical Pharmacokinetics and Metabolism

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.

For further detail, please refer to Section 5.2 of the Investigator's Brochure in Appendix 1.

4.3. Toxicology

To enable the rapid development of prophylactic vaccines during public health emergencies, as is the case for the current SARS-CoV-2 outbreak, the WHO has published recommendations on the content of a non-clinical safety package to support initiation of clinical testing.[8] This guideline is considered applicable for the BNT162 vaccines 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.[9] The study design is summarised in Table 3.

Table 3. Design of the GLP Compliant Repeat-Dose Toxicity Study (Study No. 38166)

Test Items	[redacted]	
Species(age)	Wistar Han rat (10-14 weeks)	
Administrations	Three [redacted] or two [redacted] 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**
[redacted]	Control = Buffer	/
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Satellite group	Cytokine response analysis	3/sex/group

Table 3. Design of the GLP Compliant Repeat-Dose Toxicity Study (Study No. 38166)		
Group size	Group 1-7	10 (+ 5 recovery)/sex/group

a. 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 neutralisation-sensitive sites.

The repeat-dose nonclinical toxicity study in rats evaluated the safety and immunogenicity of three different RNA modalities [redacted] nucleoside modified [modRNA], [redacted] formulated in LNPs and administered intramuscularly. The study design was based on regulatory guidance for vaccines,[10,11] results of all parameters assessed are summarised in Table 4 and further detail is presented in Section 5.3.1 of the Investigator's Brochure in Appendix 1.

Table 4. 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 hour 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 immunised 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	No difference in food consumption was observed

Table 4. Outcomes for Parameters Assessed in the Repeat-Dose Toxicity Study (Study No. 38166)

Parameter	Time of Assessment	Dosing Phase	Recovery phase
		animals receiving 30 µg BNT162a1 in comparison with control group.	between control and immunised groups.
Body temperature	+4 h and 24 hour post each administration, weekly during recovery.	A slight increase of body temperature was noted 24 hour post administration compared to 4 hour 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 hour 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.
Local tolerance	+4 hour and 24 hour post each administration, then every 48 hour until end of dosing/recovery.	The majority of immunised animals developed very slight to slight oedema at the injection site 24 hour 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 [redacted] 100 µg BNT162b2) 6 days after the second dose. For rats given a third dose, all findings resolved prior to the third administration. [redacted]	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. [redacted] 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 immunisation. 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.

Table 4. Outcomes for Parameters Assessed in the Repeat-Dose Toxicity Study (Study No. 38166)

Parameter	Time of Assessment	Dosing Phase	Recovery phase
Cytokines	Prior to and 6 hour post each dosing and at the end of dosing.	No vaccine-related changes observed.	Not assessed.
Clinical chemistry incl. acute phase proteins	3 day 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 immunised groups.
Haematology	3 day 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 [redacted] 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 immunised groups.

Table 4. Outcomes for Parameters Assessed in the Repeat-Dose Toxicity Study (Study No. 38166)

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 immunised 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 immunised groups.	No differences observed between buffer control and immunised 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 immunised groups.
Macroscopic pathology	At the end of dosing/recovery.	A thickened injection site was the most common observation in all vaccine treated animals [redacted] 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. [redacted] Enlarged iliac lymph nodes were observed in some BNT162b treated animals [redacted] 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 [redacted], 100 µg	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).

Table 4. Outcomes for Parameters Assessed in the Repeat-Dose Toxicity Study (Study No. 38166)

Parameter	Time of Assessment	Dosing Phase	Recovery phase
		BNT162b2 [redacted] Bone marrow: minimal to mild increases in the cellularity (all BNT162 vaccines) Spleen: extramedullary haematopoiesis in the spleen [redacted] Liver: vacuolation of hepatocytes in the portal regions in either all animals [redacted] and 100 µg BNT162b2) [redacted]	
Dose exposure serology	At the end of dosing/recovery.	Treatment with all BNT162 vaccine candidates resulted in the formation of neutralising antibodies protecting against pseudovirus infection. No antibody response or neutralisation 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 [redacted] The strongest responses were seen in animals treated with [redacted] and BNT162b2. No antibody response or neutralisation was observed in any of the buffer control animals.

For further detail, please refer to Section 5.3.1 of the Investigator's Brochure in Appendix 1.

4.3.2. 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,[9] no genotoxicity studies were performed.

4.3.3. Carcinogenicity

RNA itself, and the lipids used in the BNT162 vaccines have no carcinogenic or tumorigenic potential. Furthermore, according to ICH S1A,[12] no carcinogenicity studies are required for therapeutics that are not continuously administered. Therefore, no carcinogenicity studies were performed.

4.3.4. Reproductive and Developmental Toxicity

Macroscopic and microscopic evaluation of male and female reproductive tissues were included in the GLP repeat-dose toxicity study testing [redacted] BNT162b2, and BNT162c1 in rat (Section 4.3.1). No changes in these tissues were reported.

Specific fertility and embryofetal development studies are ongoing.

4.3.5. Immunotoxicology

No dedicated immunotoxicity study was conducted, however immunotoxicity of [redacted] BNT162b2, and [redacted] 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 5.3.1.4 of the Investigator's Brochure. 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 of the Investigator's Brochure, August 2020).

An increase of body temperature was noted at 24 hours post each administration in all groups. This increase was generally higher in immunised 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 hour 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 immunisation. The temperature increase was fully reversible within 48 to 72 hours post immunisation.

All cytokines assessed displayed high background levels/variability and were similarly elevated in control and vaccinated animals.

5. CLINICAL DEVELOPMENT

5.1. Ongoing Clinical Studies

5.1.1. German Phase 1 FIH Study BNT162-01

BioNTech is conducting a first-in-human (FIH) dose level-finding Phase 1/2 study (BNT162-01) in Germany in which all participants are 18-85 years of age and receive active vaccine. The objective of the study is to gather safety and immunogenicity data to enable evaluation of each of the vaccine candidates individually to inform the overall clinical development of a COVID-19 Vaccine. Additional information on these vaccine candidates can be found in Section 6 of the Investigator's Brochure in Appendix 1.

5.1.2. Global Phase 1/2/3 Study C4591001

Pfizer and BioNTech initiated global study C4591001 as a large Phase 1/2 clinical study using a flexible and stepwise study design to evaluate the safety and immunogenicity of the same prophylactic COVID-19 vaccine candidates that were also evaluated in the German study, using a range of dosage levels and dosing regimens. To gather appropriate dose level information quickly, some dose levels evaluated in the German or US studies were not the same.

Subsequently, a decision was taken, and agreed to by the US FDA Center for Biologics Evaluation and Research (CBER), to incorporate a Phase 2/3 efficacy study design as an amendment to the ongoing Phase 1/2 study to create a Phase 1/2/3 study. A description of the revised protocol design, including the incorporation of the Phase 2/3 part of the study is provided herein (the current approved protocol amendment for Study C4591001 is provided in Appendix 2. C4591001 Study Protocol Amendment 5).

Based on review of available Phase 1 safety and immunogenicity data, BNT162b2 at the 30 µg dose level was selected as the final vaccine candidate and proceeded into Phase 2/3 of Study C4591001:

- BNT162b2-vaccinated human participants displayed a favorable breadth of epitopes recognised in T cell responses specific to the SARS-CoV-2 spike antigen, and that BNT162b2 demonstrated concurrent induction of high magnitude CD4+ and CD8+ T cell responses against the receptor binding domain (RBD) and against the remainder of the spike glycoprotein.
- Across all populations, BNT162b2 administration was well tolerated with mild to moderate fever in fewer than 20% of the participants.

The Phase 2/3 part of study C4591001 commenced on 27 July 2020 and is designed to evaluate the safety, efficacy and immunogenicity of BNT162b2 in participants ≥18 years of age. Phase 2/3 is currently being conducted in the US, Brazil, Argentina, and South Africa, with sites to be added in Germany and Turkey in the near future. A total of ~30,000 participants, ≥18 years of age, randomised in a 1:1 ratio with placebo are planned to be enrolled by early October 2020. There have been 5 amendments to the protocol for study

C4591001 which are described in Protocol Amendment Summary of Changes Table in Protocol C4591001 Amendment 5, provided in Appendix 2. On 18 August 2020 (SN 0060) a Request for Comments & Advice was submitted to the FDA regarding a proposed amendment, Protocol Amendment 6. The Sponsor is currently in discussion with FDA on the following 2 changes:

1) to reduce the minimum age for participants to be eligible for C4591001 Phase 3 from 18 years to 12 years and;

2) to modify exclusion criterion #2 such that "Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV)" are no longer exclusionary in Phase 2/3.

Study C4591001 includes four planned Interim Analyses (to be conducted at accrual of 32, 62, 92, and 120 confirmed COVID-19 cases) and targets 164 cases in total at the Final Analysis. Based on anticipated enrollment rates and disease incidence of 0.9% per month in the placebo group, demonstration of the primary and key secondary study endpoints for safety and efficacy is anticipated by early November 2020. The Sponsor proposes to submit an initial dossier based on Interim Analysis in which efficacy is demonstrated, and to submit the Final Analysis of efficacy in addition to safety data when available (see Table 5).

The first 6000 subjects will record immunogenicity in an e-diary and a safety analysis of these 6000 will provide the main safety analysis at the time of filing, with adverse event data for all enrolled subjects.

Table 5. Interim Analysis and Final Analysis Timing and Data Availability

Interim Analysis[a]	Efficacy Data Availability	Safety Data Availability for the Analysis[b]
#1 late Sep 2020	32 COVID-19 cases; seronegative participants only	Safety data through 7 days post-dose 2 from the first 6000 participants enrolled All available safety data collected for participants enrolled
#2 early/mid Oct 2020	62 COVID-19 cases; sero-negative participants only	Safety data through 7 days post-dose 2 from the first 6000 participants enrolled All available safety data collected for participants enrolled
#3 mid Oct 2020	92 COVID-19 cases; sero-negative participants only	Updated safety data through 1 month post-dose 2 from the first 6000 participants enrolled

Table 5. Interim Analysis and Final Analysis Timing and Data Availability

Interim Analysis[a]	Efficacy Data Availability	Safety Data Availability for the Analysis[b]
		All available safety data collected for participants enrolled Safety data 3 months post-dose 2 for the BNT162b2 construct from Phase 1 and safety data 4 months post-dose 2 for the BNT162b1 construct for individuals ≤ 55 years of age.
#4 Mid/late Oct 2020	120 COVID-19 cases; sero-negative participants only	Updated safety data through 1 month post-dose 2 from the first 6000 participants enrolled All available safety data collected for participants enrolled Safety data for BNT162b1 and BNT162b2 constructs from Phase 1 for individuals ≤ 55 years of age.
Final Analysis early Nov 2020	164 COVID-19 cases; seronegative and seropositive participants	Updated safety data through 1 month post-dose 2 from the first 6000 participants enrolled All available safety data collected for participants enrolled Safety data for BNT162b1 and BNT162b2 constructs from Phase 1 for individuals ≤ 55 years of age.

a. Interim analysis timing is event-driven; represents projected timing.

b. Safety data presented in the table shows the latest amount of safety data; the interim analysis package will contain earlier phases of safety data

5.1.2.1. Analyses During Phase 2b/3

Objectives, estimands and endpoints were presented in the synopsis for a Phase 2/3 randomised, placebo-controlled, observer-blinded study of the efficacy and safety of one or more COVID-19 Vaccine candidates in individuals ≥18 years of age (C4591001). At CBER's suggestion, additional objectives and associated estimands and endpoints will be included to assess safety, immunogenicity, and efficacy in subjects with evidence of prior infection at baseline.

Three types of analyses are proposed during the Phase 2b/3 portion of the study:

- Phase 2 safety and immunogenicity analysis on the first 360 subjects (90 active and 9-0 placebo in each age stratum)
- Phase 3 safety including reactogenicity on the first 6000 subjects and adverse events in all enrolled subjects
- Efficacy interim and final analyses to support Traditional Approval.
    - The primary efficacy analysis will be efficacy against COVID-19 at least 14 days after the last dose of vaccine in participants without evidence of prior SARS-CoV-2 infection at baseline, as such infection induces strong neutralising antibody responses likely to prevent further infection.[13]

5.1.2.2. Interim Results from Ongoing Studies

A summary of available data can be found in Section 6 of the Investigators Brochure in Appendix 1.

5.2. Planned Clinical Studies

5.2.1. Pregnancy

COVID-19 infections have been described in pregnant women, often with good outcomes following Caesarean section.[14] Neonatal infection has followed in some but generally without adverse outcomes.[14,15] However, poor outcomes in both mother and neonate have been reported.[16] As a result, it would be desirable to protect women with a vaccine during the second half of pregnancy and this may also have the advantage of protecting neonates from COVID-19, even though neonatal disease has not generally been severe. Therefore, the Sponsor plans to include proposed use in pregnant women 18-45 years of age based on demonstration of adequate safety and effectiveness inferred from immunobinding based on the same immune markers to be used in the application for adults.

Before starting a study of vaccination in pregnancy, results from a DART study will be submitted. The results of this would also be reassuring for advising women following accidental exposure in early pregnancy, which is very likely to occur in the event of a large-scale general population immunisation program.

A two-step safety and immunogenicity study is anticipated, bridging to immunogenicity data in age-matched non-pregnant adults in Study C4591001. Initially up to 40 pregnant women 18-40 years of age would be randomised to receive a first dose of COVID-19 vaccine or TdaP (Tetanus toxoid, low dose diphtheria toxoid, acellular pertussis vaccine) between 27 0/7 and 35 6/7 weeks gestation and a second dose 3 weeks later, with the control group receiving placebo.

In a second step, the study would expand to 200 participants randomised to two doses of COVID-19 vaccine candidate or TdaP followed by placebo. Numbers may be adjusted based on assay characteristics and risk of safety events. Consideration would be given to including some participants to receive their first dose from 24 0/7 gestational age.

In addition to safety, reactogenicity, and immunogenicity assessments in maternal participants we would record pregnancy and neonatal outcome, with cord blood and 6-month infant blood for SARS-CoV-2 serology. Mothers and neonates would be followed for up to 6 months after birth for serious adverse effects (SAEs) and clinical COVID-19 episodes.

Licensure for use in pregnancy would follow approval of the candidate vaccine in adult subjects following demonstration of acceptable clinical efficacy.

A pregnancy register capturing maternal, birth, and infant outcomes will be created for inadvertently exposed pregnant women during development but particularly for anticipated exposures in pregnancy during post-approval use of the vaccine.

5.2.2. Paediatric Plan

Pfizer is currently amending the C4591001 study protocol to add participants 16-17 years of age into the younger adult cohort. This is intended to support an initial indication for use in people aged ≥16 years of age. The amendment will also add a separate cohort of adolescents 12-15 years of age. An immunobridging comparison is planned to infer effectiveness of the candidate vaccine in participants 12-15 years of age by comparison to 16-25 year old subjects. This will support a post-approval submission to reduce the age of the indication down to 12 years of age. A subsequent study will be developed with age de-escalation and dose-ranging in children and infants <12 years of age.

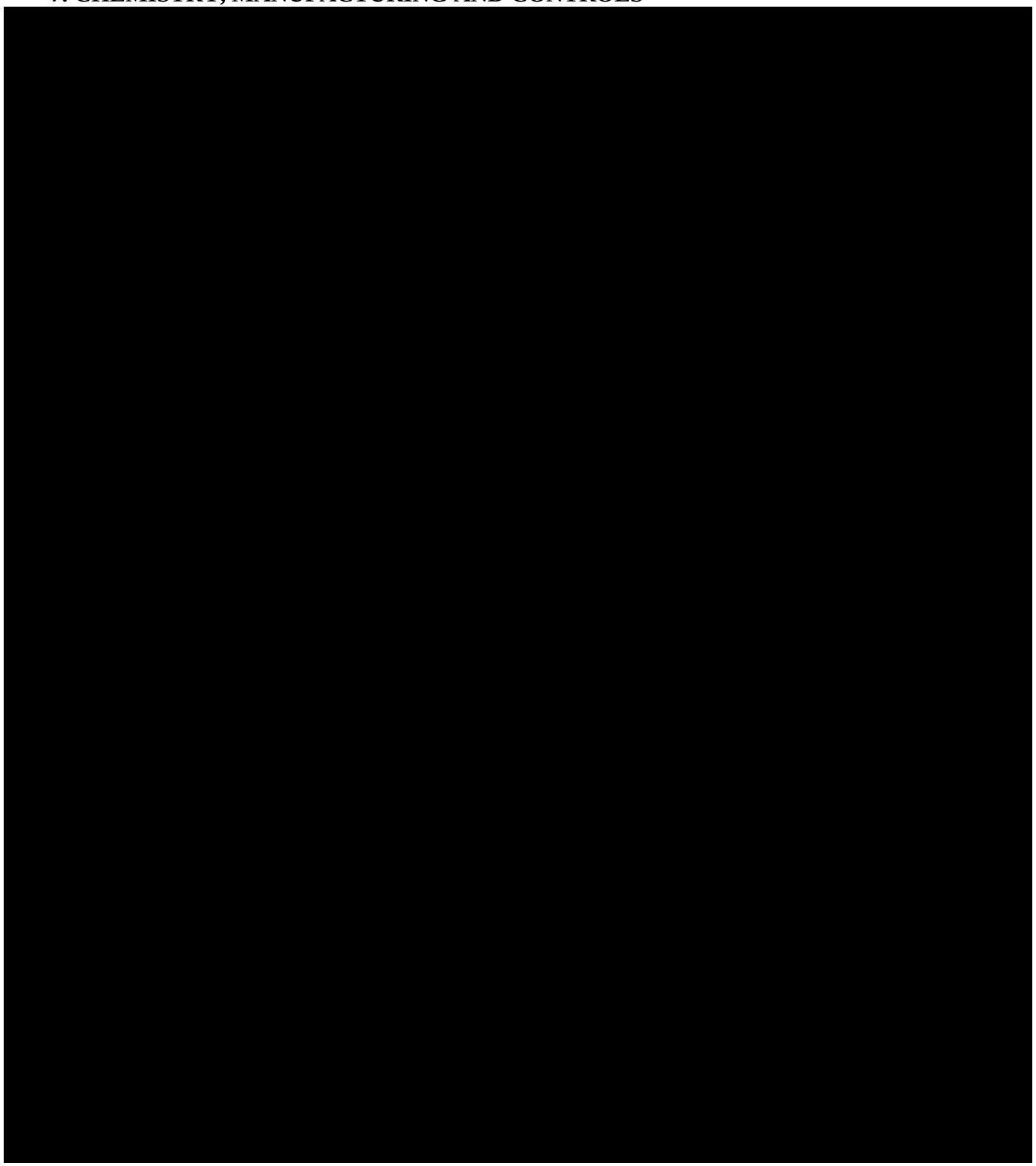
6. RISK MANAGEMENT PLAN

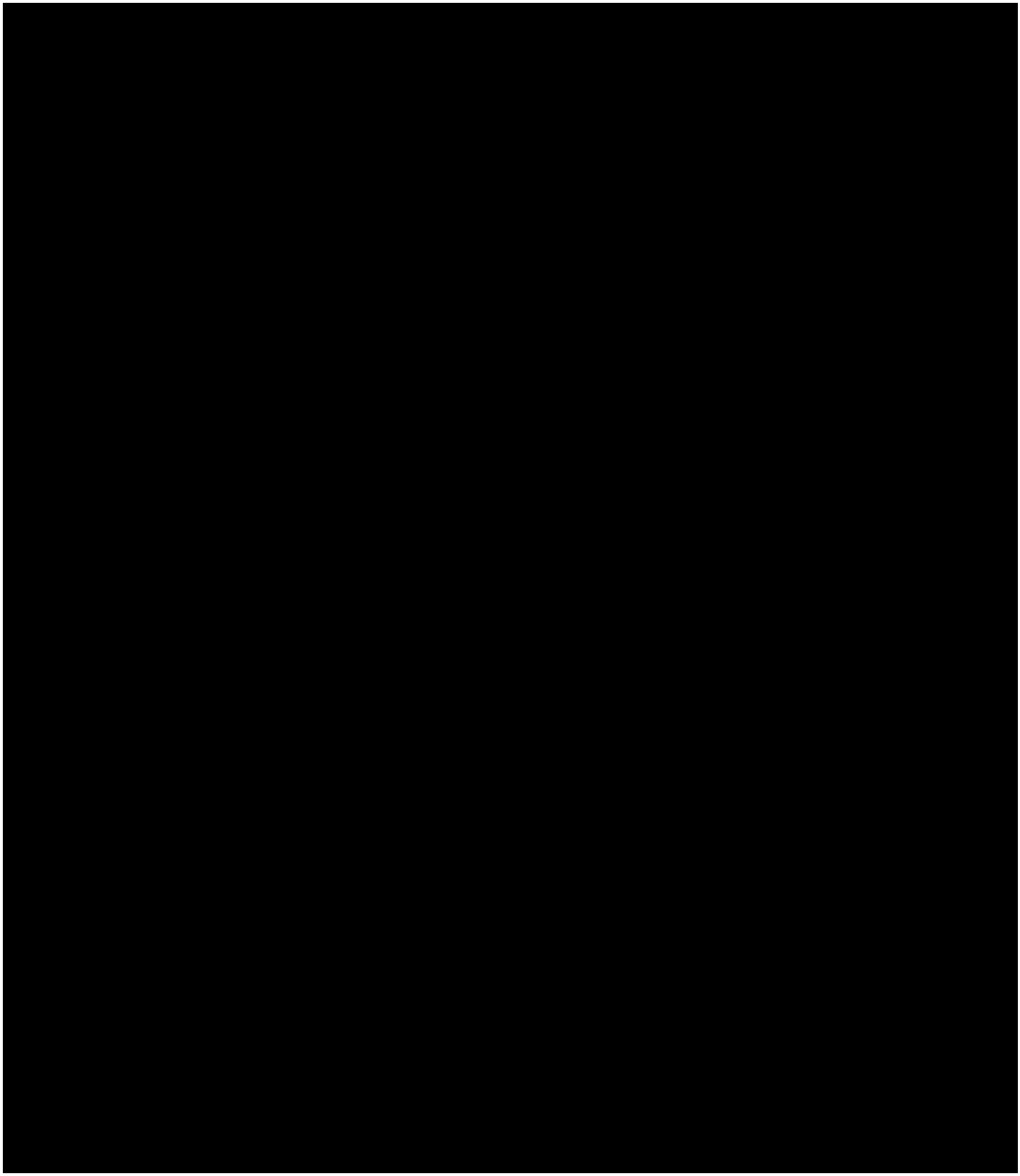
As exposure to the COVID-19 vaccine increases and understanding of the safety profile evolves, the RMP will be updated.

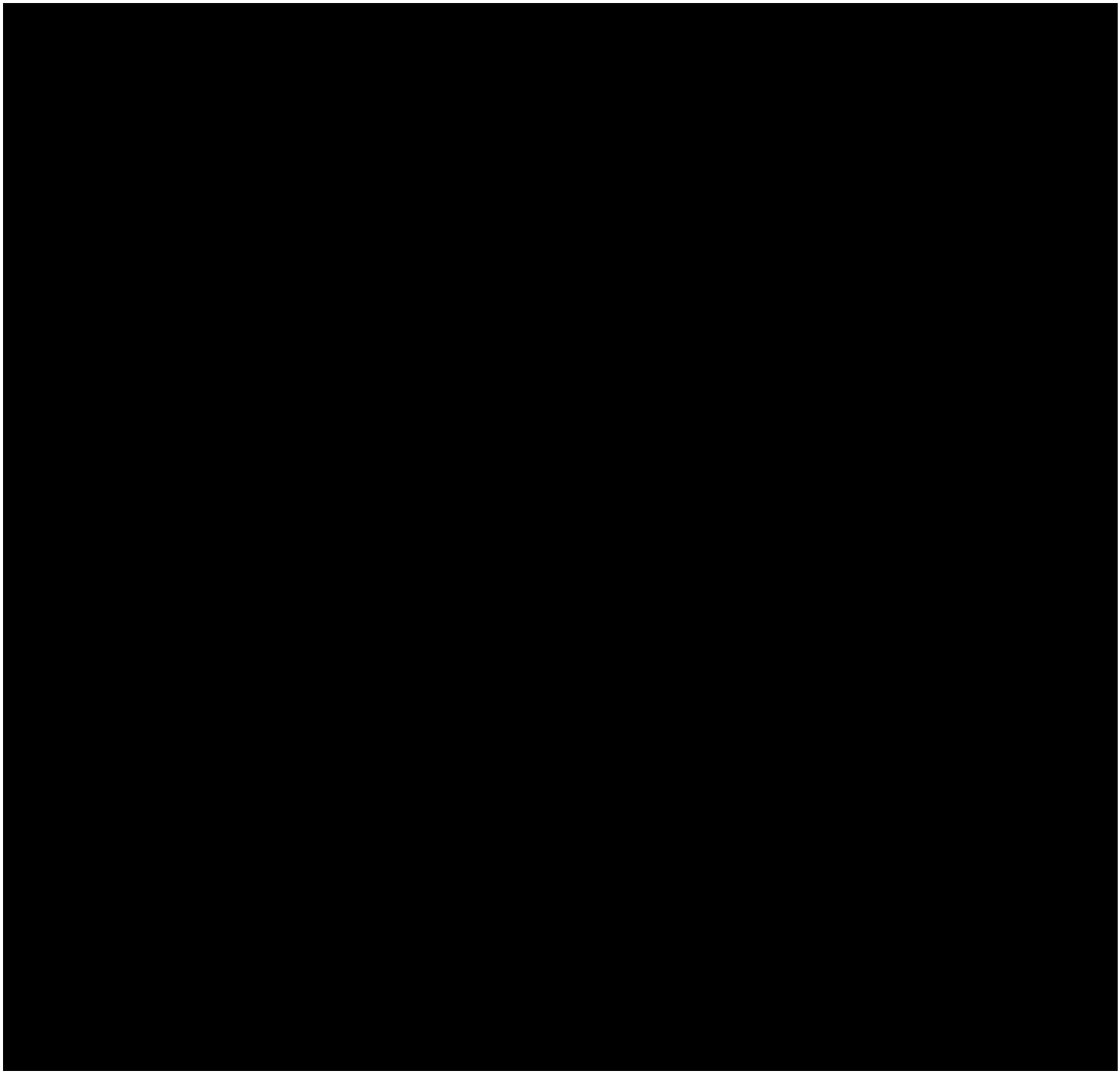
Pfizer/BioNTech plan to include vaccine-associated enhanced disease (VAED), including vaccine-enhanced respiratory disease (VAERD) as an important potential risk. Missing information will include use in pregnancy and lactation, use in children, use in immunocompromised individuals, use in individuals with chronic disease and vaccine effectiveness. These safety concerns may be updated during evaluation based on data collected from the ongoing Phase 3 study.

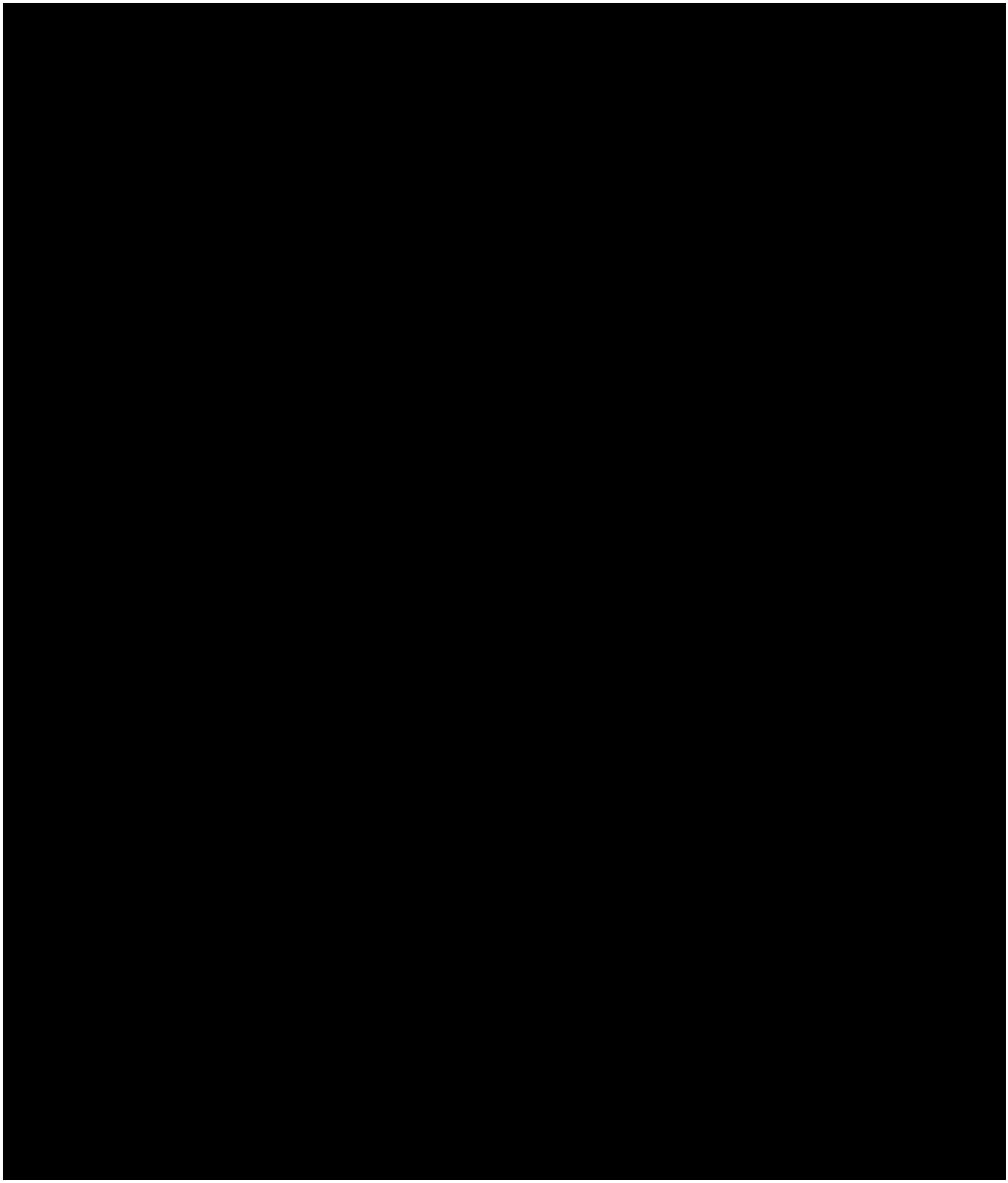
To date, there have been no identified Australia-specific considerations or epidemiology related to COVID-19, however the Sponsor acknowledges the importance of monitoring exposure in Aboriginal or Torres Strait Islander peoples to ensure any additional risks related to missing information are managed.

7. CHEMISTRY, MANUFACTURING AND CONTROLS









[redacted]

7.3. Comparability Strategy

The analytical comparability plan proposed in this document will support the use of Process 2 drug substance materials and drug product manufactured from these batches. Process 2 drug substance incorporates the use of plasmid DNA and TFF purification steps and is scalable, to maximise production capacity. Similarly, the changes associated with drug product manufacturing processes are related to production scale and manufacturing site to increase capacity for supply of the drug product.

All Process 1 and Process 2 data available at the time of initial submission, including stability data, will be provided to support the analytical comparability assessment. Supplements are planned to provide additional Process 2 data as they become available.

At the time of submission, the drug substance comparability assessment will minimally include Process 1 and 2 drug substance batches, including representative drug substance batches from the Pfizer, Andover site. The drug product comparability assessment will include lots manufactured from Process 1 and 2 drug substance batches. Commercial drug product quality will be confirmed based on release testing against the specifications that will be proposed in the Application and a future comparability assessment once commercial materials are available.

The comparability plan includes the following elements:

- Drug substance release testing against proposed commercial acceptance criteria and heightened characterisation tests with the addition of select side-by-side testing

- Drug product release testing against proposed commercial acceptance criteria and heightened characterisation tests with the addition of select side-by-side testing.

7.3.1. Drug Substance Release and Heightened Characterisation Testing

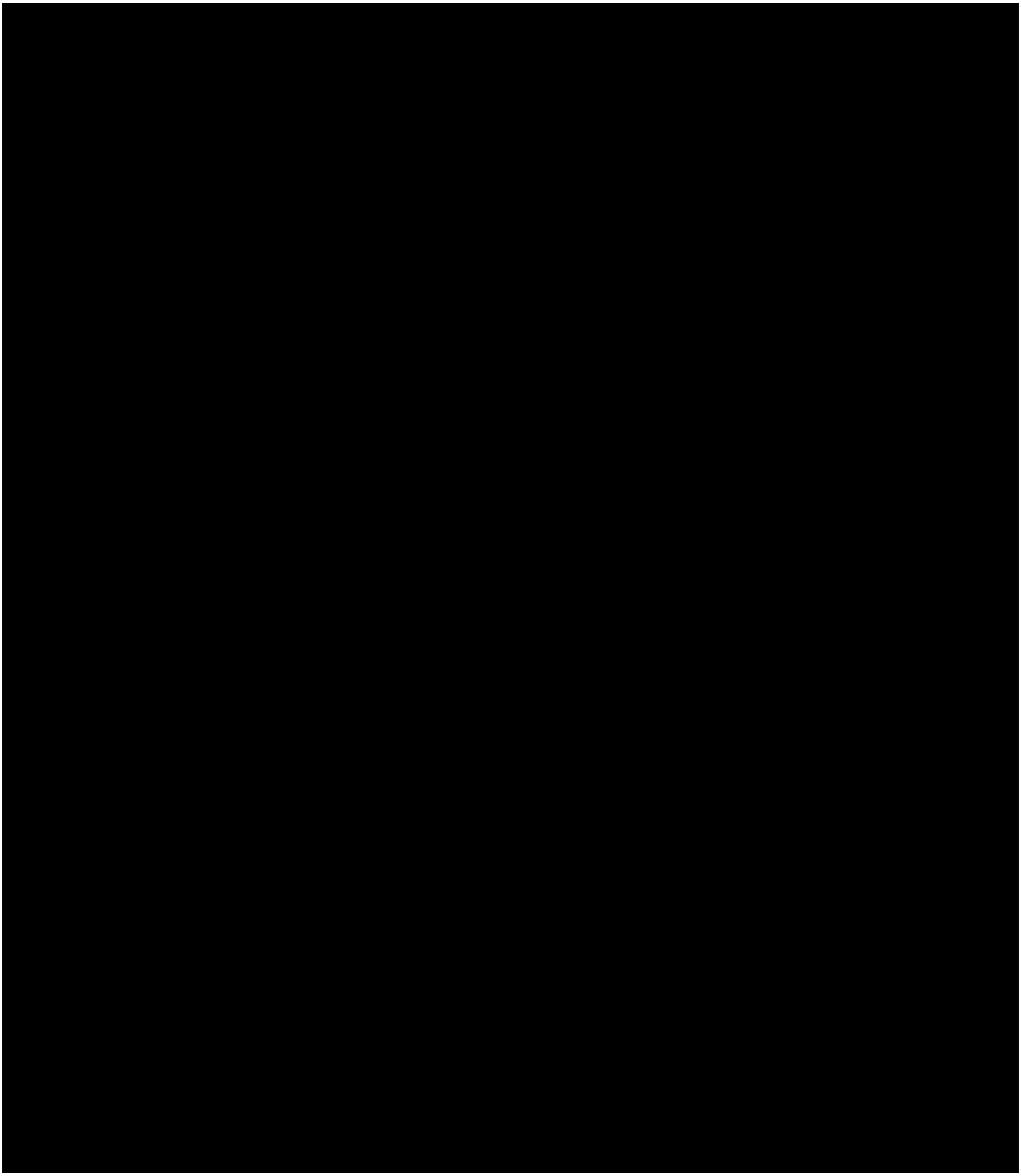
Release and heightened characterisation test results will be compared for Process 1 and 2 materials. In instances where new release test methods have been introduced subsequent to manufacture of prior material, side-by-side testing of DS will be performed.

7.3.1.1. DS Batches Included in Comparability Assessment

Representative batches of Process 1 and Process 2, including materials from clinical supply and initial commercial drug substance supply will be included in the comparability assessment. The assessment is intended to be conducted for license application with the first successful Process 2 drug substance batch manufactured at the Pfizer, Andover site, though ongoing monitoring will continue through process performance qualification (PPQ) and a continued process verification program.

7.3.1.2. Overview of Tests for PF-07302048 Drug Substance Comparability

Table 9 contains the panel of tests, both release and heightened characterisation, that will be performed.



7.3.1.3. Evaluation of Drug Substance Comparability Testing

Establishment of comparability will be based upon comparison of Process 1 and Process 2 comparability testing including release and characterisation testing, as well as comparison of chromatograms/ electropherograms with the following expected results:

- All materials should meet release specifications
- Similar peak/species distributions in each assay
- No significant detectable new species in Process 2 material
- For mass spectrometry measurements, measured masses should agree with theoretical masses according to instrument specifications.

If differences are observed, the relevance of those differences will be evaluated for their expected impact on safety and efficacy and that evaluation would be documented as part of the comparability assessment.

7.3.2. Drug Product Release and Heightened Characterisation Testing

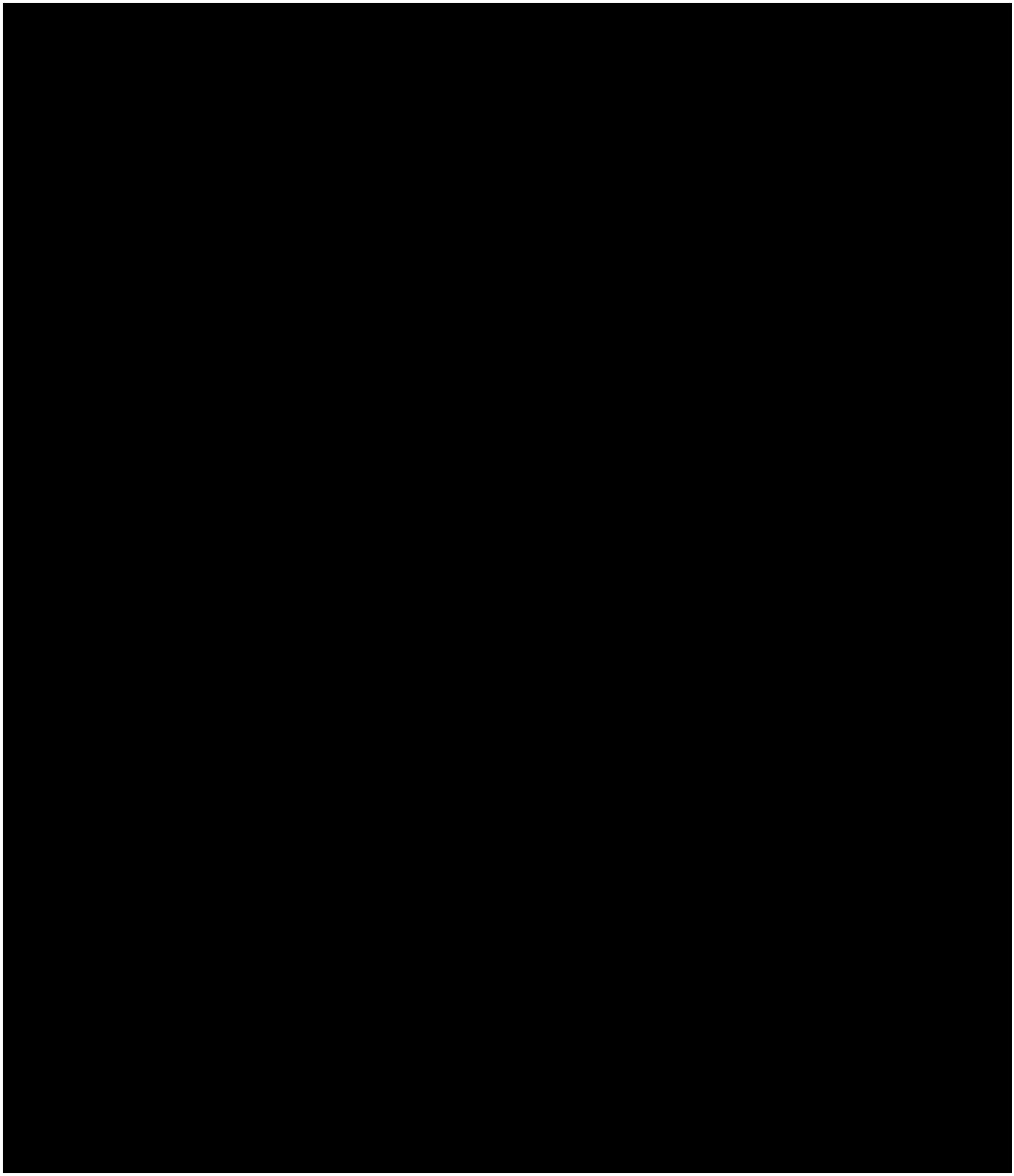
Release and heightened characterisation test results will be compared for drug product used for Phase 1, 2 and 3 clinical trials. Product quality data for initial and commercial drug product supplies will be provided as it becomes available and before lot release. In some instances, such as when a new method has been introduced, side-by-side testing will be performed.

7.3.2.1. Drug Product Lots Included in Comparability Assessment

At least one lot of drug product used in Phase 1, Phase 2 and Phase 3 clinical studies will be included in the comparability assessment. Because the changes implemented for initial supply and commercial supply involve manufacturing scale and site, acceptability of these supplies will be based on acceptable release testing against the proposed specifications that will be provided in the Application. Expanded evaluation through ongoing monitoring will continue through PPQ and a continued process verification program.

7.3.2.2. Overview of Tests for PF-07302048 Drug Product Comparability

Table 10 contains the panel of tests, both release and heightened characterisation, that will be performed.



7.3.2.3. Evaluation of Drug Product Comparability Testing

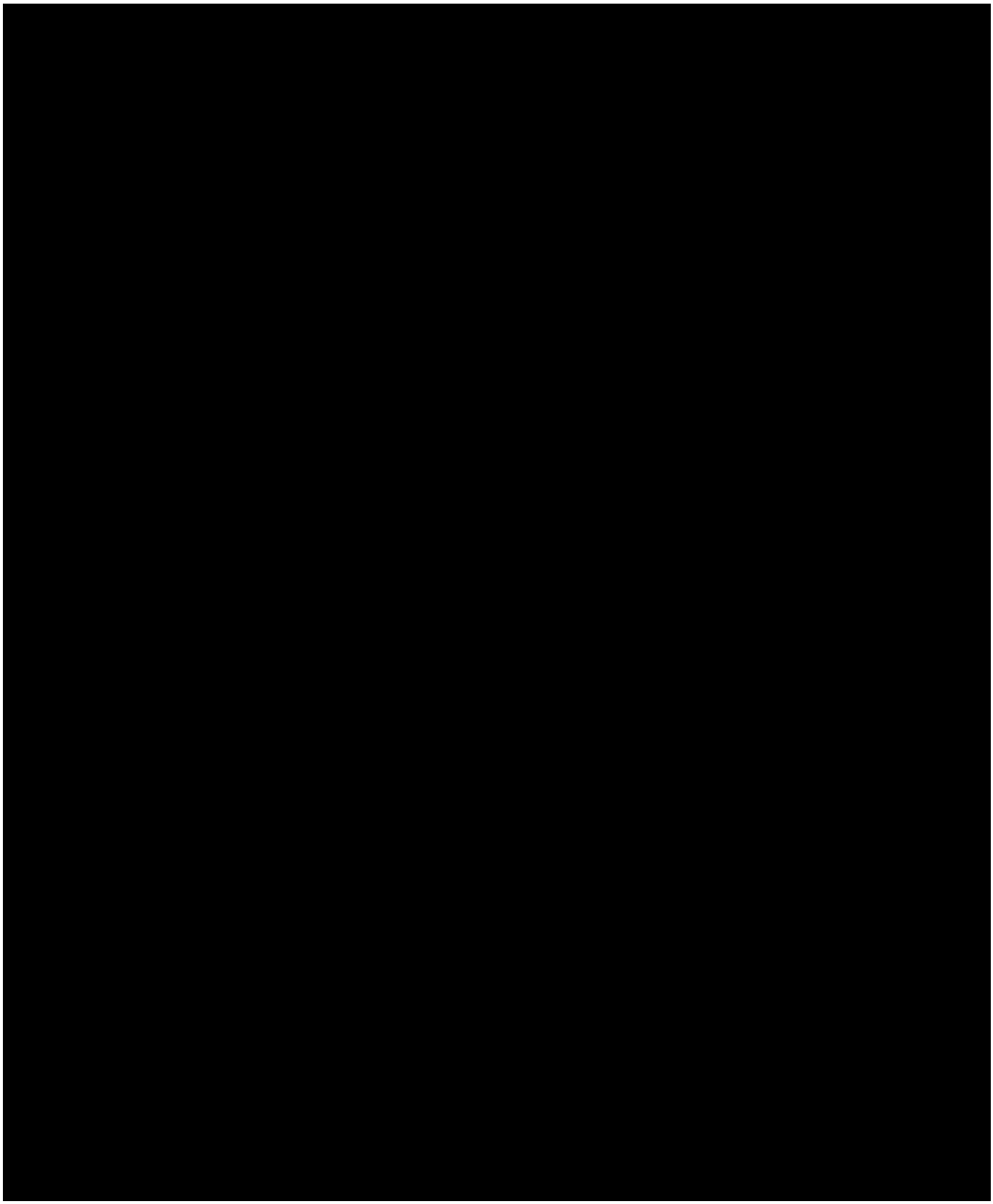
Establishment of comparability will be based upon comparison of Phase 1, Phase 2, Phase 3 clinical materials and initial and commercial supply materials including results from release and characterisation testing, as well as comparison of chromatograms/electropherograms with the following expected results:

- All materials should meet release specifications
- Similar peak/species distributions in each assay
- No significant detectable new species in initial supply and commercial materials
- For mass spectrometry measurements, measured masses should agree with theoretical masses according to instrument specifications

If differences are observed, the relevance of those differences will be evaluated for their expected impact on safety and efficacy and that evaluation would be documented as part of the comparability assessment.

Initial supply and commercial drug product will be assessed against the release specifications that will be proposed within the Application. Comparability for initial supply and commercial drug product supplies will be provided when data become available and before lot release.

7.4. Materials



[redacted]

7.4.2. Starting Materials and Ancillary Materials, and Other Excipients

Starting materials are materials used during manufacturing that are intended to be part of the final product.

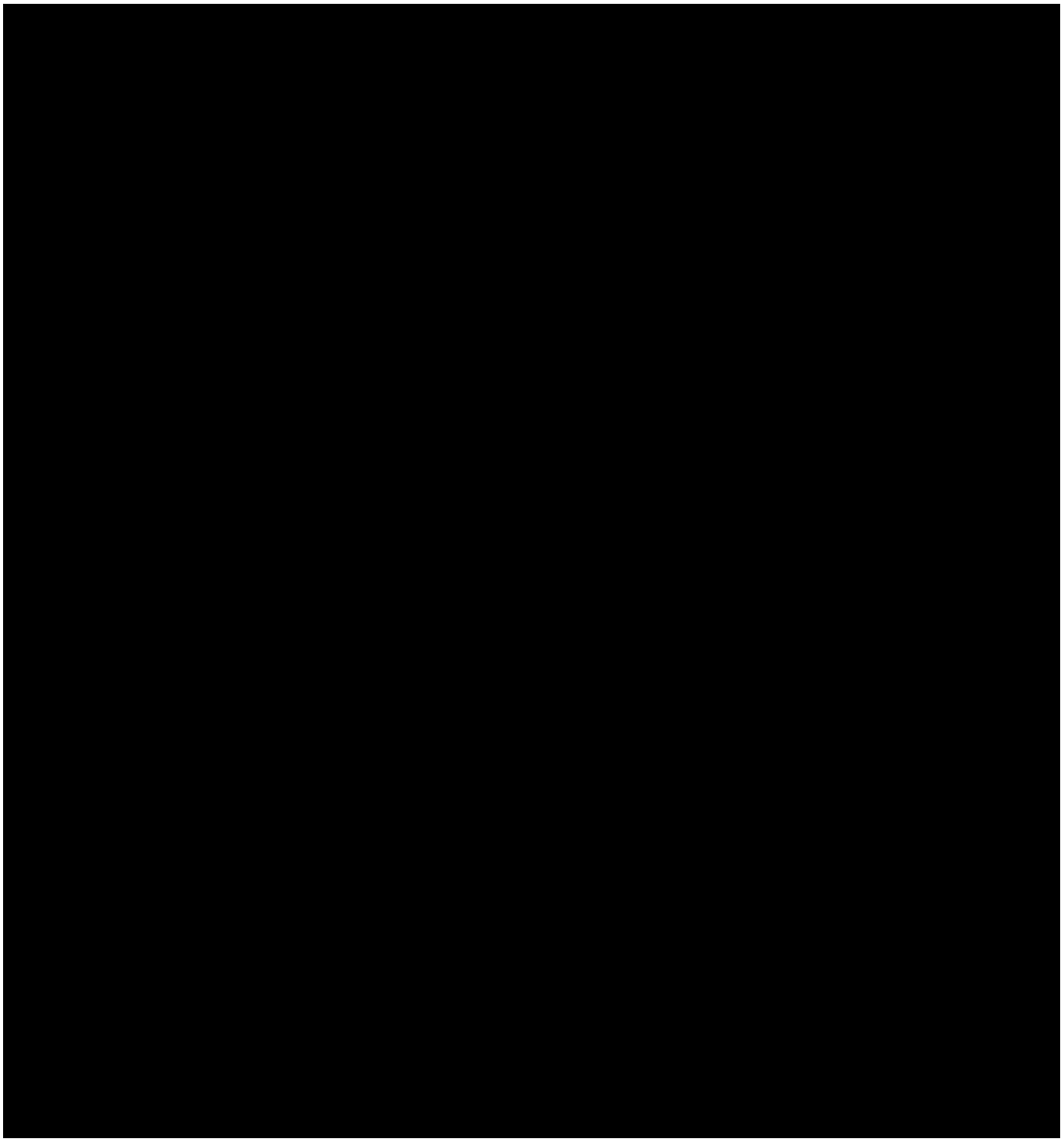
[redacted]

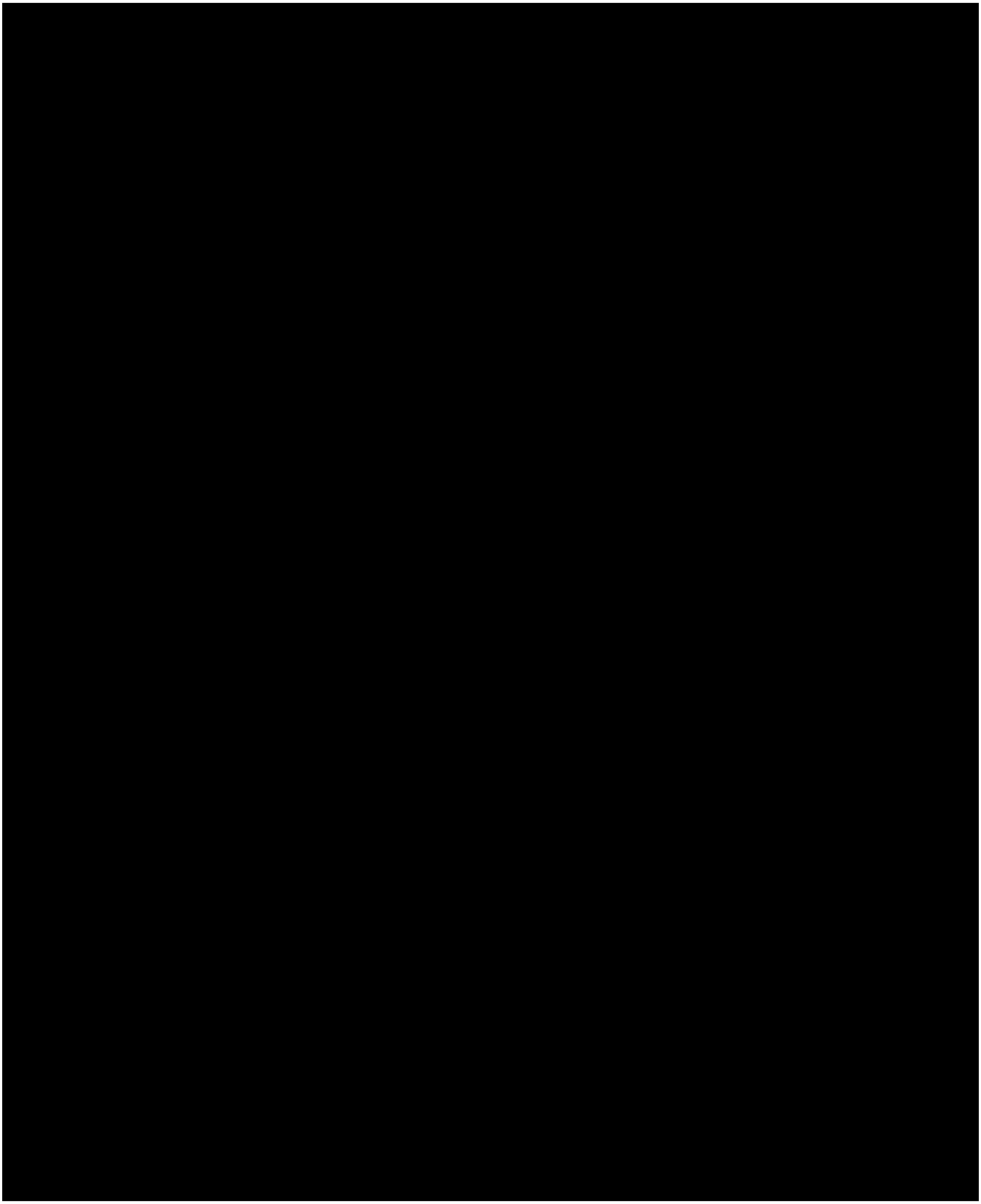
7.5. Analytical Testing and Specifications

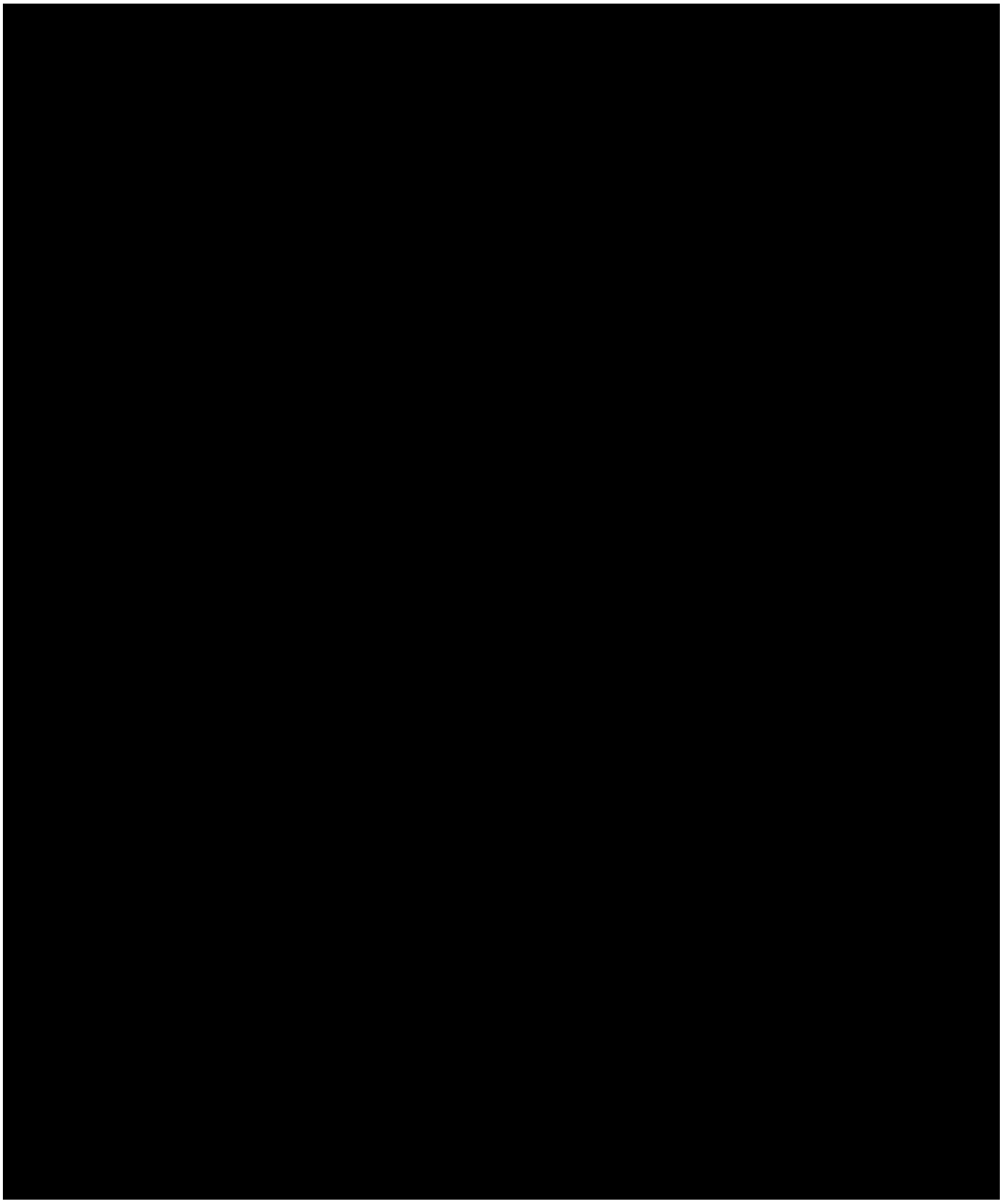
The following sub-sections provide a high-level overview of analytical testing, methods, testing for initial commercial supply as well as specification strategies that may be employed for a mRNA vaccine product. Some of these methods may be informational/characterisation tests while others are qualified for lot release.

7.5.1. Drug Substance Testing

[redacted]







[redacted]

7.6. Stability and Shelf-life

7.6.1. Drug Substance

Drug substance is held for a limited time period prior to converting into drug product. Drug substance stability studies are on-going for clinical materials. A minimum of three commercial batches will be placed on formal stability according to the ICH guidelines (and include long term, accelerated, stressed, photostability and thermal cycling studies). All stability data available at the time of dossier submission will be provided.

Developmental studies, using representative material, will also support drug substance hold time duration prior to and during drug product manufacturing. These studies may be performed using available pilot or non-GMP material that is representative of the GMP process. Data from these studies shall be used to justify the drug substance hold time period for the commercial supply.

7.6.2. Drug Product

Drug product stability studies are on-going for clinical materials. A minimum of three commercial drug product lots will be placed on formal stability according to the ICH

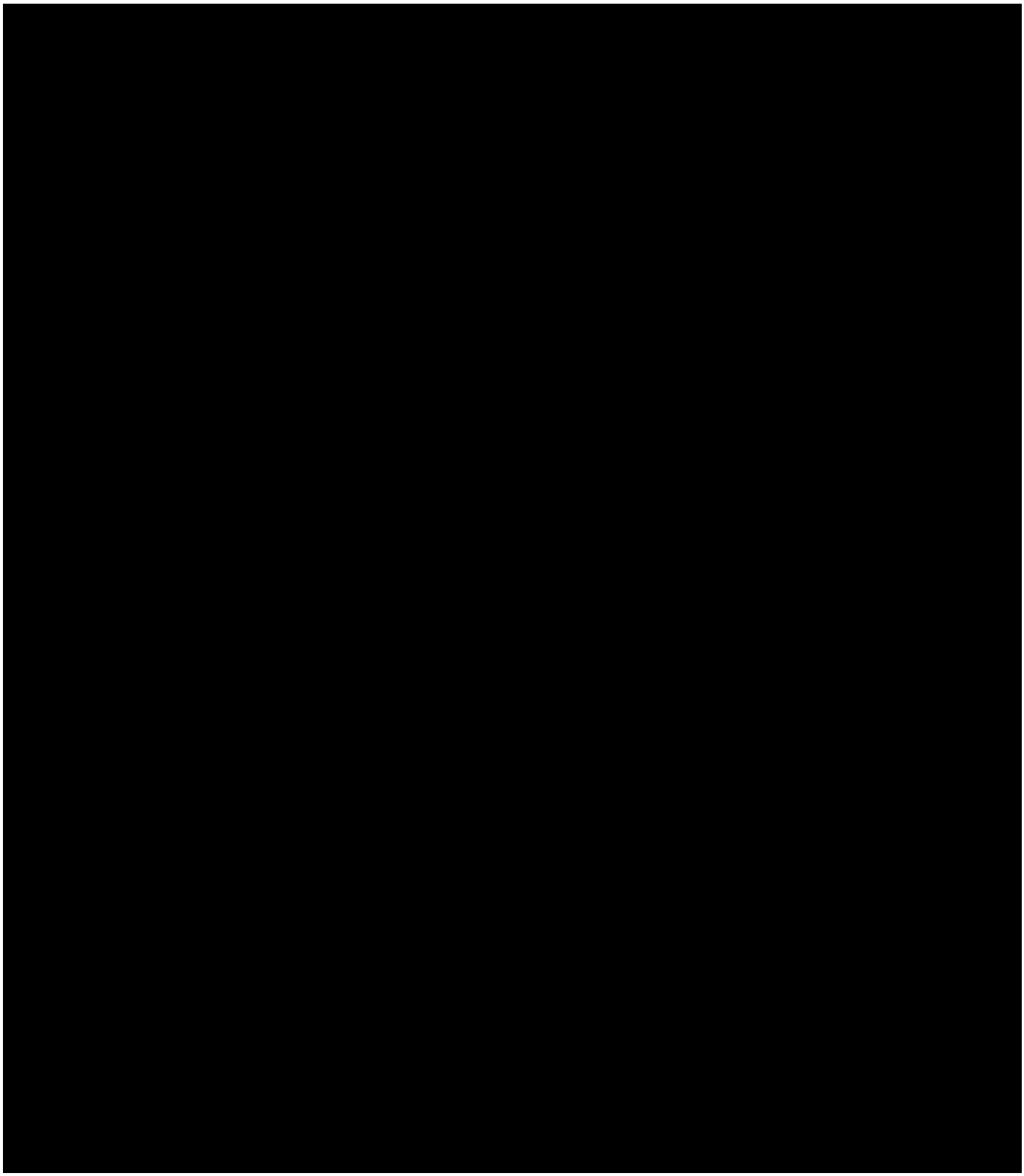
guidelines (and include long term, accelerated, stressed, photostability and thermal cycling studies). Minimally, the stability program shall cover the time period proposed for a commercial period of use and shall employ the methods, sampling times, temperatures and testing required that are stability indicating. The drug product stability program will be conducted using representative materials to establish the use period and need not be repeated for every lot manufactured by the same process. A GMP lot shall be enrolled in the stability program as confirmatory stability for drug product and annually thereafter.

7.7. Quality Assurance

7.7.1. Materials

7.7.2. Batch/Lot Release

7.8. Shipping and Distribution



8. PRODUCT DESCRIPTION

8.1. Chemical Name and Structure

Sponsor Compound Number: BNT162, PF-07302048.

Pfizer has applied for an INN and a proposed tradename is under consideration. In the interest of simplicity, the Sponsor will refer to the proposed vaccine as *TRADENAME*/*COVID-19 Vaccine* until further information is made available, at which point, the TGA will be informed.

8.2. Dosage Form, Route of Administration, and Dosing Regimen

The vaccine drug product is a preservative-free concentrated liquid formulation stored frozen at - 70 °C (± 10 ° C) for storage and distribution until the time of use. On the day of administration, the vaccine vial is to be removed from frozen storage and allowed to thaw for approximately 30 minutes at room temperature. Vials thawed at room temperature must be diluted within 2 hours or transferred to a refrigerator. Undiluted vials may be stored for up to 48 hours in the refrigerator. Sterile 0.9% sodium chloride Solution for Injection, USP is added to the vial to increase the volume of the vaccine solution and the vial is stored at 2- 30°C until administration. The vial is labelled with the time of dilution and must be discarded no longer than 6 hours after initial dilution. Dose administration of the COVID-19 vaccine product involves withdrawal of the prescribed dose from the vial into a delivery system such as a syringe.

The Sponsor intends to commercialise the current formulation and initially plans to provide a single vial from which multiple doses would be drawn. The multi-dose vial presentation is planned to be preservative-free.

The 5-dose vial is supplied as a white to off-white sterile frozen liquid, packaged in a 2 mL clear Type I glass vial with a rubber stopper, aluminum overseal and flip off cap. Note: the vial stopper is composed of Datwyler FM457 gray bromobutyl rubber that is not manufactured from dry natural rubber (latex).

The 1.8 mL of saline diluent is added directly to the concentrated multidose vaccine concentrate. After dilution, the vials contain a sufficient volume to supply 5 doses, where each 0.3 mL dose contains 30 µg vaccine for IM injection. The 0.9% Sodium Chloride Injection, USP will not be supplied with the vaccine. Healthcare professionals will be instructed to use locally sourced saline.

The vaccine will be administered intramuscularly (IM) in the upper arm (deltoid muscle) as a series of two 30 µg doses of the diluted vaccine solution (0.3 mL each) according to the following schedule: a single 0.3 mL dose followed by a second 0.3 mL dose 21 days later (prime/boost regimen).

Dosage and administration instructions are proposed to be supplied in the form of a product 'Fact Sheet', see Appendix 3. Vaccine Dosage and Administration Instructions.

8.3. Packaging and Labelling

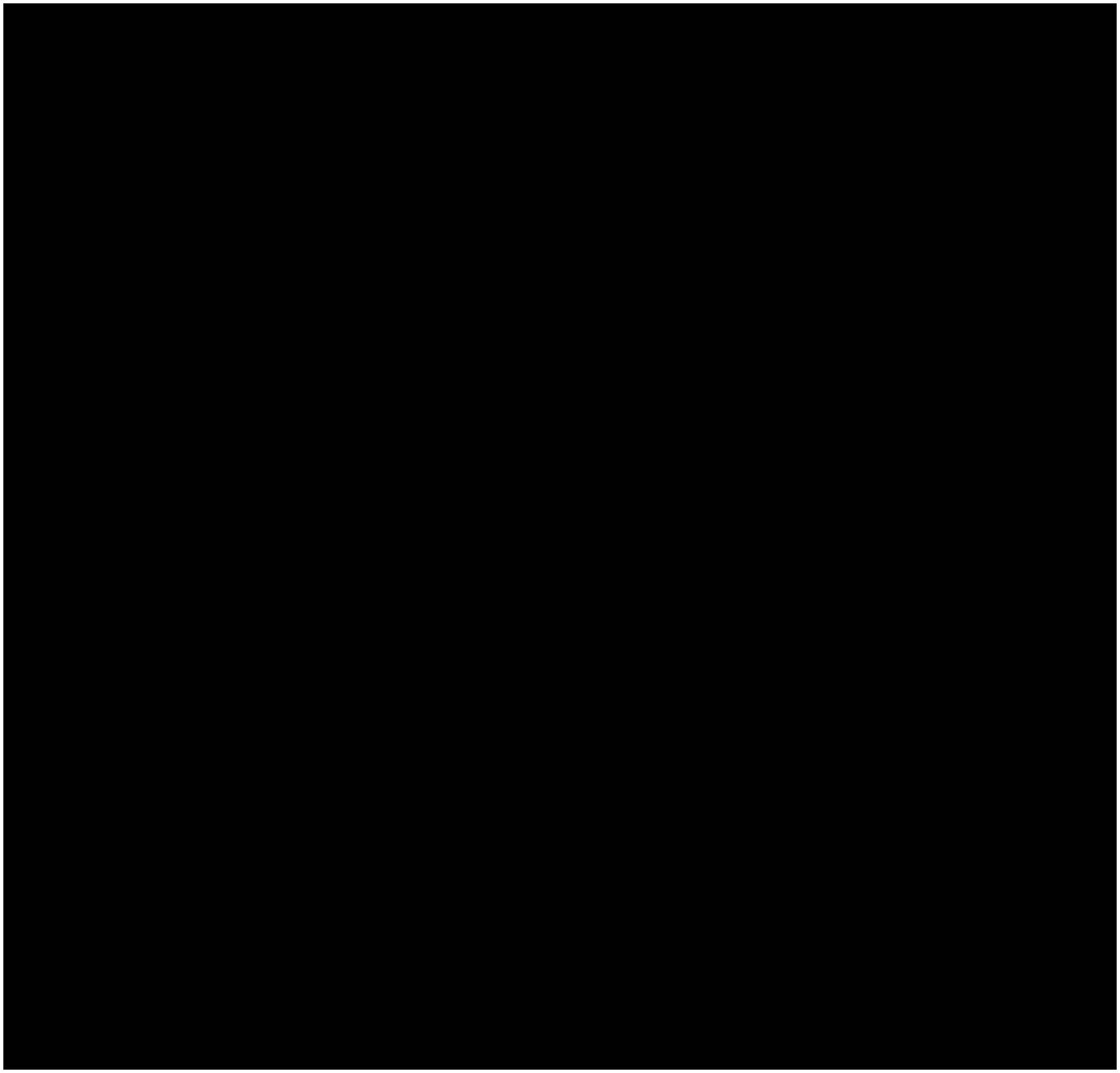
To increase the speed and agility of providing the vaccine, the multi-dose vials supplied in Australia will be in US English labelling common to all markets. Examples of the proposed vial label and carton mock-ups are provided in Appendix 4. Indicative Draft US Vial and Carton Label Mock-ups.

8.4. Use of Locally Sourced Saline

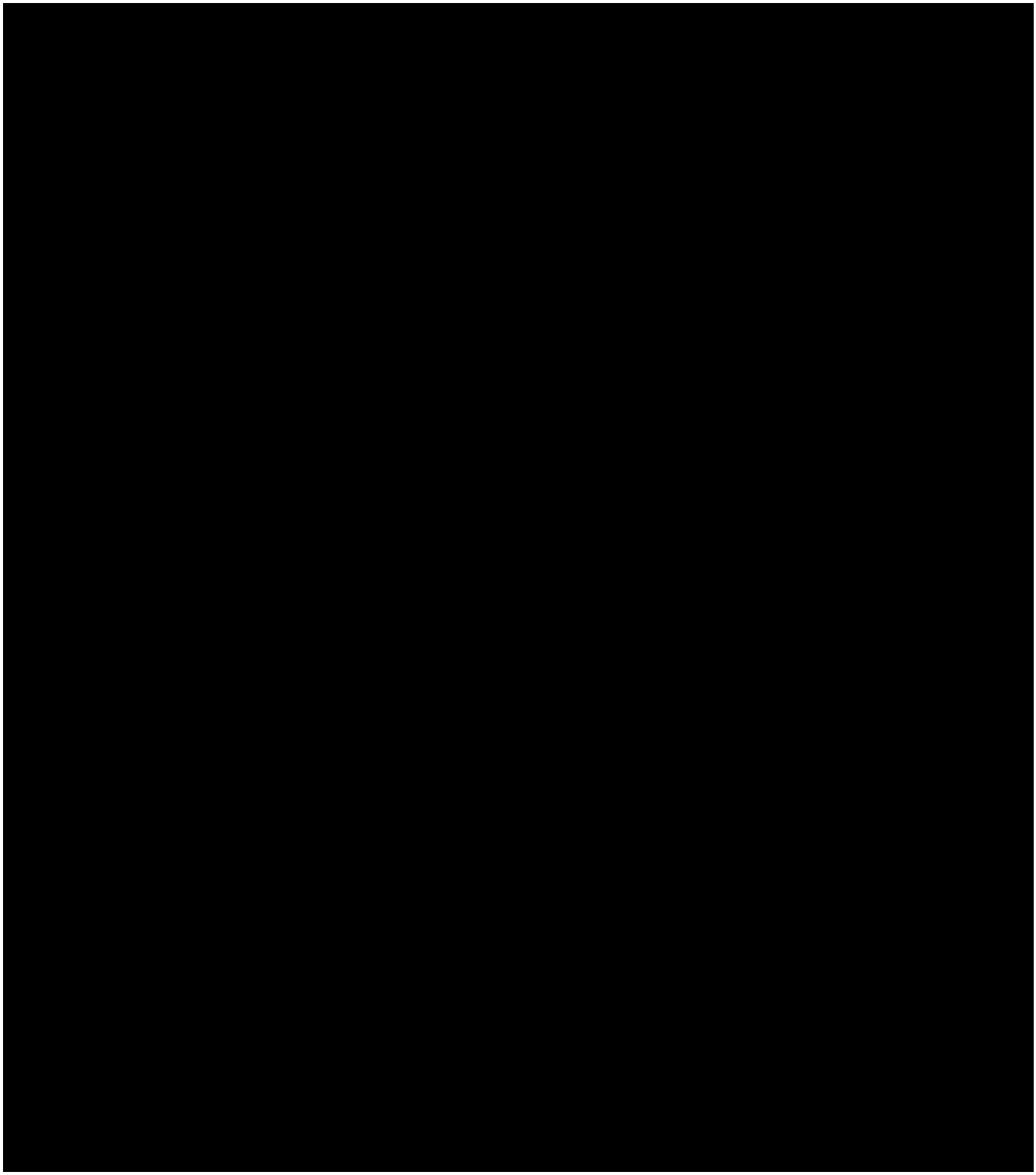
Normal Saline, syringes and needles will be provided by the clinical site, pharmacy or hospital. Since the vaccine drug product must be maintained as a frozen concentrate at - 70 ºC immediately prior to administration, co-packaging or co-kitting saline diluent is not viable or practical. Including a diluent with this product poses several challenges. In addition to occupying limited freezer capacity at - 70 ºC which is needed for drug product vial storage, co-packaging diluent requires significant additional time to thaw creating logistical complexity in dosing preparation and scheduling at administration sites.

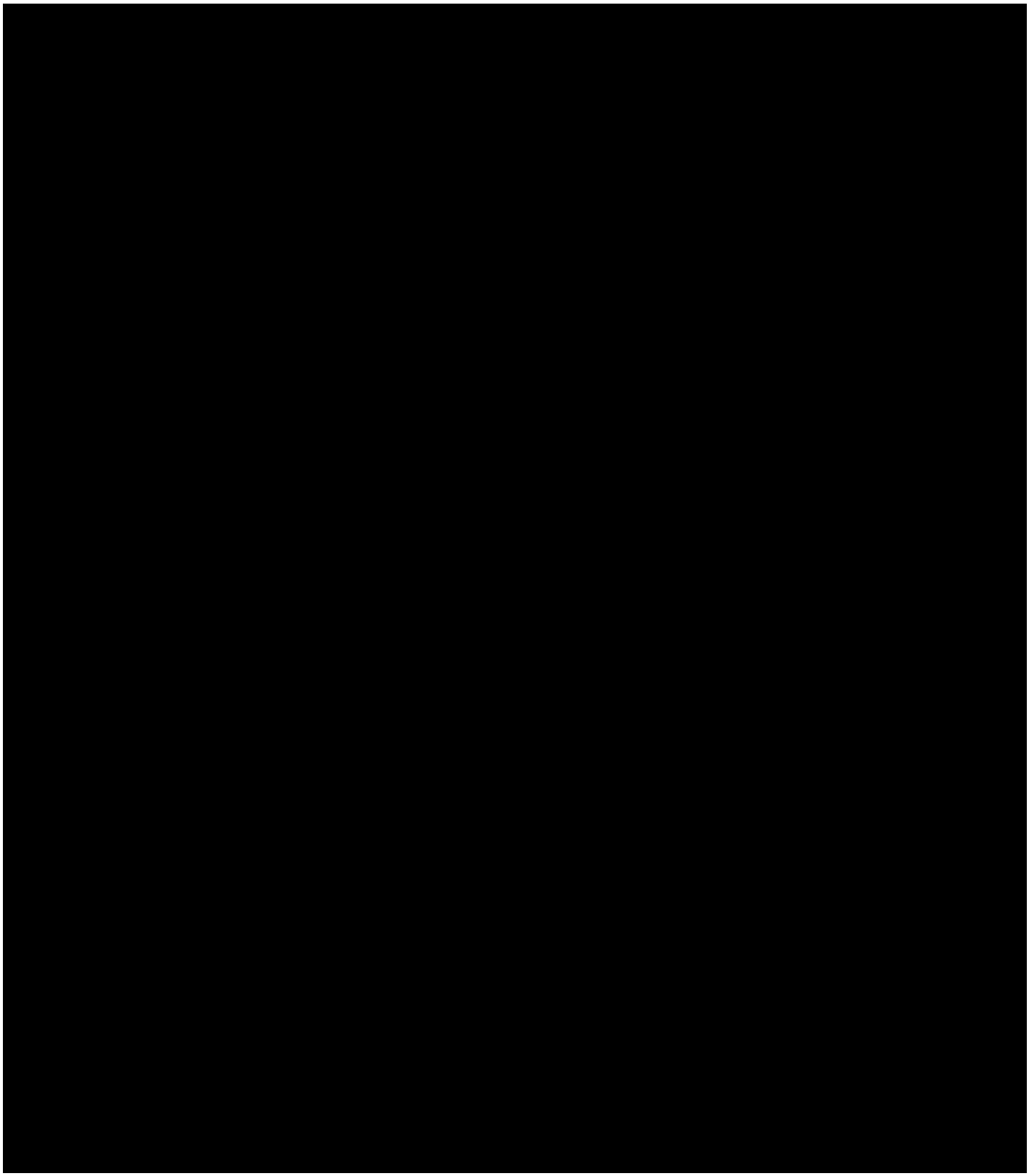
9. PROPOSED AUSTRALIAN APPLICATION

[redacted]



10. QUESTIONS FOR DISCUSSION





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11. LIST OF APPENDICES

Appendix 1. Investigator's Brochure: BNT162/PF-07302048, Version 5.0 (12 Aug 2020)

Appendix 2. C4591001 Study Protocol Amendment 5

Appendix 3. Vaccine Dosage and Administration Instructions.

Appendix 4. Indicative Draft US Vial and Carton Label Mock-ups

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INVESTIGATOR'S BROCHURE

BNT162/PF-07302048

Version: 5.0 **Date:** 12 AUG 2020

Sponsor: BioNTech RNA Pharmaceuticals GmbH
An der Goldgrube 12,
55131 Mainz,
Germany

Reference safety information 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

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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 spike-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)***	[redacted]	[redacted]	**BNT162b2**	[redacted]	
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.

[redacted]

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).

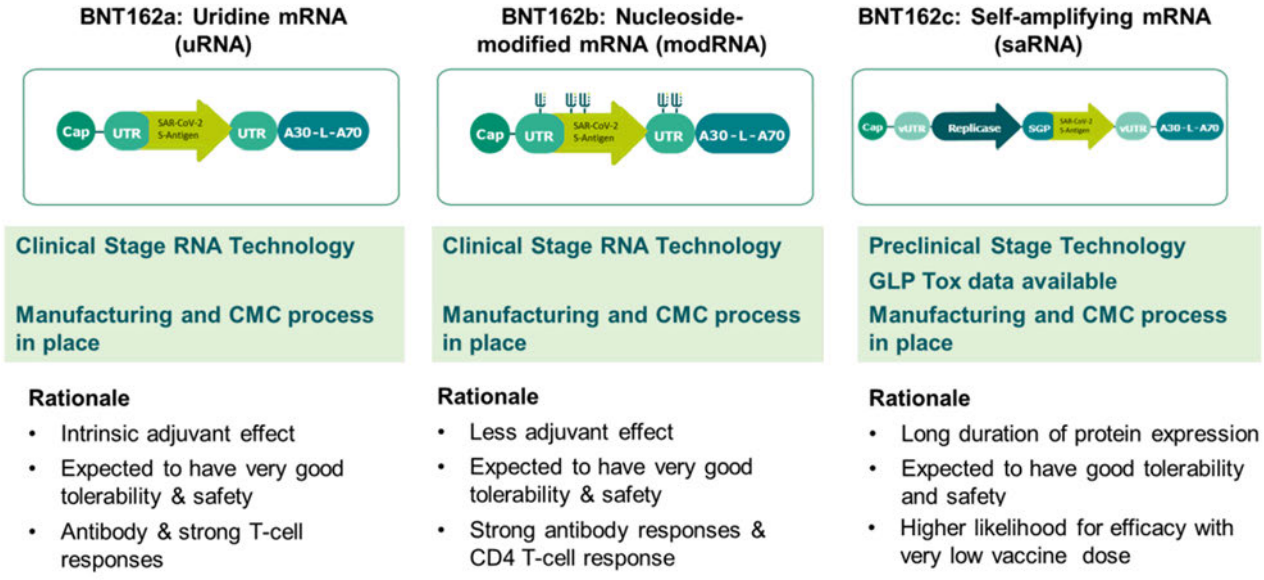


Figure 1: Overview of the three RNA platforms

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.

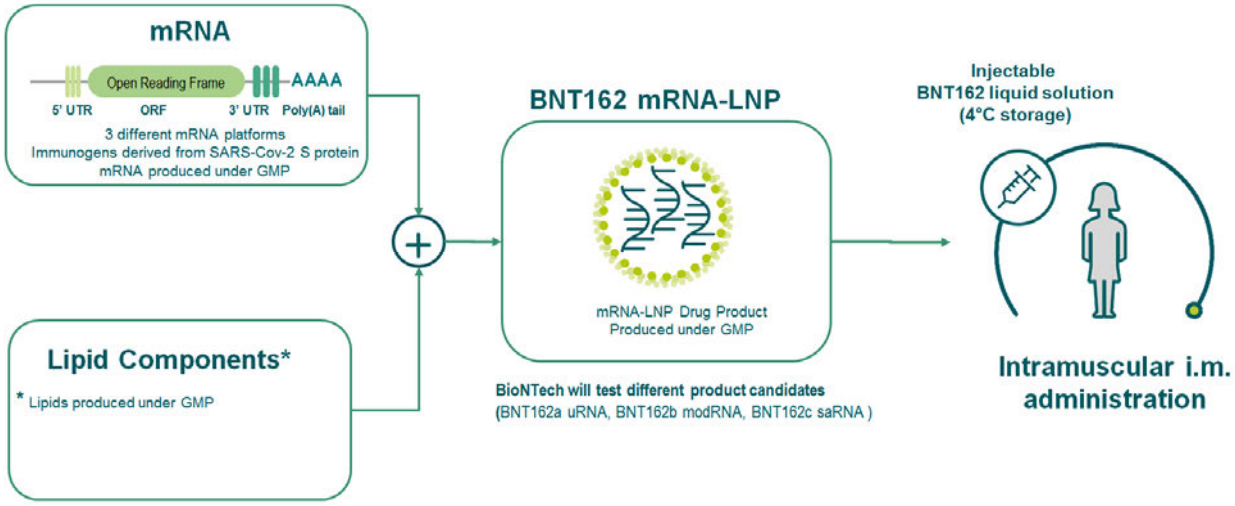


Figure 2: RNA-LNP-based BNT162 vaccines

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).

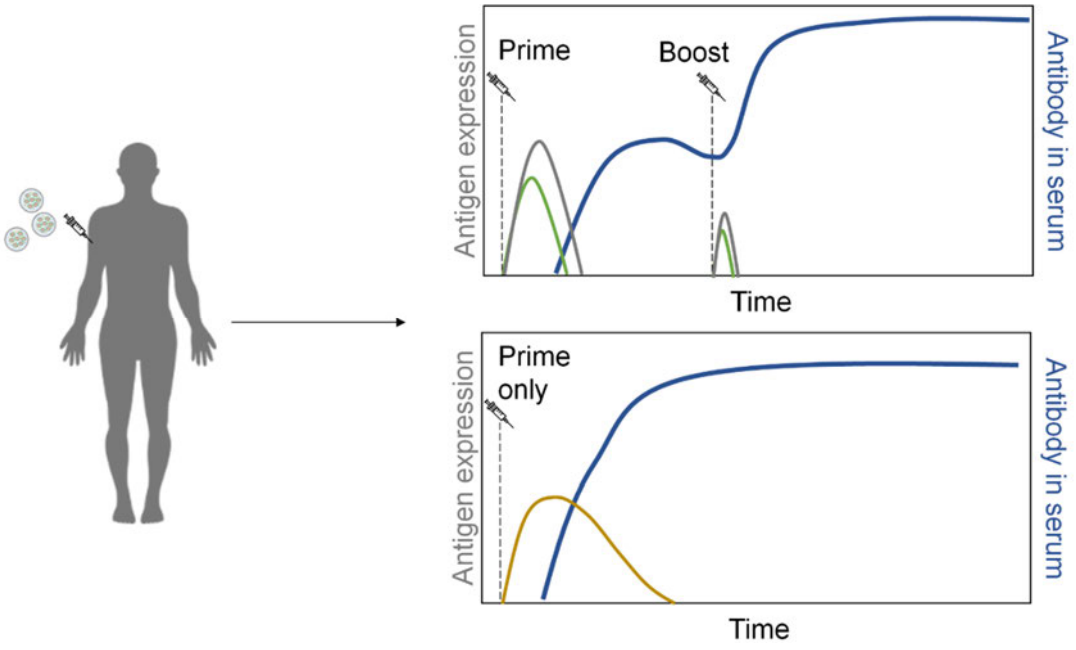


Figure 3: Rationale for the administration schema of BNT162 vaccines

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).

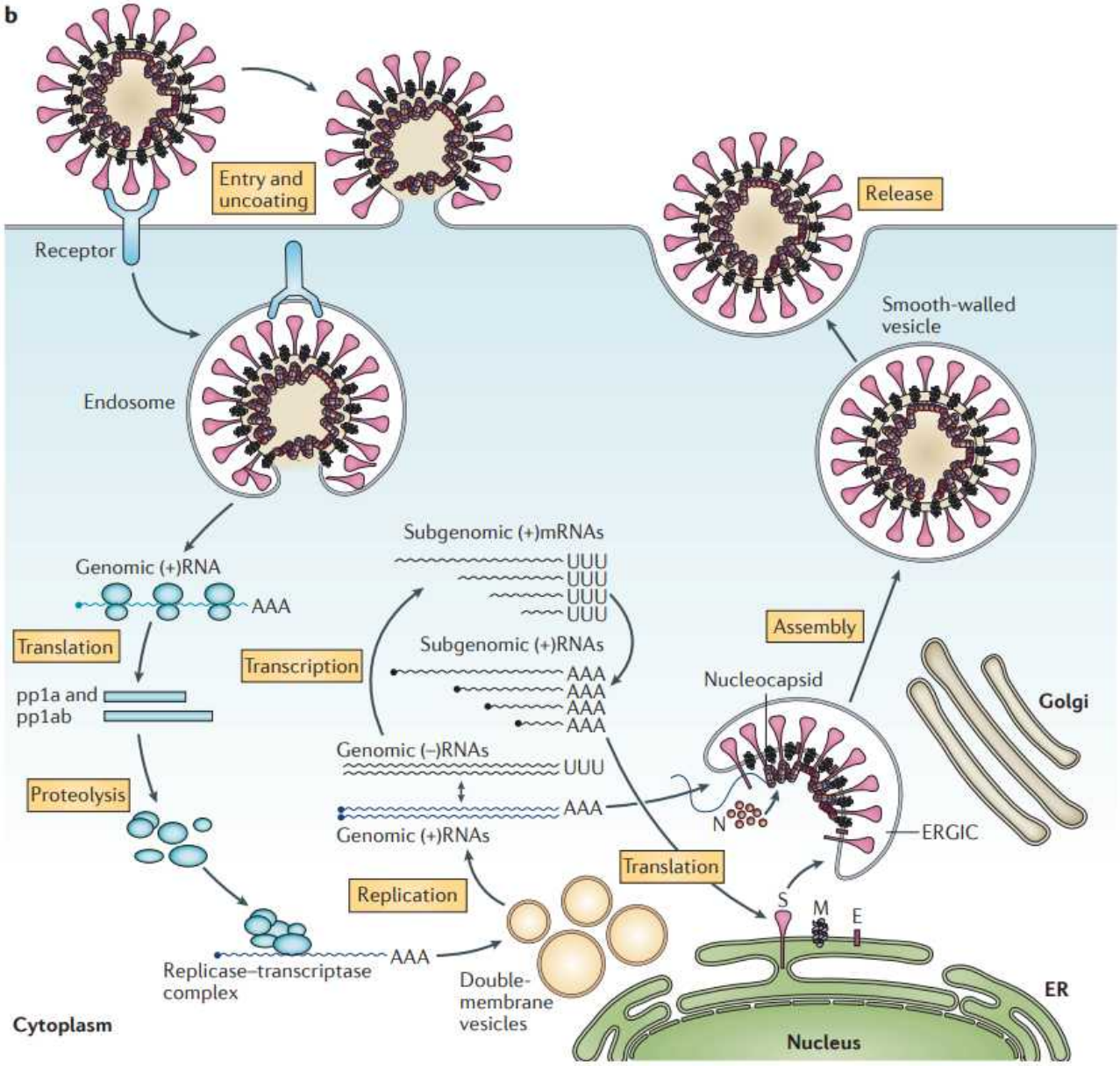


Figure 4: Schematic lifecycle of a Coronavirus

(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).

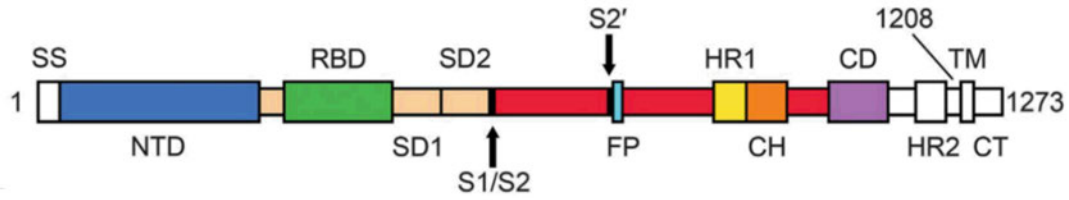


Figure 5: Schematic overview of the organization of the SARS-CoV-2 S glycoprotein

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).

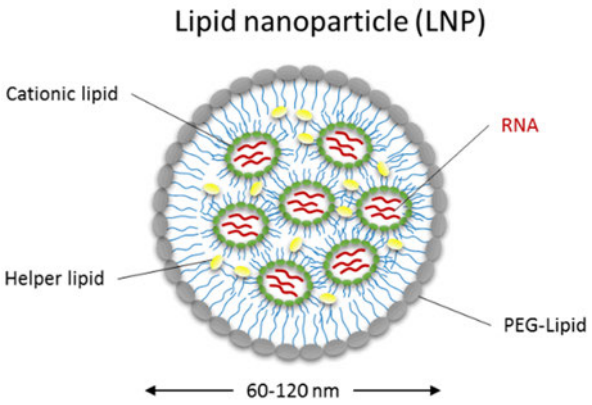


Figure 6: Schematic overview of a LNP

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	[redacted]	BNT162-01 (GER)
modRNA	BNT162b1	[redacted]	BNT162-01 (GER) and C4591001 (USA) BNT162-03 (CHN)
	BNT162b2	Full length SARS-CoV-2 spike protein bearing mutations preserving neutralization-sensitive sites	BNT162-01 (GER) and BNT162-02/C4591001 (USA, BRA, ARG, TUR, GER)
	[redacted]	[redacted]	BNT162-04 (GER) – trial set up is ongoing
saRNA	BNT162c2	[redacted]	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 [redacted] 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 [redacted]

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	
	[redacted] modRNA	[redacted]
Appearance	Clear, colorless liquid	
Theoretical length	~1200 to 4500 nucleotides *	[redacted]
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 [redacted]

Physicochemical properties and the structures of the four lipids are shown in Table 4.

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 *
	[redacted]	[redacted]	[redacted]
modRNA	BNT162b2	Full length SARS-CoV-2 spike protein bearing mutations preserving neutralization-sensitive sites[#]	V8 and V9 [#]
	[redacted]	[redacted]	[redacted]
saRNA	BNT162c2	[redacted]	[redacted]

* 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.

§ [redacted]

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 [redacted] 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.

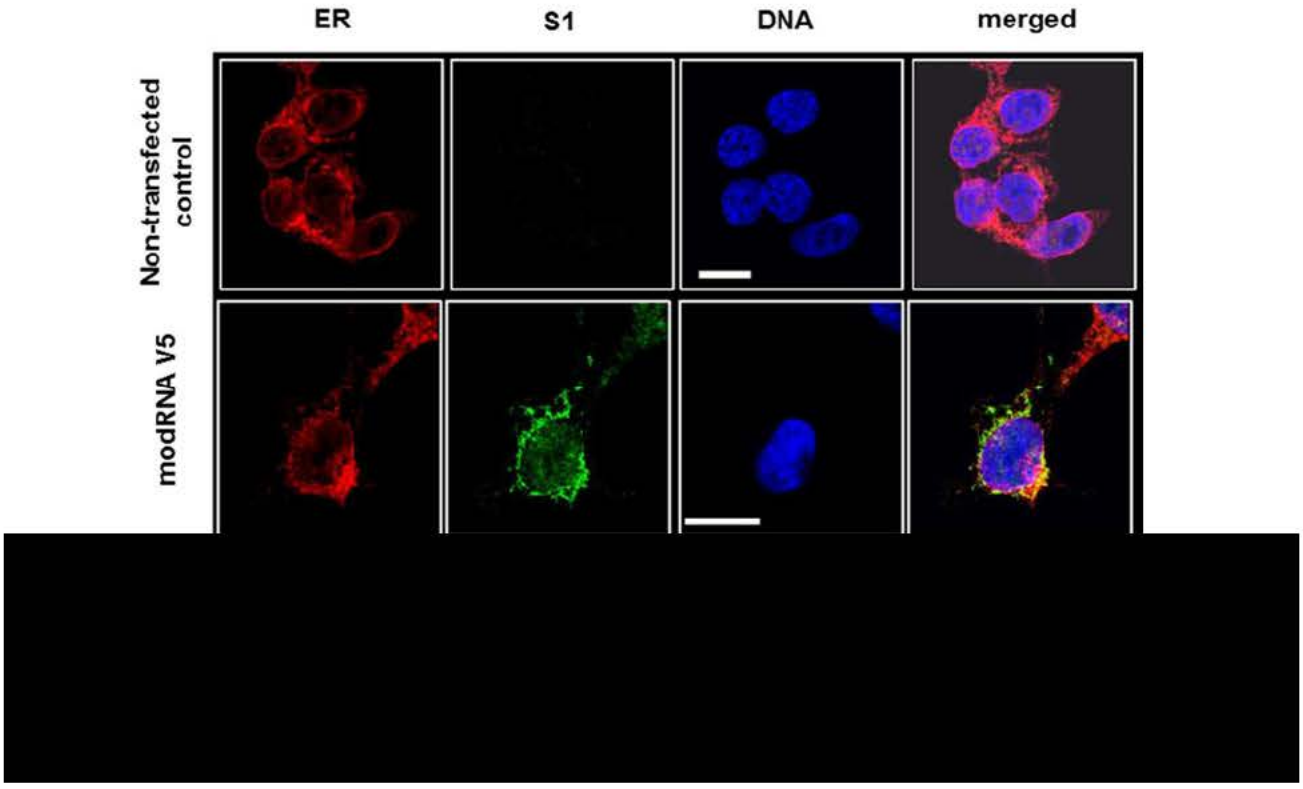


Figure 7: Immunofluorescence staining of cells transfected with BNT162b1 (modRNA encoding V5) and [redacted]

HEK293T cells were transfected with 2.5 µg of modRNA encoding the secreted, trimerized RBD (V5) or [redacted] 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 [redacted] 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, [redacted]

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).

[redacted]

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).

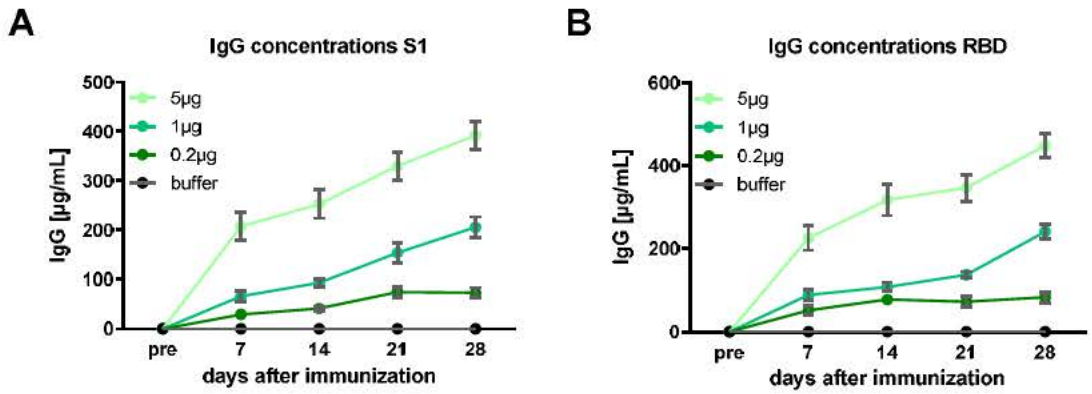


Figure 10: Anti-S IgG response 7, 14, 21, and 28 d after immunization with BNT162b2

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.

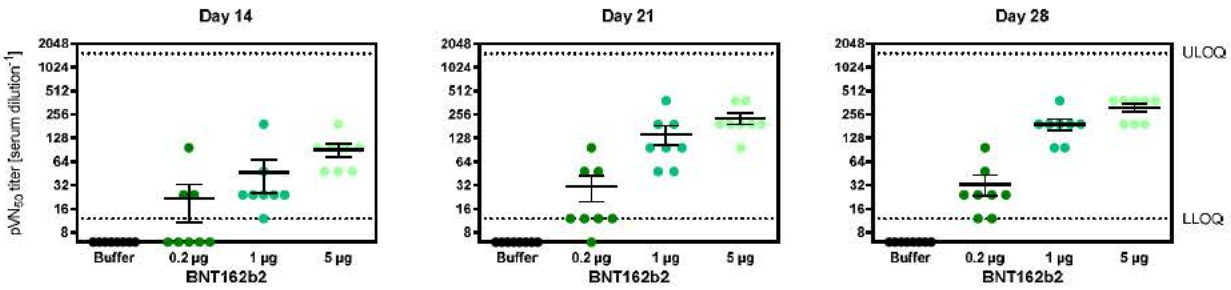
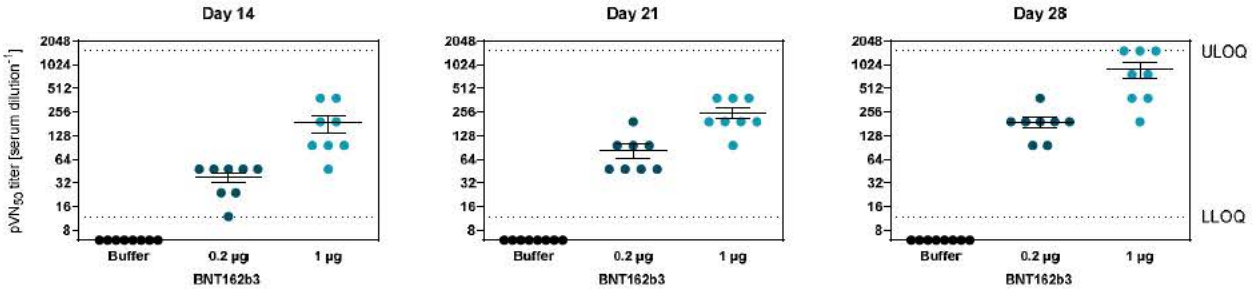


Figure 11: Neutralization of SARS-CoV-2 pseudovirus 14, 21, and 28 d after immunization with BNT162b2

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


Day 14
Day 21
Day 28
pVN50 titer [serum dilution-1]
2048
1024
512
256
128
64
32
16
8
ULOQ
LLOQ
Buffer
0.2 µg
1 µg
BNT162b3

[redacted]

5.1.4 *In vivo* immunogenicity in non-human primates

5.1.4.1 Immunogenicity of [redacted] BNT162b2 (modRNA encoding V9) and [redacted]

Six rhesus macaques (non-human primates, NHP) per group were immunized IM with [redacted] BNT162b2 (V9), [redacted] 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 [redacted] and on day 7 after BNT162b2 or [redacted] virus antigen binding IgG were present in sera of modRNA-immunized macaques (Figure 14).

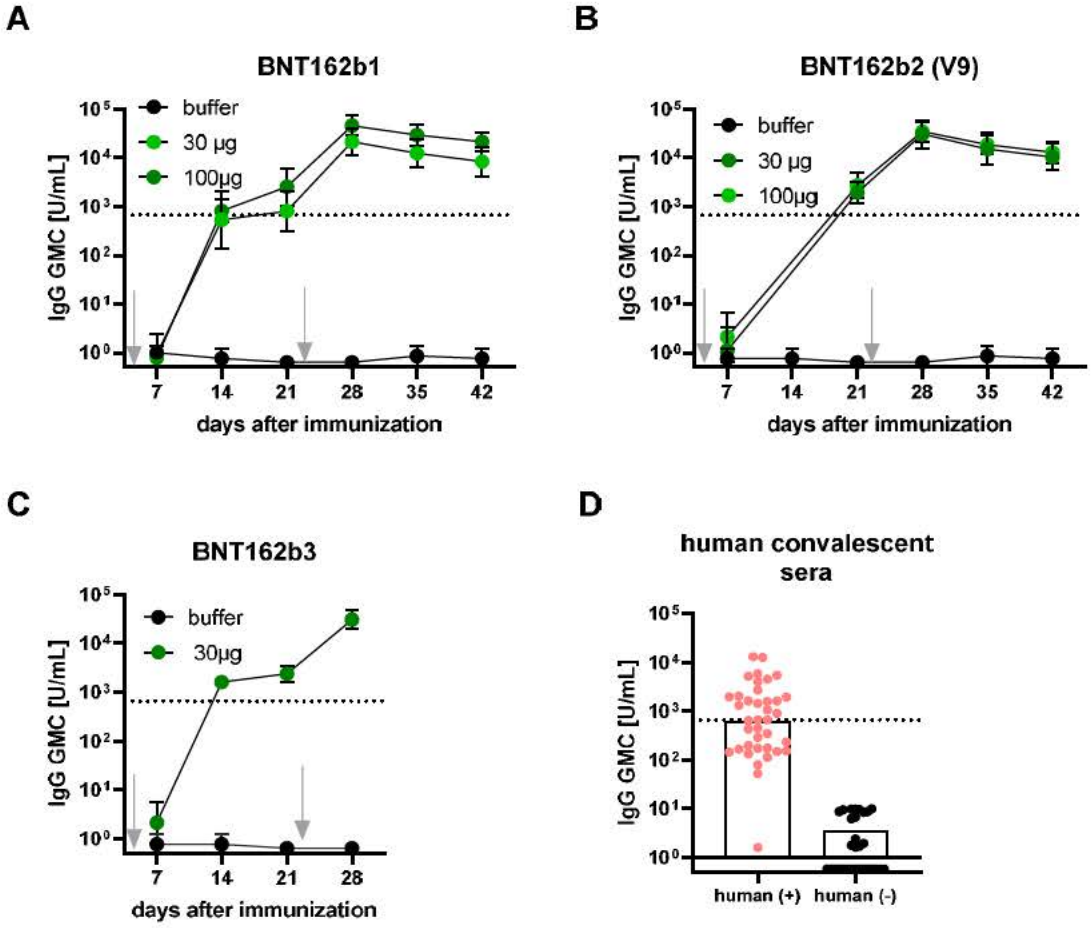


Figure 14: Anti-S IgG response after immunization with the different BNT162b candidates in NHP

Rhesus macaques were immunized IM on day 0 and 21 as indicated by grey arrows with buffer, [redacted] or (B) BNT162b2 (V9) [redacted] 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 [redacted] 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).

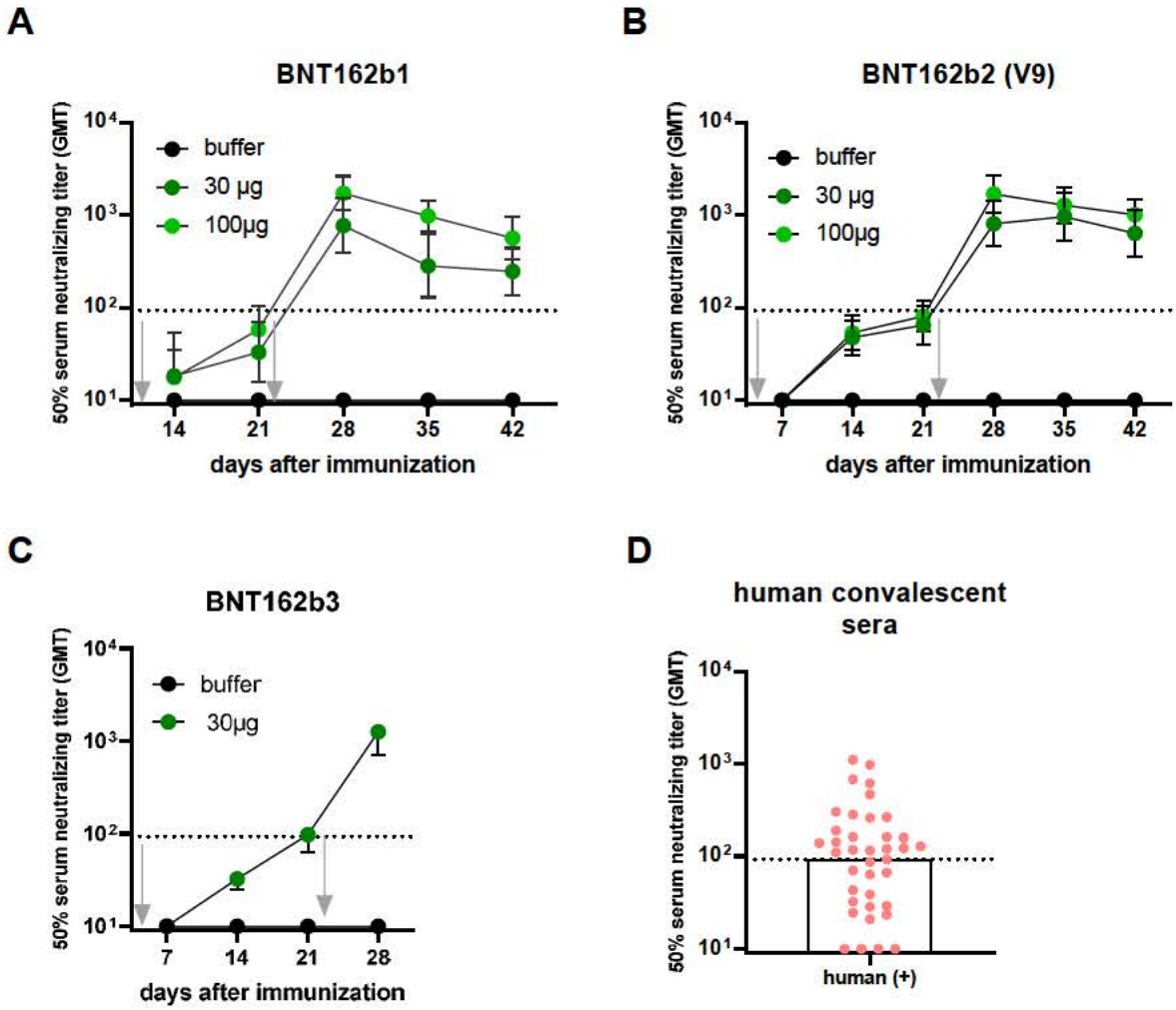


Figure 15: NT50 titer after immunization with the different BNT162b candidates in NHP

Rhesus macaques were immunized IM on day 0 and 21 as indicated by grey arrows with buffer, [redacted] B) BNT162b2 (V9) or [redacted] Weekly after immunization, animals were bled and the serum samples were analyzed for neutralizing antibodies. 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 antibodies (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

[redacted]

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 [redacted] on day 10 and 31and a high viral-neutralization response by 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. [redacted] a strong pseudovirus neutralization effect is mediated by sera obtained from [redacted] and BNT162b2-treated rats. For [redacted] 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.

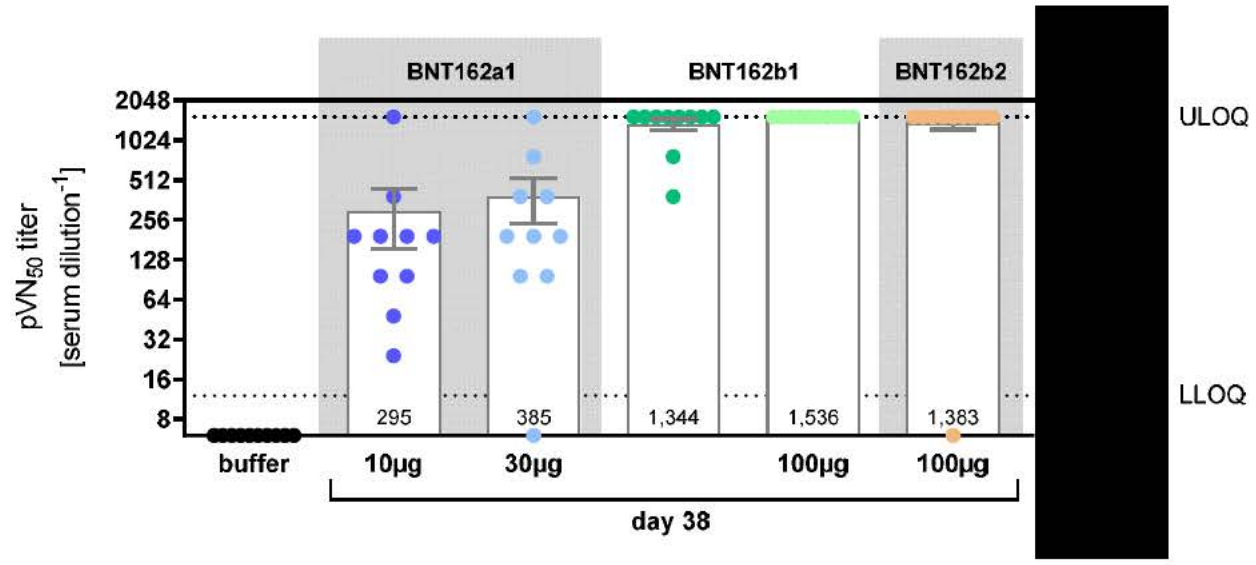


Figure 16: Pseudovirus neutralization activity of recovery cohort sera plotted as pVN50 titer

Serum samples were collected on day 31 [redacted]) 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 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, [redacted] are capable of inducing robust immune responses in mice, [redacted] 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 [redacted] BNT162b2, and [redacted] 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
[redacted]	[redacted]
BNT162b2	192
[redacted]	[redacted]
[redacted]	[redacted]

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
[redacted]	[redacted]
BNT162b2	809
[redacted]	[redacted]

Overall, all BNT162b candidates were highly immunogenic with [redacted] inducing the highest virus neutralization titer.

[redacted]

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.

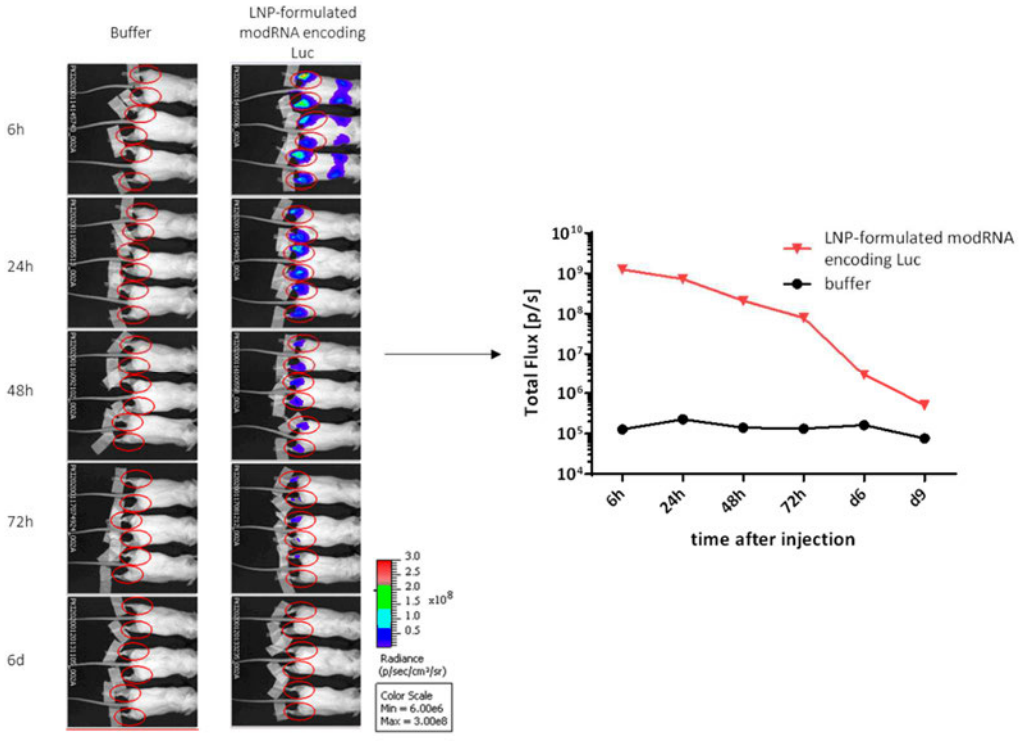


Figure 17: Bioluminescence imaging measurement using the LNP-candidate formulated BNT162b encoding luciferase

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	[redacted] • BNT162b2 [V8] (LNP formulated modRNA encoding antigen V8) * [redacted]	
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	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
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 sp ke 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. [redacted] Vaccine candidates were administered once weekly for 3 ([redacted] BNT162b2) or [redacted] 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 (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 (was seen. The injection site appeared to be painful for 4/15 male animals and 12/15 female animals (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 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 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 [redacted] 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, [redacted] Enlarged iliac lymph nodes were observed in some BNT162b treated animals [redacted] /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 ([redacted] 100 µg BNT162b2 and [redacted]) Bone marrow: minimal to mild increases in the cellularity (all BNT162 vaccines) Spleen: extramedullary hematopoiesis in the spleen [redacted] 100 µg BNT162b2) Liver: vacuolation of hepatocytes in the portal regions in either all animals ([redacted] and 100 µg BNT162b2) or females only [redacted]	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 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 [redacted] where a neutralization titer was only detectable in a few animals. The strongest responses were seen in animals treated with [redacted] 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 [redacted] BNT162b2, and [redacted] 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
[redacted]						
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, [redacted] starting at 96 h after administration. Occasionally these observations of severe erythema continued over several days and/or [redacted]

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 [redacted] 100 µg BNT162b2, followed by animals administered [redacted] 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 [redacted]

[redacted] one animal administered [redacted] 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.

[redacted]

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 [redacted]

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 [redacted] 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
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Group	Findings in male and female animals
[redacted]	[redacted]
[redacted]	[redacted]
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 [redacted] Enlarged iliac lymph nodes were observed in some BNT162b treated animals ([redacted] 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 [redacted] 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 [redacted] BNT162b2, and [redacted] 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 [redacted] 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)

[redacted]

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)

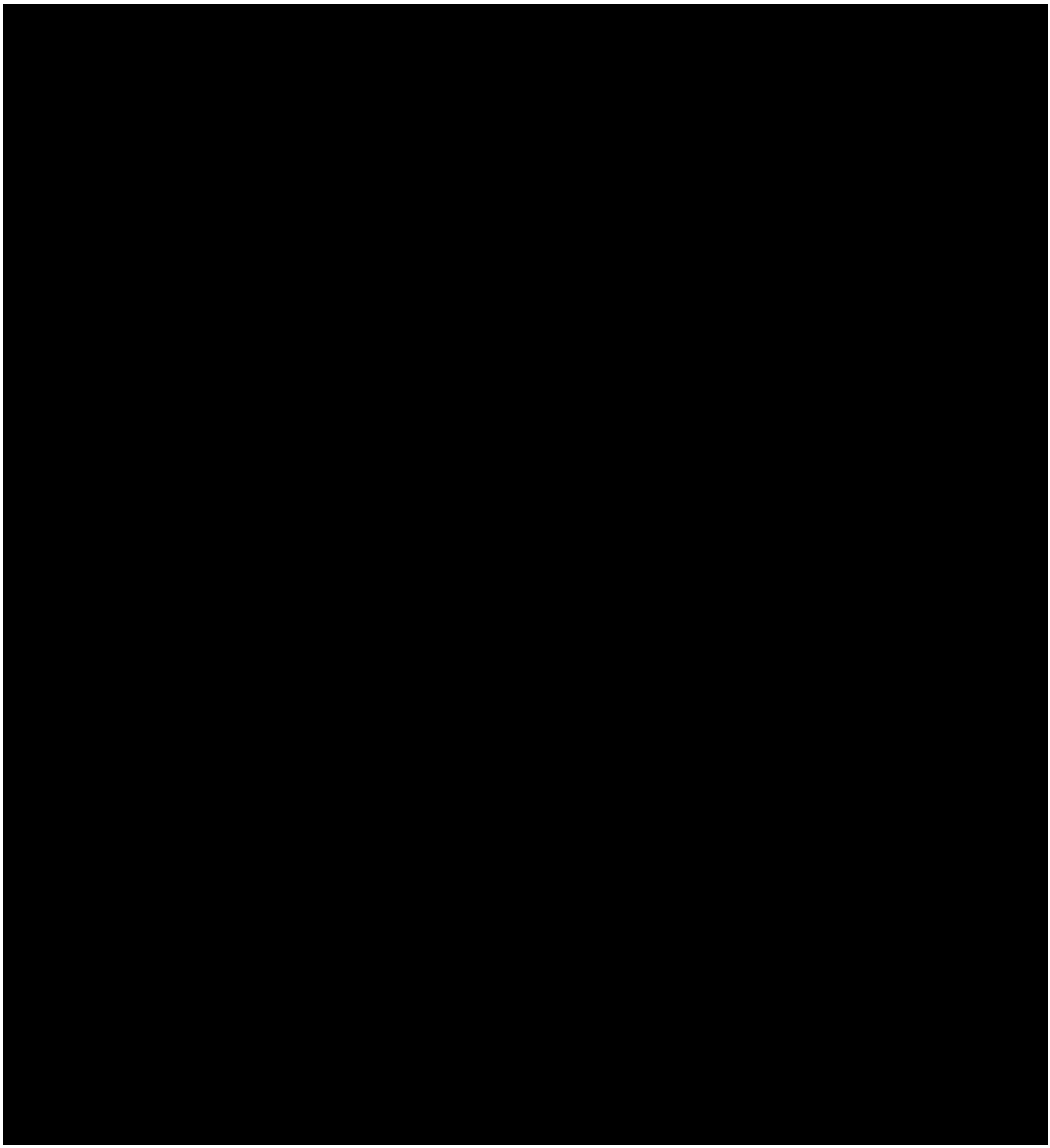
To evaluate the T cell phenotype elicited by immunization of humans with BNT162b2, IFNγ ELISpot was performed on peripheral blood mononuclear cells (PBMCs) obtained from younger adults dosed P/B with either BNT162b1 or BNT162b2.

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).

[redacted]

[redacted]



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.

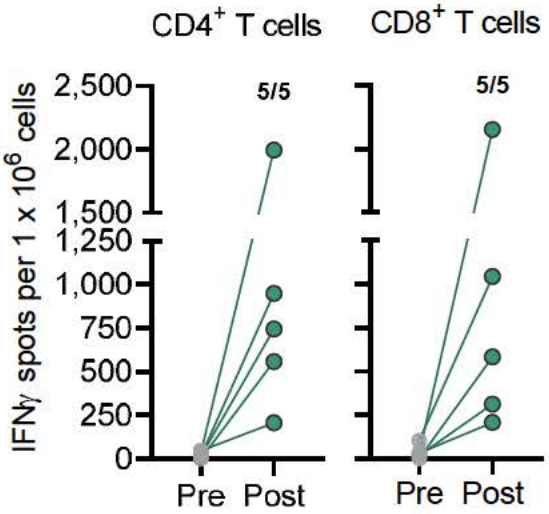


Figure 22: IFNγ ELISpot data for 5 subjects dosed with 10 µg BNT162b2 (BNT162-01)

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 spike 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 (distr bution 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).

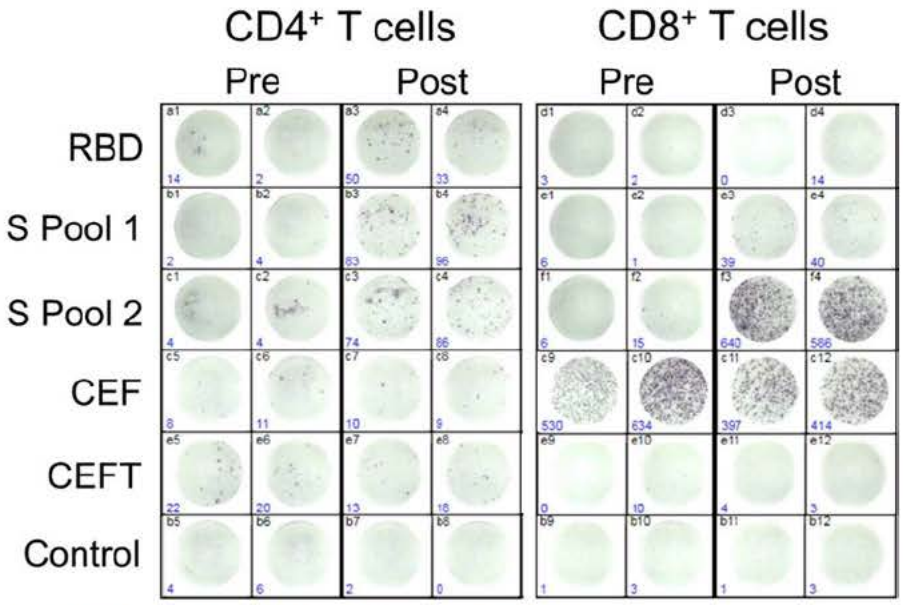


Figure 23: Example of CD4+ and CD8+ IFNγ ELISpot data (BNT162-01)

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.

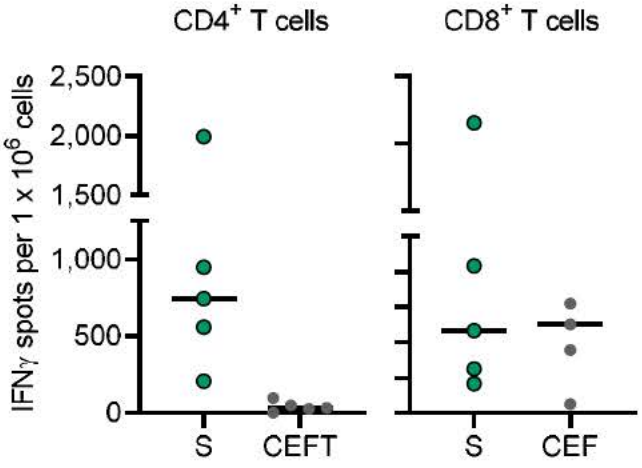


Figure 24: Comparison of BNT162b2-elicited and benchmark INFγ ELISpot responses (BNT162-01)

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.

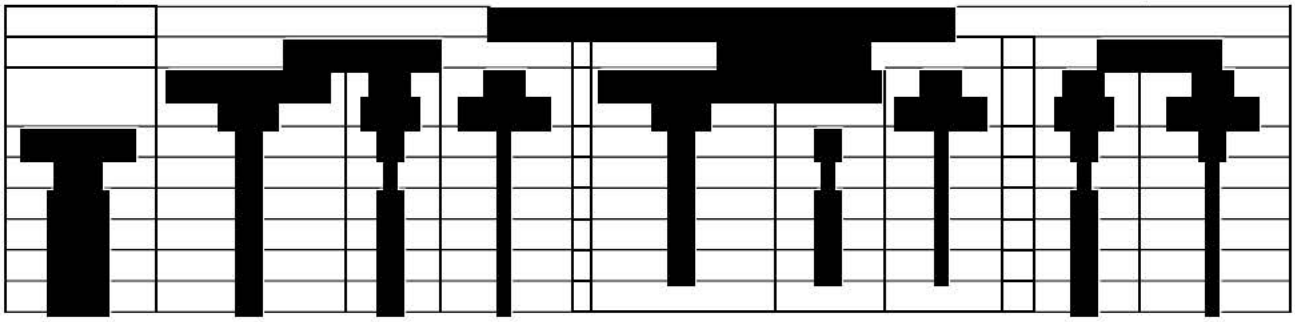
6.1.1.2.1 [redacted]

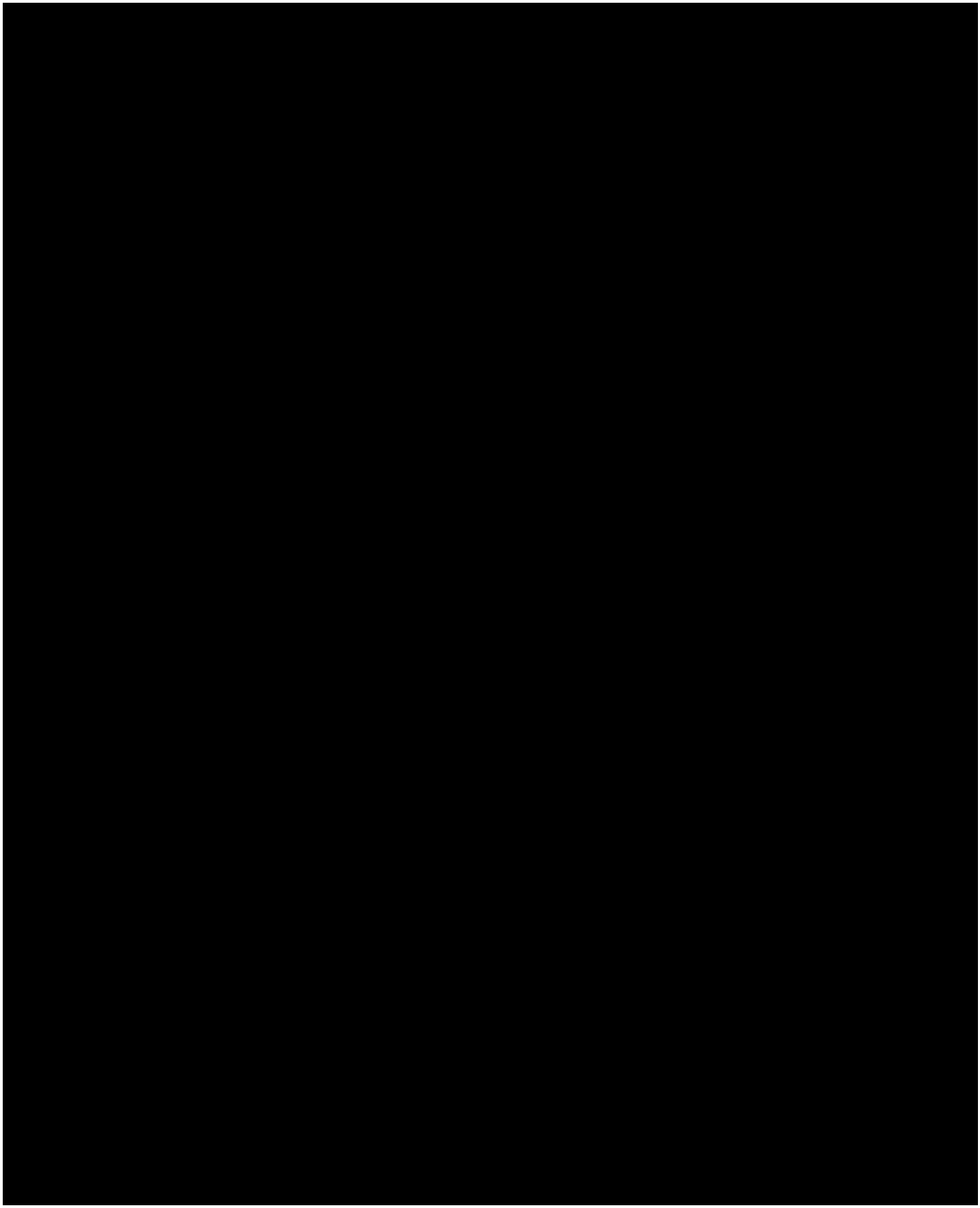
[redacted]

6.1.1.2.2 [redacted]

[redacted]

[redacted]





[redacted]

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

[redacted]

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

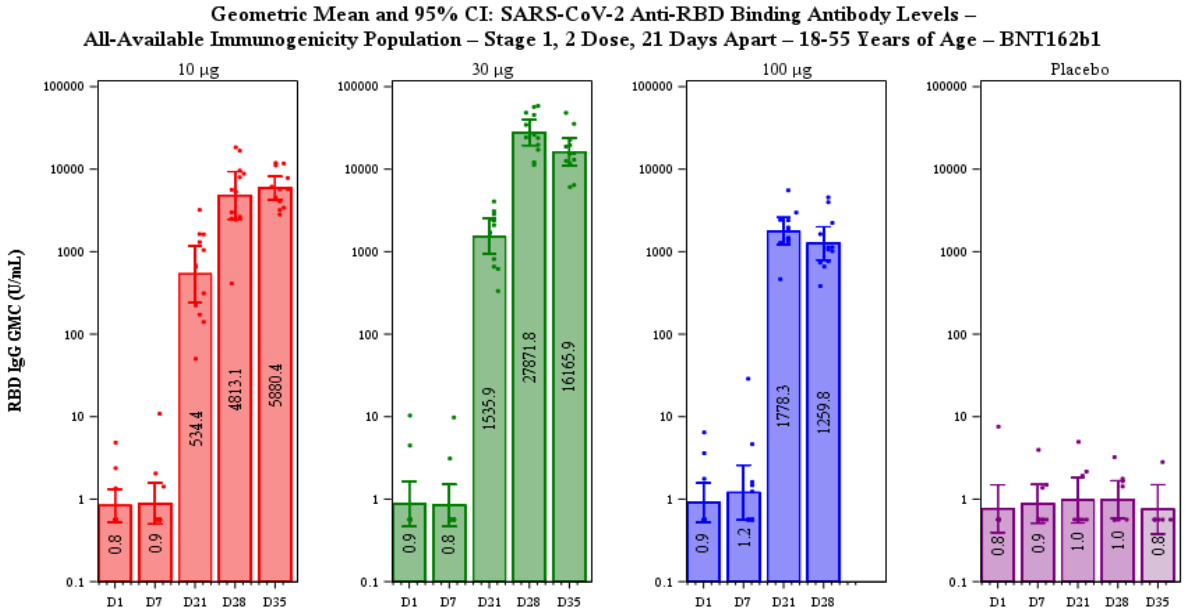
As shown for BNT162b1 in Figure 25 for younger adults and Figure 26 for elderly adults, substantial RBD-binding IgG was induced by Day 21 in all dosed subjects.

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.

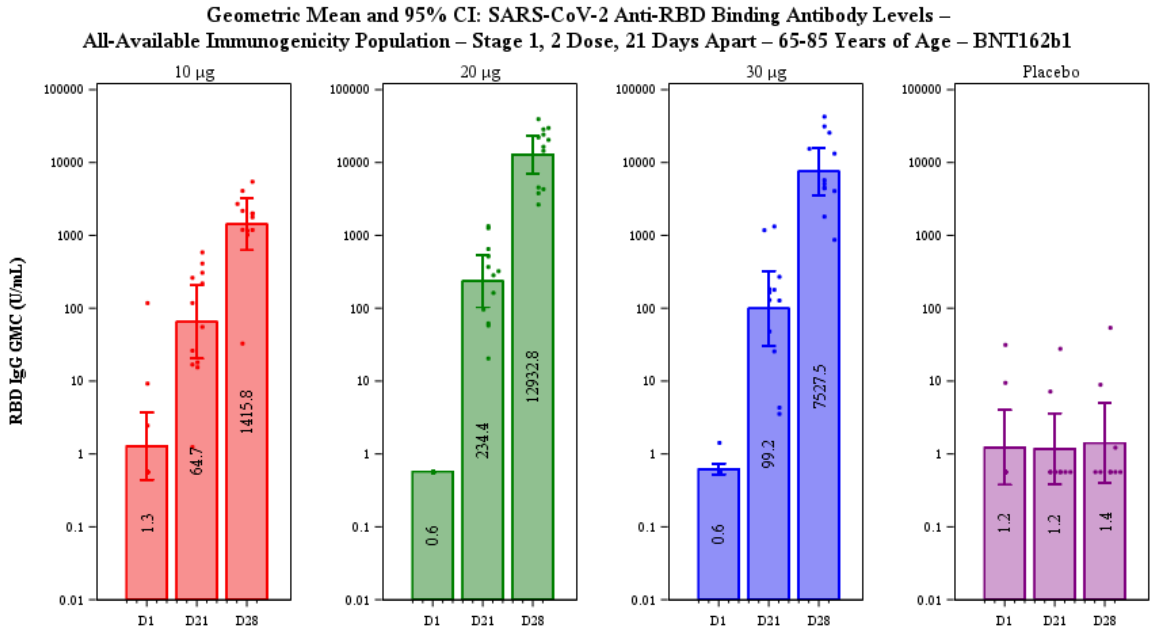
For younger adults, the GMT in the 30 µg group was approximately 2.3-times that of the 10 µg group; GMTs in 30 µg and 100 µg groups were similar, suggesting there may be little benefit in doses above 30 µg. The second doses of 10 µg and 30 µg resulted in a substantial booster response, with Day 28 GMTs 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: ./ndal/C4591001_IRC9/adva_f002_rbd_18_b1 Date of Generation: 09JUL2020 (02:59)

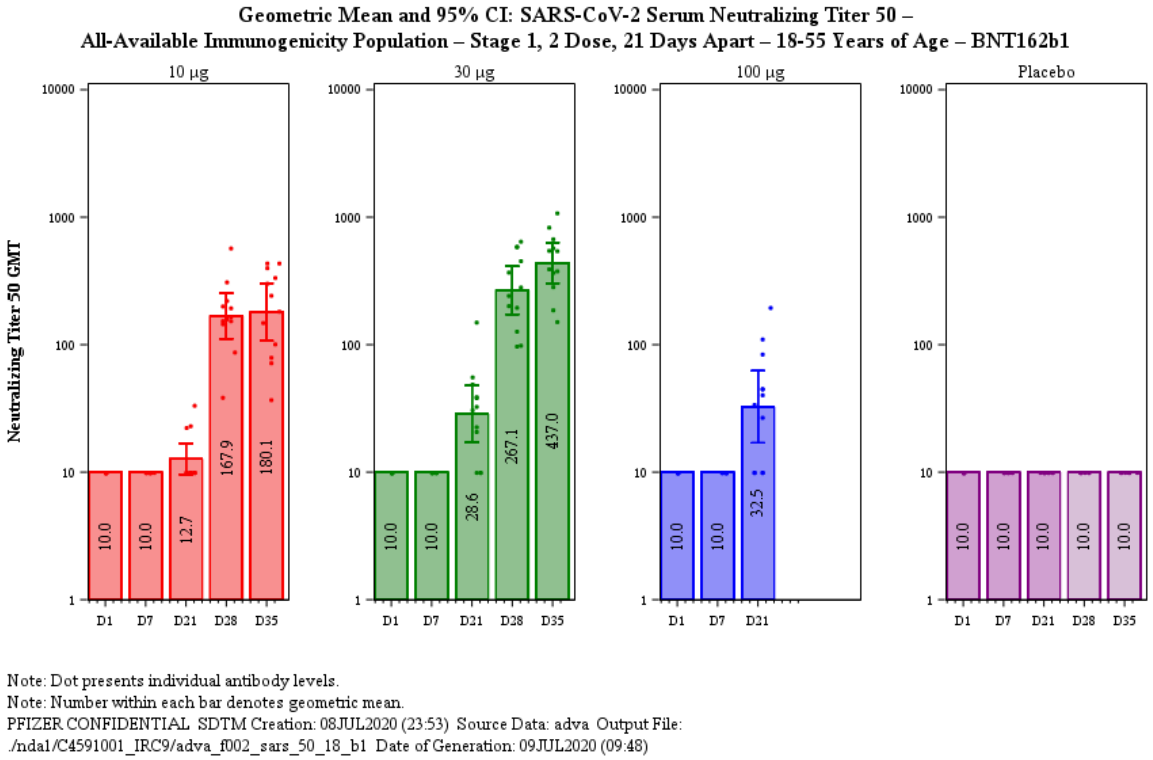
Figure 25: BNT162b1 in younger adults: RBD-binding IgG GMCs (BNT162-02)



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: ./ndal/C4591001_Phase1_22JUL2020/adva_f002_rbd_65_b1 Date of Generation: 21JUL2020 (15:30)

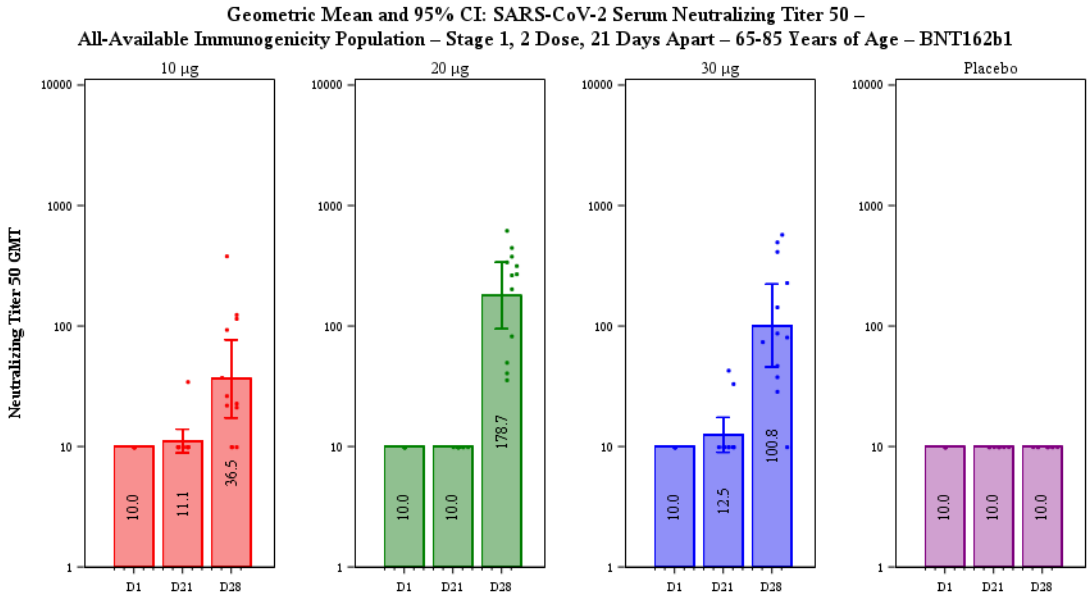
Figure 26: BNT162b1 in elderly adults: RBD-binding IgG GMCs (BNT162-02)

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)

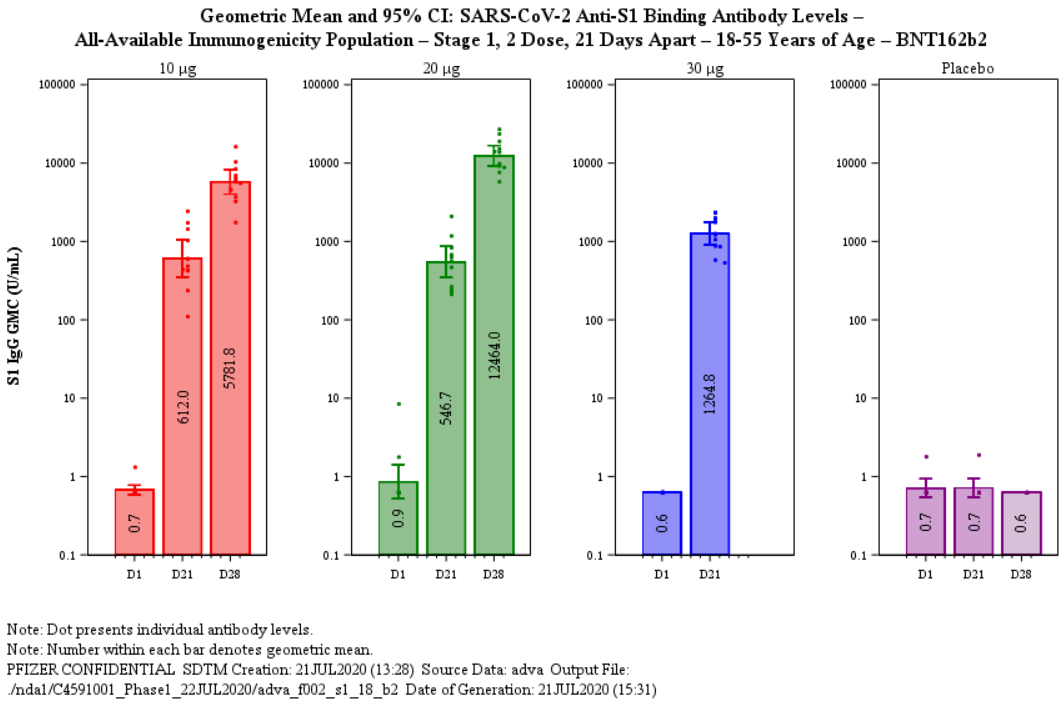
On this page, each data point represents a serum sample; each vertical bar represents a geometric mean with 95% CI. Numbers within bars are GMC or GMT for the group. Note that trial subjects in the 100 µg group only received 1 dose of vaccine.

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.

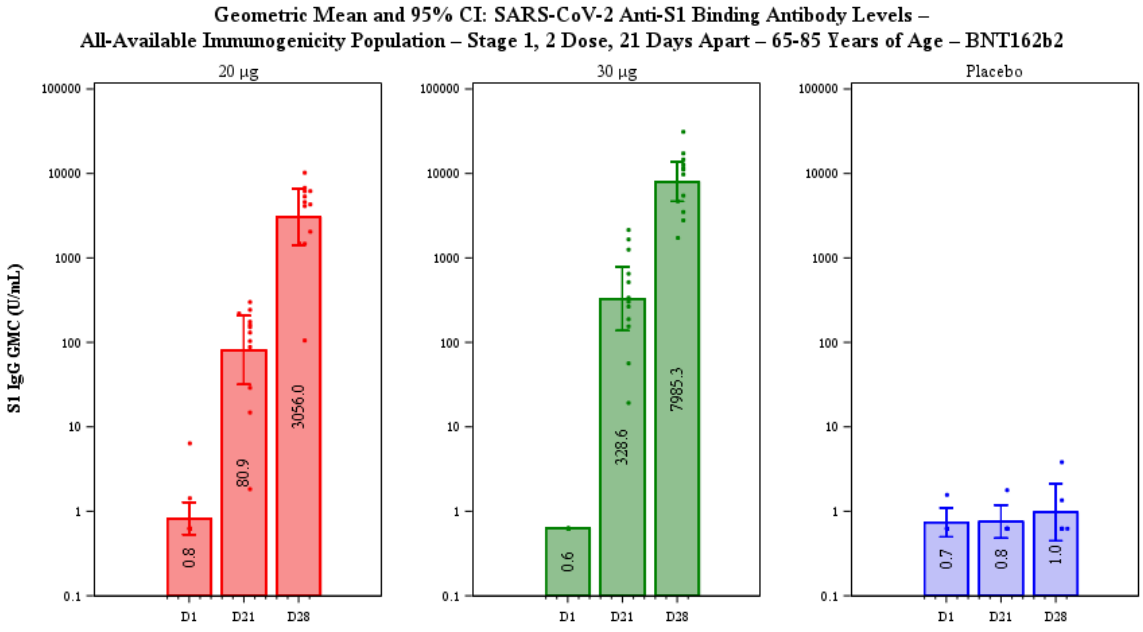
As seen for BNT162b2 in Figure 31 for younger adults and Figure 32 for elderly adults, all BNT162b1 groups showed modest increases in SARS-CoV-2 neutralization GMTs after a single dose.

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.



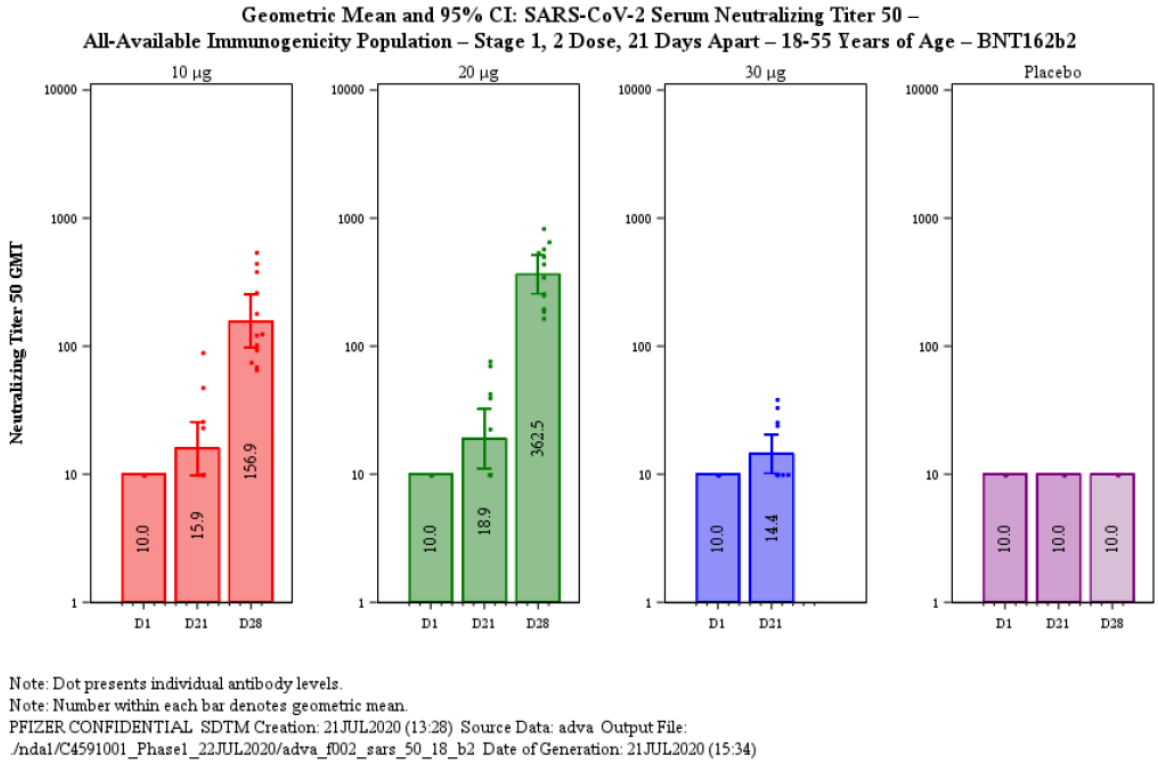
Note: Dot presents individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 21JUL2020 (13:28) Source Data: adva Output File:
./ndal/C4591001_Phase1_22JUL2020/adva_f002_s1_18_b2 Date of Generation: 21JUL2020 (15:31)

Figure 29: BNT162b2 in younger adults: S1-binding IgG GMCs (BNT162-02)



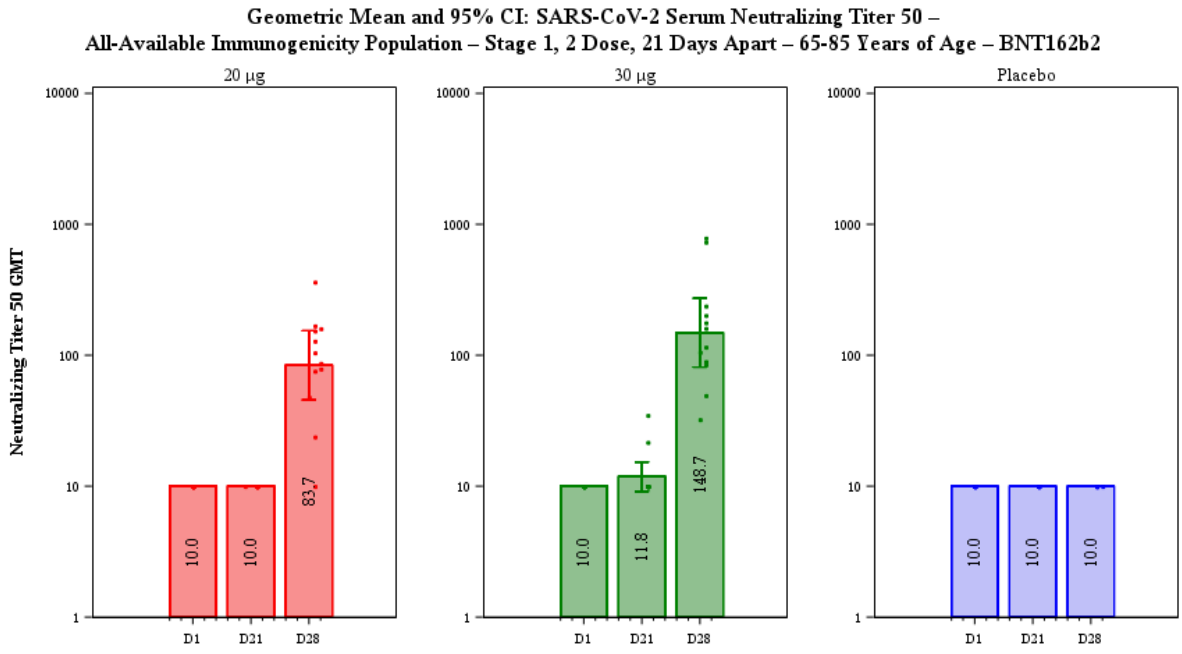
Note: Dot presents individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 21JUL2020 (13:28) Source Data: adva Output File:
./ndal/C4591001_Phase1_22JUL2020/adva_f002_s1_65_b2 Date of Generation: 21JUL2020 (15:33)

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:
./nda1/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:
./nda1/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

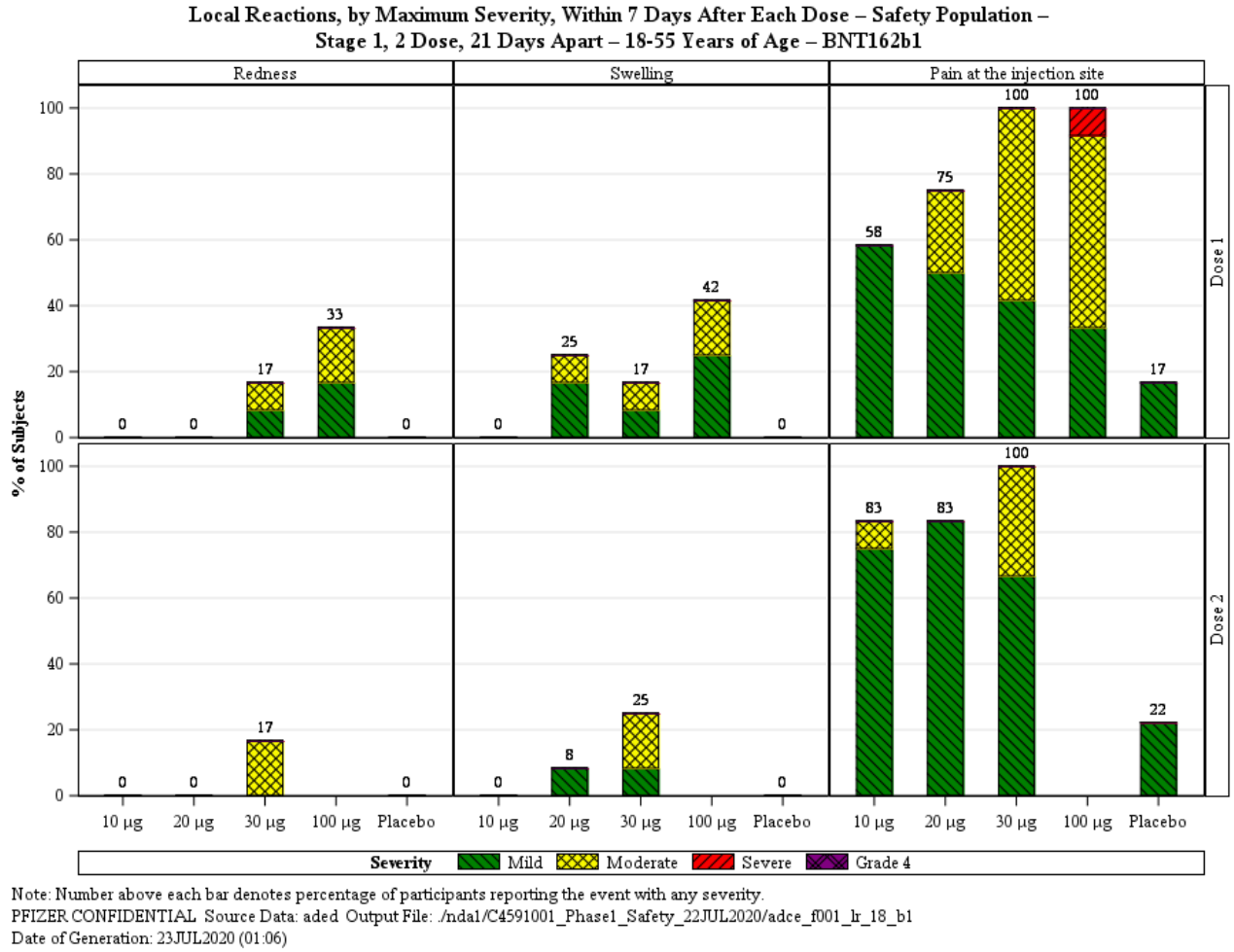
For the dose levels 10 µg to 30 µg, the three most frequent prompted systemic reactions were fatigue, headache, and chills (Figure 34). All systemic reactions were mild or moderate, arose within the first 1 to 2 d after dosing, and were short-lived. Systemic reactions were infrequent in placebo recipients 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.

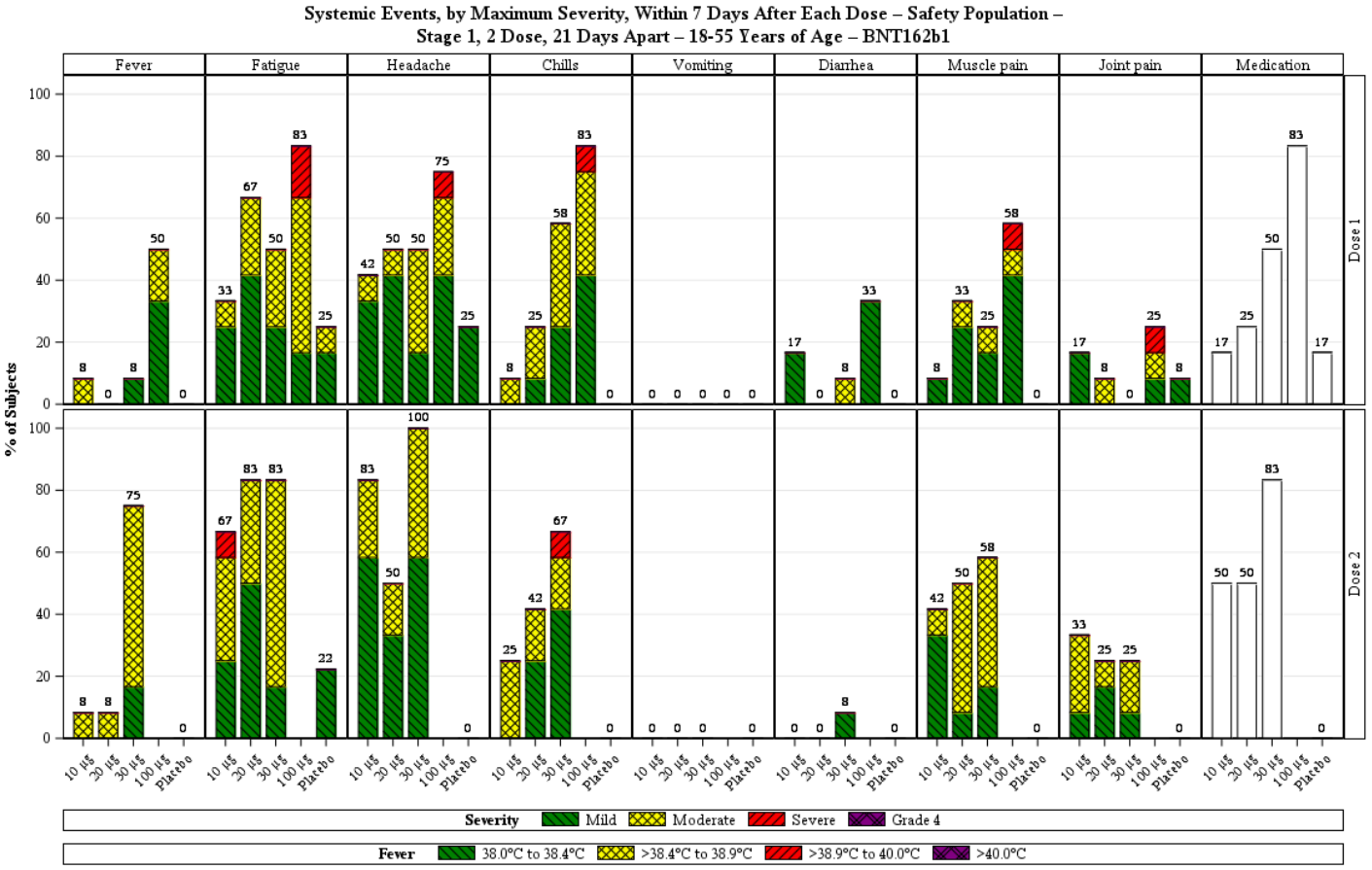
The observed poor tolerability after BNT162b1 Dose 1 at 100 µg, led to a decision not to administer Doe 2 at this dose level. Acceptable tolerability was shown after Doses 1 and 2 at 30 µg BNT162b1.

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: /nda1/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

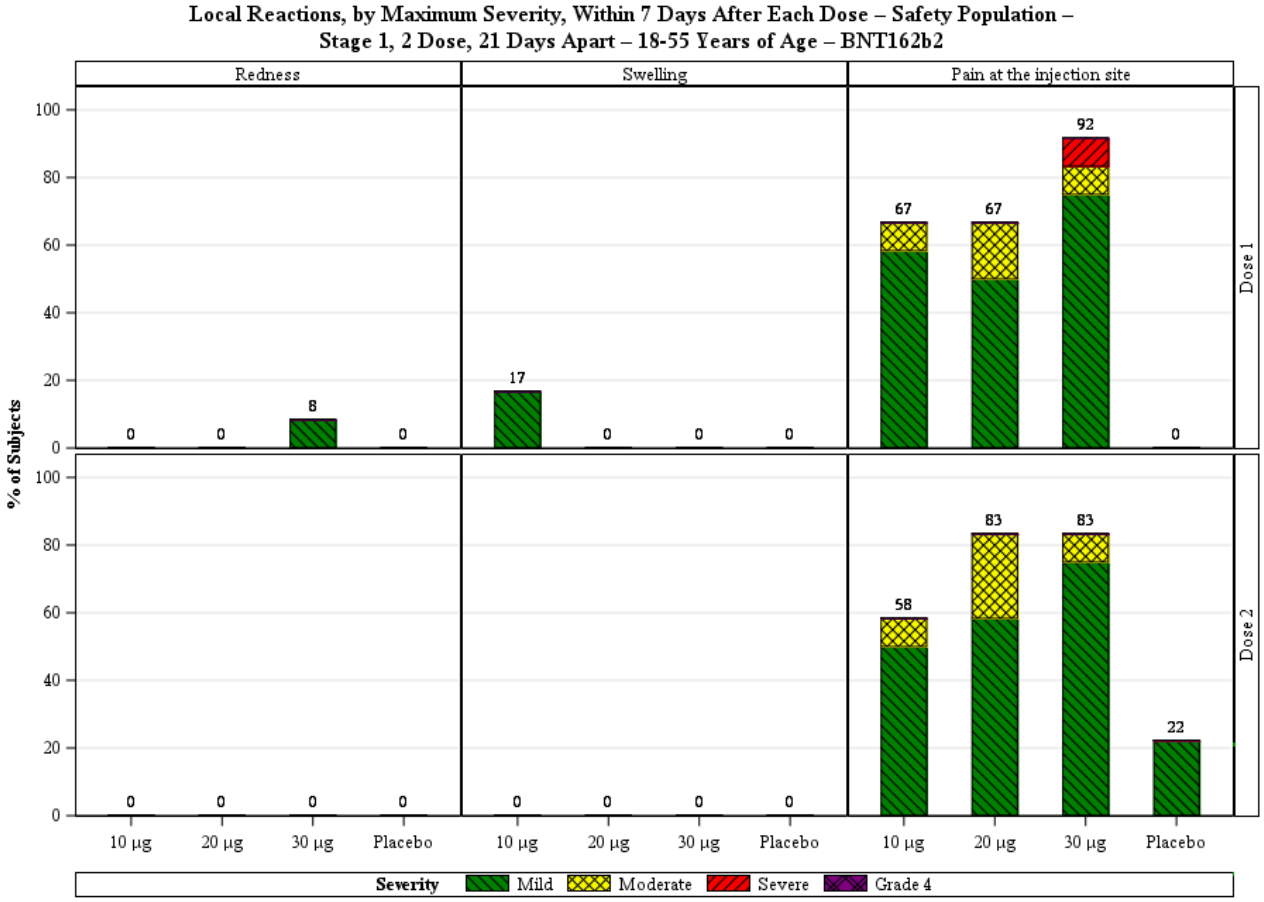
As shown in Figure 35 (younger adults) and Figure 36 (elderly adults), pain at the injection site was the most frequent prompted local reaction, increasing in frequency. Dose level- and dose number-dependent increases in reactogenicity were minimal to modest in either age group. The majority of prompted 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.

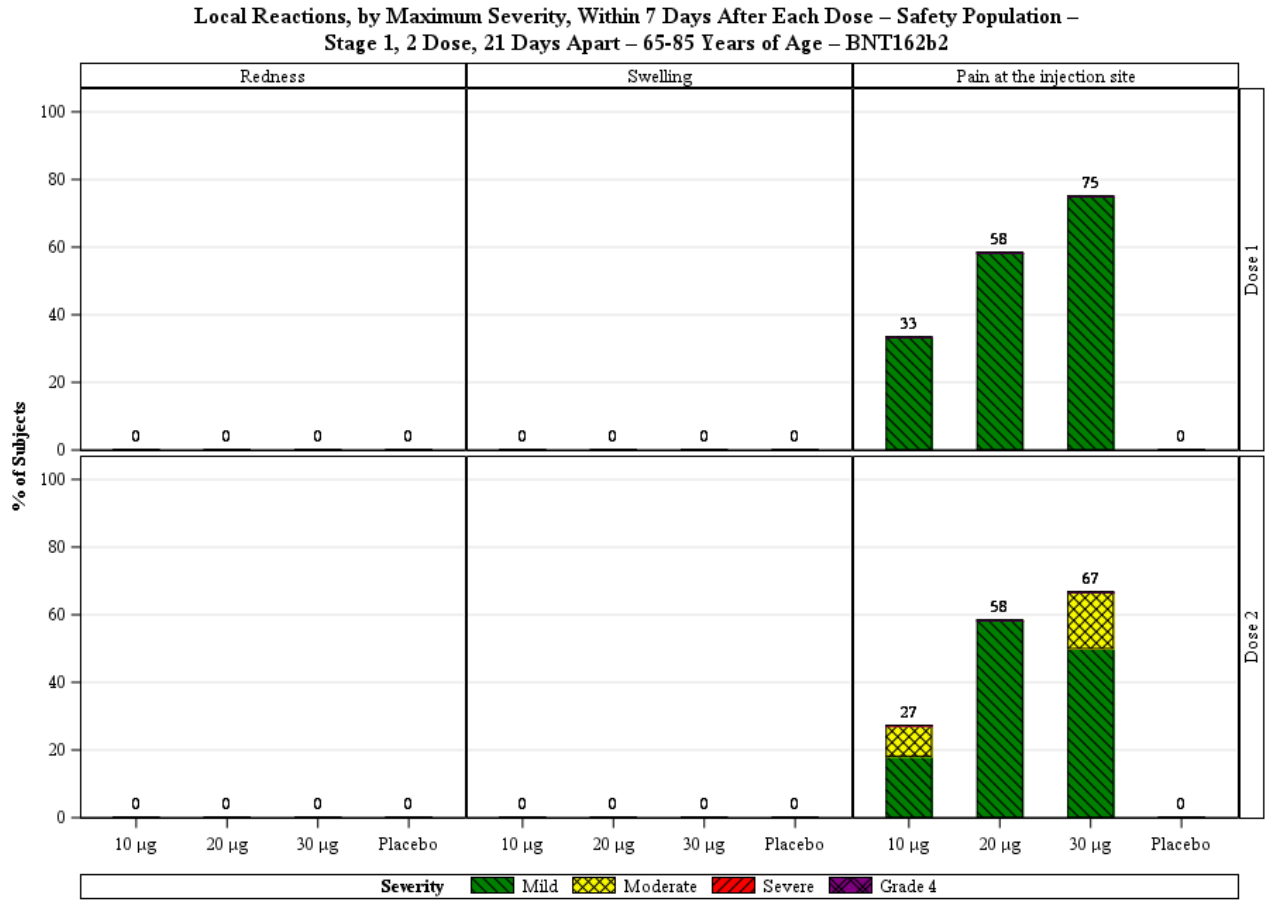
Adverse events & laboratory assessments - BNT162b2

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.



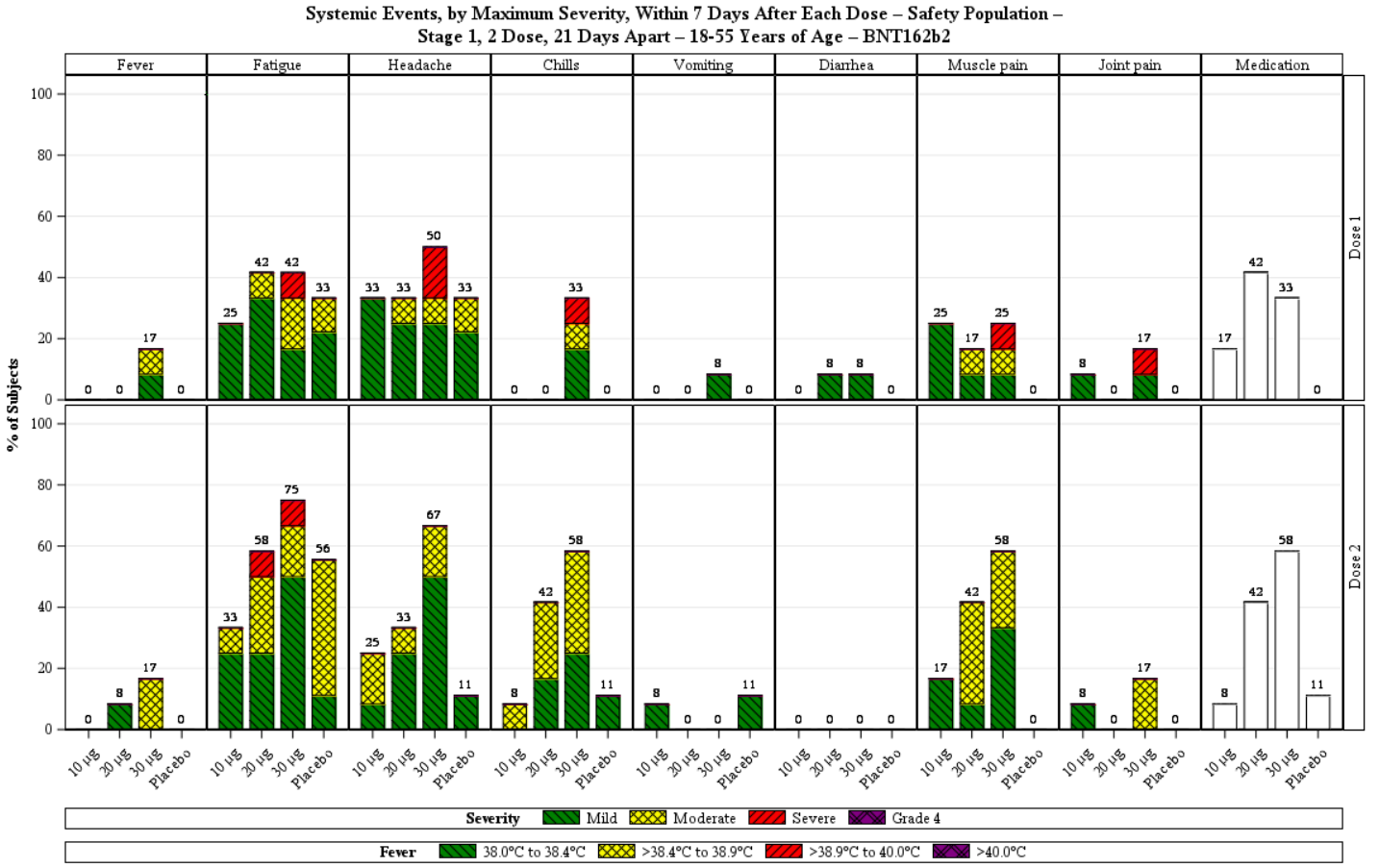
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL Source Data: aded Output File: /ndal/C4591001_Phase1_Safety_22JUL2020/adce_f001_lr_18_b2
Date of Generation: 23JUL2020 (01:07)

Figure 35: BNT162b2 in younger adults: Local reactions after doses 1 and 2 (BNT162-02)



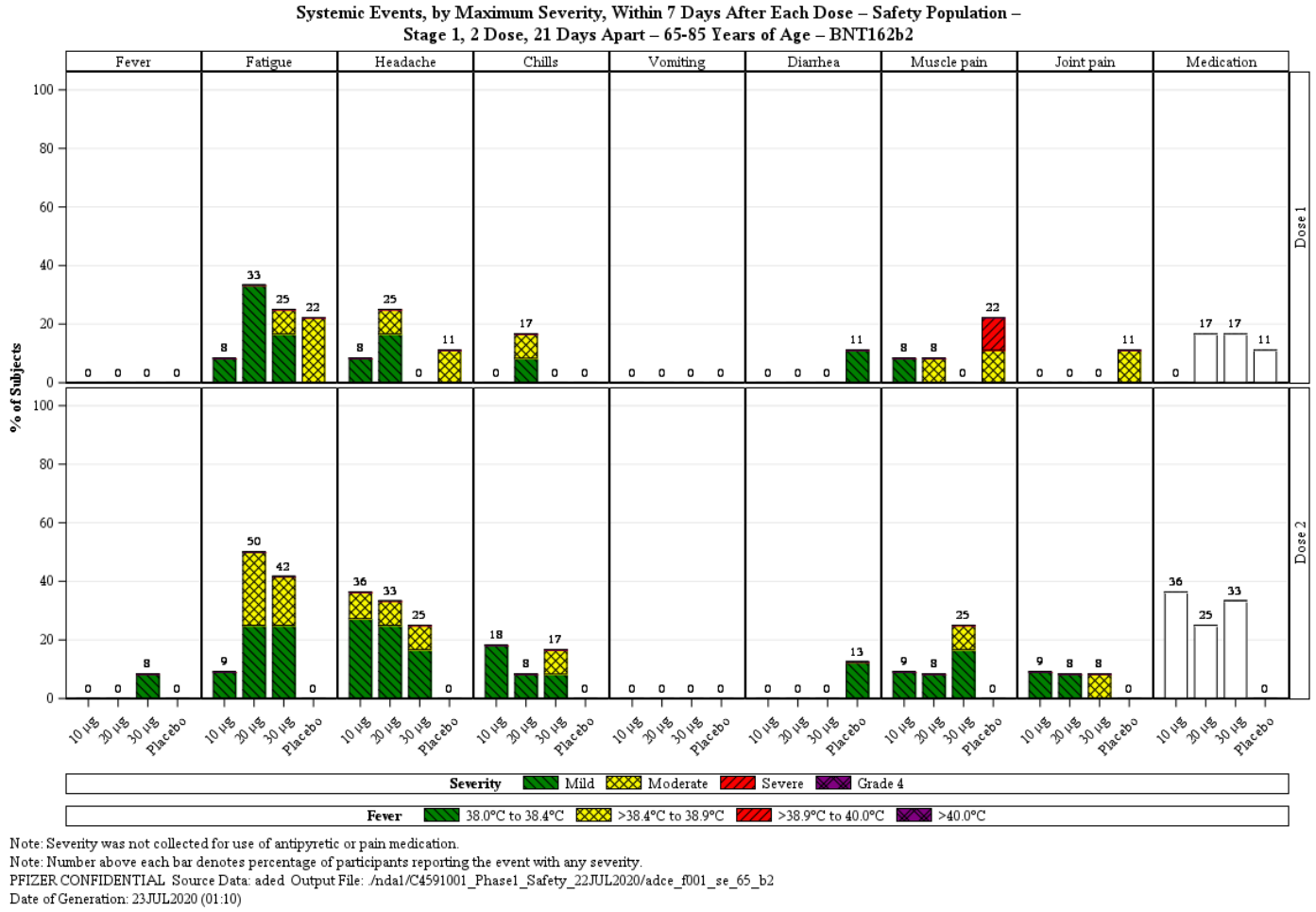
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL Source Data: aded Output File: /ndal/C4591001_Phase1_Safety_22JUL2020/adce_f001_lr_65_b2
Date of Generation: 23JUL2020 (01:08)

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: /nda1/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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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	[redacted] BNT162b2	[redacted] modRNA 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	[redacted]	[redacted]	[redacted]	[redacted]	n.a.
R-20-0041	*In vivo* immunogenicity	Mice BALB/c	[redacted]	[redacted]	[redacted]	[redacted]	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 distribution 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.

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 ADULTS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
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Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol amendment 5	24 July 2020	Following regulatory feedback: • Renamed Stage 1 to Phase 1, removed Stage 2, and renamed Stage 3 to Phase 2/3. • Clarified that a single vaccine candidate, administered as 2 doses 21 days apart, will be studied in Phase 2/3. • Stated that the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg. • Removed the potential to study BNT162b3. • Immunogenicity data will be summarized for the first 360 participants through 1 month after Dose 2, rather than through 21 days after Dose 1. • Provided further details of sponsor staff that will be unblinded in Phase 2/3. • Clarified which stopping rules apply to which phase of the study. In addition: • Clarified the AE reporting requirements for potential COVID-19 illnesses. • Updated that Visit 1 may be conducted across 2 consecutive days in Phase 2/3. • Moved the immunogenicity objectives in Phase 2/3 to become exploratory. • Added an additional inclusion criterion to enroll participants who, in the judgment of the investigator, are at risk for acquiring COVID-19. • Modified exclusion criterion 5, so that participants with a previous clinical or microbiological diagnosis of COVID-19 are excluded from all phases of the study. • Clarified that there will be 2 all-available efficacy populations. • Clarified that immunogenicity samples will be drawn for all participants; analyses will be based upon results from subsets of samples, according to the purpose. • Updated that the 3-tier approach to summarizing AEs will only be performed in Phase 2/3. • Updated that at each interim analysis for efficacy, only the first primary objective will be evaluated. • Changed to use the same posterior probability (99.5%) for all interim analyses, resulting in case split changes in Tables 5, 6, and 7.

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		• Updated the stopping and alert rule parameters for enhanced COVID-19.
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation, and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment. AEs that occur between consent and dosing will now be reported on the AE (rather than Medical History) CRF, to align with the latest Pfizer protocol template. Changes have been made to the headings to align with the latest Pfizer protocol template. Clarified that only an unblinded site staff member may obtain the participant's randomization number and study intervention allocation. Additional interim analyses have been added to evaluate VE and futility during the study. As a result of regulatory feedback, an appendix has been added to outline the stopping and alert rules to monitor for potential enhanced COVID-19.
Protocol amendment 3	10 June 2020	As data have become available from this study and the BNT162-01 study in Germany, the following decisions were made: • Not to study the BNT162a1 and BNT162c2 vaccine candidates at this time. Therefore, these

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		candidates have been removed from the protocol. • To study further lower dose levels of the modRNA candidates. Therefore, a 20-µg dose level is formally included for BNT162b1 and BNT162b2. • To permit individual and group dosing alterations for the second dose of study intervention. Following regulatory feedback, the BNT162b3 vaccine candidate has been removed from the protocol until further nonclinical data are available to support study in humans. Given the rapidly evolving pandemic situation, additional blood draws for exploratory COVID-19 research, intended to establish an immunological surrogate of protection, will be taken from selected participants who consent. In order to increase flexibility enrolling participants, an extended screening window (increased from 14 to 28 days) for sentinel participants in Stage 1 has been added. This is considered acceptable since eligible participants are expected to be either healthy or have stable medical conditions. To increase the number of doses that can be obtained from available vaccine vials, not all dose levels will result in a dosing volume of 0.5 mL. Precise dosing instructions will be provided in the IP manual. To facilitate the reporting of COVID-19 illness diagnoses and potential symptoms to the investigator, participants may utilize a COVID-19 illness e-diary.
Protocol amendment 2	27 May 2020	Given the urgent nature of the pandemic situation, the following changes allow determination of the appropriate human dose level for both younger and older adults to move speedily into the next phase of clinical evaluation: • Added a new vaccine candidate, BNT162b3, modRNA encoding a membrane-anchored RBD • Added a 50-µg dose level for vaccine candidates based on the modRNA platform (ie, BNT162b1, BNT162b2, and BNT162b3) • Modified the criteria required for the IRC to determine dose escalation in the 18- to 55-year