CLINICAL TRIAL PROTOCOL
INCLUDING AMENDMENTS NOS. 01 TO 06
BNT162-01

Version: 9.0 **Date:** 05 OCT 2020

Sponsor: BioNTech RNA Pharmaceuticals GmbH

Trial title:	A multi-site, Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy and immunocompromised adults
Brief title:	A multi-site Phase I/II trial investigating the safety and effects of four BNT162 vaccines against COVID-19 in healthy and immunocompromised adults
Trial phase:	Phase I/II
Indication:	Protection against COVID-19
Product:	BNT162: SARS-CoV-2 - RNA lipid nanoparticle (RNA-LNP) vaccines utilizing different RNA formats, i.e., BNT162a1, BNT162b1, BNT162b2 and BNT162c2.
Coordinating and Principal investigator:	Dr. Dr. med. Armin Schultz, CRS Clinical Research Services Mannheim GmbH, Germany (tel.: +49 621 15045 165)
Trial sites:	Multiple sites in Germany. For further details of the study sites and site personnel, see the Trial Master File (TMF).
Contract research organization (CRO):	CRS Clinical Research Services Mannheim GmbH, Germany
Sponsor's responsible person:	Özlem Türeci, MD, Chief Medical Officer, BioNTech SE
Sponsor:	BioNTech RNA Pharmaceuticals GmbH, An der Goldgrube 12, 55131 Mainz, Germany
Regulatory identifiers:	EudraCT no.: 2020-001038-36; ClinicalTrials.gov NCT: 04380701; WHO UTN: U1111-1249-4220
Medical Monitor:	The sponsor's Medical Monitor name and contact information will be provided separately

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Amendment No. 3	26 May 2020	5.0	Germany
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Amendment No. 4	26 Jun 2020	7.0	Germany
Amendment No. 5	21 Jul 2020	8.0	Germany
Amendment No. 6	05 OCT 2020	9.0	Germany

Statement of Compliance: This trial will be conducted in according to this protocol, the ethical principles that have their origin in the Declaration of Helsinki, good clinical practice (GCP), and applicable regulatory requirements.

1 PROTOCOL SUMMARY

1.1 Trial synopsis

Trial number: BNT162-01

Trial title

A multi-site, Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy and immunocompromised adults

Objectives and endpoints

Objectives	Endpoints [a]
Primary objective	
(All cohorts) To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after single dose (SD; prime only) or prime/boost (P/B) immunization.	• Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7 d after each immunization (trial days 8 and 29). • Solicited systemic reactions (nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever) recorded up to 7 d after each immunization (trial days 8 and 29). • The proportion of subjects with at least 1 unsolicited treatment-emergent adverse event (TEAE): o For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): occurring up to 21 d after the prime immunization (trial day 22) and 28 d after the boost immunization (trial day 50). o For BNT162c2 (SD): The proportion of subjects with at least 1 unsolicited TEAE occurring up to 28 d after the immunization (trial day 29).
Secondary objectives	
(All cohorts) To describe the immune response in healthy adults after SD or P/B immunization measured by a functional antibody titer, e.g., virus neutralization test (VNT) or an equivalent assay available by the time of trial conduct.	<u>For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B):</u> As compared to baseline at 7 and 21 d after primary immunization (trial days 8 and 22) and at 7, 14 [b], 21, 28, 63, and 162 d after the boost immunization (trial days 5 to 9): • Functional antibody responses (titers). • Fold increase in functional antibody titers. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline. <u>For BNT162c2 (SD):</u> As compared to baseline at 7, 21, 28, 42, 84, and 183 d after the primary immunization (trial days 8 to 184): • Functional antibody responses (titers). • Fold increase in functional antibody titers. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline.

Objectives	Endpoints [a]
Exploratory objectives	
(All cohorts) To describe the immune response in healthy adults after SD or P/B immunization measured by an antibody binding assay, e.g., enzyme-linked immunosorbent assay (ELISA) or an equivalent assay available by the time of trial conduct.	<u>For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B)</u> As compared to baseline at 7 and 21 d after primary immunization (trial days 8 and 22) and at 7, 14 [b], 21, 28, 63, and 162 d after the boost immunization (trial days 8 to 184). • Antibody responses measured (concentrations/titers). • Fold increase in antibody (concentrations/titers). • Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody concentrations/titers. <u>For BNT162c2 (SD)</u> As compared to baseline at 7, 21, 28, 42, 84, and 183 d after the primary immunization (trial days 8 to 184): • Antibody responses measured (concentrations). • Fold increase in antibody (concentrations). • Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody concentrations.
(All cohorts) To describe the cell-mediated immune (CMI) responses.	<u>For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B) and BNT162c2 (SD)</u> At baseline and at 28 d after the primary immunization (trial day 29): • CMI responses measured, e.g., by enzyme-linked immuno-spot (ELISpot) and intracellular cytokine staining (ICS).

Additional exploratory objective
(Only for the Expansion cohorts [Cohorts 11 to 13])
To further characterize the long term adaptive immune response after P/B immunization with 30 µg BNT162b2.
	As compared to baseline at 7 and 21 d after primary immunization (trial days 8 and 22) and at 7, 14 [b], 21, 28, 63, and 162, 343, 525, and 708 d after the boost immunization (trial days 8 to 730).
	• Functional antibody titers measured (e.g.) using VNT.
	  o Measured cross-neutralization of viruses from other coronavirus families.
	• Further assays for:
	  o Antibody-dependent cellular cytotoxicity (ADCC).
	  o Antibody induced phagocytosis.
	  o Immune cell degranulation.
	  o Activation of immune cells such as lymphocytes and granulocytes.
	  o Antibody mediated uptake and formation of immune complexes.

Objectives	Endpoints [a]
Additional exploratory objectives only for the Expansion cohorts [Cohorts 11 to 13]) To further characterize the long term adaptive immune response after P/B immunization with 30 µg BNT162b2.	As compared to baseline at 364, 546, and 729 d after the primary immunization (trial days 365 to 730): • Functional antibody titers measured (e.g.) using VNT. o Antibody responses measured (titers). o Fold increase in antibody titers. o Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers. • Functional antibody binding concentrations measured (e.g.) using ELISA. o Antibody responses measured. o Fold increase in antibody titers. o Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers. • CMI responses measured (e.g.) using ELISpot and ICS.
(Only for the Expansion cohorts [Cohorts 11 to 13]) To further characterize the adaptive immune response: Assessment of cell-mediated immunity	• Further characterization of vaccine and SARS-CoV-2 specific antigen-specific CD4 and CD8 T-cells, e.g., using ELISpot, ICS. • Functional characterization of T-cells (e.g. antigen dependent cytokine secretion, activation, proliferation, cytotoxicity, determination of human leukocyte antigen [HLA] restriction). • Cellular and molecular phenotyping of immune cells using e.g., immunophenotypic characterization of T-cells to define reactive T-cell subsets. • Bulk or single cell T-cell receptor (TCR) and transcriptome sequencing, quantitative polymerase chain reaction (qt-PCR) studies to profile and characterize and track TCRs and quantify the number of antigen-specific T-cells.

a) The given days are approximate; the respective schedule of activities defines assessment windows.
b) Only cohorts starting prime dosing after approval of amendment 09.

The additional exploratory objectives apply for subjects included in the expansion cohorts in addition to all primary, secondary, and exploratory endpoints defined for other trial subjects.

Trial design

This trial has two parts. Part A and Part B. Due to changes in the overall clinical development plan, Part B will no longer be conducted. The objective originally described for Part B have been implemented in the ongoing development via a pivotal Phase I/II/III trial BNT162-02/C4591001 (ClinicalTrials.gov NCT: 04368728).

Part A is for dose ranging of four different vaccines (BNT162a1, BNT162b1, BNT162b2, and BNT162c2) will be undertaken with dose escalation and de-escalation plus the evaluation of interim dose levels. It also includes dose ranging in older subjects.

The vaccines BNT162a1, BNT162b1, BNT162b2, and BNT162c2 will be administered using a P/B regimen. The vaccine BNT162c2 will also be administered using a SD regimen.

BNT162b2, for which the dose regimen has been determined in the dose ranging in Part A of this trial, has now entered efficacy evaluation in the ongoing development via a pivotal Phase I/II/III trial BNT162-02/C4591001 (ClinicalTrials.gov NCT: 04368728). Therefore, for BNT162b2, amendment 09 of this trial introduces expansion cohorts designed to expand the existing safety profiling to a broader population and to enable detailed characterization of the adaptive immune responses, including determine factors that impact them. These cohorts will involve healthy and immunocompromised populations treated according to the selected dosing posology and exploring an alternative posology.

The chosen trial design reflects discussion and advice from the Paul-Ehrlich Institute (PEI) obtained in scientific advice meetings held in February, March, and June 2020 in response to a fast-changing situation.

For a summary of the trial as a flow diagram, see the Schema in Section 1.2. For the planned assessments and visits, see the Schedule of Activities (SoA) in Section 1.3.

Part A

The first part of the trial (Part A) will follow a dose escalation design. Discretionary dose de-escalation and refinement is also planned. Part A will consist of a screening/treatment phase and a follow-up phase.

Dose ranging cohorts:

Trial subjects with the first-in-human [FIH] immunization will be immunized using a sentinel dosing/subject staggering (EMA 2017 guidance "Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products"). The FIH starting dose and the planned escalation/de-escalation doses are given in Table 1. Dose escalation rules have been defined in this protocol to guide dose escalation.

For all cohorts, if the investigator considers necessary, the planned observation periods before proceeding to dose further subjects in the same group may be prolonged by 24 h.

Dose de-escalation in the case of possible vaccine-related toxicities will be guided by the Safety Review Committee (SRC), as required.

In Cohort 1, the sentinel dosing/subject staggering process will be as follows:

- One sentinel subject will be dosed on one day.
- If the dosing in this subject was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 5 further subjects will be dosed (with intervals of at least 1 h between subjects).
- If the dosing in these 5 subjects was considered to be safe and well tolerated by the investigator based on 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48±2 h data from the sentinel subject):
    - The remaining 6 subjects in the group will be dosed (with intervals of at least 30 min between subjects).
    - If approved by the SRC, the next planned escalation dose (see Table 1) will be initiated. The data assessed by the SRC comprises 48 h data for 6

subjects including observation on site, short summary of phone interview (including statement about diary reports), vital signs, investigator reported local and systemic reactions, TEAEs, solicited local & systemic reactions, blood/clinical laboratory data, and brief physical examination outcome.

- If approved by the SRC, the planned de-escalation dose in Cohort 3 will be initiated.

For any subsequent dose escalation cohorts (to doses higher than the maximum already tested for a vaccine candidate), the sentinel/subject staggering process will be as follows:

- Two sentinel subjects will be dosed on one day (with intervals of at least 30 min between subjects).
- If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 4 further subjects will be dosed (with intervals of at least 15 min between subjects).
- If the dosing in these 4 subjects was considered to be safe and well tolerated by the investigator based on 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48 h data from the sentinel subjects):
  - The remaining 6 subjects in the group will be dosed (with intervals of at least 15 min between subjects).
  - If approved by the SRC, the next planned escalation dose (see Table 1) will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects including observation on site, short summary of phone interview (including statement about diary reports), vital signs, investigator reported local and systemic reactions, TEAEs, solicited local & systemic reactions, blood/clinical laboratory data, and brief physical examination outcome.

The maximum allowed dose for each vaccine candidate is defined in Table 1.

For the planned dose de-escalation cohorts, 12 subjects may be dosed on one day (with intervals of at least 15 min between subjects). The doses in these cohorts in younger adults must be lower than doses than doses that have shown acceptable tolerability in younger adults (based on the data from 12 subjects up until 48 h after the first dose). The same dose will not be administered twice, i.e., in two cohorts.

For BNT162b1 and BNT162b2, administration of the planned 10 µg dose in older subjects (Cohort 8) may start once at least a 30 µg dose has shown acceptable tolerability in younger adults (based on the data from 12 subjects up until 48 h after the boost dose).

The dose in Cohort 8 must also be confirmed by the SRC. In Cohort 8, 12 subjects will be dosed using a sentinel dosing/subject staggering (2-4-6) process with intervals of at least 1 h between the first 6 subjects and then at least 30 min intervals for the remaining 6 subjects.

For BNT162b1 and BNT162b2, administration of the planned dose escalation cohorts in older adults (Cohorts 9 and 10), 12 subjects will be dosed using a sentinel dosing/subject

staggering (2-4-6) process with intervals of at least 30 min between subjects. The doses planned in these cohorts will only be administered if the dose is confirmed by the SRC.

The doses planned for Cohorts 8 to 10 are defined in Table 2.

For the unplanned dose de-escalation cohorts, i.e., where the SRC requests the use of a reduced dose for safety reasons, 12 subjects may be dosed on one day with intervals of at least 15 min between subjects (as for planned de-escalation cohorts).

Note: BNT162b1 and BNT162b2 are nucleoside modified RNAs, while BNT162a1 and BNT162c2 are both non-modified uridine containing RNAs. RNA modification is known to impact the extent of innate immune activation at a given dose level, and thus potentially the extent of reactogenicity. Therefore, tolerability data obtained with one of the vaccine variants of each of these pairs may be potentially informative for the respective other one and should be taken in consideration by the SRC for recommendations of lower or interim doses.

In the case that an individual experiences dose limiting toxicities or that the frequency or pattern of adverse events (AEs) within a sub-cohort gives cause for concern, the investigator may request by phone an ad hoc review by the SRC, at any time, before further doses of a given vaccine construct are administered.

Expansion cohorts:

Protocol amendment 6.0 implemented three additional cohorts (Cohorts 11, 12, and 13) comprising additional 150 trial subjects aged from 18 to 85 years receiving BNT162b2 only.

BNT162b2 has entered a Phase II/III evaluation of efficacy, with the intent to support an application for marketing authorization. The dosing regimen under investigation is two 30 µg BNT162b2 doses given ~21 d apart.

The expansion cohorts are intended to provide a more in depth characterization of the adaptive immune responses induced by BNT162b2, associated vaccine safety, and the impact of factors such as subject disposition and dosing posology on humoral and cell-mediated immunity. These cohorts will extend the safety data of BNT162b2 to a broader trial population and thus closer to the vaccine target population.

Moreover, each of these cohorts will add to a more differentiated understanding of the BNT162b2-induced adaptive immune response composed of antigen-specific antibodies, CD4 and CD8 T-cells, with a view to developing insights into the mechanisms by which immunity to SARS-CoV-2 may be induced and factors driving any variability in response. Alternative treatment approaches for difficult to treat or high risk subjects may be determined. In each of these dose cohorts, a broader characterization of T-cell and antibody responses and their inter-individual variation will be performed. This will include the characterization of the dependency of adaptive immune responses on factors such as age, HLA haplotype, body mass index (BMI) and gender.

The planned dose of BNT162b2, two 30 µg BNT162b2 doses given 21 d apart, is the same regimen that has already been tested in the dose escalation phase of this trial and in almost 17,000 adult subjects, including those with acute and chronic illnesses, in the ongoing global Phase I/II/III trial BNT162-02/C4591001 (ClinicalTrials.gov NCT:

04368728). As such, all trial subjects in the three expansion cohorts can be treated in parallel.

For Cohort 13, the interval between prime immunizations will be at least 15 min. For prime immunization in Cohorts 11 and 12 and for all cohorts after the boost immunization, the interval will be at least 5 min.

The three expansion cohorts (with comparable numbers of male and female subjects for each of the defined age groups, see the section Population below) are as follows:

- Cohort 11: Alternative posology cohort with 30 healthy adults who will receive BNT162b2 using one 3 µg prime dose and one 30 µg boost dose of BNT162b2 given approximately 21 d apart (P/B regimen).
- Cohort 12: Adaptive immune response cohort (including safety and long term immune response) with 90 healthy adults who will receive two 30 µg BNT162b2 doses given approximately 21 d apart (P/B regimen).
- Cohort 13: Population expansion cohort (including safety and long term immune response) with 30 immunocompromised adults who will receive of two 30 µg BNT162b2 doses given approximately 21 d apart (P/B regimen).

For the scientific rational for the expansion cohorts, see Section 4.2.

All trial site visits for subjects in the expansion cohorts will be conducted on an outpatient basis, with the clinical judgment of the investigator determining whether a period of observation beyond that required for completion of study procedures is required, on a case by case basis. Standard measures to avoid cross-contamination of immunocompromised individuals with high risk pathogens should be followed for 24 months after the primary immunization.

Part B

Due to changes in the overall clinical development plan, Part B will no longer be conducted.

Table 1: Dose ranging: vaccine dose regimens for younger adults aged 18 to 55 years in Part A (Cohorts 1 to 7)

Vaccine / mRNA type	Vaccine-encoded antigen	Vaccine IM dosing regimen	Part A – Cohort numbers & Dose (µg) (12 subjects per cohort)						
			1 Starting dose	**2**	**3 De-escalation dose**	**4**	**5 Optional de-escalation dose**	**6**	**7**
BNT162a1 / uRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	**1A** **3 µg** [b]	2A 0.6 µg [a]	3A 0.1 µg	4A [a] 2 µg [e]	5A 0.3 µg	6A 1 µg	
BNT162b1 / modRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	1B 10 µg	2B 30 µg	3B 1 µg	**4B** **60 µg** [d]	5B 50 µg	6B 3 µg	7B 20 µg
BNT162b2 / modRNA	Modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	1C 10 µg	2C 30 µg	3C 1 µg	**4C** [a] **60 µg** [d]	5C [a] 20 µg	6C [a] 3 µg	7C [a] 50 µg
BNT162c2 / saRNA	Modified version of the full length SARS-CoV-2 S protein	Prime only: Day 1	1D 0.1 µg	2D 0.3 µg	3D 0.1 µg to <3 µg [c]	4D 1 µg	5D [a] 0.6 µg	**6D** [a] **3 µg** [d]	
BNT162c2 / saRNA	Modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	1E 0.1 µg	2E [a] 0.3 µg	3E 1 µg	**4E** [a] **3 µg**	5E [a] 0.6 µg	6E [a] 5-10 µg [d]	7E 5-10 µg

[a] All dose escalation doses used must be judged acceptable by the Safety Review Committee (SRC) before use.

[b] Status 08 JUN 2020: This cohort was set on hold by the SRC after 6 subjects had been received their Day 1 dose, furthermore the SRC decided not to perform Day 22 dosing for these 6 subjects. Due to this hold, the starting dose is also the maximum dose.

[c] Specific doses to be defined, but in the range given. Already given doses will not be repeated.

[d] The planned maximum doses per vaccine candidate.

[e] Dosing with this vaccine variant has been put on hold. Dosing may be resumed if disease prevention data for the other vaccine candidates suggest the need for additional vaccine candidates.

IM = intramuscular; RBD = Receptor Binding Domain; S protein = SARS-CoV-2 sp ke protein: tbd = to be defined.

Note: Currently, dosing with BNT162a1 has been deferred. Dosing may be resumed if disease prevention data for the other vaccine candidates suggest the need for additional vaccine candidates.

Table 2: Dose ranging: vaccine dose regimens for older adults aged 56 to 85 years in Part A (Cohorts 8 to 10)

Vaccine / mRNA type	Vaccine-encoded antigen	Vaccine IM dosing regimen	Part A – Cohort numbers & Dose (µg) (12 subjects per cohort)[a]		
			8 Older adults	9 Older adults	10 Older adults
BNT162b1 / modRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	8B 10 µg	9B[a] 20 µg	10B[a] 30 µg
BNT162b2 / modRNA	Modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	8C 10 µg	9C[a] 20 µg	10C[a] 30 µg

[a] All dose escalation doses used must be judged acceptable by the Safety Review Committee (SRC) before use.
IM = intramuscular; RBD = Receptor Binding Domain; S protein = SARS-CoV-2 sp ke protein.

Note: The doses planned in this trial for older adults (i.e., adults aged between 55 and 85 years) reflect clinical data from the ongoing BNT162-01 and BNT162-02 trials with the vaccine candidates BNT162b1 and BNT162b2 in younger adults (aged between 18 and 55 years) and elderly (adults aged between 65 and 85 years). For details, see the BNT162 IB.

BNT162b1:

- BNT162b1 P/B doses of 1, 10, 30, and 50 µg showed acceptable tolerability in younger adults.
- Based on the tolerability profile after the prime dose at 60 µg (BNT162-01 trial) and 100 µg (BNT162-02 trial), the respective boost doses were not administered.
- BNT162b1 P/B doses of 10, 20, and 30 µg showed acceptable tolerability in elderly adults. This tolerability appears to be better than seen in younger adults at the same doses.

BNT162b2:

- BNT162b2 P/B doses of 1, 10, and 30 µg showed acceptable tolerability in younger adults.
- BNT162b2 P/B doses of 10, 20, and 30 µg showed acceptable tolerability in elderly adults. This tolerability appears to be better than seen in younger adults at the same doses.

Based on the tolerability data summarized above, and the implemented safety measures (sentinel/staggered subject dosing, post-dose observations period, wellbeing questioning, etc.) as described in the section Risk assessment, the planned doses in older subjects in this trial are expected to show acceptable tolerability.

Based on the available immunogenicity data after dosing with BNT162b1 and BNT162b2 in younger adults in the BNT162-02 trial (see the BNT162 IB), the doses planned in this trial in older subjects are expected to show lower but measurable immunogenicity than in younger adults.

Altogether, the doses planned in older subjects in this trial are considered adequate to support the trial objectives and to pose an acceptable risk to trial subjects.

Table 3: Expansion cohorts for BNT162b2 (age 18 to 85 years) in Part A (Cohorts 11 to 13)

Vaccine / mRNA type	Vaccine-encoded antigen	Vaccine IM dosing regimen	Part A –-- Cohort numbers & Dose (µg) (number subjects per cohort)		
			11C (N = 30) Healthy adults (Alternative posology)	12C (N = 90) Healthy adults (Adaptive immune response cohort)	13C (N = 30) Immunocompromised but otherwise healthy adults (Population expansion cohort)
BNT162b2 / modRNA	Modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	3 µg 30 µg	30 µg 30 µg	30 µg 30 µg

S protein = SARS-CoV-2 spike protein.

Trial duration

In total, the planned trial duration (i.e., the sum of the screening, treatment, and follow-up phases) for subjects is expected to be approximately 214 d for Cohorts 1 to 10 and 738 d Cohorts 11 to 13.

For logistical reasons, investigation of the different vaccines may not be able to start at the same time.

Population

Dose ranging Cohorts (Cohorts 1 to 10)

- Healthy adults aged 18 to 55 years (Cohorts 1 to 7; younger adults) or aged 56 to 85 years (Cohorts 8 to 10; older adults). Subjects aged 56 to 85 years must be enrolled such that at least 6 subjects per cohort are aged 65 to 85 years (i.e., are elderly).

For each vaccine, 12 subjects are required for each of the dose ranging cohorts.

Expansion cohorts (Cohorts 11 to 13)

- Cohort 11 - Alternative posology cohort: 30 healthy adults aged 18 to 85 years with comparable numbers of male and female subjects for each of the following age groups: 18 to 55 years, 56 to 85 years (15 per age group).
- Cohort 12 - Adaptive immune response cohort: 90 healthy adults, with comparable numbers of male and female subjects for each of the following age groups: 18 to 55 years, 56 to 65 years, and 65 to 85 years (30 per age group).
- Cohort 13 - Population expansion cohort: 30 immunocompromised adults aged 18 to 85 years with comparable numbers of male and female subjects for each of the following age groups: 18 to 55 years, 56 to 85 years (15 per age group).

Table 4: Overview of the total number of subjects for each vaccine in Part A

Vaccine / mRNA type	Vaccine dosing regimen	Maximum number of subjects (assuming all cohorts planned in Table 1, Table 2, and Table 3 are performed)
BNT162a1 / uRNA	Prime/Boost	72 (6 cohorts)
BNT162b1 / modRNA	Prime/Boost	120 (10 cohorts)
BNT162b2 / modRNA	Prime/Boost	270 (13 cohorts)
BNT162c2 / saRNA	Prime only	72 (6 cohorts)
BNT162c2 / saRNA	Prime/Boost	84 (7 cohorts)

Key inclusion criteria

Volunteers are only eligible to be enrolled in the trial if they meet the following criteria:

- For younger adult cohorts, volunteers must be aged 18 to 55 years, have a BMI over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0.
  OR
  For older adult cohorts, volunteers must be aged 56 to 85 years, have a BMI over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0.
  OR
  For the immunocompromised adult cohort (Cohort 13), volunteers must be aged 18 to 85 years, have a BMI over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0.
- They must be healthy, in the clinical judgment of the investigator, based on medical history, physical examination, 12-lead ECG, vital signs (systolic/diastolic blood pressure, pulse rate, body temperature, respiratory rate), and clinical laboratory tests (blood chemistry, hematology, and urine chemistry) at Visit 0.
  Note: Healthy volunteers with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks (wks) before enrollment, can be included.
  OR
  For the immunocompromised cohort (Cohort 13); volunteers who have previously received solid organ transplant, or peripheral blood stem cell transplantation ≥6 months after transplantation, or individuals with human immunodeficiency virus (HIV) infection with a CD4$^+$ T-cell count of ≥200 x 10^6 /L. Individuals with lower T-cell counts will be excluded from the trial on the basis that this represents a significant medical complication. In the clinical judgment of the investigator, volunteers must be immunocompromised but otherwise healthy. After consultation with the Medical Monitor, this may include individuals receiving immunosuppressant therapy due to another confounding disease at least 2 wks prior to enrollment and/or at least 6 wks following immunization with BNT162b2, and/or individuals with immunosuppressive treatment of an autoimmune disease if the disease is stable.
- Women of childbearing potential (WOCBP) must have a negative beta-human chorionic gonadotropin urine test at Visit 0 and Visit 1. Women that are postmenopausal or permanently sterilized will be considered as not having reproductive potential.

Key exclusion criteria

Volunteers are excluded from the trial if they present any of the following criteria:

- Have had any acute illness, as determined by the investigator, with or without fever, within 72 h prior to any immunization. An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the investigator, the residual symptoms will not compromise their wellbeing if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.

- Have a known allergy, hypersensitivity, or intolerance to the planned investigational medicinal product (IMP) including any excipients of the IMP.
- Had any medical condition or any major surgery (e.g., requiring general anesthesia) within the past 5 years which, in the opinion of the investigator, could compromise their wellbeing if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments. See the inclusion criteria for non-excluded medical conditions for Cohort 13.
- Have any surgery planned during the trial, starting after Visit 0 and continuously until at least 90 d after receiving the last immunization.
- Had any chronic use (more than 21 continuous days) of any systemic medications, including immunosuppressants or other immune-modifying drugs (except for Cohort 13), within the 6 months prior to Visit 0 unless in the opinion of the investigator the medication would not prevent, limit, or confound the protocol-specified assessments or could compromise subject safety.

  Note: Healthy volunteers with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 wks before enrollment, can be included.
- Regular receipt of inhaled/nebulized corticosteroids (except for Cohort 13).
- Had any vaccination within the 28 d prior to Visit 0.
- Had administration of any immunoglobulins and/or any blood products within the 3 months prior to Visit 0.
- Had administration of another IMP including vaccines within 60 d or 5 half-lives (whichever is longer), prior to Visit 0.
- Have a known history or a positive test for any of Hepatitis B, or Hepatitis C, or (except for Cohort 13) HIV 1 or 2 within the 30 d prior to Visit 0.
- Have a positive PCR-based test for SARS-CoV-2 within the 30 d prior to Visit 1.
- Previously participated in an investigational trial involving lipid nanoparticles.
- Have a history (within the past 5 years) of substance abuse or known medical, psychological, or social conditions which, in the opinion of the investigator, could compromise their wellbeing if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.
- Have a history of hypersensitivity or serious reactions to previous vaccinations.
- Have a history of Guillain-Barré syndrome within 6 wks following a previous vaccination.
- Have a history of narcolepsy.
- (Except for Cohort 13) Have a history of or suspected immunosuppressive condition, acquired or congenital, as determined by medical history and/or physical examination at Visit 0.

- Have symptoms of the coronavirus disease 2019 (COVID-19), e.g., respiratory symptoms, fever, cough, shortness of breath and breathing difficulties.
- Have had contact with persons diagnosed with COVID-19 or who tested positive for SARS-CoV-2 by any diagnostic test within the 30 d prior to Visit 1.
- Are soldiers, volunteers in detention, CRO or sponsor staff or their family members.
- For older volunteers: Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors:
  - Hypertension
  - Diabetes mellitus
  - Chronic obstructive pulmonary disease
  - Asthma
  - Chronic liver disease
  - Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
  - Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
  - Sickle cell disease
  - Cancer (except for Cohort 13)
  - Are immune compromised due to stem cell or organ-transplantation with significant medical complications such as acute or chronic graft rejection or graft versus host disease requiring intensive immunosuppressive treatment, transplant failure or infectious complications or other conditions that would be considered a contraindication for vaccination
  - Are immune compromised due to HIV infection with a $CD4^+$ count of < 200 x 10^6 /L at screening or significant medical complications such as opportunistic infections, malignant complications (e.g., lymphoma, Kaposi sarcoma), other organ manifestations consistent with advanced acquired immunodeficiency syndrome (AIDS) or other conditions that would be considered a contraindication for vaccination
  - Resident in a long term facility
  - Current vaping or smoking (occasional smoking is acceptable)
  - History of chronic smoking within the prior year

Trial treatments (BNT162 vaccines)

Name:	BNT162 vaccines - Antiviral RNA vaccines for active immunization against COVID-19
Type:	RNA-LNP vaccines utilizing different BioNTech RNA formats, i.e., uRNA (product code BNT162a1), modRNA (two variants, product codes BNT162b1 and BNT162b2), saRNA (product code BNT162c2)

Dosage levels:	Part A cohorts: See Table 1, Table 2, and Table 3. The planned dose per vaccine candidate will not exceed the listed pre-defined maximum doses.
Dosage frequency:	One injection or two injections 21 d apart. Injection volumes will be up to 1.5 mL.
Administration route:	Intramuscular (IM); upper arm, musculus deltoideus. For the P/B regimens the same arm may be used for both immunizations. The non-dominant arm is preferred.

Statistics

The final analysis will be performed once all subjects have completed the End of Treatment (EoT visit; Visit 7). An analysis update will be performed once all subjects will have completed the last planned visit. No formal interim statistical analysis will be performed. However, preliminary analyses based on all data collected until a pre-defined data cut-off date (snapshot analyses) may be performed for each cohort once subjects within a cohort will have been followed up for at least 7 d following each dose.

Data Monitoring Committee (DMC)/SRC

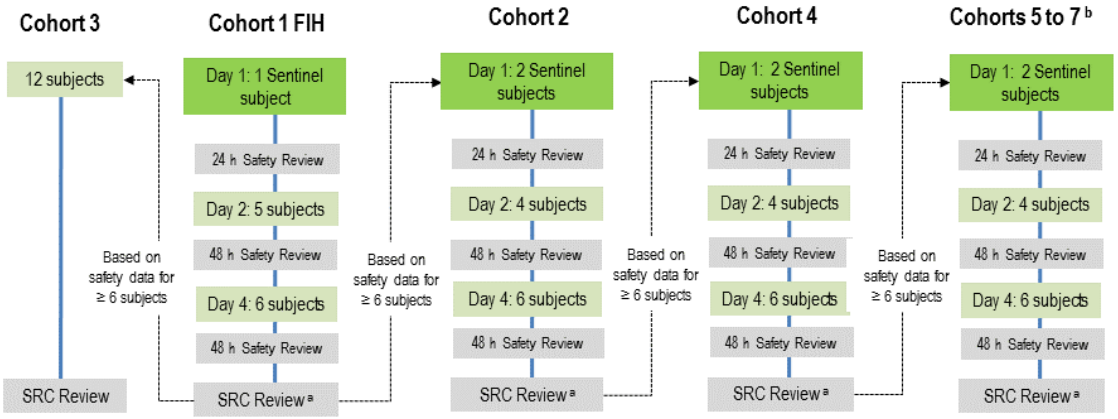
A DMC is not planned. A SRC is planned.

1.2 Schema (graphical representation of the trial)

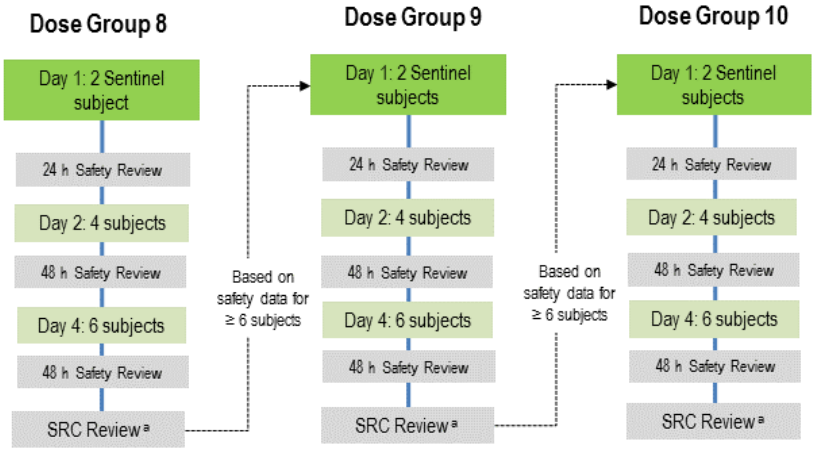
For a graphical depiction of the cohorts in Part A, see Figure 1. For logistical reasons, investigation of the different vaccines may not be able to start at the same time. Should this happen, the expected overall trial duration may be extended.

Dose ranging cohort schema for BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B) [c]

Cohorts 1 to 7 with younger adults



Cohorts 8 to 10 with older adults

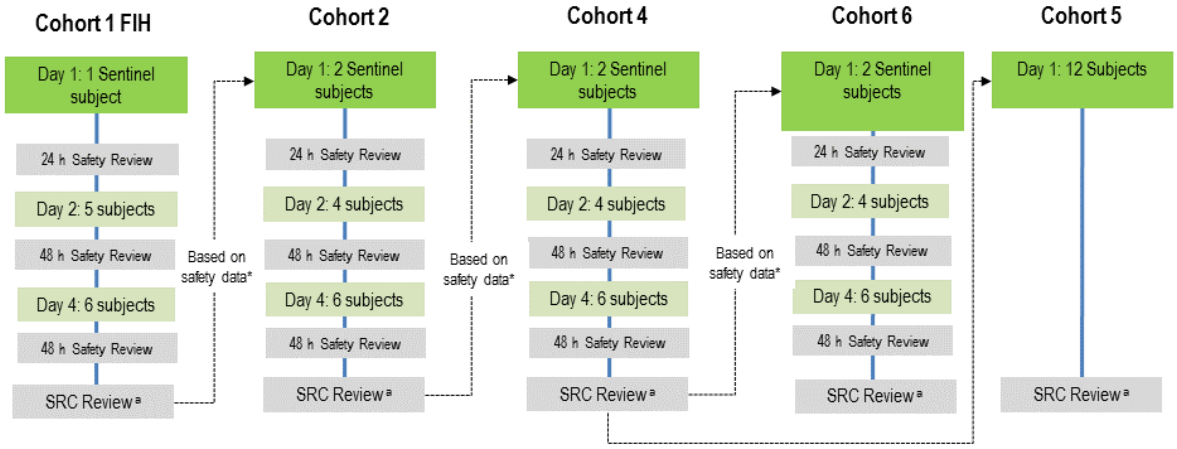


a) The data assessed by the SRC for progressing comprises 48 h data for 6 subjects.

b) Subjects will be dosed using a sentinel dosing/subject (2-4-6) staggering process unless the planned dose is the same or lower than previously found to show acceptable tolerability (in which case, all subjects may be dosed on one day).

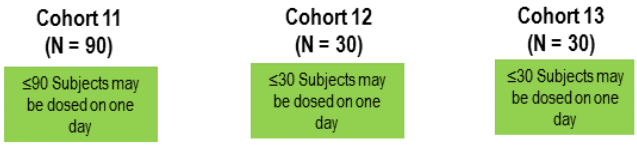
c) For the dose regimens, see Table 1 and Table 2.

Dose ranging cohort schema for BNT162c2 (SD) [b]



a) The data assessed by the SRC for progressing comprises 48 h data for 6 subjects.
b) For the dose regimens, see Table 1.

Expansion cohorts - Cohorts 11 to 13 [a]



a) For the dose regimens, see Table 3.

Figure 1: Graphical depiction of the dose-finding process in Part A

FIH = First-in-humans; h = hour(s); SRC = Safety Review Committee.

1.3 Schedule of activities

Table 5: Schedule of trial procedures and assessments – BNT162a1, BNT162b1, BNT162b2, and BNT162c2 when tested P/B (excluding Cohorts 11 to 13)

Procedure / Assessment	Visit 0	Visit 1 Pre-dose	Visit 1 (Post-) dosing	Visit 2 at 24±2h	Phone call at 48±2h	Visit 3	Visit 4 Pre-dose	Visit 4 Dosing & Post-dose	Phone call at 48±2h	Visit 5	Visit 5a	Visit 6	Visit 7 (EoT Visit)	Visit 8 (FU Visit)	Visit 9 (FU Visit)
Day [h]	**-30 to 0**	**1**	**1**	**2**		**8**	**22**	**22**		**29**	**36 [q]**	**43**	**50 [r]**	**85**	**184**
Days to last dose [h]		**0**	**0**			**7**	**21**	**0**		**7**	**14**	**21**	**28**	**63**	**162**
Informed consent	X														
Inclusion/exclusion criteria	X	X (review)													
Medical history	X	X (update)													
Physical examination incl. height	X	X [a]		X [a]		X [a]	X [a]			X [a]		X [a]	X [a]		
Vital signs, body weight [c]	X	X	X [b]	X		X	X	X [b]		X		X	X	X	X
12-lead ECG	X	X													
Urine pregnancy test for WOCBP	X	X					X								
Urine drugs of abuse screen [d]	X	X													
Alcohol breath test	X	X													
Urine collection for clinical laboratory [e]	X	X		X		X				X			X		
Blood draw for clinical laboratory (15 mL) [f]	X	X		X		X				X			X		

Procedure / Assessment	Visit 0	Visit 1 Pre-dose	Visit 1 (Post-) dosing	Visit 2 at 24±2h	Phone call at 48±2h	Visit 3	Visit 4 Pre-dose	Visit 4 Dosing & Post-dose	Phone call at 48±2h	Visit 5	Visit 5a	Visit 6	Visit 7 (EoT Visit)	Visit 8 (FU Visit)	Visit 9 (FU Visit)
Day [h]	**-30 to 0**	**1**	**1**	**2**		**8**	**22**	**22**		**29**	**36 [q]**	**43**	**50 [r]**	**85**	**184**
Days to last dose [h]		**0**	**0**			**7**	**21**	**0**		**7**	**14**	**21**	**28**	**63**	**162**
Blood draw for viral screening [g]	X (5 mL)														
Blood draw for SARS-CoV-2 testing [k]	X (2.6 mL)														
Oral swipe for SARS-CoV-2 testing		X [m]													
Allocation to IMP		X													
Immunization			X [l]					X							
Blood draw for immunogenicity (10 mL) [n]		X				X	X			X	X	X	X	X	X
Blood draw for HLA			X (4 mL EDTA-blood) [p]												
Blood draw for CMI (100 mL) [n, o]		X								X					
Blood draw for research												X (≤100 mL)		X (≤50 mL)	X (≤50 mL)
Subject hotline availability	Start	=>	=>	=>		=>	=>	=>		=>	=>	=>	=>	=>	End
Issue subject diaries		X		X		X	X			X		X	X		
Collect subject diaries				X	X [i]	X	X			X		X	X	X	

Procedure / Assessment	Visit 0	Visit 1 Pre-dose	Visit 1 (Post-) dosing	Visit 2 at 24±2h	Phone call at 48±2h	Visit 3	Visit 4 Pre-dose	Visit 4 Dosing & Post-dose	Phone call at 48±2h	Visit 5	Visit 5a	Visit 6	Visit 7 (EoT Visit)	Visit 8 (FU Visit)	Visit 9 (FU Visit)
Day [h]	**-30 to 0**	**1**	**1**	**2**		**8**	**22**	**22**		**29**	**36 [q]**	**43**	**50 [r]**	**85**	**184**
Days to last dose [h]		**0**	**0**			**7**	**21**	**0**		**7**	**14**	**21**	**28**	**63**	**162**
Record AEs since last visit		X		X		X	X			X	X	X	X	X [j]	X [j]
Local reaction assessment/ systemic events			X [b]	X		X	X	X [b]		X		X	X		
Concomitant medication	X	X		X		X	X			X		X	X		
Subject wellbeing questioning					X [i]				X [i]						

[a] Brief (symptom-directed) physical examination; no height measurement.

[b] At 1, 3, and 6 h (±15 min) after immunization.

[c] Vital signs: systolic/diastolic blood pressure, pulse rate, respiratory rate, and body temperature; body weight only at Visit 0.

[d] Urine screening for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cocaine, cannabinoids, opiates, methadone, methamphetamines, phencyclidine, tricyclic antidepressants).

[e] Dipstick urine analysis: glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrite, and leukocytes. Microscopic urinalysis: if warranted by dipstick results, urine sediment will be microscopically examined for the presence of red blood cells, white blood cells, casts, crystals, epithelial cells, and bacteria.

[f] Clinical laboratory tests: (Chemistry) alkaline phosphatase, creatinine, ferritin, C-reactive protein, albumin, alanine aminotransferase, amylase, aspartate aminotransferase, gamma glutamyl transpeptidase, total bilirubin, blood urea nitrogen, glucose, lipase, sodium, potassium, calcium; (Hematology) hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count. Only in women who are not WOCBP (to confirm postmenopausal status): follicle stimulating hormone at Visit 0.

[g] Viral screening for human immunodeficiency virus (HIV) 1 or 2, hepatitis B, hepatitis C.

[h] Flex bility for visit days: Visit 3 Day 8±1 d; Visit 4 Day 22±2 d; Visit 5 Day 29±3 d; Visit 6 Day 43±4 d; Visit 7 Day 50±4 d; Visit 8 Day 85±7 d; Visit 9 Day 184±9d.

[i] Only for the first 6 subjects per group. Questioning on and documentation of AEs as well as systemic and local reactions, the latter in case of upcoming dose decision meetings.

[j] Only IMP-related AEs and any SAEs.

[k] Blood draw for anti-SARS-CoV-2 ant bodies (samples will be stored until a test is commercially available).

[l] For Cohorts 1 and 8, immunization with at least 1 h intervals between subjects for the first 6 subjects and then with of at least 30 min intervals for the remaining 6 subject. For all other cohorts, immunization with at least 15 min intervals between subjects and for the boost injections.

[m] Oral swipe for SARS-CoV-2 testing either on Day -1 or at the Visit 1 on Day 1.

[n] The listed blood draw days may be adapted if justified by the collected data. Leftover blood after completion of the immunogenicity assessments may be used for additional analyses as descr bed in Section 8.7 (Genetics) and/or Section 8.8 (Biomarkers).

[o] For subjects who have given consent, one aliquot of the blood sample drawn for analysis of CMI may be used for HLA typing to allow additional analysis of T-cell receptor repertoire and / or phenotypic characterization of T-cells specific to vaccine-encoded antigens.

[p] If HLA typing using the blood sample collected with Lithium Heparin is not conclusive, EDTA-blood will be drawn for HLA testing.

[q] Only cohorts starting prime dosing after approval of protocol amendment 06.

[r] When entering the follow-up phase, i.e., after completing the EoT visit, subjects are allowed to participate in other clinical trials not investigating COVID-19 vaccines or treatments.

Notes:

If the boost dose is not administered or if trial subjects permanently discontinued from IMP administration, subjects will complete all assessments planned for that visit and for the EoT Visit as listed in the SoA.

The additional Visit 5a added by protocol amendment 06 will only apply for subjects who give consent.

Abbreviations: AE = adverse event; CMI = cell-mediated immune testing; D or d = day; ECG = electrocardiogram; EDTA = ethylenediamine tetraacetic acid; EoT = end of treatment (Visit); FU = follow-up (visit); h = hour(s); HLA = human leukocyte antigen; Day 0 = one day before Day 1; IMP = investigational medicinal product; min = minute(s); SARS-CoV-2 = the virus leading to COVID-19; WOCBP = women of childbearing potential.

Table 6: Schedule of trial procedures and assessments – BNT162c2

Procedure/Assessment	Visit 0	Visit 1 Pre-dose	Visit 1 Dosing & Post-dose	Visit 2 at 24±2h	Phone call at 48±2 h	Visit 3	Visit 4	Visit 5	Visit 6 (EoT Visit)	Visit 7 (FU Visit)	Visit 8 (FU Visit)
Day [a]	**-30 to 0**	**1**	**1**	**2**		**8**	**22**	**29**	**43 [q]**	**85**	**184**
Informed consent	X										
Inclusion/exclusion criteria	X	X (review)									
Medical history	X	X (update)									
Physical examination incl. height	X	X [b]		X [b]		X [b]	X [b]	X [b]	X [b]		
Vital signs, body weight [c]	X	X	X [d]	X		X	X	X	X		
12-lead ECG	X	X									
Urine pregnancy test (for WOCBP)	X	X					X				
Urine drugs of abuse screen [e]	X	X									
Alcohol breath test	X	X									
Urine for clinical laboratory [f]	X	X		X		X		X	X		
Blood draw for clinical laboratory [g]	X (15 mL)	X (15 mL)		X (15 mL)		X (15 mL)		X (15 mL)	X (15 mL)		
Blood draw for viral screening [h]	X (5 mL)										
Blood draw for SARS-CoV-2 testing [i]	X (2.6 mL)										
Oral swipe for SARS-CoV-2 testing [j]		X									
Allocation to IMP		X									
Immunization [k]			X								
Blood draw for immunogenicity		X (10 mL)				X (10 mL)	X (10 mL)	X (10 mL)	X (10 mL)	X (10 mL)	X (10 mL)

Procedure/Assessment	Visit 0	Visit 1 Pre-dose	Visit 1 Dosing & Post-dose	Visit 2 at 24±2h	Phone call at 48±2 h	Visit 3	Visit 4	Visit 5	Visit 6 (EoT Visit)	Visit 7 (FU Visit)	Visit 8 (FU Visit)
Day [a]	**-30 to 0**	**1**	**1**	**2**		**8**	**22**	**29**	**43 [q]**	**85**	**184**
Blood draw for HLA testing [p]		X (4 mL EDTA-blood)									
Blood draw for CMI testing (100 mL) [l, m]		X						X			
Blood draws for research									X (≤100 mL)	X (≤50 mL)	X (≤50 mL)
Subject hotline availability	Start	=>	=>	=>		=>	=>	=>	=>	=>	End
Issue subject diaries		X		X		X	X	X			
Collect subject diaries				X	X [o]	X	X	X	X		
Record AEs since last visit		X		X		X	X	X	X	X [n]	X [n]
Local reaction assessment/ systemic events			X [d]	X		X	X	X			
Concomitant medication	X	X		X		X	X	X	X		
Subject wellbeing questioning					X [o]						

[a] Flex bility for visit days: Visit 3 Day 8±1 d; Visit 4 Day 22±2 d; Visit 5 Day 29±3 d; Visit 6 Day 43±4 d; Visit 7 Day 85±7 d; Visit 8 Day 184±9d.

[b] Brief (symptom-directed) physical examination; no height measurement.

[c] Vital signs: systolic/diastolic blood pressure, pulse rate, respiratory rate, and body temperature; body weight only Visit 0.

[d] At 1, 3, and 6 h (±15 min) after immunization.

[e] Urine screening for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cocaine, cannabinoids, opiates, methadone, methamphetamines, phencyclidine, tricyclic antidepressants).

[f] Dipstick urine analysis: glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrite, and leukocytes. Microscopic urinalysis: if warranted by dipstick results, urine sediment will be microscopically examined for the presence of red blood cells, white blood cells, casts, crystals, epithelial cells, and bacteria.

[g] Clinical laboratory tests: (Chemistry) alkaline phosphatase, creatinine, ferritin, C-reactive protein, albumin, alanine aminotransferase, amylase, aspartate aminotransferase, gamma glutamyl transpeptidase, total bilirubin, blood urea nitrogen, glucose, lipase, sodium, potassium, calcium; (Hematology) hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count. Only in women who are not WOCBP (to confirm postmenopausal status): follicle stimulating hormone at Visit 0.

[h] Viral screening for human immunodeficiency virus (HIV) 1 or 2, hepatitis B, hepatitis C.

[i] Blood draw for anti-SARS-CoV-2 ant bodies.

[j] Oral swipe for SARS-CoV-2 testing either on Day -1 or at the Visit 1 on Day 1.

[k] For Cohort 1, immunization with at least 1 h intervals between subjects for the first 6 subjects and then with at least 30 min intervals for the remaining 6 subjects. For all other cohorts, immunization with 15 min intervals between subjects.

[l] The listed blood draw days may be adapted if justified by the collected data. Leftover blood after completion of the immunogenicity assessments may be used for additional analyses as descr bed in Section 8.7 (Genetics) and/or Section 8.8 (Biomarkers).

[m] For subjects who have given consent, one aliquot of the blood sample drawn for analysis of CMI may be used for human leukocyte antigen typing to allow additional analysis of T-cell receptor repertoire and / or phenotypic characterization of T-cells specific to vaccine-encoded antigens.

[n] Only IMP-related AEs and any SAEs.

[o] Only for the first 6 subjects per group. Questioning on and documentation of AEs as well as systemic and local reactions, the latter in case of upcoming dose decision meetings.

[p] If HLA typing using the blood sample collected with Lithium Heparin is not conclusive, EDTA-blood will be drawn for HLA testing.

[q] When entering the follow-up phase, i.e., after completing the EoT visit, subjects are allowed to participate in other clinical trials not investigating COVID-19 vaccines or treatments.

Abbreviations: AE = adverse event; CMI = cell-mediated immune testing; d = day; ECG = electrocardiogram; EDTA = ethylenediamine tetraacetic acid; EoT = end of treatment (Visit); FU = follow-up (visit); h = hour(s); HLA = human leukocyte antigen; IMP = investigational medicinal product; min = minute(s); SARS-CoV-2 = the virus leading to COVID-19; WOBCBP = women of childbearing potential.

Table 7: Schedule of trial procedures and assessments – Cohorts 11 to 13 (Expansion cohorts only)

Procedure / Assessment	Visit 0	Visit 1 Pre-dose	Visit 1 (Post-) dosing	Visit 2	Visit 3	Visit 4 Pre-dose	Visit 4 (Post-) dosing	Visit 5	Visit 5a	Visit 6	Visit 7 (EoT Visit)	Visit 8 (FU Visit)	Visit 9 (FU Visit)	Visit 10 (FU Visit)	Visit 11 (FU Visit)	Visit 12 (FU Visit)
Day [h]	**-30 to 0**	**1**	**1**	**2**	**8**	**22**	**22**	**29**	**36**	**43**	**50 [r]**	**85**	**184**	**365**	**547**	**730**
Days to last dose [h]		**0**	**0**	**1**	**7**	**21**	**0**	**7**	**14**	**21**	**28**	**63**	**162**	**343**	**525**	**708**
Informed consent	X															
Inclusion/ exclusion criteria	X	X (review)														
Medical history	X	X (update)														
Physical exam. incl. height	X	X [a]		X [a]	X [a]	X [a]		X [a]		X [a]	X [a]					
Vital signs, body weight [c]	X	X	X [b]	X	X	X	X [b]	X		X	X	X	X			
12-lead ECG	X	X														
Urine pregnancy test for WOCBP	X	X				X										
Urine drugs of abuse screen [d]	X	X														
Alcohol breath test	X	X														
Urine collection for clinical lab. [e]	X	X		X	X			X			X					
Blood draw for clin. lab. (15 mL) [f]	X	X		X	X			X			X					
Blood draw for viral screening [g]	X (5 mL)															
Blood draw for SARS-CoV-2 testing (2.6 mL) [k]	X															
Swipe for SARS-CoV-2 testing		X [m]														

Procedure / Assessment	Visit 0	Visit 1 Pre-dose	Visit 1 (Post-) dosing	Visit 2	Visit 3	Visit 4 Pre-dose	Visit 4 (Post-) dosing	Visit 5	Visit 5a	Visit 6	Visit 7 (EoT Visit)	Visit 8 (FU Visit)	Visit 9 (FU Visit)	Visit 10 (FU Visit)	Visit 11 (FU Visit)	Visit 12 (FU Visit)
Day [h]	**-30 to 0**	**1**	**1**	**2**	**8**	**22**	**22**	**29**	**36**	**43**	**50 [r]**	**85**	**184**	**365**	**547**	**730**
Days to last dose [h]		**0**	**0**	**1**	**7**	**21**	**0**	**7**	**14**	**21**	**28**	**63**	**162**	**343**	**525**	**708**
Allocation to IMP		X														
Immunization			X [l]				X									
Blood draw for immunogenicity [n]		X (10 mL)			X (10 mL)	X (10 mL)		X (10 mL)	X (10 mL)	X (10 mL)	X (10 mL)	X (10 mL)	X (10 mL)	X (10 mL)	X (10 mL)	X (10 mL)
Blood draw for HLA		X (4 mL EDTA-blood)														
Blood draw for CMI (100 mL) [n, o]		X						X					X	X	X	X
Blood draw for research											X (≤100 mL)	X (≤50 mL)	X (≤50 mL)			
Subject hotline availability	Start	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	End
Issue subject diaries		X		X	X	X		X		X	X					
Collect subject diaries				X	X	X		X		X	X	X				
Record AEs since last visit		X		X	X	X		X		X	X	X [j]	X [j]	X [j]	X [j]	X [j]
Local reaction assessment/ systemic events			X [b]	X	X	X	X [b]	X		X	X					
Concomitant medication	X	X		X	X	X		X		X	X					
Subject wellbeing questioning by phone				24 h post-dose				24 h post-dose								

[a] Brief (symptom-directed) physical examination; no height measurement.

[b] At 1, 3, and 6 h (±15 min) after immunization.

[c] Vital signs: systolic/diastolic blood pressure, pulse rate, respiratory rate, and body temperature; body weight only at Visit 0.

[d] Urine screening for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cocaine, cannabinoids, opiates, methadone, methamphetamines, phencyclidine, tricyclic antidepressants).

[e] Dipstick urine analysis: glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrite, and leukocytes. Microscopic urinalysis: if warranted by dipstick results, urine sediment will be microscopically examined for the presence of red blood cells, white blood cells, casts, crystals, epithelial cells, and bacteria.

[f] Clinical laboratory tests: (Chemistry) alkaline phosphatase, creatinine, ferritin, C-reactive protein, albumin, alanine aminotransferase, amylase, aspartate aminotransferase, gamma glutamyl transpeptidase, total bilirubin, blood urea nitrogen, glucose, lipase, sodium, potassium, calcium; (Hematology) hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count. Only in women who are not WOCBP (to confirm postmenopausal status): follicle stimulating hormone at Visit 0.

[g] Viral screening for human immunodeficiency virus (HIV) 1 or 2, hepatitis B, hepatitis C.

[h] Flex bility for visit days: Visit 3 Day 8±1 d; Visit 4 Day 22±2 d; Visit 5 Day 29±3 d; Visit 5.1 Day 36±3 d; Visit 6 Day 43±4 d; Visit 7 Day 50±4 d; Visit 8 Day 85±7 d; Visit 9 Day 184±9d; Visit 10 Day 365±14d; Visit 11 Day 547±14d; Visit 12 Day 730±14d.

[i] Only for the first 6 subjects per group. Questioning on and documentation of AEs as well as systemic and local reactions, the latter in case of upcoming dose decision meetings.

[j] Visits 8 and 9, only IMP-related AEs and any SAEs. Visits 10, 11 and 12, only any SAEs.

[k] Blood draw for anti-SARS-CoV-2 ant bodies (samples will be stored until a test is commercially available).

[l] For Cohort 13, first immunization with at least 15 min intervals between subjects. For first immunization in Cohorts 11 and 12 and for all cohorts after the boost immunization, immunization with at least 5 min intervals between subjects.

[m] Oral swipe for SARS-CoV-2 testing either on Day -1 or at the Visit 1 on Day 1.

[n] The listed blood draw days may be adapted if justified by the collected data. Leftover blood after completion of the immunogenicity assessments may be used for additional analyses as descr bed in Section 8.7 (Genetics) and/or Section 8.8 (Biomarkers).

[o] For subjects who have given consent, one aliquot of the blood sample drawn for analysis of CMI may be used for HLA typing to allow additional analysis of T-cell receptor repertoire and / or phenotypic characterization of T-cells specific to vaccine-encoded antigens.

[p] If HLA typing using the blood sample collected with Lithium Heparin is not conclusive, EDTA-blood will be drawn for HLA testing.

[r] When entering the follow-up phase, i.e., after completing the EoT visit, subjects are allowed to participate in other clinical trials not investigating COVID-19 vaccines or treatments (including immunosuppressants).

If the boost dose is not administered or if trial subjects permanently discontinued from IMP administration, subjects will complete all assessments planned for that visit and for the EoT Visit as listed in the SoA.

Abbreviations: AE = adverse event; CMI = cell-mediated immune testing; D or d = day; ECG = electrocardiogram; EDTA = ethylenediamine tetraacetic acid; EoT = end of treatment (Visit); FU = follow-up (visit); h = hour(s); HLA = human leukocyte antigen; Day 0 = one day before Day 1; IMP = investigational medicinal product; min = minute(s); SARS-CoV-2 = the virus leading to COVID-19; WOCBP = women of childbearing potential.

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TRIAL-SPECIFIC ABBREVIATIONS/TERMS

Abbreviation/Term	Explanation
Allocated subject	Enrolled subjects who are allocated to IMP
BNT162-02	C4591001 according to the Pfizer trial code
BNT162a	BNT162 RNA-LNP vaccine utilizing uRNA (the variant BNT162a1 will be tested in this trial)
BNT162b	BNT162 RNA-LNP vaccine utilizing nucleoside modified mRNA (the variants BNT162b1 and BNT162b2 will be tested in this trial)
BNT162c	BNT162 RNA-LNP vaccine utilizing self-amplifying mRNA (the variant BNT162c2 will be tested in this trial)
C4591001	BNT162-02 according to the BioNTech trial code
CMI	Cell-Mediated Immunity
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
Elderly (adults)	As defined in ICH E7, individuals aged 65 years or older
ELISA	Enzyme-Linked Immunosorbent Assay
ELISpot	Enzyme-Linked Immuno-Spot
Enrolled subjects	Subjects who signed an informed consent form, i.e., who gave informed consent
HCS	Convalescent human serum
HLA	Human leukocyte antigen
IM	Intramuscular(ly)
IV	Intravenous(ly)
modRNA	Nucleoside modified messenger RNA
mRNA	Messenger RNA
Older (adults)	Defined in this document to be individuals aged 56 to 85 years
P/B	Prime/Boost: a dosing regimen, comprising a priming immunization and a boost immunization
PEI	(German) Paul-Ehrlich-Institute
qt-PCR	Quantitative polymerase chain reaction
RNA-LNP	RNA lipid nanoparticle
RNA-LPX	RNA lipoplex
saRNA	Self-amplifying messenger RNA
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	The virus leading to COVID-19
SD	Single dose (also referred to as “single priming dose” or “single immunization”)
uRNA	Non-modified uridine containing mRNA
VNT	Virus neutralization test
Younger (adults)	Defined in this document to be individuals aged 18 to 55 years

For standard abbreviations, see Section 10.9.

NOTES FOR THE READER

When the term “must” is used, the action/item is always mandatory. Non-compliance with this instruction constitutes a protocol deviation. When the term “should” is used, the action/item is recommended but not mandatory. Non-compliance with this instruction does not constitute a protocol deviation.

The BioNTech SE group is a holding comprising several subsidiaries including BioNTech RNA Pharmaceuticals GmbH, the sponsor of this clinical trial.

2 INTRODUCTION

2.1 Background

2.1.1 Overview of the disease

Severe Acute Respiratory Syndrome (SARS) -CoV-2 infections and the caused disease Coronavirus Disease 2019 (COVID-19) are increasing every day and spreading globally, affecting more and more countries.

On March 11th, 2020 the World Health Organization (WHO) characterized the COVID-19 outbreak as pandemic.

The WHO Situation Update Report dated April 15th, 2020 noted 1,914,916 confirmed cases with 123,010 deaths globally, including 977,596 confirmed cases with 84,607 deaths in the European region (WHO Situation Report Nr. 85).

There are currently no approved vaccines or antiviral drugs to prevent or treat SARS-CoV-2 infections or its associated disease COVID-19 (Habibzadeh and Stoneman 2020).

2.1.2 Introduction to BioNTech RNA-based vaccines

An LNP-formulated RNA-based vaccine would provide one of the most flexible, scalable and fastest approaches to provide protection against the emerging viruses like SARS-CoV-2 (Rauch et al. 2018; Sahin et al. 2014).

The development of an RNA-based vaccine encoding a viral antigen that is translated to protein by the vaccinated organism 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 via a cell-free *in vitro* transcription process, which allows an easy and rapid production, and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with conventional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

The development of *in vitro* transcribed RNA as an active platform for the use in infectious disease vaccines is based on the extensive knowledge of the company in RNA technology, which has been gained over the last decade. The core innovation is based on *in vivo* delivery of a pharmacologically optimized, antigen-encoding RNA to induce robust neutralizing antibodies and a concomitant T-cell response to achieve protective immunization with minimal vaccine doses (Vogel et al. 2018; Moyo et al. 2018; Pardi et al. 2017).

At BioNTech, there are three different RNA platforms under development, namely non-modified uridine containing mRNA (uRNA, BNT162a), nucleoside modified mRNA (modRNA, BNT162b), and self-amplifying mRNA (saRNA, BNT162c).

All three RNA platforms have been tested in more than a dozen non-clinical GLP safety studies and, for uRNA and modRNA, there is pre-existing clinical safety data (see the BNT162 investigator's brochure [IB]). These data have been obtained primarily with RNAs formulated with liposomes which are related, but not identical, to those to be used in this trial.

The non-clinical toxicity data generated by BioNTech suggest a favorable safety profile for uRNA and modRNA, as well as saRNA formulated with different nanoparticles for various administration routes, including intravenous (IV) injection. The favorable safety profile after IV dosing is notable because it results in a higher systemic exposure than the planned IM dosing in this trial. Overall, the findings were mild and mostly related to the mode-of-action and the RNA-intrinsic stimulation of innate immune sensors. No unsuspected target organs of toxicity were identified. The non-clinical safety profile of uRNA and modRNA in rodents was predictive for clinical safety. For further details, see the BNT162 IB.

The safety and toxicity of the lipid nanoparticle enveloped uRNA, modRNA, and saRNA vaccines encoding coronavirus antigens is currently being analyzed in a GLP-compliant repeated-dose toxicity study.

A recently published clinical trial using an influenza vaccine based on modRNA encapsulated in LNPs highly related to those used in this trial and also administered IM reported good safety and well tolerability (Feldman et al. 2019).

2.2 Trial rationale

SARS-CoV-2 infections and the caused disease COVID-19 are increasing every day and spreading globally, affecting more and more countries, and carrying a high risk of rapidly becoming pandemic (for more details, see Section 2.1.1). There are currently no vaccines or antiviral drugs to treat these infections or its caused disease COVID-19. Therefore, there is an unmet need for the rapid development of effective prophylactic vaccines.

BioNTech has developed a technology platform of RNA-based vaccines which enables the rapid development of vaccines against emerging viral diseases (for more details, see Section 2.1.2). This technology platform is especially attractive because it has the ability to deliver high numbers of vaccine doses rapidly in a single production campaign.

This trial investigates the potential safety and immunogenicity of four prophylactic BNT162 vaccines against SARS-CoV-2, BNT162a1, BNT162b1, BNT162b2, and BNT162c2. The two variants of the BNT162b vaccines, BNT162b1 and BNT162b2, differ in the encoded antigen.

Some of the prophylactic BNT162 vaccines against SARS-CoV-2 investigated in this trial are under investigation in other ongoing trials (see Table 8). The status and preliminary results from all of these are trials are summarized in the following sections.

For the status of ongoing and planned clinical trials, see Table 8.

Table 8: Status of ongoing and planned clinical trials (as of 24 SEP 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: Due to changes in the overall clinical development plan, Part B will no longer be conducted.	<u>BNT162a1 (age 18 to 55 years):</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 years):</u> 1 µg 12 subjects prime / 12 boost 3 µg 12 subjects prime / 12 boost 10 µg 12 subjects prime / 11 boost 20 µg 12 subjects prime / 11 boost 30 µg 12 subjects prime / 12 boost 50 µg 12 subjects prime / 11 boost 60 µg 12 subjects prime (Further dosing with BNT162b1 at 60 µg and the boost dose for already dosed subjects was cancelled) <u>BNT162b1 (age 56 to 85 years):</u> 10 µg 12 subjects prime / 6 boost 20 µg 12 subjects prime / 0 boost 30 µg 2 subjects prime / 0 boost <u>BNT162b2 (age 18 to 55 years):</u> 1 µg 12 subjects prime / 11 boost 3 µg 12 subjects prime / 12 boost 10 µg 12 subjects prime / 11 boost 20 µg 12 subjects prime / 12 boost 30 µg 12 subjects prime / 12 boost <u>BNT162b2 (age 56 to 85 years):</u> 10 µg 12 subjects prime / 12 boost 20 µg 12 subjects prime / 12 boost 30 µg 12 subjects prime / 2 boost <u>BNT162c2 SD (age 18 to 55 years):</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) <u>BNT162c2 P/B (age 18 to 55 years):</u> 0.1 µg 12 subjects prime / 12 boost 0.3 µg 12 subjects prime / 12 boost 1 µg 12 subjects prime / 12 boost 3 µg 12 subjects prime / 0 boost

Trial number	Design	Current number dosed (subject age)
BNT162-02 / C4591001 (NCT 04368728) US, Argentina, Brazil, Turkey, Germany	Phase I/II/III, placebo-controlled, randomized, observer-blind, dose-finding trial. (Subjects are randomized: 4 active vaccine to 1 placebo)	**Phase I** BNT162b1 (age 18 to 55 years): 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 (Further dosing with BNT162b1 at 100 µg and the boost dose for already dosed subjects was cancelled) BNT162b1 (age 65 to 85 years): 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 years): 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 years): 10 µg 15 subjects prime / 15 boost 20 µg 15 subjects prime / 15 boost 30 µg 15 subjects prime / 15 boost **Phase II-III** BNT162b2 (age 18 to 85 years) 30 µg 33,346 subjects (split P/B not available) (Assuming 50% of the subjects are on BNT162b2 30 µg 16,673 subjects)
BNT162-03 (NCT 04523571) China	Phase I, randomized, placebo-controlled, observer-blind trial.	BNT162b1 (age 18 to 55 years): 10 µg 24 subjects prime / 24 boost 30 µg 24 subjects prime / 24 boost BNT162b1 (age >55 years): 10 µg 24 subjects prime / 0 boost 30 µg 24 subjects prime / 0 boost
BNT162-04 (NCT 04537949) 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.	BNT162b3 (age 18 to 55 years): 10 µg 6 subjects prime / 0 boost BNT162b3 (age 56 to 85 years): Recruiting.

Note: For the BNT162-02/C4591001 trial, the term “stage” was replaced by “phase” by an amendment.
NCT = ClinicalTrials.gov identify identifier.

See Table 9 for the number of trial subjects dosed at least once with BNT162 vaccine candidates in the ongoing clinical trials.

Table 9: Number of trial subjects dosed at least once with BNT162 vaccine candidates in the ongoing clinical trials (status 24 SEP 2020)

BNT162 vaccine candidate ***Dosing regimen (age group)***	**BNT162a1**	**BNT162b1**	**BNT162b2**	**BNT162c2**	
Phase I					
SD (younger adults)	30	177	105	72	
SD (older adults)	0	119	81	0	
Phase II/III					
SD (younger and elderly adults)			16,673*		
Total all adults dosed at least once in Phase I & II/III	**30**	**296**	**16,859***	**72**	**Sum = 17,257**
		Sum BNT162b1 + BNT162b2 = 17,155*			

* Estimated / includes estimated number based on 1:1 active:placebo assignment.
Older adults = adults aged 56 to 85 years; SD = single dose; Younger adults = adults aged 18 to 55 years.

For a summary of the available results from the ongoing trials, see the BNT162 IB.

2.3 Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected TEAEs for this trial are given in the BNT162 IB.

2.3.1 Risk assessment

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

- The volume of blood drawn will be kept to a minimum and will remain less than that drawn when donating blood:
    - For subjects in Cohorts 1 to 10, up to approximately 592 mL blood will be drawn per subject over the complete trial, i.e., over approximately 223 d.
    - For subjects in Cohorts 11 to 13, up to approximately 1022 mL blood will be drawn per subject over the complete trial, i.e., over approximately 760 d.
- All trial-specific procedures will be performed by qualified trial site personnel.
- Immunization will be done by a physician.
- Human experience with BNT162 vaccines was not available prior to this trial. However, clinical data was available for RNAs formulated with related but not identical liposomal compositions or non-formulated RNAs and can support risk assessment of the BNT162 vaccines.

Based on such data, the risks linked to the immunization with the BNT162 vaccines are as follows:

- Due to the IM route of administration, there is the risk of local reactions at the injection site, e.g., erythema, pruritus, pain, tenderness, swelling, sweating.

- Due to their immune-modulatory effect, vaccines may cause systemic flu-like reactions such as temporary headache, fatigue, loss of appetite, myalgia, arthralgia, fever. Rarely, with certain prophylactic vaccines (e.g., as seen for vaccines using attenuated viruses) severe allergic reaction or a neurological side effects, such as a seizure, were seen. Although these rare side effects are a concern, the risk of a vaccine causing serious harm or death is considered to be extremely small, in particular for BNT162 vaccines, which are molecularly defined, highly purified and based on RNA, which naturally occurs and is metabolized in the human organism.
- Due to the IM route the risk of systemic reactions is considered low.
- As with other vaccines, and with single stranded RNA being an innate immune sensor-agonist, BNT162 vaccine administration may cause temporary headache, fatigue or loss of appetite. Rarely, with certain prophylactic vaccines (e.g., as seen for vaccines using attenuated viruses) severe allergic reactions or neurological side effects, such as seizures, were seen. Although these rare side effects are a concern, the risk of a vaccine causing serious harm or death is considered to be extremely small, in particular for BNT162 vaccines, which are molecularly defined, highly purified, subunit vaccines.

The available non-clinical data of BNT162a, BNT162b, and BNT162c suggest a favorable safety profile with events that are mild and mostly related to the mode-of-action and the RNA-intrinsic stimulation of innate immune sensors.

- Based on the available clinical and non-clinical data on the individual components (uRNA, modRNA, saRNA, the specific LNP formulation), that are combined within the BNT162 products, a favorable safety profile of BNT162 products is expected with mild and localized effects (see the BNT162 IB for details on these trials).

To date, based on available clinical experience with BNT162 vaccines in human subjects.

- Generally, good tolerability was observed. Overall, many of the reported TEAEs appear to be similar to reactogenicity events anticipated for IM-administered vaccines, typically with an onset within first 24 h post immunization. All events / 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. Most TEAEs were managed with simple measures and resolved spontaneously.
- The adverse reactions (AEs for which there is a reason to conclude that the vaccine caused the events) identified for BNT162 vaccines at this time are: injection site pain, fever, fatigue, headache, chills, and muscle pain.
- While the general risk of effects potentially associated with the innate immune activation and transient secretion of associated cytokines are defined above based on the described data, the dose response-relationship, and thus the tolerability for the BNT162 vaccine candidates will only be defined by the ongoing trials (for a summary of the ongoing trials, see Table 8 and the BNT162 IB).

The clinical experience after P/B dosing with BNT162b1 at 10, 20, and 30 µg and single doses of BNT162b2 at 10, 20, and 30 µg, in healthy elderly adults aged 65 to 85 years is summarized in the BNT162 IB.

The local tolerability of BNT162b1 and BNT162b2 in elderly adults seemed comparable to that recorded in younger adults aged 18 to 55 years. Likewise, the pattern of systemic reactogenicity appeared similar between the 2 age groups, possibly with a lower overall incidence in the elderly adults in comparison to the younger adults at equal doses (for details, see the BNT162 IB).

Preliminary data in elderly adults, show lower but measurable antibody responses in older adults than in younger adults (for details, see the BNT162 IB). The investigation of higher dose range in older adults in this trial may therefore be required to support the Phase III program planned to support marketing approval.

When assessing the risk for dosing of older subjects with BNT162 vaccine candidates in this trial, the follow information is relevant:

- Preliminary data in subjects treated in the ongoing BNT162 trials backed by non-human primate (rhesus macaque) immunogenicity data have shown that BNT162b1 in the tested dose range is immunogenic.
- The risk that older adults may be under dosed with the vaccine doses chosen based on data for younger adults (as was observed for other vaccines).
- Preliminary data in elderly show a comparable to lower reactogenicity based on the observed local reactions and system events in similar doses. This observation may indicate a lower innate response in younger adults.
- In this trial, the P/B BNT162b1 and BNT162b2 doses planned in older adults (10, 20, and 30 µg) are within the range already shown to show acceptable tolerability in younger adults and in elderly adults in this trial and/or BNT162-02 trial (for details, see the BNT162 IB). This tolerability in elderly adults appears to be better than seen in younger adults at the same doses.
- Although using doses already found to show acceptable tolerability in younger adults and an even better tolerability in elderly adults, this trial implements numerous safety measures (e.g., sentinel dosing/staggering of subjects, on site observation periods after each immunization, wellbeing questioning, frequent on site visits after immunization).
- This trial includes inclusion/exclusion criteria to exclude potential risk factors relevant for all adults, but additional criteria have been included to further protect the safety of enrolled older adults.

- The listed risks can be managed using routine symptom driven standard of care as described in Section 6.6.3. Treatment of these events is dependent on the discretion of the investigators.
- Since this trial involves the first immunization of humans with the BNT162 vaccines, in the FIH cohorts and all dose escalation cohorts use a sentinel dosing/staggering

of subjects (EMA 2017 guidance "Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products").

To further ensure trial subject safety during dose ranging cohorts, the trial protocol foresees that:

- On site observation periods after each immunization (i.e., 24 h for the first 6 subjects per group and 6 h for other subjects in the same group) that are much longer than used in recently completed FIH clinical trials investigating related RNA-based vaccines. For example, the 2 Moderna trials investigating mRNA vaccines against avian H10N8 and H7N9 influenza viruses in healthy adults (Feldman et al. 2019) that observed trial subjects on site for only 1 h after each immunization before discharge from the trial site.
- More frequent on site visits after immunization (i.e., on Days 2 and 8) than used in recently completed FIH clinical trials investigating with related RNA-based vaccines, e.g., the 2 Moderna trials investigating mRNA vaccines against avian H10N8 and H7N9 influenza viruses in healthy adults (Feldman et al. 2019) that used on site visits on Day 8.
- Subject wellbeing questioning by telephone at 48±2 h after each immunization (where applicable, after both the prime and boost immunizations) will be performed for the first 6 subjects per cohort. Additional subject wellbeing calls may be included at the discretion of the SRC.
- In the case that an individual experiences dose limiting toxicities or that the frequency or pattern of AEs within a sub-cohort gives cause for concern, the investigator may request an ad hoc review by the SRC before further doses of a given vaccine construct are administered.
- If the investigator considers necessary, the planned observation periods before proceeding to dose further subjects in the same group may be prolonged by 24 h.
- The SRC must assess the safety and tolerability data of the first 6 subjects before allowing progression to the next cohort, for each vaccine per cohort/dose level.
- After each assessment, the SRC may request a prolongation of the observation periods to up to Day 7 for later cohorts. Experience in this ongoing trial and in the ongoing BNT162-02 trial, has confirmed the adequacy of the implemented observations periods.
- The SRC may make recommendations on increasing observation periods and additional subject wellbeing calls may be included at the discretion of the SRC.
- To ensure trial subject safety during the trial, their safety will be monitored from Visit 0 (screening) until approximately 6 months after the last immunization.

For the expansion cohorts:

- Due to the extensive experience and exposure already achieved with BNT162b2 at 30 µg in the ongoing global Phase II/III trial (from which frequent, rolling safety data submissions to health authorities are being made) the measures implemented for

dose ranging cohorts are deemed unnecessary for the expansion cohorts (by 24 SEP 2020, almost 17,000 trial subjects have been dosed at least once with BNT162b2, see Table 9).

- Immunocompromised individuals are considered at increased risk from infection with SARS-CoV-2 and of infections in general. Risk minimization measures already in place for the protection of all subjects in this trial are also considered sufficient to protect this increased risk group, who are generally regarded as ambulatory in nature. Care should however be taken to avoid unnecessary extension of on site time and site visits for these subjects, to minimize their risk of exposure to high risk pathogens.

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

The risks linked to the pandemic COVID-19 outbreak will be managed by requiring that the trial subjects:

- Avoid contact with persons tested positive for SARS-CoV-2 antibodies or have an increased risk for infection during their participation in the trial.
- Practice social distancing and follow good practices to reduce their chances of being infected or spreading COVID-19 during their participation in the trial.
- Complete health status checks which include symptom-directed physical examinations, vital signs assessments, and clinical laboratory tests at the planned visit days.
- Use the Subject Hotline to contact the trial site during their participation in the trial should they require guidance or should they experience any symptoms of illness. The reporting of any symptoms of illness, e.g., enhanced respiratory disease or flu-like symptoms, may trigger diagnostic measures at the discretion of the investigator.

To minimize the risk to trial subjects in this trial, an SRC will regularly review and evaluate the safety and immunogenicity data. For details, see Section 10.1.5.

2.3.2 Benefit assessment

After participating in this trial, depending on the immunization regimen followed, some trial subjects should be immune against SARS-CoV-2 infection.

There is an urgent need for the development of new prophylactic vaccines given the threat posed by the increasing number of globally distributed outbreaks of SARS-CoV-2 infection. The BioNTech platform of RNA-based vaccines being tested in this trial is especially attractive because it has the ability to deliver high numbers of vaccine doses rapidly in a single production campaign. This platform has the added advantage of not employing live virus and could therefore potentially be used for immuno-compromised populations.

By participating in this trial, the trial subjects will support the development of one or more prophylactic vaccines against SARS-CoV-2 infection.

2.3.3 Overall benefit/risk conclusion

Overall, the sponsor considers the benefit/risk ratio to be acceptable for a trial of this type.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints [a]
Primary objective	
(All cohorts) To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after single dose (SD; prime only) or prime/boost (P/B) immunization.	• Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7 d after each immunization (trial days 8 and 29). • Solicited systemic reactions (nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever) recorded up to 7 d after each immunization (trial days 8 and 29). • The proportion of subjects with at least 1 unsolicited TEAE: o For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): occurring up to 21 d after the prime immunization (trial day 22) and 28 d after the boost immunization (trial day 50). o For BNT162c2 (SD): The proportion of subjects with at least 1 unsolicited TEAE occurring up to 28 d after the immunization (trial day 29).
Secondary objectives	
(All cohorts) To describe the immune response in healthy adults after SD or P/B immunization measured by a functional antibody titer, e.g., VNT or an equivalent assay available by the time of trial conduct.	<u>For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B):</u> As compared to baseline at 7 and 21 d after primary immunization (trial days 8 and 22) and at 7, 14 [b], 21, 28, 63, and 162 d after the boost immunization (trial days 5 to 9): • Functional antibody responses (titers). • Fold increase in functional antibody titers. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline. <u>For BNT162c2 (SD):</u> As compared to baseline at 7, 21, 28, 42, 84, and 183 d after the primary immunization (trial days 8 to 184): • Functional antibody responses (titers). • Fold increase in functional antibody titers. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline.
Exploratory objectives	
(All cohorts) To describe the immune response in healthy adults after SD or P/B immunization measured by an antibody binding assay, e.g., ELISA or an equivalent assay available by the time of trial conduct.	<u>For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B)</u> As compared to baseline at 7 and 21 d after primary immunization (trial days 8 and 22) and at 7, 14 [b], 21, 28, 63, and 162 d after the boost immunization (trial days 8 to 184). • Antibody responses measured (concentrations/titers). • Fold increase in antibody (concentrations/titers). • Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody concentrations/titers. <u>For BNT162c2 (SD)</u> As compared to baseline at 7, 21, 28, 42, 84, and 183 d after the primary immunization (trial days 8 to 184): • Antibody responses measured (concentrations). • Fold increase in antibody (concentrations).

Objectives	Endpoints [a]
	• Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody concentrations.
(All cohorts) To describe the CMI responses.	For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B) and BNT162c2 (SD) At baseline and at 28 d after the primary immunization (trial day 29): • CMI responses measured, e.g., by enzyme-linked immuno-spot (ELISpot) and ICS.
Additional exploratory objective (Only for the Expansion cohorts [Cohorts 11 to 13]) To further characterize the long term adaptive immune response after P/B immunization with 30 µg BNT162b2.	As compared to baseline at 7 and 21 d after primary immunization (trial days 8 and 22) and at 7, 14 [b], 21, 28, 63, and 162, 343, 525, and 708 d after the boost immunization (trial days 8 to 730). • Functional antibody titers measured (e.g.) using VNT. o Measured cross-neutralization of viruses from other coronavirus families. • Further assays for: o Antibody-dependent cellular cytotoxicity (ADCC). o Antibody induced phagocytosis. o Immune cell degranulation. o Activation of immune cells such as lymphocytes and granulocytes. o Antibody mediated uptake and formation of immune complexes.
Additional exploratory objectives only for the Expansion cohorts [Cohorts 11 to 13]) To further characterize the long term adaptive immune response after P/B immunization with 30 µg BNT162b2.	As compared to baseline at 364, 546, and 729 d after the primary immunization (trial days 365 to 730): • Functional antibody titers measured (e.g.) using VNT. o Antibody responses measured (titers). o Fold increase in antibody titers. o Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers. • Functional antibody binding concentrations measured (e.g.) using ELISA. o Antibody responses measured. o Fold increase in antibody titers. o Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers. • CMI responses measured (e.g.) using ELISpot and ICS.
(Only for the Expansion cohorts [Cohorts 11 to 13]) To further characterize the adaptive immune response: Assessment of cell-mediated immunity	• Further characterization of vaccine and SARS-CoV-2 specific antigen-specific CD4 and CD8 T-cells, e.g., using ELISpot, ICS. • Functional characterization of T-cells (e.g. antigen dependent cytokine secretion, activation, proliferation, cytotoxicity, determination of HLA restriction). • Cellular and molecular phenotyping of immune cells using e.g., immunophenotypic characterization of T-cells to define reactive T-cell subsets. • Bulk or single cell TCR and transcriptome sequencing, quantitative polymerase chain reaction (qt-PCR) studies to profile and characterize and track TCRs and quantify the number of antigen-specific T-cells.

a) The given days are approximate; the respective schedule of activities defines assessment windows.
b) Only cohorts starting prime dosing after approval of amendment 09.

4 TRIAL DESIGN

4.1 Overall design

This trial has two parts. Part A and Part B. Due to changes in the overall clinical development plan, Part B will no longer be conducted. The objective originally described for Part B have been implemented in the ongoing development via a pivotal Phase I/II/III trial BNT162-02/C4591001 (ClinicalTrials.gov NCT: 04368728).

Part A is for dose ranging of four different vaccines (BNT162a1, BNT162b1, BNT162b2, and BNT162c2) will be undertaken with dose escalation and de-escalation plus the evaluation of interim dose levels. It also includes dose ranging in older subjects.

The vaccines BNT162a1, BNT162b1, BNT162b2, and BNT162c2 will be administered using a P/B regimen. The vaccine BNT162c2 will also be administered using a SD regimen.

BNT162b2, for which the dose regimen has been determined in the dose ranging in Part A of this trial, has now entered efficacy evaluation in the ongoing development via a pivotal Phase I/II/III trial BNT162-02/C4591001 (ClinicalTrials.gov NCT: 04368728). Therefore, for BNT162b2, amendment 09 of this trial introduces expansion cohorts designed to expand the existing safety profiling to a broader population and to enable detailed characterization of the adaptive immune responses, including determine factors that impact them. These cohorts will involve healthy and immunocompromised populations treated according to the selected dosing posology and exploring an alternative posology.

The chosen trial design reflects discussion and advice from the PEI obtained in scientific advice meetings held in February, March, and June 2020 in response to a fast-changing situation.

For a summary of the trial as a flow diagram, see the Schema in Section 1.2. For the planned assessments and visits, see the Schedule of Activities (SoA) in Section 1.3.

Part A

The first part of the trial (Part A) will follow a dose escalation design. Discretionary dose de-escalation and refinement is also planned. Part A will consist of a screening/treatment phase and a follow-up phase.

Dose ranging cohorts:

Trial subjects with the FIH immunization will be immunized using a sentinel dosing/subject staggering (EMA 2017 guidance “Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products”). The FIH starting dose and the planned escalation/de-escalation doses are given in Table 1. Dose escalation rules have been defined in this protocol to guide dose escalation.

For all cohorts, if the investigator considers necessary, the planned observation periods before proceeding to dose further subjects in the same group may be prolonged by 24 h.

Dose de-escalation in the case of possible vaccine-related toxicities will be guided by the Safety Review Committee (SRC), as required.

In Cohort 1, the sentinel dosing/subject staggering process will be as follows:

- One sentinel subject will be dosed on one day.
- If the dosing in this subject was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 5 further subjects will be dosed (with intervals of at least 1 h between subjects).
- If the dosing in these 5 subjects was considered to be safe and well tolerated by the investigator based on 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48±2 h data from the sentinel subject):
    - The remaining 6 subjects in the group will be dosed (with intervals of at least 30 min between subjects).
    - If approved by the SRC, the next planned escalation dose (see Table 1) will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects including observation on site, short summary of phone interview (including statement about diary reports), vital signs, investigator reported local and systemic reactions, TEAEs, solicited local & systemic reactions, blood/clinical laboratory data, and brief physical examination outcome.
    - If approved by the SRC, the planned de-escalation dose in Cohort 3 will be initiated.

For any subsequent dose escalation cohorts (to doses higher than the maximum already tested for a vaccine candidate), the sentinel/subject staggering process will be as follows:

- Two sentinel subjects will be dosed on one day (with intervals of at least 30 min between subjects).
- If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 4 further subjects will be dosed (with intervals of at least 15 min between subjects).
- If the dosing in these 4 subjects was considered to be safe and well tolerated by the investigator based on 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48 h data from the sentinel subjects):
    - The remaining 6 subjects in the group will be dosed (with intervals of at least 15 min between subjects).
    - If approved by the SRC, the next planned escalation dose (see Table 1) will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects including observation on site, short summary of phone interview (including statement about diary reports), vital signs, investigator reported local and systemic reactions, TEAEs, solicited local & systemic reactions, blood/clinical laboratory data, and brief physical examination outcome.

The maximum allowed dose for each vaccine candidate is defined in Table 1.

For the planned dose de-escalation cohorts, 12 subjects may be dosed on one day (with intervals of at least 15 min between subjects). The doses in these cohorts in younger adults must be lower than doses than doses that have shown acceptable tolerability in younger adults (based on the data from 12 subjects up until 48 h after the first dose). The same dose will not be administered twice, i.e., in two cohorts.

For BNT162b1 and BNT162b2, administration of the planned 10 µg dose in older subjects (Cohort 8) may start once at least a 30 µg dose has shown acceptable tolerability in younger adults (based on the data from 12 subjects up until 48 h after the boost dose).

The dose in Cohort 8 must also be confirmed by the SRC. In Cohort 8, 12 subjects will be dosed using a sentinel dosing/subject staggering (2-4-6) process with intervals of at least 1 h between the first 6 subjects and then at least 30 min intervals for the remaining 6 subjects.

For BNT162b1 and BNT162b2, administration of the planned dose escalation cohorts in older adults (Cohorts 9 and 10), 12 subjects will be dosed using a sentinel dosing/subject staggering (2-4-6) process with intervals of at least 30 min between subjects. The doses planned in these cohorts will only be administered if the dose is confirmed by the SRC.

The doses planned for Cohorts 8 to 10 are defined in Table 2.

For the unplanned dose de-escalation cohorts, i.e., where the SRC requests the use of a reduced dose for safety reasons, 12 subjects may be dosed on one day with intervals of at least 15 min between subjects (as for planned de-escalation cohorts).

Note: BNT162b1 and BNT162b2 are nucleoside modified RNAs, while BNT162a1 and BNT162c2 are both non-modified uridine containing RNAs. RNA modification is known to impact the extent of innate immune activation at a given dose level, and thus potentially the extent of reactogenicity. Therefore, tolerability data obtained with one of the vaccine variants of each of these pairs may be potentially informative for the respective other one and should be taken in consideration by the SRC for recommendations of lower or interim doses.

In the case that an individual experiences dose limiting toxicities or that the frequency or pattern of AEs within a sub-cohort gives cause for concern, the investigator may request by phone an ad hoc review by the SRC, at any time, before further doses of a given vaccine construct are administered.

Expansion cohorts:

Protocol amendment 6.0 implemented three additional cohorts (Cohorts 11, 12, and 13) comprising additional 150 trial subjects aged from 18 to 85 years receiving BNT162b2 only.

BNT162b2 has entered a Phase II/III evaluation of efficacy, with the intent to support an application for marketing authorization. The dosing regimen under investigation is two 30 µg BNT162b2 doses given ~21 d apart.

The expansion cohorts are intended to provide a more in depth characterization of the adaptive immune responses induced by BNT162b2, associated vaccine safety, and the impact of factors such as subject disposition and dosing posology on humoral and cell-

mediated immunity. These cohorts will extend the safety data of BNT162b2 to a broader trial population and thus closer to the vaccine target population.

Moreover, each of these cohorts will add to a more differentiated understanding of the BNT162b2-induced adaptive immune response composed of antigen-specific antibodies, CD4 and CD8 T-cells, with a view to developing insights into the mechanisms by which immunity to SARS-CoV-2 may be induced and factors driving any variability in response. Alternative treatment approaches for difficult to treat or high risk subjects may be determined. In each of these dose cohorts, a broader characterization of T-cell and antibody responses and their inter-individual variation will be performed. This will include the characterization of the dependency of adaptive immune responses on factors such as age, HLA haplotype, BMI and gender.

The planned dose of BNT162b2, two 30 µg BNT162b2 doses given 21 d apart, is the same regimen that has already been tested in the dose escalation phase of this trial and in almost 17,000 adult subjects, including those with acute and chronic illnesses, in the ongoing global Phase I/II/III trial BNT162-02/C4591001 (ClinicalTrials.gov NCT: 04368728). As such, all trial subjects in the three expansion cohorts can be treated in parallel.

For Cohort 13, the interval between prime immunizations will be at least 15 min. For prime immunization in Cohorts 11 and 12 and for all cohorts after the boost immunization, the interval will be at least 5 min.

The three expansion cohorts (with comparable numbers of male and female subjects for each of the defined age groups, see the section Population) are as follows:

- Cohort 11: Alternative posology cohort with 30 healthy adults who will receive BNT162b2 using one 3 µg prime dose and one 30 µg boost dose of BNT162b2 given approximately 21 d apart (P/B regimen).
- Cohort 12: Adaptive immune response cohort (including safety and long term immune response) with 90 healthy adults who will receive two 30 µg BNT162b2 doses given approximately 21 d apart (P/B regimen).
- Cohort 13: Population expansion cohort (including safety and long term immune response) with 30 immunocompromised adults who will receive of two 30 µg BNT162b2 doses given approximately 21 d apart (P/B regimen).

For the scientific rational for the expansion cohorts, see Section 4.2.

All trial site visits for subjects in the expansion cohorts will be conducted on an outpatient basis, with the clinical judgment of the investigator determining whether a period of observation beyond that required for completion of study procedures is required, on a case by case basis. Standard measures to avoid cross-contamination of immunocompromised individuals with high risk pathogens should be followed for 24 months after the primary immunization.

Part B

Due to changes in the overall clinical development plan, Part B will no longer be conducted.

4.1.1 Adaptive trial design elements

Dose de-escalation and escalation rules have been defined in this protocol (see Section 6.6.2).

4.1.2 Planned number of trial subjects

See Table 4.

4.2 Scientific rationale for the trial design

The trial design is based on the sponsor's experience with trials of this type and other published trials for vaccine development.

The chosen trial design reflects discussion and advice from the PEI obtained in two scientific advice meetings held in February and March 2020. At these meetings, the PEI supported the high-level design of this trial, specifically the staggered approach, single dose (single immunization dose) and P/B testing, conditional to performance of lower dose exploration if appropriate and re-consideration of the dose regimens for Part B if appropriate.

Part A of the trial is designed as a classical dose escalation, investigating the dose range which is most likely to be well tolerated and induce a virus neutralizing response. To ensure trial subject safety, a staggered approach has been chosen starting with a defined low standard dose. Use of the overlapping escalating doses in Cohorts 1 to 3, i.e., progression to initiation of dosing at the next higher dose when data is available for 6 of 12 trial subjects per group, allows a faster dose escalation while ensuring trial subject safety.

Trial subjects in Cohort 1 (with the FIH immunization), will be immunized using a sentinel dosing/staggering of subjects (EMA 2017 guidance "Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products").

The expansion cohorts (Cohorts 11 to 13) are designed to be complementary to the ongoing global Phase I/II/III trial BNT162-02/C4591001 (ClinicalTrials.gov NCT: 04368728), to demonstrate clinical efficacy and safety for two 30 µg BNT162b2 doses given ~21 d apart, which will enroll over 40'000 subjects. The Phase I/II/III trial does not include the detailed immunogenicity assessments needed to better understand the mode-of-action of the vaccine and approaches for potential improvements, e.g., in defined populations (by age, gender, immunocompromised status, certain ethnicity-associated HLA, etc.). This trial will therefore include such immunogenicity assessments, including detailed characterization of immune responses to BNT162b2 in respect of binding antibodies, neutralizing antibodies, and cell-mediated immunity, including evaluation of CD4 and CD8 T-cell responses.

Cohort 11 aims to determine whether a lower prime dose may further improve vaccine tolerability (reactogenicity), without compromising immunogenicity whilst exploring whether this alternative posology promotes a more favorable pattern of composite immune response modulation. A lower prime dose may further improve reactogenicity and may modulate the pattern of the composite immune response towards a more pronounced B cell response. This alternative posology, if proven effective, could support future ring-

vaccination strategies and substantial dose efficiencies. The latter could be important during the scale-up phase at the beginning of a pandemic. It has previously been demonstrated for non-RNA vaccines that an asymmetric prime-boost strategy does not adversely impact the resulting immunogenicity. The use of a lower prime dose may enable optimization of the initial CMI response, when it is most beneficial for acute patient protection, without compromising the overall humoral response. This cohort will include long term monitoring of the immune response and immune-defense.

Cohort 12 is intended to complement the ongoing Phase II/III evaluation of efficacy by including assessment of the immune mechanisms induced by this unique class of vaccine. The data from this cohort addresses the expected dynamic range of inter-individual variability and could provide insights into treatment success factors and/or development strategies for future vaccine candidate design/selection for the current pandemic and future COVID-19 outbreaks. This cohort will include long term monitoring of the immune response and immune-defense.

Cohort 13 will comprise immunocompromised adults, a population that has a particular risk in the current pandemic for contracting COVID-19 and for severe complications. The reactogenicity but also the immune response to BNT162b2 may be dampened in immunocompromised individuals. This cohort will show whether the immune response is indeed compromised and if yes to which extent and in which of its components and thus allow rational approaches to also serve this population of subjects. It is crucial that the priority vaccination of high risk populations is supported by data demonstrating that vaccination will be well tolerated and clinically beneficial.

BNT162b2 was selected for Phase II/III evaluation of efficacy, in part, due to its superior performance in elderly subjects, who typically demonstrate lower reactogenicity than younger subjects, but also lower levels of immunogenicity than younger subjects. The objective of Cohort 13 is to characterize the immune responses in a population with both the age-related lower immunogenicity and the lower immunogenicity linked to being immunocompromised. This knowledge could help guide future treatment optimization strategies. This cohort will include long term monitoring of the immune response and immune-defense.

Part B of the trial will no longer be conducted due to changes in the global clinical development plan in a rapidly evolving situation.

4.3 Justification for dose

Given that BioNTech proposes a rapid response scenario to a newly emerged pandemic outbreak, sufficient data is currently not available to experimentally validate the dose selection and initial starting dose. Therefore, BioNTech proposed a starting dose of 0.1 µg (for BNT162c2), 3 µg (for BNT162a1) and 10 µg (for BNT162b1 and BNT162b2) in this trial based on non-clinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). Based on preliminary data from this trial, as explained below, the planned doses for the BNT162a1 and BNT162c2 vaccine candidates were reduced (see Table 1).

The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (RB_0003-01 N [NCT02410733], SAR441000 [NCT03871348]). Doses of up to 400 µg total uRNA administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA administered intratumorally, have not demonstrated signs of unpredictable overstimulation of the immune system.

The BNT162 vaccines will be administered IM as this route has been demonstrated to lead to efficient induction of antigen-specific cellular and humoral immunity and *in vivo* protein expression of comparable drug products (as shown by other companies, i.e., Moderna and CureVAC).

The doses planned in this trial were discussed with the PEI in a Scientific Advice Meeting on February 6th, 2020. At this meeting, the PEI supported the high-level design of this trial, conditional to dose exploration and, if appropriate, re-consideration of the dose regimens for Part B. This protocol reflects this advice.

As discussed in Section 2.3.1, to date, there is very limited clinical experience with BNT162 vaccines in human subjects. Reactogenicity is anticipated and considered to contribute to the mode-of-action of inducing vaccine immune responses. Initial dose ranging studies have suggested AE profiles consistent with previous usage of similar constructs in cancer patients, with AEs generally dividing into 2 groups: local injection site reactions and systemic flu-like illness.

As summarized in the BNT162 IB, to date most of the AEs reported after immunization with BNT162 vaccine candidates have been mild to moderate in intensity and no SAEs have been reported. Fever of severe intensity has been reported. Most AEs were managed with simple measures and resolved spontaneously.

Based on the available clinical and non-clinical data experience, the sponsor expects the planned maximal doses (see Table 1) to be safe.

The doses planned in this trial for older adults (i.e., adults aged between 55 and 85 years) reflect clinical data from the ongoing BNT162-01 and BNT162-02 trials with the vaccine candidates BNT162b1 and BNT162b2 in younger adults and elderly (adults aged between 65 and 85 years). After P/B dosing, these doses (10, 20, and 30 µg) showed acceptable tolerability in younger adults and in elderly adults. For details, see the BNT162 IB.

The dosing regimen planned in this trial for the expansion cohorts (Cohort 12 and 13), two 30 µg BNT162b2 doses given ~21 d apart (P/B regimen), is the dosing regimen currently being tested in the ongoing global Phase II/III trial BNT162-02. Status 24 SEP 2020, almost 17,000 trial subjects have been dosed with 30 µg BNT162b2 P/B.

Cohort 12 will explore an alternative posology with low dose prime (3 µg) and standard dose boost (30 µg) as described elsewhere.

Taken together, the planned starting doses in this trial are considered to be safe, but still sufficient to induce an antiviral immune response.

4.4 End of treatment (EoT) and end of trial definition

A trial subject is considered to have completed the trial if they have completed all planned visits as listed in the SoA, including all follow-up visits (see Section 1.3).

The EoT is defined as the date the last subject completed the EoT Visit (for BNT162c2 given SD Visit 6, for all cohorts with P/B dosing Visit 7).

The end of trial is defined as the date when the last subject completed the last planned visit given in the SoA (see Section 1.3).

5 TRIAL POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

5.1.1 Inclusion criteria Part A

Volunteers are only eligible to be enrolled in the trial if they meet all of the following criteria:

1. Have given informed consent by signing the informed consent form (ICF) before initiation of any trial-specific procedures.
2. They must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, lifestyle restrictions (e.g., to practice social distancing and to follow good practices to reduce their chances of being infected or spreading COVID-19), and other requirements of the trial.
3. They must be able to understand and follow trial-related instructions.
4. For younger subject cohorts, volunteers must be aged 18 to 55 years, have a BMI over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0.

   OR

   For older adult cohorts, volunteers must be aged 56 to 85 years, have a BMI over
   OR

   For the immunocompromised adult cohort (Cohort 13), volunteers must be aged 18 to 85 years, have a BMI over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0.
5. They must be healthy, in the clinical judgment of the investigator, based on medical history, physical examination, 12-lead ECG, vital signs (systolic/diastolic blood pressure, pulse rate, body temperature, respiratory rate), and clinical laboratory tests (blood chemistry, hematology, and urine chemistry) at Visit 0.

   Note: Healthy volunteers with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 wks before enrollment, can be included.

   OR

   For the immunocompromised cohort (Cohort 13); volunteers who have previously received solid organ transplant, or peripheral blood stem cell transplantation ≥6 months after transplantation, or individuals with HIV infection with a $CD4^+$ T-cell count of ≥200 x 10^6 /L. Individuals with lower T-cell counts will be excluded from the trial on the basis that this represents a significant medical complication. In the clinical judgment of the investigator, volunteers must be immunocompromised but otherwise healthy. After consultation with the Medical Monitor, this may include individuals receiving immunosuppressant therapy due to another confounding disease at least

2 wks prior to enrollment and/or at least 6 wks following immunization with BNT162b2, and/or individuals with immunosuppressive treatment of an autoimmune disease if the disease is stable.

6. WOCBP must have a negative beta-human chorionic gonadotropin urine test at Visit 0 and Visit 1. Women that are postmenopausal or permanently sterilized will be considered as not having reproductive potential.
7. WOCBP must agree to practice a highly effective form of contraception during the trial, starting after Visit 0 and continuously until 60 d after receiving the last immunization. WOCBP must agree to require their male partners to use condoms during sexual contact (unless male partners are sterilized or infertile).
8. WOCBP must confirm that they practiced at least one highly effective form of contraception for the 14 d prior to Visit 0.
9. WOCBP must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during trial, starting after Visit 0 and continuously until 60 d after receiving the last immunization.
10. Men who are sexually active with a WOCBP and have not had a vasectomy must agree to practice a highly effective form of contraception with their female partner of childbearing potential during the trial, starting after Visit 0 and continuously until 60 d after receiving the last immunization.
11. Men must be willing to refrain from sperm donation, starting after Visit 0 and continuously until 60 d after receiving the last immunization.
12. They must have confirmation of their health insurance coverage prior to Visit 0.
13. They must agree to not be vaccinated during the trial, starting after Visit 0 and continuously until 28 d after receiving the last immunization.

5.2 Exclusion criteria

5.2.1 Exclusion criteria Part A

Volunteers are excluded from the trial if they meet or present any of the following criteria:

1. Have had any acute illness, as determined by the investigator, with or without fever, within 72 h prior to the first immunization. An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the investigator, the residual symptoms will not compromise their wellbeing if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.
2. Are breastfeeding on the day of Visit 0 or who plan to breastfeed during the trial, starting after Visit 0 and continuously until at least 90 d after receiving the last immunization.
3. Have a known allergy, hypersensitivity, or intolerance to the planned IMP including any excipients of the IMP.

4. Had any medical condition or any major surgery (e.g., requiring general anesthesia) within the past 5 years which, in the opinion of the investigator, could compromise their wellbeing if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments. See the inclusion criteria 5 for non-excluded medical conditions for Cohort 13.
5. Have any surgery planned during the trial, starting after Visit 0 and continuously until at least 90 d after receiving the last immunization.
6. Had any chronic use (more than 21 continuous days) of any systemic medications, including immunosuppressants or other immune-modifying drugs (except for Cohort 13), within the 6 months prior to Visit 0 unless in the opinion of the investigator, the medication would not prevent, limit, or confound the protocol-specified assessments or could compromise subject safety.
   Note: Healthy volunteers with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 wks before enrollment, can be included.
7. Received any vaccination within the 28 d prior to Visit 0.
8. Had administration of any immunoglobulins and/or any blood products within the 3 months prior to Visit 0.
9. Had administration of another investigational medicinal product including vaccines within 60 d or 5 half-lives (whichever is longer), prior to Visit 0.
10. Have a known history or a positive test for any of Hepatitis B, or Hepatitis C, or HIV 1 or 2 (except for Cohort 13) within the 30 d prior to Visit 0.
11. Have a positive PCR-based test for SARS-CoV-2 within the 30 d prior to Visit 1.
12. Have a positive drugs of abuse (for amphetamines, benzodiazepines, barbiturates, cocaine, cannabinoids, opiates, methadone, methamphetamines, phencyclidine, and tricyclic antidepressants) result at Visit 0 or Visit 1.
13. Have a positive breath alcohol test at Visit 0 or Visit 1.
14. Previously participated in an investigational trial involving lipid nanoparticles.
15. Are subject to exclusion periods from other investigational trials or simultaneous participation in another clinical trial. When entering the follow-up phase, i.e., after completing the EoT visit, subjects are allowed to participate in other clinical trials not investigating COVID-19 vaccines or treatments.
16. Have any affiliation with the trial site (e.g., are close relative of the investigator or dependent person, such as an employee or student of the trial site).
17. Have a history (within the past 5 years) of substance abuse or known medical, psychological, or social conditions which, in the opinion of the investigator, could compromise their wellbeing if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.
18. Have a history of hypersensitivity or serious reactions to previous vaccinations.

19. Have a history of Guillain-Barré syndrome within 6 wks following a previous vaccination.
20. Have a history of narcolepsy.
21. Have history of alcohol abuse or drug addiction within 1 year before Visit 0.
22. (Except for Cohort 13) Have a history of or suspected immunosuppressive condition, acquired or congenital, as determined by medical history and/or physical examination at Visit 0.
23. Have any abnormality or permanent body art (e.g., tattoo) that, in the opinion of the investigator, would obstruct the ability to observe local reactions at the injection site.
24. Have had any blood loss >450 mL, e.g., due to donation of blood or blood products or injury, within the 7 d prior to Visit 0 or plan to donate blood during the trial, starting after Visit 0 and continuously until at least 7 d after receiving the last immunization.
25. Symptoms of COVID-19, e.g., respiratory symptoms, fever, cough, shortness of breath and breathing difficulties.
26. Have had contact with persons diagnosed with COVID-19 or who tested positive for SARS-CoV-2 by any diagnostic test within the 30 d prior to Visit 1.
27. Are soldiers, volunteers in detention, CRO or sponsor staff or their family members.
28. Regular receipt of inhaled/nebulized corticosteroids.
29. For older volunteers and for Cohort 13 only: Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors:
    - Hypertension.
    - Diabetes mellitus.
    - Chronic obstructive pulmonary disease.
    - Asthma.
    - Chronic liver disease.
    - Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2).
    - Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies.
    - Sickle cell disease.
    - Cancer (except for Cohort 13).
    - Are immune compromised due to stem cell or organ-transplantation with significant medical complications such as acute or chronic graft rejection or graft versus host disease requiring intensive immunosuppressive treatment, transplant failure or infectious complications or other conditions that would be considered a contraindication for vaccination.

- Are immune compromised due to HIV infection with a $CD4^+$ count of $< 200 \times 10^6$ /L at screening or significant medical complications such as opportunistic infections, malignant complications (e.g., lymphoma, Kaposi sarcoma), other organ manifestations consistent with advanced AIDS or other conditions that would be considered a contraindication for vaccination.
- Resident in a long term facility.
- Current vaping or smoking (occasional smoking is acceptable).
- History of chronic smoking within the prior year.

5.3 Lifestyle considerations

Strenuous physical activity will not be allowed on visit days. When at the trial site, trial subjects will not be allowed to smoke or to drink alcohol.

Trial subjects will be required to practice social distancing and to follow good practices to reduce their chances of being infected or spreading COVID-19, e.g., as described in the WHO guidance "Protection measures for persons who are in or have recently visited (past 14 d) areas where COVID-19 is spreading or regional equivalents.

Trial subjects will be warned to avoid contact with persons tested positive for SARS-CoV-2 antibodies or those who have an increased risk for infection.

Dose ranging (Cohorts 1 to 10)

For Cohort 1 and any subsequent dose escalation cohort (in younger adults or older adults), the first 6 subjects dosed in each group will be required to remain at the site for approximately 24 h after the first immunization. The remaining trial subjects in these cohorts will be required to remain at the site for approximately 6 h after the first immunization.

For any dose de-escalation or dose-refinement cohorts, i.e., cohorts with doses lower than previously tested and found to be acceptable, trial subjects will be required to remain at the site for approximately 6 h after the first immunization.

For all cohorts with P/B dosing (irrespective of whether dose escalation, dose de-escalation, or dose-refinement cohorts), all trial subjects will be required to remain at the site for approximately 6 h after the boost immunization.

Expansion for BNT162b2 (Cohorts 11 to 13)

For Cohorts 11 to 13, all trial subjects will not be required to remain at the site beyond the time required for all trial-visit-related procedures to be completed. Care should be taken with Cohort 13 subjects (immunocompromised) to minimize duration of site visits.

5.4 Screen failures

Screen failures are defined as individuals who consent to participate in the trial but who are not subsequently assigned to IMP.

A minimal set of screen failure information is required to ensure transparent reporting of screening failures to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, date the ICF was signed, the reasons for screen failures, and any serious AEs (SAEs), if applicable.

6 TRIAL TREATMENTS

Trial treatment is defined as any IMP intended to be administered to a trial subject according to the trial protocol. Trial treatment must be administered a physician.

6.1 IMP administered

IMP name:	BNT162 vaccines - Antiviral RNA vaccines for active immunization against COVID-19
Type:	RNA-LNP vaccines utilizing different BioNTech RNA formats, i.e., uRNA (product code BNT162a1), modRNA (2 variants, product codes BNT162b1 and BNT162b2), saRNA (product code BNT162c2)
Dosage levels:	See Table 1, Table 2, and Table 3. The planned dose per vaccine candidate will not exceed the pre-defined maximum dose (see Table 1 and Table 2).
Dosage frequency:	One injection or two injections 21 d apart. Injection volumes will be up to 1.5 mL
Administration route:	Intramuscular (IM); upper arm, musculus deltoideus. For the P/B regimens the same arm may be used for both immunizations. The non-dominant arm is preferred.

6.2 Preparation/handling/storage/accountability

The preparation of solution for injection will be performed by aseptic handling procedures by pharmaceutical personnel or other trained personnel at the trial site.

For instructions on IMP (BNT162 vaccine) preparation, handling, and storage, see the Pharmacy Manual.

The investigator or a physician must confirm appropriate temperature conditions have been maintained during transit for all trial intervention received and any discrepancies are reported and resolved before use of the trial intervention.

Only trial subjects enrolled in the trial may receive IMP and only authorized site personnel may administer IMP. All IMP (and any components thereof) must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized trial site personnel.

The investigator, nominated site personnel, or the head of the site (where applicable) is responsible for IMP (and any components thereof) accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IMP (and any components thereof) is provided in the Pharmacy Manual.

6.3 Measures to minimize bias: randomization and blinding

Not applicable.

6.4 Trial treatment compliance

Trial subjects will be immunized by a physician.

The date and time of each immunization must be recorded in the source documents and recorded in the case report form (CRF). The IMP dose and trial subject identification will be confirmed at the time of administration by a member of the trial site personnel other than the person administering the IMP.

6.5 Concomitant therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest) that the trial subject receives during the trial, i.e., starting after Visit 0 and until the EoT Visit**,** must be recorded along with the:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The sponsor's Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Trial subjects must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), unless, in the opinion of the investigator and sponsor, the medication will not compromise their wellbeing, or could prevent, limit, or confound the protocol-specified assessments.

Trial subjects are required to agree to not be vaccinated during the trial, starting after Visit 0 and continuously until 28 d after receiving the last immunization (see the inclusion criterion 13).

Nonsteroidal anti-inflammatory drugs (NSAIDs), e.g., paracetamol/acetaminophen at doses of up to 4 g/day is permitted for use any time during the trial. Other concomitant medication may be considered on a case by case basis by the investigator, if required after consultation with the sponsor's Medical Monitor.

6.5.1 Premedication

Not applicable.

6.5.2 Rescue medication

Not applicable.

6.6 Dose modifications

The trial design allows for a flexible dosing which allows a better evaluation on the optimal dose range. For details, see Section 4.1.

The decision to make dose adaptions or to initiate a cohort for each vaccine will be made by the SRC (for details, see Section 10.1.5). Dose de-escalation and escalation rules have been defined in this protocol (see Section 6.6.2).

6.6.1 Dose limiting toxicity

Applicable to dose ranging cohorts only

During the time of enrollment into a given dose escalation cohort in Part A, if any of the following events occur, it will be considered an individual dose limiting toxicity and further dosing in that cohort will be stopped:

- Anaphylactic reaction considered related.
- Generalized urticaria considered related.
- Four trial subjects in that cohort with any severe unsolicited local event, if considered related and not manageable with simple measures (e.g., cooling, analgesia, nonsteroidal anti-inflammatory drugs [NSAIDs]).
- AEs within 7 d of vaccination assessed by the investigator to be potentially life-threatening (Grade 4) and that are possibly related, or for which there is no alternative, plausible, attributable cause.
- Any systemic SAE within 7 d of vaccination that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.
- Any fever >40.0°C (>104.0°F) within 7 d of vaccination considered related and confirmed by an investigator or medically qualified person.
- Two trial subjects (at any dose level) with the same or similar severe (Grade 3 or higher) AE (including reactogenicity reported as AEs and clinically significant laboratory abnormalities) within 7 d of vaccination, considered related, or for which there is no alternative, plausible, attributable cause (for severity grading of AEs see Section 10.3.1.7).

For the cohorts with BNT162c2 P/B dosing, dosing with the boost dose will only start after SRC assessment of Day 28 safety data (solicited and unsolicited) for the cohort testing BNT162c2 (SD).

Approval from the SRC will be required prior to any further dosing in the affected cohort. The SRC may call for the opening of a lower dose level cohort.

The same events will prompt IMP discontinuation for individual subjects as described in Section 6.6.4. Tasks connected to the discontinuation of IMP are described in Section 7.1.

The above guidance regulates how potential dose limiting toxicities may influence the decisions to further enroll trial subjects in any cohort. These decisions are taken by the SRC based on the 48 h safety data from the first 6 subjects of each cohort (see Section 4.1). Due to the staggered sentinel dosing design, subjects will have been followed for 4 d for the sentinel subjects when this SRC decision is made.

The above guidance also regulates how potential dose limiting toxicities may influence the decisions to enroll subjects into the next cohort for that vaccine, i.e., to progress to the next cohort. These decisions are taken by the SRC based on the 48 h safety data from all 12 subjects of each cohort (see Section 4.1). Due to the staggered sentinel dosing design, subjects will have been followed for 6 d for the sentinel subjects when this SRC decision is made.

The sum of the above events occurring at any time during the trial conduct (i.e., not just with 7 d of vaccination) will be used for the overall assessment of the candidate vaccine safety profile, i.e., to assess whether any of the observed side effects are possibly linked to vaccination.

The assessment of dose limiting toxicity should be done consistently for all subjects treated with the same treatment and dose.

In addition to data entry in the CRF, DLTs will be reported within 24 h via SAE Report Form as described in Section 10.3.1.10 and forwarded to the safety contacts listed in the same section.

6.6.2 Dose modification guidance/rules

Part A

See Section 10.1.5 for the data set upon which SRC decisions described below for Part A are made.

- The decision to test reduced or intermediate doses will be made for each vaccine independently.
- Any proposal to alter the planned escalation dose, or to test an additional de-escalation dose, must be approved by the SRC.

Dose escalation:

- Dose escalation will only continue if the previous dose was considered safe and well tolerated by the SRC.
- Any proposal to alter the planned escalation doses must be approved by the SRC.

6.6.3 Mitigation plans for specific AEs

Based on experience with other BioNTech RNA-based vaccines and published data from other RNA-based vaccines, it is anticipated that subjects may experience TEAEs of flu-like symptomatology following the administration of RNA vaccines due to the mechanism of action of RNA vaccines. This may include fever, chills, rigors, tachycardia, arthralgia, myalgia, headache, nausea. Treatment of these events is dependent on the discretion of the investigators; however, the following management suggestions are provided:

- Treat fever with acetaminophen or NSAIDs with a dose per trial site recommendation.
- After the first occurrence of flu-like symptomatology, subjects can be treated with standard therapeutic dose of acetaminophen, or NSAIDs, starting at least 2 h after the immunization.
- Corticosteroids should be avoided as either prophylaxis or treatment as it counteracts the effects of immunization.

- Ensure adequate hydration of trial subjects on the day of immunization. Consider administering fluids (e.g., water for drinking, 0.5 - 1.0 L) within approximately 2 h following the immunization per trial site standard.

If subjects experience enhanced respiratory disease or progression of flu-like symptomatology, such as non-resolution of the symptoms after 7 d, symptom kinetics that are inconsistent with a relationship to RNA immunization, additional diagnostic measures should be considered and the Medical Monitor should be informed.

6.6.4 Safety stopping criteria

See Section 6.6.1 for the list of events that must prompt discontinuation for the individual subjects.

The SRC will review and evaluate the collected safety data periodically during the trial (see Section 10.1.5 for details). A decision to stop treatment for an individual subject or to terminate the trial may be taken if safety concerns are identified by the SRC.

Suspected unexpected serious adverse reactions (SUSARs) will immediately be reviewed by the SRC. They will trigger a temporary stop of IMP administration to new subjects in the respective dose level cohort for that vaccine until the SRC recommendation to continue or to permanently stop IMP administration of new subjects in the respective dose level cohort for that vaccine.

Guidance for discontinuation of trial treatment is provided in Section 7.1.

6.7 Treatment after the end of the trial

Not applicable.

7 DISCONTINUATION OF TRIAL TREATMENT AND TRIAL SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of trial treatment

In rare instances, it may be necessary for a trial subject to permanently discontinue IMP administration (i.e., to not receive the boost dose for groups with P/B regimens). If IMP administration is definitively discontinued, the trial subject will remain in the trial to be evaluated for safety. For cohorts with P/B dosing, if the boost dose is not administered, subjects should still complete all assessments planned in the SoA (Section 1.3).

IMP administration must be stopped if dose limiting toxicities described in Section 6.6.1 are observed.

If any of the above are observed, an unscheduled safety analysis by the SRC will be required. Trial subjects who tolerated initial vaccinations will be allowed to receive a second vaccination during this time.

Trial subjects permanently discontinued from IMP administration will complete all assessments planned for that visit and for the EoT Visit as listed in the SoA (Section 1.3).

In the event of discontinuation of trial treatment, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of trial treatment or also from trial procedures, post-treatment follow-up, and/or future collection of additional information.

Trial subjects permanently discontinued from IMP administration will complete all assessments planned for that visit and for the EoT Visit as listed in the SoA (Section 1.3).

7.1.1 Temporary discontinuation

Not applicable. For the Cohorts 11 to 13 (inclusive), temporary delays to the boost doses due to intercurrent illness (i.e., immunization with the boost dose within 1 wk of the scheduled day) are allowed.

7.1.2 Rechallenge

Not applicable.

7.2 Trial subject discontinuation/withdrawal from the trial

A trial subject may withdraw from the trial at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. Withdrawals are expected to be uncommon.

If the trial subject withdraws consent for data processing, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a trial subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document sample destruction in the investigator's site file (ISF).

If the trial subject withdraws consent or is permanently discontinued from the trial, the trial subject will be permanently discontinued both from IMP administration and from the trial at that time.

If possible, permanently discontinued trial subjects will:

- Complete all assessments planned for that visit and for the EoT Visit, if discontinued on a visit day.
- Complete all assessments planned for the EoT Visit, if not discontinued on a visit day.

7.3 Lost to follow-up

A trial subject will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a trial subject fails to return to the trial site for a required trial visit:

- The trial site must attempt to contact the trial subject and reschedule the missed visit as soon as possible and counsel the trial subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the trial subject wishes to and/or should continue in the trial.
- Before a trial subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the trial subject (where possible, three telephone calls and, if necessary, a certified letter to the trial subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the trial subject's medical record.
- If the trial subject continues to be unreachable, they will be considered to have withdrawn from the trial.

7.4 Replacement of permanently discontinued trial subjects

Permanently discontinued trial subjects will be replaced to ensure that the 12 subjects complete the trial as planned up to Visit 3 for each group unless permanently discontinued due to safety issues; in the latter cases, the SRC will decide whether to replace the discontinued trial subjects. Trial subjects permanently discontinued after Visit 3 will not be replaced.

8 TRIAL ASSESSMENTS AND PROCEDURES

See the SoA (Section 1.3) for all planned time points for assessments.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the trial subject should continue or discontinue IMP administration (i.e., to administer the boost administration for groups with the P/B regimen).

Adherence to the trial protocol requirements, including those specified in the SoA, is essential and required for trial conduct.

All screening evaluations must be completed and reviewed to confirm that potential trial subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all trial subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

For the baseline assessments (demographics, medical history), see Section 10.12.

The listed trial assessments and procedures will be updated to reflect the needs of Part B in the planned protocol amendment.

8.1 Efficacy assessments

Not applicable.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

Complete physical examinations will be performed at screening. Brief physical examinations will be performed at later time points including prior boost immunizations (see the SoA in Section 1.3).

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height (in cm) will also be measured and recorded during complete physical examinations.
- A brief (symptom-directed) physical examination. The brief physical examination includes an overall health judgment. In depth physical examinations are required if obvious pathological signs are visible or in the case the subject states any signs or symptoms.

8.2.2 Vital signs

Body temperature (in °C), pulse rate, respiratory rate, and blood pressure will be assessed at the times given in the SoA (Section 1.3). Body weight (in kg) will also be measured and recorded.

Blood pressure (systolic/diastolic, in mmHg) and pulse (in bpm) measurements will be assessed while the trial subject is in a supine position/at rest. If available, a completely automated device should be used, otherwise manual techniques can be used. The same method of measurement should be used for the trial subject during the course of the trial.

Blood pressure and pulse measurements should be preceded by at least 5 min of rest for the trial subject in a quiet setting without distractions (e.g., television, cell phones).

Vital signs should be taken before any blood collection.

8.2.3 Electrocardiograms

Standard 12-lead ECGs will be recorded at the times given in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc; according to Bazett) intervals.

ECGs will be judged by the investigator as clinically significant (yes/no); only the investigator assessment and heart rate will be recorded in the CRF.

8.2.4 Clinical laboratory tests

See Section 10.2 for the list of clinical laboratory tests to be performed at the times given in the SoA (Section 1.3).

The investigator must review the laboratory report, document this review with signature and date, and record any clinically relevant changes occurring during the trial in the AE section of the CRF. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the trial should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the sponsor's Medical Monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required clinical laboratory tests (see Section 10.2) must be conducted in accordance with the trial site standard.

If laboratory values from non-protocol-specified laboratory assessments performed at the laboratory require a change in trial subject management or are considered clinically significant by the investigator (e.g., SAE, AE or dose modification), then the results must be recorded in the CRF.

8.2.5 Drugs of abuse screening

Screening for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cocaine, cannabinoids, opiates, methadone, methamphetamines, phencyclidine, and tricyclic antidepressants) will be performed using a commercially available kit at the times given in the SoA (Section 1.3).

8.2.6 Testing for alcohol use

Breath testing for alcohol use will be performed at the times given in the SoA (Section 1.3).

8.2.7 Viral screening (for blood-borne viruses)

The screen will test for: Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis C antibodies, and HIV-1 and HIV-2 antibodies. For SARS-CoV-2 testing, see Section 8.2.10.

8.2.8 Subject diaries

Trial subjects will be given subject diaries at Visit 1 and be asked to record any reactions between visits, solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) and solicited systemic reactions (nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever [i.e., ≥38°C]).

Subject diaries may include App-supported electronic documentation in compliance with the applicable data protection regulations.

Trial site personnel will collect subject diaries at the visits given in the SoA (Section 1.3).

8.2.9 Assessment of local reactions

Local reactions after IM immunization will be assessed by the investigator at the times given in the SoA (Section 1.3). This information will be used to validate the solicited assessment of local reactions in the patient diary and potentially support AE reporting.

Local reactions (both investigator assessed and solicited in the subject diaries) will be graded using criteria based on the guidance given in US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" for "Local Reaction to Injectable Products" (see the section "Assessment of intensity" in Section 10.3.1.11).

8.2.10 SARS-CoV-2 testing

SARS-CoV-2 testing (PCR-based and antibody-based) will be performed at the time points provided in the SoA (Section 1.3).

This includes PCR-based testing for SARS-CoV-2 as an eligibility criterion and blood draws for anti-SARS-CoV-2 antibody testing as baseline reference for immunogenicity analysis.

If required, this reference will allow the discrimination between vaccinated and infected subjects.

The screen for SARS-CoV-2 by PCR-based test using oral swipe sample can be performed by either a central laboratory or a "point of care" device at the trial site.

- If a central laboratory is used: Only the SARS-CoV-2 status will be tested and no further data will be generated.

- If a point of care device is used: The most commonly used devices come with pre-defined test panels that test for a range of pathogens and not just for SARS-CoV-2. Thus, inevitably and automatically, incidental data for the pathogens other than SARS-CoV-2 will be generated when using such devices. Since this incidental data is not required by this trial, only the results for SARS-CoV-2 will be recorded in the CRF, analyzed, and reported as described in this protocol. If a test result for SARS-CoV-2 or another pathogen must be reported to relevant authorities, this notification will be done by the trial site.

The anti-SARS-CoV-2 antibody testing will be performed with a commercially available antibody test. In case this commercial antibody test can, discriminate between vaccine-specific and infection-specific antibody responses (based on the antigens used), it will be used to test subjects who may have experienced enhanced respiratory disease or progression of flu-like symptomatology, such as non-resolution of the symptoms after 7 d, symptom kinetics that are inconsistent with a relationship to RNA immunization, as might be expected with a COVID-19 disease (see Section 6.6.3).

In these cases, ad hoc anti-SARS-CoV-2 antibody testing will be performed to test for the development and presence of SARS-CoV-2-specific antibodies, ideally at approximately 14 d and 28 d after the last immunization with the BNT162 candidate vaccine. This data will be used to evaluate the development and progression of an antibody response allowing the diagnosis of a manifest infection.

In case this commercially available test cannot discriminate between vaccine-specific and infection-specific antibody responses, the same kind of analysis will be performed with a custom-made assay specifically developed by the CRO.

8.2.11 Subject hotline

Subjects will be provided with contact details for a Subject Hotline, which can be used to contact the trial site during their participation in the trial should they require guidance or should they experience any symptoms of illness. The reporting of any symptoms of illness, e.g., flu-like symptoms, may trigger diagnostic measures (including ad hoc site visits) at the discretion of the investigator. For guidance for specific AEs, see Section 6.6.3.

8.2.12 Subject wellbeing questioning

Structured non-leading subject wellbeing questioning will be performed at the time given in the SoA (Section 1.3). Subject responses may trigger more in depth questioning on specific topics, and may trigger diagnostic measures (including ad hoc site visits) at the discretion of the investigator.

8.2.13 Assessment of systemic reactions

Systemic reactions after IM immunization will be assessed via daily solicited reports in the subject diaries and at the times given in the SoA (Section 1.3).

Systemic reactions will be graded using criteria based on the guidance given in US FDA Guidance for Industry “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers

Enrolled in Preventive Vaccine Clinical Trials" for "Systemic reaction grading scale" (see the section "Assessment of intensity" in Section 10.3.1.11).

8.3 Adverse events and serious adverse events

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs and SAEs.

8.3.1 Time period and frequency for collecting AE and SAE information

For Cohorts 1 to 10, all AEs and SAEs will be collected from the date of subject consent until discharge from the trial only IMP-related AEs and any SAEs will be collected.

For Cohorts 11 to 13, all AEs and SAEs will be collected from the date of subject consent until Visit 7. Thereafter, at Visits 8 and 9 only IMP-related AEs and any SAEs will be collected. At Visits 10, 11, and 12, only any SAEs will be collected.

All SAEs (initial and follow-up reports) will be recorded and reported to the sponsor or designee within 24 h after becoming aware of the event, as indicated in Section 10.3.1.10.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a trial subject has been discharged from the trial, and he/she considers the event to be reasonably related to the IMP administration or trial participation, the investigator must promptly notify the sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the trial subject is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each trial subject at subsequent visits/contacts. All AEs/SAEs/dose limiting toxicities (DLTs) will be followed until resolution, stabilization, the event is otherwise explained, or the trial subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.1.7.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to the sponsor within 24 h of receipt of the information as indicated in Section 10.3.1.10.

All ongoing AEs/SAEs will be followed until resolution, considered by the investigator to be stable or chronic (resolved with sequelae), the trial subject is lost to follow-up or the trial subject withdraws consent. If no final status is reached by the time of discharge from the trial, the investigator must confirm the unavailability of a final status.

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of trial subjects and the safety of a trial treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Independent Ethics Committees (IECs), and investigators. The execution of expedited reporting to the different entities may be delegated as detailed in the trial Safety Management Plan.

Safety reports will be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

For the IMP, it is the sponsor's or delegate's responsibility to perform SUSAR reporting to the regulatory authority, the IEC and the other investigators as required by national law and applicable guidelines.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor should review it and then file it together with the IB. If required by local requirements, the investigator will notify the relevant IEC.

8.3.5 Pregnancy

For WOCBP, urine pregnancy tests will be performed using a commercial kit at the times given in the SoA (see Section 1.3).

Pregnancy information will only be collected after obtaining written informed consent from the pregnant female subject (or if a male subjects' partner becomes pregnant, written informed consent from both).

Pregnancy information will be collected for pregnancies that occurred after the date of the first dose of trial treatment until 60 d after the last dose of trial treatment for pregnant subjects (or until 60 d after the last immunization of the male subject for pregnant female partners).

If a pregnancy is reported, the investigator should inform the sponsor within 24 h of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Death events

Any death that occurs within the observation period will be reported as an SAE.

In case of a fatal event, the event term should not be “death” but the underlying event which led to death (death = outcome). If there is more than one AE in a fatal case, only for the AE leading to death the outcome “fatal” should be selected. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be documented as event term.

8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable, this trial will only enroll healthy trial subjects.

8.3.8 Adverse events of special interest

Enhanced respiratory disease or flu-like symptomatology not resolved after 7 d or with symptom kinetics that are inconsistent with a relationship to RNA immunization will considered adverse events of special interest (AESI).

8.4 Treatment of overdose

Any dose of trial treatment above the planned dose specified in this protocol will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the sponsor’s Medical Monitor immediately.
- Closely monitor the trial subject for any AE/SAE and laboratory abnormalities (at least for 7 d).
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the sponsor’s Medical Monitor based on the clinical evaluation of the trial subject.

8.5 Pharmacokinetics

Not applicable.

8.6 Pharmacodynamics

Not applicable.

8.7 Genetics

For Cohorts 1 to 10, a blood sample (blood and / or isolated PBMCs) may be used for HLA typing of a subject to allow additional analysis, e.g., characterization of TCR repertoire and/or phenotypic characterization of antigen-specific T-cells as further specified in Section 8.8 (Biomarkers). Data generated with these additional analyses may provide information about the HLA dependency of immune response (e.g., if distinct HLA types have stronger / better immune response towards SARS-CoV-2).

For Cohorts 11 to 13, a blood sample (blood and / or isolated PBMCs) will be used for HLA typing of a subject to allow additional analysis. HLA analysis will be conducted in all subjects in the Cohorts 11 to 13.

Further, an additional blood sample may also be used for profiling (e.g., by use of next generation sequencing) of TCRs in peripheral blood after vaccination.

Blood samples will only be used for genetic analysis if the trial subjects have provided informed consent for this genetic analysis.

Leftover blood after completion of the immunogenicity assessments may be used for the genetic analyses as described here.

8.8 Biomarkers (CMI responses, explorative biomarker, immunogenicity research purposes)

Three additional blood draws (with up to 200 mL in total) will be taken at the times listed in the SoA (Section 1.3) for explorative biomarker/immunogenicity research purposes, these will be in addition to standard trial assessments in selected dose ranging cohorts, and as core elements of the assessments of the expansion cohorts.

Research samples will be collected in order to investigate vaccine-induced immune responses by use of, but not limited to, phenotypic or functional characterization of antigen-specific T-cells (e.g., by flow cytometry-based phenotyping including multimer staining), analysis of TCR repertoire (e.g., by next generation sequencing) and multiplex-cytokine analysis.

In addition, samples may be stored and analysis may be performed on biomarker variants thought to play a role in the mechanism of action of BNT162 to evaluate their association with observed clinical responses to BNT162. Furthermore, samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to BNT162.

Samples for biomarker analysis will be retained for use for up to 5 years after the end of the trial. The tube with the sample will be labeled with a number (optionally also with a bar code) to keep the subject's identity confidential; the tube label will not include information that could be used to identify the subject. Results of the blood analyses will be linked to the clinical information collected during the trial using this specific number. The analysis will only be carried out on the basis of the label data and samples. Biomarker samples and all data generated using the samples, will be handled in accordance with applicable laws and regulations; this includes requirements applicable for data protection, for sample shipment outside Germany, and a potential withdrawal of consent.

Blood samples will only be used for biomarker analysis if the trial subjects have provided informed consent for this biomarker analysis.

8.9 Immunogenicity assessments

Immune responses as laid down in the trial objectives will be assessed at the times listed in the SoA (Section 1.3) using:

1) A functional antibody titer determined, e.g., via VNT or an equivalent assay.
   - Sero negative is defined as titers below the starting dilution (i.e., below the LOD [limit of detection] of the assay).
   - Seroconversion after immunization is defined as a 4-fold increase in titer.
     - for seronegative pre-immunization sera: a titer ≥ 4-times the LOD.
     - for seropositive pre-immunization sera: a titer which is 4-fold higher than the measured pre-immunization titer.
2) An antibody binding assay, e.g., ELISA or an equivalent assay.
   - Seroconversion after immunization is defined as a 4-fold increase in titer/antibody concentration.
3) CMI/responses mediated by immune cells such as CD4 and CD8 T-cells and their functional phenotypic subset by, e.g., ELISpot, ICS, multimer analyses, cytokine secretion assays, flow cytometry and other tests.

   CMI analysis will include among others CD4 and CD8 T-cells, Th1-specific cytokines (e.g., IFN-gamma, TNF-alpha, IL-2, or IL-12) and Th2-specific cytokines (e.g., IL-4, IL-5, IL-10, IL-13) to analyze the induction of either balanced Th1/Th2 responses, or of unbalanced Th1-dominant or Th2-dominant immune responses, respectively.

Additional exploratory analyses of IMP-induced antibody responses with selected samples may include:

- Assessing neutralization activity against variant spike proteins from other SARS-CoV-2 strains or other coronavirus families.
- Antibody affinity, isotype and subclass analysis / functional assessment of antibodies, e.g., ADCC, antibody induced phagocytosis, immune cell degranulation, activation of immune cells such as lymphocytes and granulocytes.
- Mechanisms that are potentially associated with antibody-dependent enhancement (ADE), e.g., antibody mediated uptake of (pseudo)-virus-particles into cells, formation of immune complexes.

Additional exploratory analyses of vaccine-induced CMI (including non-T-cell based) responses with selected samples may include:

- Analysis of immune activation, proliferation, cytotoxicity and cellular, molecular of immune cells subsets.

- Bulk or single cell TCR and transcriptome sequencing, qt-PCR studies to profile and characterize, and track TCRs and to quantify the number of antigen-specific T-cells.
- Analyses of polymorphism in immune response genes.

Correlations will be described – in particular for Cohorts 11 to 13 – between these immune responses and different subject disposition / characterization parameters such as age, gender, HLA, in relation to each other with further exploration as scientifically determined.

Instructions on the sample collection, handling, and shipping will be provided in a Laboratory Manual. The methodology used for these assessments will be documented in the Biomarker Manual.

Leftover blood after completion of the immunogenicity assessments may be used for additional analyses as described in Section 8.7 (Genetics) and/or Section 8.8 (Biomarkers).

Blood samples will only be used for additional analyses if the trial subjects have provided informed consent for these additional analyses.

8.10 Blood collection

For subjects in Cohorts 1 to 10, up to approximately 592 mL blood will be drawn per subject over the complete trial, i.e., over approximately 223 d.

For subjects in Cohorts 11 to 13, up to approximately 1022 mL blood will be drawn per subject over the complete trial, i.e., over approximately 760 d.

Additional blood samples may be taken, e.g., for safety assessments after AEs or SAEs.

For enrolled subjects who have not completed the EoT visit (see the SoA in Section 1.3) before approval of Protocol Amendment 04, the optional additional blood draws added by protocol amendment 04 will only apply for subjects who give consent.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

There is no formal statistical hypothesis under test.

9.2 Sample size determination

No formal sample size calculations have been performed.

For Part A, the inclusion of 12 subjects per group is considered to be adequate for a safety assessment of each vaccine per dose level. The probability to observe a particular TEAE with incidence of 15% at least once in 12 subjects per group is 85.8%.

For the expansion cohorts the probability to observe a particular TEAE with incidence of 5% at least once in 30 and 90 subjects per group, respectively, is 78.5% and 99.0% respectively (see Table 10).

Table 10: Probability to observe a particular TEAE at least once

Number of subjects	TEAE incidence	Probability to observe a particular TEAE at least once
12	15%	85.8%
30	15%	99.2%
	10%	95.8%
	5%	78.5%
90	15%	>99.9%
	10%	>99.9%
	5%	99.0%

9.3 Analysis sets

The following analyses sets are defined:

Analysis set	Description
Screened Set	The screened set is defined as all subjects who signed informed consent
Safety Set	The safety set is defined as all subjects who received at least one dose of IMP.

9.4 Statistical analyses

Statistical analyses will be performed by BioNTech or a designated CRO. All statistical analyses will be carried out using SAS®, Version 9.3 or higher, and/or other statistical software as required.

The statistical analysis plan (SAP) will be finalized prior to database snapshot for the primary analysis and it will include a more technical and detailed description of the

statistical analyses described in this section. Any deviations from the planned analyses described in the final SAP will be described and justified in the clinical trial report.

This section gives a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General considerations

In general, data will be summarized by groups and groups may be combined as appropriate.

Continuous variables will be summarized by group using the following descriptive statistics: number of subjects (n), mean, standard deviation, median, minimum and maximum.

Categorical variables will be summarized by group presenting absolute and relative frequencies (n and %) of subjects in each category.

Baseline is defined as last available value prior to first dose of IMP.

9.4.2 Primary endpoints

The primary endpoints are defined in Section 3.

All AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA®) coding system to get a system organ class (SOC) and preferred term (PT) for each AE.

Treatment-emergent AEs (TEAE) are defined in Section 10.3.1.1 and will be summarized using the Safety Set. In general, AEs will be analyzed by group (i.e., by type [BNT162a1, BNT162b1, BNT162b2, BNT162c2 SD, and BNT162c2 P/B] and dose level) and for each immunization, i.e., for:

- Prime immunization up to 7 d after initial immunization
- Prime immunization up to boost immunization or 28 d after initial immunization (whatever comes first)
- Boost immunization up to 7 d after boost immunization (only for P/B regimens)
- Boost immunization up to 28 d after boost immunization (only for P/B regimens)
- Prime immunization up to 28 d after boost immunization or after prime immunization (if no boost was given)

Additionally, AEs will be summarized for all dose levels combined for each type.

For each analysis, the number and percentage of subjects reporting at least one AE will be summarized by PT nested within SOC for each of the following AE types using the Safety Set:

- Any AE
- Any AE excluding AEs based on solicited reporting via subject diaries

- Related AE
- Grade ≥3 AE
- Related Grade ≥3 AE
- Any SAE
- Related SAE

Moreover, the number and percentage of subjects with any AE will be summarized by worst grade by PT nested within SOC.

Local reactions and systemic reactions will be graded using criteria based on the guidance given in US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (see Section 10.3.1.11).

For each immunization, the number and percentage of subjects reporting at least one local reaction or systemic reaction (i.e., solicited data collected using subject diaries) will be summarized for each of the following types using the Safety Set:

- Any local reactions or systemic reactions
- Grade ≥3 local reactions or systemic reactions

The analysis of local and systemic reactions will be repeated with a reduced set of terms (called the "comparability analysis"), to facilitate like-for-like comparisons between different trials in the clinical development program for BNT162 vaccines.

Moreover, the number and percentage of subjects reporting at least one local reaction will be summarized by worst grade using the Safety Set.

9.4.3 Secondary endpoints

The secondary endpoints are defined in Section 3.

The binary secondary endpoints will be summarized by group presenting absolute and relative frequencies (n and %) of subjects in each category for each assessment. The continuous secondary endpoints will be summarized by group using summary statistics. The scheduled time points for assessment are given in the SoA (see Section 1.3).

9.4.4 Exploratory endpoints

The exploratory endpoints are defined in Section 3. Exploratory analyses will be described in the SAP.

9.4.5 Other safety analyses

Safety data other than AEs that will be summarized includes clinical laboratory parameters, vital signs, and ECGs. All safety analyses will be based on the safety set and will be summarized descriptively by group unless otherwise stated.

Clinical laboratory parameters

The clinical laboratory parameters to be summarized and assessed are listed in Section 10.2. The scheduled time points for assessment are given in the SoA (see Section 1.3).

Clinical laboratory parameters at each timepoint and change from baseline to each post-baseline time point will be summarized using descriptive summary statistics for each parameter by group.

Shift tables from baseline to worst intensity grade will be provided for each laboratory parameter by group.

Additionally, the occurrence of clinically significant abnormal laboratory results within a trial subject will be analyzed using descriptive summary statistics for each parameter and visit by group.

Abnormal laboratory results will be graded using criteria based on the guidance given in US FDA Guidance for Industry 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials' (see Section 10.3.1.11).

Laboratory parameter results will be listed along with the normal ranges. Values that are below or above the normal ranges will be flagged.

Clinical laboratory analysis details will be described in the SAP.

Vital signs

The vital sign parameters to be summarized and assessed are given in Section 8.2.2. The scheduled time points for assessment are given in the SoA (see Section 1.3).

Vital sign parameters at each time point and change from baseline to each post-baseline time point will be summarized using descriptive summary statistics for each parameter by group.

ECG

ECG parameters to be summarized and assessed are given in Section 8.2.3. The scheduled time points for assessment are given in the SoA (see Section 1.3).

ECGs will be judged by the investigator as clinically significant (yes/no).

9.4.6 Other analyses

Other analyses will be described in the SAP.

9.5 Interim analyses

The final analysis will be performed once all subjects have completed Visit 7 (EoT). An analysis update will be performed once all subjects will have completed Visit 10. No formal interim statistical analysis will be performed. However, preliminary analyses based on all data collected until a pre-defined data cut-off date (snapshot analyses) may be performed

for each cohort once subjects within a cohort will have been followed up for at least 7 d following the dose.

9.6 Data Monitoring Committee

A DMC is not planned. An SRC is planned, for details see Section 10.1.5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, ethical, and trial oversight considerations

This trial will be conducted in according to this protocol, the ethical principles that have their origin in the Declaration of Helsinki, Good Clinical Practice (GCP), and applicable regulatory requirements.

10.1.1 Regulatory and ethical considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable GCP guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IEC and reviewed and approved by the IEC before the trial is initiated.

Any amendments to the protocol will require IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial subjects.

The coordinating investigator or delegate will be responsible for the following:

- Providing written summaries of the status of the trial to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC.
- Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures.
- Providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IEC, European regulation 536/2014 (if applicable), and all other applicable local regulations.

The principal investigator, any investigator(s), the sponsor, or personnel at other establishments must cooperate with any inspection of the documents, facilities, records, and other resources deemed appropriate by the inspecting authorities to be related to the trial and that may be located at the trial site, at the sponsor, or at other establishments.

The sponsor must be notified as soon as possible about any upcoming regulatory authority inspection.

10.1.2 Financial disclosure

All investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.3 Informed consent process

Informed consent must be obtained before any trial-specific screening procedure is performed.

The investigator or his/her representative will explain the nature of the trial to the trial subject and answer all questions regarding the trial.

Trial subjects must be informed that their participation is voluntary.

Trial subjects will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IEC or trial site.

The medical record must include a statement that written informed consent was obtained using a sponsor-approved ICF before the trial subject was enrolled in the trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Trial subjects must be re-consented to the most current version of the ICF during their participation in the trial.

Informed consent will be obtained for the use of residual biosamples collected for further explorative investigations of the immune response in healthy adults after SD or P/B immunization, e.g., using new assays that become available after completion of trial conduct.

10.1.4 Data protection

Trial subjects will be assigned a unique identifier by the investigator according to the sponsor specifications on unique identifier assignment. Any trial subject records or datasets that are transferred to the sponsor will contain the identifier only; trial subject names or any information which would make the trial subject identifiable will not be transferred.

Trial subjects must be informed that his/her personal trial-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the trial subject who will be required to give consent for their data to be used as described in the informed consent.

Trial subjects who withdraw consent must be informed that the data collected up until consent was withdrawn will still be used by the sponsor as described in the ICF.

Trial subjects who withdraw consent must be informed that, unless they agree otherwise, any biosamples collected will be destroyed.

Trial subjects must be informed that their medical records may be examined by sponsor Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees - SRC

For Part A, the SRC will be comprised by a sponsor medical representative, the Medical Monitor, a sponsor-independent investigator, and a site representative.

Key roles of the SRC are as follows:

- Before progression to the next cohort, for each vaccine per cohort/dose level, assess the data, decide whether to approve initiation of the next cohort/dose level and to confirm the planned dose or define another dose for use. The data assessed by the SRC is defined in Section 1.1.
- After completing its evaluation of the 48 h data for the first 6 subjects per group in cohort, the SRC may request a prolongation of the observation period to up to Day 7 data for later cohorts or other similar adaptions to protect subject wellbeing.
- Throughout the trial, assess whether to replace trial subjects permanently discontinued due to safety issues.
- Throughout the trial, approval from the SRC will be required prior to resuming any dosing in a “stopped” cohort (see Section 6.6.1). The SRC may call for the opening of a lower dose level cohort.
- SRC may make recommendations on increasing the length of the observation periods and additional subject wellbeing calls may be included at the discretion of the SRC.

The SRC will act according to its own written procedures described in a charter, and will prepare written minutes of its meetings.

10.1.6 Dissemination of clinical trial data

A final clinical trial report integrating all trial results will be prepared by the sponsor.

This trial will be registered and trial results be posted on publicly accessible trial registries (e.g., the EU Clinical Trial Register) in accordance with the applicable regulations.

10.1.7 Data quality assurance

All trial subject data relating to the trial will be recorded in a CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit trial-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on site monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this trial including quality checking of the data.

The sponsor assumes accountability for actions delegated to other parties (e.g., CRO).

Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of trial subjects are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for 25 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source documents

Source documents provide evidence for the existence of the trial subject and substantiate the integrity of the data collected. Source documents are filed in the ISF.

Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source documents are original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

10.1.9 Trial and site start and closure

The trial start date is the date on which the trial will be open for enrollment of trial subjects.

The sponsor designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial

completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of trial subjects by the investigator.
- Discontinuation of further trial treatment development.

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs, the regulatory authorities, and any CROs used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the trial subject and should assure appropriate follow-up.

10.1.10 Publication policy

The results of this trial may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This will allow the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for the publication of trial results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-site trials only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (ICMJE) authorship requirements.

10.1.11 Protocol preparation and approval

This protocol has been prepared, reviewed and approved, including wet ink sign-off by the sponsor’s responsible person, in accordance with the sponsor’s standard operating procedures. Documentation of this process is filed in the TMF.

10.2 Clinical laboratory tests

Blood will be drawn and urine will be collected for clinical laboratory tests at the times given in the SoA (Section 1.3).

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count.

Clinical chemistry

Alkaline phosphatase, creatinine, ferritin, C-reactive protein, albumin, alanine aminotransferase, amylase, aspartate aminotransferase, gamma glutamyl transpeptidase, total bilirubin, blood urea nitrogen, glucose, lipase, sodium, potassium, calcium.

Follicle stimulating hormone: Only in women who are not of childbearing potential.

Urinalysis

Dipstick: glucose, bilirubin, ketone, specific gravity (1 mL ≙ 1 g), blood, pH, protein, urobilinogen, nitrite, and leukocytes.

Microscopic urinalysis: If warranted by dipstick results, urine sediment will be microscopically examined for presence of red blood cells, white blood cells, casts, crystals, epithelial cells, and bacteria.

10.3 Adverse events: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1 Definition of AE and TEAE

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
  NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding that is clinically significant), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
- Events after signing ICF and before IMP administration will be handled as AEs.
- A TEAE is defined as any AE with an onset date on or after the first administration of IMP (if the AE was absent before the first administration of IMP) or worsened after the first administration of IMP (if the AE was present before the first administration of IMP). AEs with an onset date more than 28 d after the last administration of IMP will be considered as treatment-emergent only if assessed as related to IMP by the investigator.

10.3.1.1 Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs, physical examination, measurements), including those that worsen from baseline, and which are considered clinically significant in the medical and scientific judgment of the investigator, may be considered as AEs.
- Reactogenicity need only be reported as an AE if doing so provides clinically significant information not available elsewhere (such as the solicited reactions listings), e.g., severe reactogenicity lasting longer than the period of solicitation of symptoms in the subject diary. Diagnostic AEs for local and/or systemic

reactogenicity, e.g., “injection site reaction” or “flu-like illness”, should generally be preferred over AEs reporting of individual signs and symptoms.

- New conditions or (at the discretion of the investigator) any worsening of a pre-existing condition detected or diagnosed after Visit 0.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial treatment or a concomitant medication. Overdose *per se* will not be reported as an AE/SAE.

10.3.1.2 Events <u>not meeting</u> the AE definition

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

10.3.1.3 Suspected adverse reactions

All untoward and unintended responses to an IMP-related to any dose administered.

- The definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the IMP.
- The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

10.3.1.4 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under trial, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  The term “life-threatening” in the definition of “serious” refers to an event in which the trial subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires trial subject hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the trial subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or out trial subject setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any

other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Results in persistent disability/incapacity:
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly or a birth defect.
- Other situations:
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the trial subject or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

10.3.1.5 Suspected unexpected serious adverse reactions

All suspected adverse reactions related to an IMP (the tested drugs and comparators) that occur in this trial, and that are both unexpected and serious are "suspected unexpected serious adverse reactions" (SUSARs). SUSARs are subject to expedited reporting.

10.3.1.6 Use of the terms "severe" and "serious"

Severity and seriousness need to be assessed independently for each AE recorded on the CRF.

SAEs must be reported by the investigator to the sponsor immediately (i.e., no more than 24 h after learning of the event; see Section 10.3.1.10 for reporting instructions).

10.3.1.7 Recording and follow-up of AE and/or SAE

AE and SAE Recording

The investigator needs to assess and document any AE regardless of association with the use of the trial treatment during the period of observation (starting from Visit 0 until 21 d after the last immunization or trial subject discharge from the trial, whichever one is later). To ensure trial subject safety during the trial, safety will be monitored from Visit 0 (screening) until approximately 6 months after the last immunization.

- Data pertaining to AEs will be collected during each trial visit either based on the trial subject's spontaneous description or investigator's inquiry or discovered in the course of examinations done during the visit, clinical significance of any sign or symptom needs to be evaluated by the investigator.

- Clinically significant findings need to be documented as AEs in the source data and CRF. Findings that are evaluated and documented in the source data as not clinically significant (e.g., an abnormal laboratory value without any clinical manifestation), should not be documented as AE.
- The investigator will then record all relevant AE information in the CRF and perform an assessment on:
  - Intensity, see the section “Assessment of intensity” in Section 10.3.1.7 for guidance on the assessment of intensity
  - Seriousness
  - Outcome
  - Causal relationship of the AE to the trial treatment
  - Any trial treatment action and/or any other action taken
- All assessments as well as AE term (diagnosis/description), start date and time of onset, end date and time need to be documented in the CRF.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all trial subject identifiers, with the exception of the trial subject number, will be redacted on the copies of the medical records before submission to the sponsor.
- To avoid colloquial expressions, the AE should be reported in standard medical terminology. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded.

Assessment of AE and/or SAE intensity

For subjects in yet to be started cohorts, the assessment of AE and/or SAE intensity should be done as described in protocol version 7.0 (which includes amendment 04).

The assessment of AE and/or SAE intensity should be done consistently for all subjects treated with the same treatment and dose.

All subjects treated in completed cohorts, where the first treatment pre-dates approval of the protocol version 5.0 (i.e., including amendment 04), should continue to use the grading scheme in the earlier protocol version, such that the same grading scheme is used consistently for all subjects given the same treatment and dose.

Where applicable, retrospective re-mapping of grading from 3-point to 4-point scale will be completed prior to database lock, with definitions for mild and moderate intensity events aligned and all events previously graded as severe intensity (on 3-point scale), queried to determine whether grade 3 (severe) or 4 (potentially life-threatening) should be applied.

In case of doubt, the Medical Monitor should be consulted.

The intensity of AEs or SAEs will be graded by the investigator. For further guidance on grading of solicited reactions, please refer to guideline "US FDA Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". Where specific guidance for an adverse event term is not provided, the following general approach should be followed:

- Grade 1 - Mild; does not interfere with the subject's usual function.
- Grade 2 - Moderate; interferes to some extend with the subject's usual function.
- Grade 3 - Severe; interferes significantly with the subject's usual function.
- Grade 4 - Potentially Life-threatening; life-threatening consequences, urgent intervention required.

Please also refer to the intensity tables given in the guideline for intensity of clinical and laboratory abnormalities to be reported as AEs:

- Guideline Section III.A for assessment of clinical abnormalities (local and systemic)

Actions taken by the investigator

Actions taken by the investigator as a result of an AE must be documented.

Action(s) taken with trial treatment (IMPs) by the investigator:

- Dose not changed (= continuation of trial treatment administration according to the trial protocol)
- Dose reduced
- Drug interrupted; i.e., interruption of IMP administration during a given visit
- Drug withdrawn
- Unknown (e.g., in case the trial subject is lost to follow-up)
- Not applicable (e.g., in case treatment with trial treatment has not yet started or event starts after last trial treatment administration)

Other action(s) that may be taken by the investigator include:

- None
- Remedial drug therapy
- Other specific treatment(s) of AE (to be specified)

Outcome

The investigator has to assess the outcome of an AE (and not the trial subject's outcome) at the time of documentation based on the following criteria:

- Recovered/resolved* (= complete resolution of the AE)
- Recovering/resolving (= AEs which are improving but not yet resolved completely, e.g., decrease in an intensity grade)

- Not recovered/not resolved (= AEs which are ongoing without improving or still present when the trial subject deceases due to another cause)
- Recovered/resolved with sequelae* (= trial subject recuperated but retained pathological conditions resulting from the AE; the sequelae should be indicated)
- Fatal** (= death due to the AE)
- Unknown (e.g., in case the trial subject is lost to follow-up)

* Generally, an AE is defined as recovered/resolved if all symptoms have ceased, no medication for treatment of the event is taken anymore and no other measures (e.g., hospitalization) are ongoing.

If the trial subject has developed permanent or chronic symptoms or if the event requires long term medication(s), the AE is defined as recovered/resolved with sequelae as soon as no changes of symptoms and/or medication(s) are expected anymore.

An AE that is documented as a worsening of a medical condition already known at baseline, is defined as recovered as soon as the medical condition has returned to baseline status.

** In case of a fatal event, the event term should not be “death” but the underlying event which led to death (death = outcome). If there is more than one AE in a fatal case, only the AE leading to death will be attributed with the outcome “fatal”. All other AEs ongoing at the time of death will be attributed with the outcome “not recovered/not resolved”. A copy of an autopsy report should be submitted if available.

Assessment of causality

The investigator is obligated to assess the relationship between trial treatment/trial procedure and each occurrence of each AE/SAE.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.

It is sufficient to document the causality in the source data and CRF as:

- Related (= there is a reasonable possibility of a causal relationship) or
- Not related (= there is no reasonable possibility of a causal relationship)

Relationship to trial treatment

- The relationship or association of an AE or SAE to a trial treatment will be made by the investigator after having evaluated all accessible data and, if necessary, he/she will re-evaluate the case as new information becomes available.
- Events caused by the procedure of trial treatment administration should be differentiated from events caused by the trial treatment itself. Only events

suspected to be caused by the IMPs itself should be documented as suspected Relationship to trial procedures.

- In this trial, it cannot be excluded that during the course of the trial some procedures give rise to AEs which are related to the trial procedure and not to the trial treatment. Procedure-related AEs can occur on the site of injection of the trial treatment e.g., redness, swelling, hematoma or itching or during or after trial-specific procedure, e.g., discomfort after blood drawing.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.1.8 SAE exemptions

In general, SAEs are defined according to ICH Topic E2A (CPMP/ICH/377/95), EU Directive 2001/20/EC and ENTR/CT-3 (see Section 10.3.1.4).

In the present trial, some events are excluded from the SAE definition. The following events do not need to be reported as SAEs:

- AEs and SAEs occurring after trial subject discharge from the trial must only be reported by the investigator to the sponsor if a relationship to trial treatment or trial procedure is suspected.
- Planned hospitalizations required by the protocol (e.g., for trial treatment administration) will not be considered as reportable SAE.

10.3.1.9 Documentation of particular situations

AEs that are secondary to other events:

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be documented as an independent AE in source data and CRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be documented as AE.
- If vomiting results in severe dehydration, both events should be documented as AEs separately.

Abnormal laboratory results and vital signs values:

Not every laboratory or vital signs abnormality needs to be documented as AE. For clinically significant laboratory/vital signs abnormalities the following definitions and documentation rules apply:

- If a laboratory/vital signs abnormality is a sign of a disease or syndrome, the laboratory/vital signs abnormality is clinically significant and only the diagnosis of the causing disease or syndrome needs to be documented as AE.
- If a laboratory/vital signs abnormality results in specific symptoms but no diagnosis of a disease or syndrome can be made, the laboratory/vital signs abnormality is clinically significant and only the symptoms need to be documented as AEs.
- If a laboratory/vital signs abnormality is not a sign of a disease or syndrome and does not result in specific symptoms but leads to a change in trial treatment or in a medical intervention, the laboratory/vital signs abnormality is clinically significant and must be documented as AE.
- If a laboratory/vital signs abnormality is not considered clinically significant by the investigator, then an AE does not need to be documented.

AEs associated with an overdose or error in drug administration:

An overdose is the accidental or intentional use of a drug in an amount (per administration or cumulatively) higher than the dose being studied (for the trial treatment) or higher than the maximum recommended dose according to the authorized product information (for approved concomitant medications). An overdose or incorrect administration of a drug is not itself an AE, but it may result in an AE.

All AEs associated with an overdose or incorrect administration should be documented as AE in source data and CRF and reported as SAE if applicable.

AEs of proven COVID-19 disease of moderate or severe intensity:

Any case of proven COVID-19 disease occurring during the observation period should be reported as an SAE, where the intensity of the respective AE is rated as “moderate” or “severe” (according to the criteria provided in Section 10.3.1.7). If none of the other SAE definitions are deemed suitable, then the SAE criterion of being a “medically important event” should be applied (according to the definitions provided in Section 10.3.1.4). An SAE form should be completed, including follow-up information, as detailed in Section 10.3.1.10 such that an SAE report and narrative can be prepared and distributed.”

10.3.1.10 Reporting of SAEs

All SAEs or DLTs (even if non-serious) which occur in a trial subject during the observation period, whether considered to be associated with trial medication or not, must be reported by the investigator to the sponsor within 24 h following knowledge of the event.

All SAEs occurring after the end of the period of observation only have to be reported to the sponsor if the investigator suspects a relationship to trial medication or the trial procedure.

SAE Reporting to sponsor using a paper form (SAE Report)

For the period of observation, see Section 8.3.1.

For any SAE or DLT (even if non-serious), the investigator needs to complete the paper Serious Adverse Event Form which must be sent to the sponsor via one of the following reporting methods:

- Safety Report Fax No.: +49 (0) 231 700 118 68
- Safety Report E-Mail Address: pv-biontech@pharmsoft.de

Information for final description and evaluation of a case report may not be available within the required time frames for reporting. Nevertheless, for regulatory purposes, initial reports should be submitted if the following minimal information is available:

- An identifiable trial subject (trial subject number)
- A suspected medicinal product
- An identifiable reporting source (investigator/trial site identification)
- An event or outcome that can be identified as serious

SAE follow-up information should be sent to the sponsor (indicating that this is a "follow-up" report using the SAE Form or the Additional Information and Follow-Up Form) without delay as described above and accompanied by appropriate anonymous supporting documentation (e.g., discharge letters, medical reports or death certificates), until a final outcome and date are available. All confidential information (name, address, full day of birth) needs to be blackened before sending. In addition to a medical record, the investigator should complete an Additional Information and Follow-Up Form, which contains the SAE term and trial subject number.

A copy of the submitted SAE report must be retained on file by the investigator. If explicitly required according to national legislation, the investigator must submit copies of the SAEs to the IEC or authority and retain documentation of these submissions in the ISF.

In case an investigator or any other trial team member has questions on safety reporting the sponsor may be contacted via: E-Mail: pharmacovigilance@biontech.de

For medical questions, the sponsor's Medical Monitor for this trial should be contacted; contact details are given in the trial Safety Management Plan.

10.3.1.11 Assessments of intensity for solicited local and systemic reactions and laboratory abnormalities

The grading of solicited local and systemic reactions, recorded in the patient diaries, will be according to the following guidance, in line with Guideline Section III.A for assessment of clinical abnormalities (local and systemic).

Local reactions

Redness and swelling / induration will be measured and recorded in centimeters and then categorized during analysis as absent, mild, moderate, severe or potentially life-

threatening, based on the grading scale in Table 11. Likewise, pain (perceived) and tenderness (elicited) at the injection site will be assessed by the trial subject as absent, mild, moderate, severe or potentially life-threatening, according the grading scale in Table 11.

Table 11: Local reaction grading scale

	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-Threatening (Grade 4)**
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema / redness [a]	2.5 cm to 5.0 cm	>5.0 cm to 10.0 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration / swelling [b]	2.5 cm to 5.0 cm	>5.0 cm to 10.0 cm	>10 cm	Necrosis

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Systemic reactions (signs and symptoms)

Symptoms of vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain will be assessed by the participant as absent, mild, moderate, severe or potentially life-threatening, according to the grading scale in Table 12.

Table 12: Systemic reaction grading scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Vomiting	1-2 times in 24 h	>2 times in 24 h	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 h	4 to 5 loose stools in 24 h	6 or more loose stools in 24 h	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Fever

Fever is defined as an oral temperature of ≥38.0°C. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 13.

Table 13: Fever grading scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Fever	38.0-38.4°C	38.5-38.9°C	39.0-40.0°C	>40.0°C

If a fever of ≥39.0°C is recorded by a subject during the 7-day post-vaccination diary period, a telephone contact should occur to ascertain further details and determine whether a site or healthcare professional visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C for recording in the trial database. If a participant experiences a confirmed fever >40.0°C, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the trial intervention, further vaccinations will be discontinued in that participant (see Section 6.6.1).

Laboratory abnormalities

Laboratory abnormalities will be graded according to the grading scheme given in Table 14.

Table 14: Laboratory abnormality grading scale

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Female) change from baseline value - g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hemoglobin (Male) change from baseline value – g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
Chemistry	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

10.4 Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

WOCBP

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of trial treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For trial subjects with permanent infertility due to an alternate medical cause other than the above (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining trial entry.

Note: Documentation can come from the site personnel review of the trial subject's medical records, medical examination, or medical history interview.

Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrollment.

10.4.2 Contraception guidance

WOCBP must confirm that they practiced at least one highly effective form of contraception for the 14 d prior to Visit 0.

WOCBP must practice a highly effective form of contraception during the trial, starting after Visit 0 and continuously until 60 d after receiving the last immunization. WOCBP must agree to require their male partners to use condoms during sexual contact (unless male partners are sterilized or infertile).

Men who are sexually active with a WOCBP and have not had a vasectomy must agree to practice a highly effective form of contraception with their female partner of childbearing potential during the trial, starting after Visit 0 and continuously until 60 d after receiving the last immunization.

Subjects with bilateral tubal occlusion, previous successful vasectomy or those who are truly abstinent or exclusively homosexual are deemed as being "not of reproductive potential".

The investigator or delegate should advise the subject how to achieve highly effective contraception. The following birth control methods may be considered as highly effective:

- Intrauterine device. [a]
- Intrauterine hormone-releasing system. [a]
- Combined estrogen and progestogen-based contraception: established use of oral, intravaginal, or transdermal hormonal methods of contraception.
- Progesterone-based contraception: established use of oral, injected, or implanted [a] hormonal methods of contraception.
  [a)] Contraception methods that in the context of this guidance are considered to have low user dependency.

10.4.3 Collection of pregnancy Information

Pregnancy information will only be collected after obtaining written informed consent from the pregnant female trial subject (or if a male trial subjects' partner becomes pregnant, written informed consent from both).

Pregnancy information will be collected for pregnancies that occurred after the start of trial intervention and until 60 d after the last administration of IMP for pregnant trial subjects (or until 60 d after the last administration of IMP to the male trial subject for pregnant female partners).

The initial and follow-up information must be documented on the paper-based Pregnancy Reporting Form and submitted to the sponsor within 24 h of learning of a trial subject's pregnancy/partner's pregnancy. The completed form needs to be sent to the Safety Report Fax number or E-Mail given in Section 10.3.1.10. Completed pregnancy forms must be signed by an investigator before faxing/mailing them to the sponsor. Blank reporting forms are provided to the investigator during the site initiation visit and are filed in the ISF.

The investigator will collect follow-up information on the trial subject/trial subject's partner and the neonate and the information will be forwarded to the sponsor. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications and their presumed relation to the IMP.

Generally, the follow-up will be of a duration determined in consultation with the pediatrician.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-trial pregnancy related SAE considered reasonably related to the trial intervention by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former trial subjects, he or she may learn of an SAE through spontaneous reporting.

10.4.4 Sperm donation

Men must refrain from sperm donation, starting after Visit 0 and continuously until 60 d after receiving the last immunization.

10.5 Genetics

Not applicable.

10.6 Liver safety: Suggested actions and follow-up assessments

Not applicable.

10.7 Investigators and trial administrative structure

10.7.1 Investigators and trial site personnel

There must be an investigator at each trial site.

If the trial is conducted by a team of individuals at the trial site, the investigator leading and responsible for the team is called the principal investigator.

All persons assigned responsibility as principal investigator must sign a declaration of their responsibilities and their agreement to this protocol before any trial-related procedure is performed.

Curriculum vitae and/or other relevant documents confirming the current qualification of the investigators must be provided to the sponsor. This should include any previous training in the principles of GCP, experience obtained from work with clinical trials, and experience with trial subject care.

Documentation of all involved investigators must be maintained according to GCP and applicable regulatory requirements.

10.7.2 Trial site personnel assigned trial-related duties

The principal investigator or deputy may define appropriately qualified personnel at a trial site to perform significant trial-related procedures and/or to make trial-related decisions under his/her supervision. In this case, the principal investigator must maintain a signed

list of the persons to whom they delegate significant trial-related duties/responsibilities; the delegated trial-related duties/responsibilities must be specified in the list.

When personnel or responsibility changes are made, the principal investigator or deputy must ensure that the relevant documentation is updated before any trial-related activities are performed.

Documentation of all involved trial site personnel performing significant trial-related procedures and/or making trial-related decisions must be maintained according to GCP and applicable regulatory requirements.

10.7.3 Contract research organizations

Documentation of all involved CROs must be maintained according to GCP and applicable regulatory requirements. This includes documentation of any delegation of responsibilities to CROs.

10.7.4 The sponsor and sponsor's personnel

The trial sponsor listed on the title page accepts the responsibilities of the sponsor according to GCP and applicable regulatory requirements.

The sponsor must designate appropriately qualified personnel to advise on trial-related topics. The trial site will be provided with contact details for these personnel before any trial-related procedure is performed.

A list of key sponsor personnel involved in the preparation of this protocol and the conduct of the trial, including their full names, titles, roles, and responsibilities, must be maintained.

10.8 Country-specific requirements

Not applicable.

10.9 Other standard abbreviations and definitions

For trial-specific abbreviations, see the list of trial-specific abbreviations.

For definitions related to safety, see Section 10.3.

Abbreviation	Explanation
AE	Adverse Event
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CRO	Contract Research Organization
d	Day(s)
DLT	Dose limit toxicity(ies)
DMC	Data Monitoring Committee
EDC	Electronic Data Capture (system)
EoT	End of Treatment

Abbreviation	Explanation
FDA	(US) Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
h	Hour(s)
HIV	Human Immunodeficiency Virus
HRT	Hormonal Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation (of technical requirements for registration of pharmaceuticals for human use)
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product; in this trial, BNT162 vaccines
ISF	Investigator's Site File
min	Minute(s)
NSAID	Nonsteroidal Anti-Inflammatory Drug
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SOC	System Organ Class
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-Emergent Adverse Event
TMF	Trial Master File
US	United States (of America)
WHO	World Health Organization
wks	Week(s)
WOCBP	Women Of Child Bearing Potential

10.10 Protocol amendments

Changes made to the protocol using the protocol amendments are described in detail in the document Protocol Amendment History which is available upon request. This Protocol Amendment History is filed together with the protocol in the TMF.

10.10.1 Protocol amendment no. 01

Amendment rationale

This amendment describes the replacement of the product codes BNT162c1 with BNT162c2. The RNA component of BNT162c1 encoded only the RBD of the S protein, the

RNA component of BNT162c2 encodes a modified version of the full length S protein. BNT162c1 was replaced with BNT162c2 because of its superior immunogenicity profile in non-clinical studies.

This amendment describes changes made in response to feedback from the German PEI (April 16th, 2020).

This amendment was issued before any trial subjects were enrolled into the trial.

10.10.2 Protocol amendment no. 02

Amendment rationale

This amendment describes a dose adjustment for the vaccine BNT162c2 and the corrections of some inconsistencies and ambiguities.

This amendment was issued after some of the planned trial subjects have already been enrolled into the trial.

10.10.3 Protocol amendment no. 03

Amendment rationale

This amendment describes updates in response to PEI and IEC feedback on protocol version 4.0.

This amendment was issued after some of the planned trial subjects have already been enrolled into the trial.

10.10.4 Protocol amendment no. 04

Amendment rationale

The changes planned by amendment 04 were discussed with the PEI on the basis of the submitted protocol version 6.0. Amendment 04 was revised in response to received feedback, to yield protocol version 7.0.

This amendment describes adaption of the protocol to:

- Allow the assessment of additional intermediate and low dose cohorts for BNT162b modRNA vaccine candidates to support identification of a suitable dose for Phase II/III evaluation.
- Allow the assessment of BNT162b1 modRNA vaccine candidate in elderly subjects, given its favorable safety, tolerability, and immunogenicity profile in younger adults to date and recently available non-human primate immunogenicity data for the BNT162b1 and other modRNA vaccine candidates.
- Plan the assessment of BNT162b2 modRNA vaccine candidate in elderly subjects.
- Allow the assessment of P/B cohorts for the BNT162c2 saRNA vaccine candidate.
- Allow revision of safety assessment & dose limiting toxicity criteria.
- Add additional for blood draws for explorative biomarker/immunogenicity research purposes.

This amendment was issued after some of the planned trial subjects have already been enrolled into the trial.

10.10.5 Protocol amendment no. 05

Amendment rationale

Amendment 05 address feedback obtained from the PEI and the IEC on protocol version 7.0. Some changes were also implemented to align data collection and reporting in this trial with the data collection and reporting in other trials with BNT162 vaccines candidates (to facilitate data merging).

This amendment will be issued after some of the planned trial subjects have already been enrolled into the trial.

10.10.6 Protocol amendment no. 06

Amendment rationale

Protocol amendment 6.0 implemented three additional cohorts (Cohorts 11, 12, and 13) comprising up to additional 150 trial subjects aged from 18 to 85 years receiving BNT162b2 only.

BNT162b2 has entered a Phase II/III evaluation of efficacy, with the intent to support an application for marketing authorization. The dosing regimen under investigation is two 30 µg BNT162b2 doses given ~21 d apart.

The expansion cohorts implemented by this amendment are intended to provide a more in depth characterization of the adaptive immune responses induced by BNT162b2, associated vaccine safety, and the impact of factors such as subject disposition and dosing posology on humoral and cell-mediated immunity. These cohorts will extend the safety data of BNT162b2 to a broader trial population and thus closer to the vaccine target population.

Moreover, each of these cohorts will add to a more differentiated understanding of the BNT162b2-induced adaptive immune response composed of antigen-specific antibodies, CD4 and CD8 T-cells, with a view to developing insights into the mechanisms by which immunity to SARS-CoV-2 may be induced and factors driving any variability in response. Alternative treatment approaches for difficult to treat or high risk subjects may be determined. In each of these dose cohorts, a broader characterization of T-cell and antibody responses and their inter-individual variation will be performed. This will include the characterization of the dependency of adaptive immune responses on factors such as age and gender.

For further background on the scientific rationale for the expansion cohorts, see Section 4.2.

The planned dose of BNT162b2, two 30 µg BNT162b2 doses given ~21 d apart, the same regime that has already been tested in the dose escalation phase of this trial and in almost 17,000 adult subjects, including those with acute and chronic illnesses, in the ongoing global Phase I/II/III trial BNT162-02/C4591001 (ClinicalTrials.gov NCT: 04368728).

The three expansion cohorts are as follows:

- Cohort 11: Alternative posology cohort with 30 healthy adults who will receive BNT162b2 using one 3 µg prime dose and one 30 µg boost dose of BNT162b2 given approximately 21 d apart (P/B regimen).
- Cohort 12: Adaptive immune response cohort (including safety and long term immune response) with 90 healthy adults who will receive of two 30 µg BNT162b2 doses given approximately 21 d apart (P/B regimen).
- Cohort 13: Population expansion cohort (including safety and long term immune response) with 30 immunocompromised adults who will receive of two 30 µg BNT162b2 doses given approximately 21 d apart (P/B regimen).

This amendment also addresses feedback obtained from the PEI and the IEC on protocol version 8.0.

This amendment also introduces logistical simplifications, i.e., except for Cohorts 1 and 8, the minimum interval between dosed trial subjects has been reduced from 30 min to 15 min for the prime and boost doses in the still to be completed Cohorts 2 to 10 (inclusive). Also, the minimum interval has been set to at least 5 min for the prime and boost doses in Cohorts 11 and 12, and to 15 min (prime) and 5 min (boost for Cohort 13. This simplification/design is considered justified:

- Because all FIH cohorts for the different BNT162 vaccine variants have been completed.
- Due to the extensive experience and exposure already achieved with BNT162 vaccine candidates, including that almost 17,000 trial subjects have been dosed at least once with BNT162b2 (see Table 9).

Further changes were implemented to align data collection and reporting in this trial with the data collection and reporting in other trials with BNT162 vaccines candidates (to facilitate data merging).

This amendment will be issued after some of the planned trial subjects have already been enrolled into the trial.

10.11 Data collection and management

The trial documentation must be adequate for the reconstruction of the trial.

10.11.1 Case report forms

CRFs will be completed through use of an electronic data capture (EDC) system. Trial site personnel will receive training and have access to a manual for appropriate CRF completion. The CRFs will be submitted electronically to the sponsor via the system and should be handled in accordance with instructions from the sponsor.

All CRFs should be completed by designated, trained trial site personnel. CRFs should be reviewed, verified, and then electronically signed and dated by the investigator or a designee.

At the end of the trial, the investigator will receive trial subject data for his/her trial site in a readable format that must be kept with the trial records. Acknowledgment of receipt of the trial subject data will be required.

10.11.2 Trial subject reported outcomes

Not applicable.

10.11.3 Data management

The CRO (see the title page) will be responsible for data management of this trial, including quality checking of the data.

Data entered manually will be submitted to the sponsor through use of an EDC system, data extracts and reports. Trial sites will be responsible for data entry into the EDC system. In the event of discrepant data, the data management service provider will request data clarification from the trial sites, which the trial sites will resolve electronically in the EDC system.

The data management service provider will produce a Trial Data Validation Specification document that describes the quality checking to be performed on the data. CRFs and correction documentation will be maintained in the EDC system's audit trail.

Central laboratory data will be sent directly to the data management service provider.

System backups for data stored by the sponsor and records retention for the trial data will be in accordance with regulatory requirements.

10.11.4 Investigator's Site File and the Trial Master File

The principal investigator or deputy is responsible for the filing of all essential documents in an ISF. The sponsor is responsible for the timely filing of all essential documents in the TMF. As applicable, these files must be available at monitoring visits and during audits or regulatory inspections.

After trial completion, the principal investigator or deputy must ensure that all source data and documentation related to the trial is recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. The principal investigator or deputy must take measures to prevent accidental or premature destruction of these documents.

The principal investigator or deputy must keep the ISF, the source data/documentation arising from the trial according to the prescribed record retention period in the country and/or according to the hospital policy, but at least until informed by the sponsor that the trial-related records are no longer required.

10.12 Other data

10.12.1 Demographic data

At screening, the following demographic data will be recorded for all trial subjects:

- Age (in years/months)
- Gender (male/female)
- Ethnic group

10.12.2 Medical history

Medical history information will be recorded for at the times given in the SoA (Section 1.3).

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CRS trial no.:	049/20
Sponsor trial no.	BNT162-01
EudraCT no.	2020-001038-36
Protocol title (short version)	Multi-site Phase I/II Trial Investigating the Safety and Effects of Four BNT162 Vaccines Against COVID-19 in Healthy Adults
Original title of the protocol	A Multi-site, Phase I/II, 2-Part, Dose-Escalation Trial Investigating the Safety and Immunogenicity of Four Prophylactic SARS-CoV-2 RNA Vaccines Against COVID-19 Using Different Dosing Regimens in Healthy Adults
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Information about the trial	**Name**	**Telephone**
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Information on data privacy can be found in section 13 starting on page 22.

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I. PARTICIPANT INFORMATION

1. Introduction

Dear prospective participant,

We would like to ask you whether you are prepared to take part in this clinical drug trial (hereinafter referred to below in short as a "trial"). Clinical trials are necessary to obtain or expand knowledge about the efficacy and safety of medicines. This is why the law on medicines (section 40 AMG [German Medicines Act]) requires new drugs to undergo clinical trials. As required by law, the clinical trial described in more detail below has been approved by the competent ethics committee and by the competent authority.

Your participation in this trial is voluntary. You will be included in this trial only if you give your written consent. If you do not take part in the trial or later wish to withdraw from it, you will not suffer any disadvantages. You may end your participation in the trial at any time and without stating any reasons. This is described in more detail in section 12.

This participant information is intended to explain the trial to you in more detail. Please take your time and read through this information carefully. Do not hesitate to raise any points that are unclear to you. You will be given enough time to consider whether or not you wish to participate.

2. Why is this trial being carried out?

An infection with the SARS-CoV-2 (severe acute respiratory syndrome – coronavirus-2) virus can lead to coronavirus disease 2019 (COVID-19).
This infectious disease was observed for the first time in 2019 in China and is quickly spreading worldwide.

An infection with SARS-CoV-2 can lead to symptoms such as fever and cough. Persons affected also report sniffles, shortness of breath, muscle and joint pain, sore throat and headaches, as well as nausea/vomiting and diarrhea, and also a decreased sense of smell and taste. The course of the disease may vary in severity, from asymptomatic courses to severe lung inflammation (pneumonia) with pulmonary failure and death. Currently there are neither vaccines nor drugs available to treat the infection.

This trial is being conducted to investigate the safety and efficacy of several newly developed vaccines against SARS-CoV-2. You cannot assume that you will receive effective immunization protection by participating in the trial.

In conventional vaccinations, parts of the pathogen or attenuated pathogens are administered to the body. These are known as antigens and they are identified by the immune system of our body as foreign; the immune system forms appropriate molecules for defense, known as antibodies. If the body is exposed to the actual pathogen, the immune defense can be activated and the pathogen can be fought.

The vaccines used in this trial consist of large molecules, known as ribonucleic acids (RNA). In contrast to conventional vaccines in which the viruses are cultivated and given in killed form, RNA vaccines contain the genetic information of parts of the pathogen (RNA are molecular strands which contain genetic information). In the case of a vaccination with RNA, the information for producing the antigens is carried into the body and the body produces the antigens itself. This concept of RNA vaccine technology permits rapid manufacture of vaccines for previously unknown pathogens since the adaptation to the antigens takes place according to the modular design principle. In this trial, three building blocks – uRNA, modRNA, saRNA – are combined with information on the building blocks of SARS-CoV-2. The sponsor of the trial has already gained initial experiences in clinical trials with a part of the RNA building blocks with cancer patients, as well as with vaccines which build on RNA building blocks (BNT162a1, BNT162b1, BNT162b2, BNT162c2).

3. Trial design: Will I always receive the trial substance?

This clinical trial is an open trial, that is, the trial physicians as well as the trial participants know which dose of the vaccine you are receiving. All participants receive one of the 4 vaccines in one of several dosages specified in the protocol.

- Four newly developed vaccines against SARS-CoV-2 in several dosages are being investigated to find the best tolerated and effective dose for the vaccines. In total, the trial is being conducted in up to 37 groups, each with 12 participants. Depending on the results in the groups, additional groups may be included.

Adaptations in the dosages and vaccine schedules may be made in order to find the optimal dose and optimal schedule. The starting point is treatment group 1 for each vaccine. The next higher dose is given only after investigating the safety and tolerability. In later treatment groups, doses which are lower than the dose in treatment group 1 may also be administered.

The vaccines are injected into a muscle of the upper arm, preferably in the non-dominant arm.

4. What is the course of the trial?

This trial is being conducted at two trial centers in Germany.

Up to 384 healthy men and women aged 18 to 55 years are taking part. If good tolerability and indications of a good activation of the immune response are seen in two of the vaccines, up to 6 additional groups with up to 72 older trial participants (age 56 to 85 years) may be included.

The trial itself consists of the sections of screening, treatment and observation visits, a final examination, and a follow-up observation phase.

Your trial participation, from screening to completion of the follow-up observation phase, will last approx. 7 to 8 months.

You have the right at all times to end your participation in the clinical trial, without stating any reasons (see section 12).

A telephone hotline (see page 1) is available to you throughout the entire duration of the trial.

4.1 Information session

Prior to all trial procedures, an information session with one of the trial physicians will be held and you will receive this trial subject information leaflet which you should read carefully.
During the verbal information, the clinical trial will be explained to you by one of the trial physicians and you will have the opportunity to ask him/her all of your questions.

Prior to consent, you will have an individual informational discussion with one of the trial physicians.

If you have decided to participate in the clinical trial, you will be asked to give your consent in writing to participate in the trial before the start of the screening.

4.2 Screening (visit 0)

Prior to inclusion in this clinical trial, you will be asked about your previous illnesses and current state of health during an outpatient visit, and you will undergo a comprehensive medical examination. The results of these preliminary tests will determine whether you can continue taking part in this clinical trial.

Please come to the trial center for the screening appointment. Prior to all procedures, you voluntarily give your written consent for participation in the clinical trial.

During the screening, the following procedures will be performed:

- Documentation of past medical history
- Physical examination, including measurement of height
- Measurement of blood pressure, pulse, respiratory rate, body temperature and body weight
- ECG

- Women of childbearing age: Urine pregnancy test
- Urine drug test and alcohol breath test
- Urine sample for safety laboratory
- Blood sample for safety laboratory
- Blood sample for virus serology (liver inflammation [hepatitis B and C], immune deficiency [HIV])
- Blood sample to detect SARS-CoV-2 antibodies (due to a previous infection)
- Survey of concomitant medication and state of health
- Review of trial-specific inclusion and exclusion criteria

Test for viral infections:

During the screening, laboratory tests for certain viral infections will be performed (liver inflammation [hepatitis B and C] as well as immune deficiency [HIV]). You will be personally and confidentially informed of the result. The wide-ranging consequences which result for you in the event of a (initially documented) positive test result will be communicated to you in the verbal information about the clinical trial. The physicians in the trial center are available to hold counseling discussions both before and also after the testing.

In the event of a positive HIV test result, an anonymous report must be made to the Robert Koch Institute in Berlin, in accordance with the infection protection law.
In the event of a positive hepatitis test result, a report identifying you by name must be made to the health authorities, in accordance with the infection protection law.

In the event of a substantiated significant suspicion of SARS-CoV-2, a positive result on a throat swab of an active COVID-19 infection, or positive antibody detection prior to the start of treatment or in the course of the trial, a report identifying you by name must likewise be made to the health authorities and you must quarantine in accordance with the stipulations from the health authorities.

However, for further treatment in the event of a positive test result, we must refer you to your family doctor who will conduct further diagnostic measures and counseling.

Please note: In the event of a positive test, it is possible that you will have to declare this result, for example, if you have taken out private insurance, even if this results in disadvantages for you.

4.3 Main examination (visits 1 to 6 or visits 1 to 5)

The staff of the trial center will give you an exact schedule which reflects the chronological and organizational course of the trial upon inclusion in the administration phase. We ask you to attend the appointments scheduled by the trial staff in the trial schedule since this very important for the result of this clinical trial. If you should exceptionally be unable to keep a scheduled appointment, please notify the trial site so that an alternative appointment can be scheduled.

In order for the planned number of trial participants to be able to be included in the administration phase, additional suitable trial participants are invited as a reserve. The reserve participants take part only in the procedures of the clinical trial which are planned until the morning of day 1 (prior to the first administration of

the trial medication). The trial team will inform you in advance whether or not you are a reserve participant. Suitable reserve participants may participate in the next treatment groups, if they continue to be suitable.

- For the first 6 participants in each case of groups with two administrations of BNT162a1, BNT162b1, BNT162b2 and BNT162c2 of treatment group 1 and subsequent groups with a dose increase, the main examination consists of 1 inpatient visit with an overnight stay (visit 1), a telephone inquiry about 48 hours after the administration, and 5 outpatient visits to the trial center (visits 2 to 6). If the safety assessment committee feels it is necessary, the inpatient visit or the telephone inquiry 48 hours after the administration may also apply to other participants and treatment groups.
  For all other participants with two administrations of BNT162a1, BNT162b1, BNT162b2, and BNT162c2, the main examination consists of 6 outpatient visits (visits 1 to 6).
- For the first 6 participants in each case of groups with a single administration of BNT162c2 of treatment group 1 and subsequent groups with a dose increase, the main examination consists of 1 inpatient visit with an overnight stay (visit 1), a telephone inquiry about 48 hours after the administration, and 4 outpatient visits to the trial center (visits 2-5). If the safety assessment committee feels it is necessary, the inpatient visit or the telephone inquiry 48 hours after the administration may also apply to other participants and treatment groups.
  For all other participants with a single administration of BNT162c2, the main examination consists of 5 outpatient visits (visits 1 to 5).
- Throat swab to detect a COVID-19 infection (the test will be performed within a day either on the day prior to or on the morning before the first administration.)

Note: The throat swab to detect a COVID-19 infection will be performed in all groups within a day before the first administration. It is possible that you will have to come in to the trial center on 2 days for visit 1.

The throat swab to detect an active COVID-19 infection will be analyzed in the trial center directly or in the central laboratory.
This involves the use of point-of-care laboratory diagnostics as well as the associated test cartridges intended by the manufacturer. Depending on the manufacturer of the device, the samples will be tested not only for COVID-19, but also for other respiratory disease pathogens or pathogens causing other flu-like illnesses. Some of these pathogens cause diseases (pertussis, legionella, flu) which must be reported. This procedure is specified by the manufacturer and cannot be modified.
If you should correspondingly test positive, this result would also have to be reported to the health department and you must also quarantine, in accordance with the stipulations of the health authorities.
On day 1, it will be checked once again prior to the administration of the vaccination whether you continue to meet the inclusion and exclusion criteria and whether your past medical history has changed as compared to the previous examination.
If you are included in the trial, you will then be allocated to one of the different treatment groups.
On day 1, you will receive a trial subject diary in which you will note information on your state of health and possible reactions at the injection site. Please bring this diary to all main examination visits to the trial site.

- Participants in the groups with two administrations of BNT162a1, BNT162b1, BNT162b2 and BNT162c2 will receive a total of 2 vaccinations with an interval of 21 days (day 1 and day 22). The respective procedures are summarized in Table 1.
- Participants in the groups with a single administration of BNT162c2 receive 1 vaccination on day 1. The respective procedures are summarized in Table 2.

The first 6 participants of the respective groups remain in the trial center after the first injection for another 24 h (overnight) and are discharged if there are no medical concerns. The overnight stay following the treatment may also apply to other participants and treatment groups if the safety assessment committee feels an extension of the observation is necessary.

All other participants remain in the trial center after the injection for another 6 hours and are discharged if there are no medical concerns.

If you experience a fever of 39.0°C or higher in the period up to 7 days after the vaccination, you must report this to the trial physician via telephone.

You will be asked about your state of health during each visit to the trial site. Please report all changes to your well-being, whether or not they were expected. The more detailed information you provide, the better the trial physician can assess possible adverse effects of the trial substance.

Table 1: Procedures during the main examination (two administrations of BNT162a1, BNT162b1, BNT162b2 and BNT162c2)

Visit	**1**		**2**		**3**	**4**			**5**	**6**
Trial day	**1 (before)**	**1 (after)**	**2**	**3**	**8**	**22 (before)**	**22 (after)**	**24**	**29**	**43**
Procedures										
Physical examination	X		X		X	X			X	X
Throat swab to detect a COVID-19 infection	X[a]									
Blood pressure, pulse, body temperature, respiratory rate	X	X[b]	X		X	X	X[b]		X	X
Electrocardiogram (ECG)	X									
Urine pregnancy test	X					X				
Urine drug test	X									
Alcohol breath test	X									
Urine sample for safety laboratory	X		X		X				X	
Blood sample for safety laboratory	X		X		X				X	
Allocation to the vaccination	X									
Administration of the vaccination		**X**					**X**			
Blood sample to measure ant bodies	X				X	X			X	X
Blood sample to determine immune defense cells[d]	X								X	
Assessment of the injection site		X[b]	X		X	X	X[b]		X	X
Handout of the diary	X		X		X	X			X	X
Inquiry/collection of the diary			X	X	X	X			X	X
Survey of concomitant medication and state of health	X		X		X	X			X	X
Telephone inquiry of your state of health				X[c]				X[c]		
Telephone inquiry of the diary entries				X[c]						

[a] within a day prior to administration (the test is performed within a day either on the day before or on the morning before the first administration)

[b] 1, 3, and 6 hours after the injection

[c] approx. 48 h after the administration; only the first 6 participants of the respective groups

[d] In some cases, your genetic information from a part of the sample to determine the immune defense cells will be analyzed – if you consent to this – for certain surface proteins of the immune defense cells. It is anticipated that no additional blood sample will be necessary for this. If another blood sample is nonetheless necessary, you will be asked to provide separate consent.
Additional information on this can be found in section 14.

before: before the administration / after: administration and shortly thereafter

Table 2: Procedures during the main examination (single administration of BNT162c2)

Visit	**1**		**2**		**3**	**4**	**5**
Trial day	**1 (before)**	**1 (after)**	**2**	**3**	**8**	**22**	**29**
Procedures							
Physical examination	X		X		X	X	X
Throat swab to detect a COVID-19 infection	X [a]						
Blood pressure, pulse, body temperature, respiratory rate	X	X [b]	X		X	X	X
Electrocardiogram (ECG)	X						
Urine pregnancy test	X					X	
Urine drug test	X						
Alcohol breath test	X						
Urine sample for safety laboratory	X		X		X		X
Blood sample for safety laboratory	X		X		X		X
Allocation to treatment	X						
Administration of the vaccination		**X**					
Blood sample to measure antibodies	X				X	X	X
Blood sample to determine immune defense cells [d]	X						X
Assessment of the injection site		X [b]	X		X	X	X
Handout of the diary	X		X		X	X	X
Inquiry/collection of the diary			X	X	X	X	X
Survey of concomitant medication and state of health	X		X		X	X	X
Telephone inquiry of your state of health				X [c]			
Telephone inquiry of the diary entries				X [c]			

[a] within one day prior to administration (the test is performed within one day either on the day before or on the morning before the first administration)

[b] 1, 3, and 6 hours after the injection

[c] approx. 48 h after the administration; only the first 6 participants of the respective groups

[d] Your genetic information from a part of the sample to determine the immune defense cells will be analyzed – if you consent to this – for certain surface proteins of the immune defense cells.
It is anticipated that no additional blood sample will be necessary for this. If another blood sample is nonetheless necessary, you will be asked to provide separate consent.
Additional information on this can be found in section 14.

before: before the administration / after: administration and shortly thereafter

4.4 Final examination (visit 7, day 50 or visit 6, day 43)

During the outpatient final examination of the groups with two administrations of BNT162a1, BNT162b1, BNT162b2 and BNT162c2 (visit 7, day 50), the following examinations will be performed:

- Physical examination
- Blood pressure, pulse, body temperature, respiratory rate
- Urine sample for safety laboratory
- Blood sample for safety laboratory
- Blood sample to measure antibodies

- Assessment of the injection site
- Handout of the diary
- Inquiry/collection of the diary
- Survey of concomitant medication and state of health

During the outpatient final examination of the groups with a single administration of BNT162c2 (visit 6, day 43), the following examinations will be performed:

- Physical examination
- Blood pressure, pulse, body temperature, respiratory rate
- Urine sample for safety laboratory
- Blood sample for safety laboratory
- Blood sample to measure antibodies
- Inquiry/collection of the diary
- Survey of concomitant medication and state of health

4.5 Follow-up observation visits

During the outpatient follow-up observation visits of the groups with two administrations of BNT162a1, BNT162b1, BNT162b2 and BNT162c2 (visit 8, day 85 and visit 9, day 184), the following examinations will be performed:

- Blood pressure, pulse, body temperature, respiratory rate
- Blood sample to measure antibodies
- Inquiry/collection of the diary (only at visit 8, day 85)
- Inquiry regarding your state of health

During the outpatient follow-up observation visits of the groups with a single administration of BNT162c2 (visit 7, day 85 and visit 8, day 184), the following examinations will be performed:

- Blood sample to measure antibodies
- Inquiry regarding your state of health

After the last follow-up observation visit, you will be discharged from the trial. In the event of major changes in findings, you will be asked to come in for an outpatient checkup in the trial center or for a visit to your family doctor.

5. What personal benefit do I receive from participating in the trial?

It is anticipated that you will not have any personal health benefit from participating in this clinical trial, apart from a medical examination.

However, the results of the clinical trial may contribute to developing an effective vaccination to prevent an infection with SARS-CoV-2.

6. What risks are associated with participation?

6.1 Risks due to the trial substances

BNT162 are RNA vaccines which are to be used as a vaccination against the novel SARS-CoV-2. They have not been used in humans to date. The sponsor of the trial has already gained initial experiences in clinical trials with a part of the RNA building blocks with cancer patients, as well as with vaccines which build on RNA building blocks (BNT162a1, BNT162b1, BNT162b2, BNT162c2). Based on experiences with these, the following adverse effects may occur:

Due to administration in the muscle, there may be locally limited and mild reactions at the injection site – for example, reddening of the skin, itching, pain, touch sensitivity, sweating.

Because of the interaction with the immune system, there may be fever, headaches, fatigue or a loss of appetite, as in the case of any vaccination. Based on experience with other RNA vaccines, there may be flu-like symptoms (fever, chills, spasms, palpitations, joint pain, muscle pain, headaches, nausea). These symptoms are – as in the case of other vaccinations – transient.

In rare cases, severe allergic reactions or neurological effects (such as seizures) have been observed in the case of preventive vaccinations which are based, for example, on attenuated viruses. Although these rare adverse effects are worrying, the risk that a vaccine can cause severe damage or even lead to death is considered to be extremely low, particularly in the case of BNT162 vaccines which consist of defined, ultrapure vaccine components.

Within the scope of experimental, nonclinical trials, a vaccine-induced intensification of the disease through vaccines which can be used against diseases caused by coronaviruses was observed. Such effects have not been reported to date in the case of SARS-CoV-2. However, there are no data to date which can definitively exclude the fact that BNT162 can lead to an intensification of the disease.

To date, the BNT162 vaccines have been administered to only a small number of people in currently two trials (Germany, United States of America). The initial preliminary data on these trials are available.

Trial in Germany (BNT162-01, last updated: July 01, 2020, preliminary data):

The vaccine candidate BNT162b1 has been administered to date to 60 participants at dosages of 1, 10, 30, 50, and 60 µg. The participants of the 1, 10, 30, and 50 µg dose groups received 2 administrations and the participants of the 60 µg dose group received 1 administration.

A total of 57 out of 60 participants reported flu-like symptoms (52 out of 60 participants after the first application and 38 out of 46 participants after the second application). Locally limited reactions at the injection site were reported by 51 out of 60 participants (51 out of 60 participants after the first application and 39 out of 46 participants after the second application). The symptoms generally began within 24 hours after administration and either spontaneously resolved or resolved after simple measures (e.g. with antipyretic medications

such as paracetamol) generally within one to two days. In all dose groups, the reactions observed were generally mild to moderate. There were no serious adverse events in the follow-up observation phase after the administration. Transient changes to certain safety laboratory parameters were observed which corresponded to the effect of BNT162b1. One participant discontinued the trial due to non-trial-related symptoms. Overall, the safety observations had no influence on the benefit/risk assessment.

The vaccine candidate BNT162a1 was administered at a dosage of 3 µg to 6 participants. All 6 participants reported flu-like symptoms which began within 24 hours after administration, generally moderate fever (in more than half of the participants). One participant reported vomiting and another reported a drop in blood pressure. All reactions resolved, however some participants were still showing symptoms for several days. There were no serious adverse events at this dosage, and no participant discontinued the trial due to adverse events. Because of the reactions observed after this dose, the safety committee decided to not treat any other participants with the 3 µg dose. Lower dosages (0.1 and 0.3 µg) were tolerated well; the participants reported only local reactions at the injection site. The vaccine candidate BNT162a1 is not being pursued for the time being in the rest of the trial.

The vaccine candidate BNT162b2 was administered at dosages of 1, 10, 20 and 30 µg to 43 participants. BNT162b2 is tolerated similarly to BNT162b1. The participants reported flu-like symptoms (33 out of 43 participants) and locally limited reactions at the injection site (33 out of 43 participants) which generally began within 24 hours after administration. The reactions observed were mild to moderate.

The vaccine candidate BNT162c2 was administered at dosages of 0.1, 0.3 and 1 µg to a total of 36 participants. The participants reported flu-like symptoms which were generally mild to moderate (22 out of 36 participants), and locally limited reactions at the injection site (22 out of 36 participants) which were severe in some cases. There were no serious adverse events.

Trial in the USA (PF-07302048; NCT04380701, preliminary data)

In parallel to the trial in Germany, another trial is currently being conducted in the USA.

The vaccine candidate BNT162b1 has been investigated to date at dosages of 10 to 100 µg in younger adults (18 to 55 years) and at dosages of 10 to 30 µg in older adults (65 to 85 years). To date, BNT162b1 or placebo (dummy drug) have been administered to a total of 105 participants.

Overall, the safety and tolerability of BNT162b1 over all dose stages were like other vaccines of this type and comparable with the results of the trial in Germany. A clear connection between the observed reactions and the dose administered was observed. The reactions were more significant after the second administration of BNT162b1, but the symptoms resolved quickly within a few days. There were only two participants who complained of severe symptoms (fatigue after 10 µg, chills after 30 µg). Based on the safety observations after the 100 µg dose, it was decided to not give the second administration in this dose group.

The administrations were well tolerated by elderly participants in the trial. An 81-year-old participant reported severe muscle pain and skin rash after the administration of 20 µg, accompanied by mild fever, which suggested shingles. After treatment with an antiviral drug, the symptoms resolved within one week. The symptoms were not considered to be related to the vaccination.

Overall, the tolerability of BNT162b1 in the American trial in elderly trial participants was comparable to that of younger adults.

The vaccine candidate BNT162b2 is being investigated at dosages of 10 to 30 µg in younger adults (18 to 55 years) and at dosages of 10 to 30 µg in older adults (65 to 85 years). To date, BNT162b2 or placebo (dummy drug) have been administered to a total of 90 participants. To date, only preliminary data are available which, however, demonstrate good tolerability, comparable to BNT162b1.

Overall, the tolerability of both vaccine candidates which were previously administered in the trial in the USA was good. The initial results indicate possibly better tolerability in older adults in comparison to younger adults.

As with any new vaccine, the administration of BNT162 vaccines can lead to new, previously unknown adverse effects. As with any new medicinal product administration and vaccine, there is the possibility of developing allergic reactions. In rare cases, an acute, life-threatening, anaphylactic immediate reaction (allergic shock) can occur. Emergency equipment is available at the trial site. An on-duty doctor can be reached at all times.

Moreover, the administration of the trial substance or the trial examinations may entail risks which are not foreseeable according to the current state of knowledge.

To minimize the risks, the administration will be given in a staggered way in the respective treatment group 1 as follows:

- initially 1 participant, then 5 more participants, and then the remaining 6 participants.

In the following treatment groups, the administration will be staggered as follows if a higher dose than in the preceding groups is given:

- initially 2 participants, then 4 more participants, and then the remaining 6 participants.

This staggering is also used in treatment groups with older participants.

A dose increase takes place only if the safety data of at least 6 participants by day 3 show that the previous dosages were well tolerated.

If, in the course of the clinical trial, information becomes known which could influence your willingness to participate in the clinical trial, you will be immediately informed.

6.2 Risks due to trial-related procedures

In addition, the procedures performed for trial-related reasons within the scope of this clinical trial may involve risks or lead to discomfort.
Specifically, these involve risks and discomfort related to the blood sampling and skin reactions to adhesive patches and adhesive ECG electrodes.

In the course of this clinical trial, blood will be drawn from you several times. During the blood sampling, a circulatory reaction may occur which can lead to a change in blood pressure, dizziness, nausea and possibly fainting and seizures. The blood draws may occasionally cause local irritation, such as swelling, induration and inflammation of the vein and the formation of blood clots, as well as bleeding in the surrounding tissue (bruise). Nerve injuries may occur.

In the groups who received two administrations of BNT162a1, BNT162b1, BNT162b2, BNT162c2, the blood loss during the trial will be approximately 380 mL (18 samples), and in the groups which received a single administration of BNT162c2, approximately 370 mL (17 samples) will be drawn within about 7 to 8 months.
For comparison: in the case of a blood donation, 500 mL is generally drawn at a time).

In the event of significant changes in laboratory values, blood sampling may be necessary for reasons of safety until the changes have returned to the baseline level or until a diagnosis of a possible concomitant disease has been made. The amount of blood needed is based on the values to be determined, generally 3-6 mL per blood sample and up to 12 mL in exceptional cases.

It may be possible that, throughout the entire trial, additional blood sampling will become necessary, for example, following adverse events or to determine molecules which provide indications of the effect (biomarkers) or immunogenicity (cells or molecules of the immune system). However, not more than an additional 200 mL will be taken for these samples. If this is the case, you will provide a separate consent for this. The separate consent has no impact on your participation in this trial.

Adhesive patches and adhesive ECG electrodes: In persons with very sensitive skin, the use of adhesive ECG electrodes can cause itching and redness underneath the adhesive patch. These reactions are normally harmless and disappear after the adhesive patch is removed.

Please tell the trial site staff about all symptoms, illnesses or injuries that you experience during the course of the clinical trial. If these are severe, please report this immediately to the staff at the trial site, if necessary by telephone.

In the case of an adverse event, you may be asked, for reasons of safety, to undergo follow-up examinations or to prolong your visit at the trial site. This is necessary until this adverse event or its underlying changes have resolved or are clarified. Additional blood samples may also need to be taken.

7. Pregnancy and contraception during the trial

It is not yet known whether the use of BNT162-RNA vaccines in a parent can harm the unborn child.

Therefore, please observe the information below regarding contraception. If you have questions about reliable contraception, the trial physicians are happy to answer additional questions.

With the exception of complete abstinence (no sexual intercourse), no method of birth control always offers 100% reliable prevention of pregnancy. Most of these pregnancies occur due to improper or irregular use of a contraceptive method.

7.1 Female participants

Pregnant and breastfeeding women may therefore **not participate** in this clinical trial.

For this reason, all women must undergo a pregnancy test at the start of the clinical trial. Excluded from this are women in menopause (at least one year after the permanent absence of

menstrual periods) or those who have been surgically sterilized (ligature/dissection of the Fallopian tubes, removal of the uterus). However, pregnancy tests only confirm pregnancy reliably a few days after conception.

If you participate in the clinical trial and if you a woman of childbearing age, you must use a highly effective method of contraception (that is, with a failure rate of less than 1% per year) until 60 days after the last vaccination.

Suitable contraceptive methods for this trial – female participants of childbearing age

For the female participant of childbearing age:	◂ PLUS ▸	for the male partner:
• Hormonal contraceptives which prevent ovulation (tablets – "the pill" –, patches, vaginal ring, three-month injectable contraceptive, contraceptive implant) • Copper or hormonal IUD		• Condom

Under the following conditions, it may be sufficient that the male sexual partner of the female trial participant is sterilized:

a) the success of the sterilization has been verified (by means of semen testing)

b) a corresponding medical certificate is available, and there are no other sexual partners

Abstinence from heterosexual intercourse may also be a suitable method of contraception for this trial. Please speak to the physicians at the trial center about this, if necessary.

If you become pregnant or think that you might be pregnant during the time from the first administration until 60 days after the last administration, you must inform the trial physician immediately.

Women of childbearing age may not donate eggs until 60 days after the last vaccination.

7.2 Male trial participants

If you are a fertile man with a female partner of childbearing age and if you participate in this clinical trial, you must use a highly effective method of contraception (that is, with a failure rate of less than 1% per year) until 60 days after the last vaccination. You are not considered to be fertile if you have been successfully sterilized (e.g. vasectomy).

Suitable contraceptive methods for this trial – male participants

For the man:		For his female partner of childbearing age:
• Condom	◂ PLUS ▸	• Hormonal contraceptive (tablets – "the pill" –, patches, vaginal ring, three-month injectable contraceptive, contraceptive implant) • Copper or hormonal IUD

Under the following conditions, it may be sufficient that the male trial participant is sterilized:

a) the success of the sterilization has been verified (by means of semen testing)

b) there is a corresponding medical certificate available

Abstinence from heterosexual intercourse may also be a suitable method of contraception for this trial. Please speak to the physicians at the trial center about this, if necessary.

If your partner becomes pregnant in the time from the first administration until 60 days after the last administration, you must immediately notify one of the physicians in the trial center of this pregnancy. You will be asked to regularly inform the trial physician of the course of the pregnancy, the delivery, and the health of your child. You will receive a separate information and consent form for this purpose on which you and your partner must give your consent.

Men may not donate sperm until 60 days after the last vaccination.

8. What must I be aware of if I participate?

8.1 Participation and participation requirements

If you decide to participate, you will be asked to sign a declaration of consent and you will receive a copy of this participant information and the signed declaration of consent.

During your participation in this clinical trial (the trial begins with your signature on the declaration of consent), you may not take part in any other drug trial.

Your participation in this clinical trial is voluntary. If you participate in the clinical trial, you have the right at all times to end the clinical trial early, without indicating any reasons. If you decide to not participate or to discontinue the clinical trial early, this will not lead to any unfavorable treatment.

If you decide or the trial physician decides that you will end the trial early after the first administration of the trial substances, it will be recommended to you for your own safety to undergo a follow-up examination as planned.

The trial site does not assume any liability for personal property.

8.2 Limitations and special rules of conduct

After you have been considered for participation and decided to participate in this clinical trial, you must comply with some restrictions.

- No excessive physical activities within 2 days prior to all days on which you come to the trial center.
- During your visit to the trial center, smoking and alcohol consumption are prohibited. During the screening and on day 1, an alcohol breath test will be performed. Note: If alcohol consumption is suspected, drug tests may also be performed at other times.
- The use of all types of drugs is prohibited generally and throughout the entire clinical trial. During the screening and on day 1, a urine drug test will be performed. Since foods or drinks containing poppy seeds, such as poppy seed buns, poppy seed cake or milkshakes with poppy seeds could possibly cause a positive drug test, you should not consume these items starting at 48 hours prior to the screening or admission to the trial center.
  Note: If drug use is suspected, drug tests may also be performed at other times.
- Please drink plenty of liquid, approx. 0.5-1 L water, within the first two hours after each vaccination.
- During your visit to the trial site, only foods or beverages which are given to you by the kitchen or the staff are permitted.
- You must keep the information about the content of the clinical trial and trial substances confidential.
- During the clinical trial, trial participants must adhere to the rules described in section 7 regarding contraception and egg or sperm donation.
- From the time of the screening (visit 0) up to and including 28 days after the last immunization of this trial, you may not receive any other vaccinations.
- From the time of the screening (visit 0) up to and including 7 days after the last immunization of this trial, you may not donate any blood.
- From the time of the screening (visit 0) up to and including 14 days after the last immunization of this trial, you may not travel to countries with a high risk of infection with SARS-CoV-2 (according to the definition of the Robert Koch Institute [RKI]).

In any case, avoid contact with persons who tested positive for SARS-CoV-2 or who have a high risk of being infected.

It is mandatory to follow the recommendations of the World Health Organization (WHO) or the Federal Center for Health Education (BZgA) to decrease your risk of infection. The latter is available at https://www.infektionsschutz.de/coronavirus.html.

If you do not follow the prescribed rules of conduct and do not implement the planned measures during the clinical trial, we will be obliged to exclude you from the clinical trial.

8.3 Concomitant medication and medical care

Please do not take any corticosteroids (hormones which are formed in the adrenal cortex – that is, medications which contain these hormones, for example, artificially produced corticosteroids such as prednisone, prednisolone, methylprednisolone, triamcinolone, dexamethasone, betamethasone, or paramethasone) until the end of your participation in this trial, since these have an effect on the immunization.

Flu-like symptoms (fever, chills, spasms, heart palpitations, joint pain, muscle pain, headaches, nausea) which can be the consequence of the vaccination or caused by other viral infections, including COVID-19, can be treated with paracetamol according to the recommendations of your physician/the package leaflet (up to 4 g per day).
The paracetamol administration should start no earlier than 2 hours after the vaccination.
Please enter the administration in your participant diary.

If you receive treatment from other doctors, you must tell them that you are taking part in the clinical trial. Your trial physician must also be informed of any medical treatment that you receive from another doctor during the clinical trial. You will receive a trial ID which you should also always keep with you for emergencies.

9. Will there be any costs for me as a result of participation? Will I receive an expense allowance?

Your participation in this clinical trial is not associated with any costs to you.

Participants who take part only in the information session and screening receive compensation in the amount of € 70.00 if the drug and alcohol testing is negative.

Participants in the groups with two administrations of BNT162a1, BNT162b1, BNT162b2 and BNT162c2 which involve an inpatient admission receive compensation of € 1770.00, including screening. Participants of these groups who had only outpatient visits receive compensation of € 1700.00, including screening.

Participants in the groups with a single administration of BNT162c2 which involve an inpatient admission receive compensation of € 1670.00, including screening. Participants of these groups who had only outpatient visits receive compensation of € 1600.00, including screening.

“Reserve subjects” who are not included in the treatment phase of the clinical trial receive compensation in the amount of € 80.00.

Subjects who make an additional journey to the trial site for the throat swab receive compensation for this in the amount of € 50.00.

The compensation will be paid to you generally at the end of the clinical trial after the final visit has taken place, provided you have taken part in all examination days and followed the instructions during the clinical trial. If you end the clinical trial early, you will receive compensation which is calculated proportionately based on the number of visits which took place. You are responsible for paying any necessary taxes as well as for making any social security contributions.

10. Am I insured while taking part in the clinical trial?

10.1 Trial participant insurance

It is not expected that you will suffer health damage due to your participation in the clinical trial.

All trial participants are insured during the clinical trial of a medicine in accordance with the German Medicines Act. The scope of the insurance coverage can be found in the insurance documents which were given to you.

If you suspect that your participation in the clinical trial has damaged your health or aggravated existing symptoms, you must immediately contact the insurance company:

HDI Global SE **Tel. no.: +49 (0) 211 – 7482-246**
Postfach 10 10 27 **Fax no.: +49 (0) 211 - 1153794**
40001 Düsseldorf
Insurance certificate no.: 83-075131 -03028

with the help of your trial physician if necessary in order to maintain your insurance cover. If your trial physician helps you with this, you will receive a copy of the report. If you notify the insurance company directly, please also inform your trial physician.

You must cooperate with the investigation into the cause or extent of damage, and do everything you can to avoid and minimize the damage.

You may only undergo other medical treatment while taking part in the clinical trial after consulting the trial physician, except in an emergency. You must notify the trial physician immediately of any emergency treatment.

You will receive a copy of the insurance certificate and insurance conditions. In particular, we would like to point out to you item 1.4 (regarding the exclusions), item 3.1 (regarding the scope of the services) and item 4.3 as well as item 4.4 (regarding your obligations).

10.2 Travel accident insurance

In addition, travel accident insurance is being taken out for you with Marsh GmbH, Lyoner Straße 36, 60528 Frankfurt am Main, Germany (Mr. S. Lübstorf, telephone: +49 (0)69-6676-331 / fax: +49 (0)69 6676 555 / policy no. 403-11-518113534) under insurance number 403-11-518113534. This insurance covers all damage to your person due to accidents which you suffer throughout the entire clinical trial on the direct route to and from the trial site.

You will receive a copy of the insurance certificate and insurance conditions.

11. Will I be told about new information obtained during the clinical trial?

You will be told about new information relating to this clinical trial that might be important to your willingness to continue taking part. You can then consider whether you want to continue taking part in this clinical trial on that basis.

12. Can my participation in the clinical trial be terminated prematurely?

You can end your participation at any time, without giving reasons. This will not cause you any disadvantages.

Under certain circumstances the trial physician or the sponsor might, however, also decide to terminate your participation in the clinical trial prematurely, and you cannot affect this decision. This might be done for the following reasons, among others:

- Your continued participation in the clinical trial is no longer medically justifiable;
- You have – possibly repeatedly – violated medical instructions and rules of conduct within the scope of the trial (such as the consumption of alcohol, drugs, or unauthorized medications).
- The clinical trial is discontinued altogether.
- If illnesses, allergic reactions occur which, in the opinion of the trial physician, could damage your health or which are no longer compatible with continued participation in the trial, you will be prematurely excluded from the clinical trial.

Serious and unexpected adverse events which are definitively or likely related to the trial substance and which impact the benefit/risk assessment can lead to an early termination of the clinical trial.

New scientific findings on the trial substances which could jeopardize your safety or the appearance of a serious unexpected event can also lead to the discontinuation of the trial.

If you decide to withdraw from the clinical trial prematurely, or if your participation is terminated prematurely for one of the reasons referred to above, it is important for your own safety that you undergo a recommended final check-up as described in section 4.4.

The trial physician will discuss with you whether and when additional check-ups are necessary.

13. What will happen to my data?

Medical findings and personal information will be obtained from you ("personal data") as part of the clinical trial and recorded at the trial site in your individual record or stored electronically.

The legal basis for this data processing is your consent (art. 6 para. 1(a), art. 9 para. 2(a) General Data Protection Regulation [GDPR]).
The data are collected and used according to legal regulations (GDPR in conjunction with section 40 of the German Medicines Act [AMG] as well as section 42b AMG, provided the trial data are used for an application for approval).

The responsible party in terms of data privacy is the sponsor of this clinical trial.

The data are provided exclusively in pseudonymized form to the sponsor of the clinical trial, the examining and approving authorities, or a site commissioned by it for scientific assessment. Pseudonymized means that no information such as names or initials are used, but instead only a number and/or letter code, possibly indicating the year of birth. It is possible to

allocate these data back to you personally only with the aid of this code. Unencoded data which enable you to be personally identified are available only at the trial site. The data are protected against unauthorized access.

If trial results are published, the confidentiality of your personal data likewise remains guaranteed. Compliance with data privacy regulations is ensured to the fullest extent.

The results of this clinical trial will also be used for scientific research purposes and forwarded in this connection to infectious disease researchers within and outside of the country.

Where applicable, they will also be forwarded to cooperation partners (domestic and international cooperation partners and pharmaceutical industry companies) of the companies of the BioNTech group for the further development of the trial substance and/or the development of new therapies as well as analysis methods and, where applicable, also for commercial purposes (such as patent registration).

Pseudonymization measures for your personal data will be used for the forwarding mentioned above to domestic and international infectious disease researchers and/or cooperation partners so that your identity is not disclosed.

If forwarding of your pseudonymized personal data should be necessary in this connection to a country outside of Europe for which there is no adequacy decision of the EU Commission in accordance with art. 45 GDPR, data will be transferred only if there are suitable data privacy guarantees as defined by art. 46 GDPR. A suitable guarantee is the use of standard contractual clauses. The decision of the EU Commission on standard contractual clauses, including a copy of the standard contractual clauses, is available at https://eur-lex.europa.eu/legal-content/DE/TXT/?uri=CELEX%3A32010D0087.

If your data are presented at scientific conferences or published (disclosed) in scientific journals, these publications will take place in an exclusively anonymized manner, that is, in a form which does not allow you to be personally identified.

Your personal data will be handled confidentially. An exception is the duty of disclosure regarding participant fees paid in the event of inquiries by the employment office, tax office, and social welfare office.

You have the right to receive information about your stored data, to the free transfer of a copy of your personal data, to have your data corrected or deleted, to request a limitation of the processing, or to object to further processing. In addition, for electronic data which you yourself provided to the trial site, you have the right to transfer these data to yourself or to a third party in a common format (right to data portability). In some cases, your rights may be limited by laws (art. 17, para. 3 GDPR), especially if they would jeopardize the proper implementation of the clinical trial or in the case of mandatory archiving regulations.

The responsible party in terms of data privacy is the sponsor of this clinical trial. If you have questions about data privacy or wish to exercise your rights, you can contact the trial physician or the data privacy officer of the trial site or of the sponsor. As a general rule, please contact the data privacy officer of the trial site because only the trial site can have full access to your data and provide corresponding information because of the legally required

pseudonymization process in clinical trials. In view of this, the sponsor's data privacy officer can only provide limited help.

Contact information of the CRS data privacy officer

CRS Clinical Research Services Andernach GmbH
Data Privacy Officer
Rennweg 72
56676 Andernach, Germany
Email: datenschutzbeauftragter@crs-group.de

Contact data for the sponsor's data privacy officer

Dr. Michael Kruse
BioNTech SE
An der Goldgrube 12
55131 Mainz, Germany
Telephone: +49 (0) 6131-9084-1030,
Email: Michael.Kruse@biontech.de or data.privacy@biontech.de

You may also contact the data privacy officers directly if you have concerns regarding the handling of your personal data. The responsible party is:

a) the state data privacy officer of the federal state in which your trial site is located.

Baden-Württemberg:

The Officer for Data Privacy and Freedom of Information of the State of Baden-Württemberg
Dr. Stefan Brink
Königsstraße 10 a
70173 Stuttgart, Germany
Telephone: +49 (0)711-615541-0
Fax: +49 (0)711.615541-15
Email: poststelle@lfdi.bwl.de

Berlin:

Berlin Officer for Data Privacy and Freedom of Information
Maja Smotlczyk
Friedrichstraße 219
10969 Berlin, Germany
Telephone: +49 (0)30-138 89-0
Fax: +49 (0)30-215 50 50
Email: mailbox@datenschutz-berlin.de

b) the state data privacy officer for the sponsor:

Rhineland-Palatinate:

The Officer for Data Privacy and Freedom of Information of the State of Rhineland-Palatinate
Prof. Dr. Dieter Kugelmann
Hintere Bleiche 34
55116 Mainz, Germany
Telephone: +49 (0)6131-208 24 49
Fax: +49 (0)6131-208 24 97
Email: poststelle@datenschutz.rlp.de

c) as well as any other data privacy supervisory authority in the European Union.

The German Medicines Act and also the European General Data Protection Regulation as well as the German Federal Data Protection Act contain more information for the necessary scope of consent to data processing.

Please see the declaration of consent printed at the end of this participant information for details, in particular on the option of revocation. Please be aware that you may participate in the clinical trial only if you have given your written consent for data processing.

14. What will happen to my blood samples?

The blood samples will, like the data, be stored in pseudonymized form, thus without indicating name or initials. Your blood samples will be processed by the following institutions:

MLM Medical Labs GmbH (safety laboratory, HIV and hepatitis serology, HLA determination)
Dohrweg 63
41066 Mönchengladbach, Germany

BioNTech SE Biosampling Unit (determination of antibodies and immune defense cells)
An der Goldgrube 12
55131 Mainz, Germany
Precision for Medicine/Epiontis GmbH (determination of immune defense cells)
Barbara-McClintock- Str. 6
12489 Berlin, Germany
Vis Mederi (detection of antibodies directed against the virus)
Strada del Petriccio e Belriguardo 35
53100 Sienna, Italy
High-throughput Clinic Immunoassays & Diagnostics (repeat analyses/comparative measurements)
Pfizer Vaccine Research & Development
401 N. Middletown Rd
Pearl River, NY 10950, USA

14.1 Safety laboratory and serology for HIV and hepatitis

The blood samples for the safety laboratory and serology for HIV and hepatitis are used exclusively for this clinical trial and will be destroyed no later than the conclusion of the trial.

14.2 Pharmacogenetic testing (HLA determination)

In special cases, the sponsor of the clinical trial (BioNTech RNA Pharmaceuticals GmbH) would like to examine your genetic information for a group of certain proteins on the surface

of white blood cells (leucocyte antigens, abbreviated as HLA) (= pharmacogenetic testing) and on the surface of other nucleated cells of the body. The testing can be performed with a part of the sample for testing cell-mediated immunity. In this case, no separate blood sampling is necessary. If this is not possible, you will be asked specifically once more for your consent for a separate blood sample.

The HLA system is a group of human genes which are central to the function of the immune system and which may be important for the sponsor's analyses, for example, if particularly strong immune responses were measured.

In conducting genetic testing, parts of your genetic information will be decoded. Within the scope of these analyses, the genomic data will be used exclusively to investigate genetic characteristics of immune cells.

Even if the scientific analyses do not aim to identify disease-triggering hereditary factors, there is the possibility that hereditary factors which indicate a significantly increased risk of a disease will be discovered.

However, there are no plans to identify such findings during this clinical trial, although this is technically possible. This means that you may not be informed of any such findings indicating a need for treatment.

Participation in this pharmacogenetic testing is voluntary and does not depend on participation in the trial. You can give/not give us your consent on page 31.

14.3 Biomarkers

Up to 5 additional blood samples (totaling a maximum of 200 mL) may be taken for additional research purposes (you will be asked to provide separate consent for this). These samples will be tested for certain cells and molecules formed by the body as part of the immune response to the vaccine (known as "biomarkers").

These samples may be stored and analyzed at a later point in time to investigate, for example, which of these biomarkers are related to clinical symptoms following the administration of BNT162 vaccines, or to further develop diagnostic and analytical methods. The samples will be stored for up to 5 years after the end of the trial. The sample will be labeled (barcode or digits) such that you cannot be personally identified.

Blood samples for biomarker analyses and all of the data they yield are used taking into consideration the applicable legal regulations, including the requirements for compliance with data privacy regulations (including when sending the samples outside of Germany) and a possible withdrawal of your consent.

14.4 Antibody determination and determination of the cell-mediated immune response

The blood samples for antibody determination and to determine the cell-mediated immune response which were taken from you in this trial will initially be used for the measurements provided for in this trial. It is assumed that all of the material will be used up within the scope of the trial.

In order to prevent any leftover material from going to waste, it is planned to use it, for example, for the following additional testing and measurements:

- for comparative measurements (that is, comparability of antibody determinations or to confirm the determination of cells of the cell-mediated immune response of various laboratories. These comparative measurements may also be performed outside of Germany or the European Union, where applicable).
- for the further development of diagnostic and analytical methods.
- for genetic and biomarker testing, as described above in section 14.2 and 14.3

The samples and all of the data they yield are used taking into consideration the applicable legal regulations, including the requirements for compliance with data privacy regulations (including when sending the samples outside of Germany) and a possible withdrawal of your consent.

Leftover material is stored for a maximum of 5 years after the end of the trial.

The sample will be labeled (barcode or digits) such that you cannot be personally identified.

Early termination of trial participation

If you wish to end your participation in the clinical trial early, you may decide whether your samples are to be destroyed or whether they may continue to be used in anonymized form. The samples which were taken for HLA determination (including the remainders of samples as well as the components isolated from them) will be stored by the laboratory until the sponsor arranges for destruction. Measurement results will not be deleted.

15. Whom should I contact if I have further questions?

Counseling sessions at the trial site

You can always have further counseling sessions with the trial physician named on page 1 or another trial physician.

Contact point at the competent federal higher authority according to section 40 para. 5 AMG

There is also a contact point at the competent federal higher authority. Participants in clinical trials, their legal representatives or proxies can get in touch with this contact point.

Paul Ehrlich Institute
Clinical Trials Department
Paul-Ehrlich-Str. 51-59
63225 Langen
Tel.: 06103 / 77 1810
Fax: 06103 / 77 1277
Email: klinpruefung@pei.de

16. Address and telephone number of the trial site

CRS Clinical Research Services <site> GmbH

Address

If you have questions about the organization before and during the clinical trial, please contact the recruitment office (tel.: 0800-100 6971 (free) or <direct tel. no.)>.

You will receive an emergency card with information about the clinical trial and you will be given a telephone number at which you can reach the on-call physician of <CRS-site GmbH> at all times (24-hour emergency telephone: <tel. no. >).

The trial physician Dr. *XXXXXXX* and his/her deputy XXXX can be reached at <tel. no.>.

In case of an event which you or your family members feel is serious or life-threatening, you should immediately contact the emergency physician (tel.: 112) and do not delay the treatment in attempting to reach the on-call physician.

II. Declaration of consent with regard to data privacy

I am aware that in this clinical trial, personal data, in particular medical findings about me, are to be collected, stored and analyzed. The data regarding my health are used according to legal regulations and this use requires the following voluntarily granted declaration of consent prior to participation in the clinical trial, that is, without the following consent, I cannot participate in the clinical trial.

1. I hereby declare my consent for personal data within the scope of this clinical trial, in particular data about my health, to be collected about me and recorded in hardcopy form as well as on electronic data media at CRS Clinical Research Services <site> GmbH. If necessary, the data collected may be forwarded in pseudonymized (encoded) form:

   a) to the sponsor BioNTech RNA Pharmaceuticals or a site commissioned by it for purposes of scientific analysis,

   b) in the event of an application for approval: to the applicant and the authority responsible for the approval (e.g. Paul Ehrlich Institute [PEI] and the competent foreign authorities (e.g. the U.S. Food and Drug Administration [FDA] or the European Medicines Agency [EMA]),

   c) in the event of adverse events: to the sponsor, to the competent ethics committee in each case and the competent higher federal authority (PEI), as well as from these parties to the European database,

   d) to domestic and international infectious disease researchers for exclusively scientific purposes,

   e) to cooperation partners (domestic and international cooperation partners and pharmaceutical industry companies) of the companies of the BioNTech group for the further development of the trial substance and/or the development of new therapies as well as analysis methods and, where applicable, also for commercial purposes (such as patent registration).

2. I additionally declare my consent for authorized and confidentiality-bound representatives of the sponsor as well as the competent supervisory authorities to inspect my personal data on file with the trial physician, in particular my health data, provided this is necessary to verify the proper conduct of the trial. This may also include personal presence at trial-related activities. I release the trial physician from the obligation to maintain medical confidentiality for these measures.

3. It has been explained to me that I can end participation in the clinical trial at any time. I can likewise at any time withdraw consent for the processing of my personal data, in particular data about my health. In the event of such withdrawal of my consent, I hereby declare my consent for data stored until this point in time to continue to be processed, provided this is necessary to

   a) determine the effects of the medicinal product to be tested,

   b) ensure that my interests which are worthy of protection are not compromised,

   c) comply with the obligation to submit complete approval documentation.

4. I hereby declare my consent for my data to be stored for at least fifteen years after the end or discontinuation of the trial, as specified by the regulations on the clinical testing of medicinal products. Thereafter my personal data will be deleted, unless statutory, official or contractual retention periods stipulate otherwise.

5. I have been informed of the following legal regulation: If I withdraw my consent to participate in the trial, all sites which have stored my personal data, in particular health data, must immediately check the extent to which the stored data are still needed for the purposes listed in no. 3 a) to e).

   Data which are no longer needed must be immediately deleted.

6. I consent for my family doctor to be informed about my participation in the clinical trial (cross out if not desired).

   _____

   _____

   (Name and address of the family doctor)

III. Declaration of consent

Multi-site Phase I/II Trial Investigating the Safety and Effects of Four BNT162 Vaccines Against COVID-19 in Healthy Adults

CRS 049/20 (EudraCT: 2020-001038-36)

Participant number: xxxxx

_____

Name of trial subject (please print)

In a personal discussion, the trial physician informed me in detail and comprehensibly about the trial substance and about the nature, significance, risks and scope of the clinical trial. I have also read and understood the text of the participant information in Version 7.0 datedJuly 24, 2020 and the data protection declaration. I have had the opportunity to discuss the conduct of the clinical trial with the trial physician.

I had enough time to make a decision.

I know that I can withdraw my consent to take part in the trial at any time and without giving reasons (verbally or in writing), and that no disadvantages will arise as a result.

I confirm that I will provide complete and accurate information about my medical history, my state of health, the intake of medications, as well as any other questions related to the clinical trial.

I confirm that I have complied with and will comply with the limitations according to section 8.2 of the participant information.

I agree to voluntarily participate in the clinical trial CRS 049/20 (EudraCT: 2020-001038-36).

I have received a dated and signed copy of the participant information and informed consent form as well as the insurance documents (general insurance conditions, confirmation of insurance). One copy remains at the trial site.

All my questions have been answered to my satisfaction.

_____ _____

Place, date Signature of the trial subject

I consent to the use of a part of the sample for the pharmacogenetic testing to investigate cell-mediated immunity. I am aware that this consent for this purpose is optional and that I can withdraw this consent at any time, without any disadvantages to me.

Note: If this test cannot be performed with the sample for cell-mediated immunity, a separate blood sampling of approx. 4 mL may be performed. You will then be asked separately for your consent for this.

Yes □ **No □**

_____ _____

Place, date Signature of the trial subject

Physician conducting the information discussion

_____

First and last name of the physician (please print)

With my signature, I confirm that I conducted the information discussion, handed out the participant information, and answered any questions which arose. I obtained consent from the participant. *(applicable if the information discussion and screening are performed by the same physician; otherwise delete.)*

<location>,_____ _____

Place, date Signature of physician conducting the information discussion

(Date to be filled out personally by the trial physician)

Physician obtaining the consent prior to the start of screening

(NOT necessary if the physician conducting the information discussion and the physician conducting the screening are the same and both took place on the same day. In this case, one physician signature is sufficient: that of the physician conducting the information discussion.)

_____

First and last name of the physician (please print)

With my signature, I confirm that I answered all questions which arose and that I gave him/her a copy of this informed consent form.

☐ There were no questions

☐ The following questions were answered *(bullet points of topics covered)*:

_____

_____

_____

<location>,_____ _____

Place, date, Signature of the trial physician

(Date to be filled out personally by the trial physician)

Participant information leaflet and declaration of consent – Additional blood sampling: Immunomonitoring
CRS trial no. 049/20
EudraCT no. 2020-001038-36

CRS trial no.:	049/20
Sponsor trial no.	BNT162-01
EudraCT no.	2020-001038-36
Protocol title (short version)	Multi-site Phase I/II Trial Investigating the Safety and Effects of Four BNT162 Vaccines Against COVID-19 in Healthy Adults
Original title of the protocol	A Multi-site, Phase I/II, 2-Part, Dose-Escalation Trial Investigating the Safety and Immunogenicity of Four Prophylactic SARS-CoV-2 RNA Vaccines Against COVID-19 Using Different Dosing Regimens in Healthy Adults
Sponsor	BioNTech RNA Pharmaceuticals GmbH, An der Goldgrube 12, 55131 Mainz, Germany
Trial center	<Name> <Address> <Address>
Investigator	<Title / Name> <Address> <Address> <Telephone: 000-123 45 67 89 Fax: 000-123 45 67 899>

Information about the trial	**Name**	**Telephone**
Mon. – Fri., during the day	<Trial subject administrative office>	<123 45 67 89>
	<Physician at the trial site	*<123 45 67 89>*
Evenings, nights, weekends, holidays	< Mobile telephone >	<123 45 67 89>
	< Central trial site >	*<123 45 67 89>*

I Participant information

Dear prospective participant,

You are taking part in the clinical trial BNT162-01 and have already declared your consent to be treated within the scope of the trial.

The sponsor of the clinical trial (BioNTech RNA Pharmaceuticals GmbH) would like to investigate the function and activation status of your immune cells using various immunological tests (immunomonitoring) in order to determine the reactions of your immune system to the administration of the vaccine.

Blood sampling within the scope of the trial is planned for the visit currently taking place and we would like to ask you if more blood than previously planned can be drawn at this visit for this testing, however not more than an additional 200 mL (at the up to 5 additional blood samplings, however a total of not more than 200 mL).

This blood sample will be used for the characterization of certain immune cells and certain immune system messengers. In addition, the samples may be stored longer and used to determine certain biomarkers (biological characteristics which can be measured and analyzed) which may be connected to the observed reactions to the vaccination or be used for the development of diagnostic methods.

You will receive compensation of € 50.00 for this additional blood sample.

These additional blood samples will be analyzed in the laboratory BioNTech SE Biosampling Unit (determination of antibodies and immune defense cells), An der Goldgrube 12, 55131 Mainz, Germany.

These samples will be stored for up to 5 years after the end of the trial. More information on insurance, the handling of your data and samples, as well as information on data privacy can be found in the general participant information for participation in the clinical trial.

Your participation in this additional blood sampling is voluntary. You may refuse this at any time, also without stating any reasons, or withdraw your consent for this, without this resulting in any disadvantages for your trial participation.

II Declaration of consent

In a personal discussion, the trial physician informed me in detail and comprehensibly about the significance and risks of the additional blood sampling.

I know that I can withdraw my consent (verbally or in writing) to take part in this additional blood sampling at any time and without giving reasons and that no disadvantages will arise for me as a result.

I agree to participate in this additional blood sampling.

Participant number: _____

_____

Name of trial participant (please print)

_____ _____

Place, date Signature of the trial participant

Physician conducting the information discussion

_____

First and last name of the physician (please print)

<location>,_____ _____

Plate, date Signature of physician conducting the information discussion

(Date to be filled out personally by the investigator)

Participant information leaflet and declaration of consent – Additional blood sampling: Pharmacogenomic testing HLA
CRS trial no. 049/20
EudraCT no. 2020-001038-36

CRS trial no.:	049/20
Sponsor trial no.	BNT162-01
EudraCT no.	2020-001038-36
Protocol title (short version)	Multi-site Phase I/II Trial Investigating the Safety and Effects of Four BNT162 Vaccines Against COVID-19 in Healthy Adults
Original title of the protocol	A Multi-site, Phase I/II, 2-Part, Dose-Escalation Trial Investigating the Safety and Immunogenicity of Four Prophylactic SARS-CoV-2 RNA Vaccines Against COVID-19 Using Different Dosing Regimens in Healthy Adults
Sponsor	BioNTech RNA Pharmaceuticals GmbH, An der Goldgrube 12, 55131 Mainz, Germany
Trial center	<Name> <Address> <Address>
Investigator	<Title / Name> <Address> <Address> <Telephone: 000-123 45 67 89 Fax: 000-123 45 67 899>

Information about the trial	**Name**	**Telephone**
Mon. – Fri., during the day	<Trial subject administrative office>	<123 45 67 89>
	<Physician at the trial site	*<123 45 67 89>*
Evenings, nights, weekends, holidays	< Mobile telephone >	<123 45 67 89>
	< Central trial site >	*<123 45 67 89>*

I Participant information

Dear prospective participant,

You are taking part in the clinical trial BNT162-01 and have already declared your consent to be treated within the scope of the trial.

Blood sampling within the scope of the trial is planned for the visit currently taking place and we would like to ask you if more blood than previously planned can be drawn at this visit for further testing, however not more than an additional 4 mL.

In special cases, the sponsor of the clinical trial (BioNTech RNA Pharmaceuticals GmbH) would like to examine your genetic information for a group of certain proteins on the surface of white blood cells (leukocyte antigens, abbreviated as HLA) (= pharmacogenetic testing).

The HLA system is a group of human genes which are central to the function of the immune system and which may be important for the sponsor's analyses. In the event of results of particular interest, these genes will be subsequently analyzed.

In conducting genetic testing, parts of your genetic information will be decoded. Within the scope of these analyses, the genomic data will be used exclusively to investigate genetic characteristics of immune cells. Even if the scientific analyses do not aim to identify disease-triggering hereditary factors, there is the possibility that hereditary factors which indicate a significantly increased risk of a disease will be discovered. However, there are no plans to identify such findings during this clinical trial, although this is technically possible. This means that you may not be informed of any such findings indicating a need for treatment.

You will receive compensation of € 10.00 for this additional blood sample.

These additional blood samples will be analyzed in the laboratory MLM Medical Labs GmbH, Dohrweg 63, 41066 Mönchengladbach, Germany.

More information on insurance, the handling of your data and samples, as well as information on data privacy can be found in the general participant information for participation in the clinical trial.

Your participation in this additional blood sampling is voluntary. You may refuse this at any time, also without stating any reasons, or withdraw your consent for this, without this resulting in any disadvantages for your trial participation. The additional samples (including the remainders of samples as well as the components isolated from them) will be stored by the laboratory until the sponsor arranges for destruction. Measurement results will not be deleted.

II Declaration of consent

In a personal discussion, the trial physician informed me in detail and comprehensibly about the significance and risks of the additional blood sampling.

I know that I can withdraw my consent (verbally or in writing) to take part in this additional blood sampling at any time and without giving reasons and that no disadvantages will arise for me as a result.

I agree to participate in this additional blood sampling.

Participant number: _____

_____

Name of trial participant (please print)

_____ _____

Place, date Signature of the trial participant

Physician conducting the information discussion

_____

First and last name of the physician (please print)

<location>,_____ _____

Plate, date Signature of physician conducting the information discussion

(Date to be filled out personally by the investigator)

CLINICAL TRIAL PROTOCOL AMENDMENT HISTORY INCLUDING AMENDMENTS NOS. 01 TO 06

BNT162-01

Protocol version: 9.0 **Date:** 05 OCT 2020

Sponsor: BioNTech RNA Pharmaceuticals GmbH

Trial title:	A multi-site, Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy and immunocompromised adults
Brief title:	A multi-site Phase I/II trial investigating the safety and effects of four BNT162 vaccines against COVID-19 in healthy and immunocompromised adults
Trial phase:	Phase I/II
Indication:	Protection against COVID-19
Product:	BNT162: SARS-CoV-2 - RNA lipid nanoparticle (RNA-LNP) vaccines utilizing different RNA formats, i.e., BNT162a1, BNT162b1, BNT162b, BNT162c2
Principal investigator:	Dr. Dr. med. Armin Schultz, CRS Clinical Research Services Mannheim GmbH, Germany (tel.: +49 621 15045 165)
Trial sites:	Multiple sites in Germany. For further details of the study sites and site personnel, see the Trial Master File (TMF).
Contract research organization:	CRS Clinical Research Services Mannheim GmbH, Germany
Sponsor's responsible person:	Özlem Türeci, MD, Chief Medical Officer, BioNTech SE
Sponsor:	BioNTech RNA Pharmaceuticals GmbH, An der Goldgrube 12, 55131 Mainz, Germany
Regulatory identifiers:	EudraCT no.: 2020-001038-36; ClinicalTrials.gov NCT: 04380701; WHO UTN: U1111-1249-4220
Medical Monitor:	The sponsor's Medical Monitor name and contact information will be provided separately

Document history	Date	Version number	Valid for
First approved version	09 Apr 2020	2.0	Germany
Amendment No. 1	17 Apr 2020	3.0	Germany
Amendment No. 2	13 May 2020	4.0	Germany
Amendment No. 3	26 May 2020	5.0	Germany
Amendment No. 4	09 Jun 2020	6.0	Germany
Amendment No. 4	26 Jun 2020	7.0	Germany
Amendment No. 5	21 Jul 2020	8.0	Germany
Amendment No. 6	05 OCT 2020	9.0	Germany

Statement of Compliance: This trial will be conducted in according to this protocol, the ethical principles that have their origin in the Declaration of Helsinki, good clinical practice (GCP), and applicable regulatory requirements.

TABLE OF CONTENTS

1 PROTOCOL AMENDMENTS

1.1 Protocol amendment no. 01

Amendment rationale

This amendment describes the replacement of the product codes BNT162c1 with BNT162c2. The RNA component of BNT162c1 encoded only the RBD of the S protein, the RNA component of BNT162c2 encodes a modified version of the full length S protein. BNT162c1 was replaced with BNT162c2 because of its superior immunogenicity profile in non-clinical studies.

This amendment describes changes made in response to feedback from the German PEI (April 16th, 2020).

This amendment will be issued before any trial subjects have been enrolled into the trial. This change has no impact on the planned trial objectives or trial conduct.

Detailed description of changes

Editorial changes are not listed.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Throughout the document, the product code “BNT162c1” was replaced with “BNT162c2”.	BioNTech decision based on non-clinical data.
Section 1.1 (Trial design) & Section 4.1. The data assessed by the SRC comprises 48 h data for 6 subjects including observation on site, phone interview ~~(if available)~~, vital signs, TEAEs, local reactions…	PEI feedback.
Section 1.1 (Trial design) & Section 4.1. Details of Part B will be defined after evaluation of aggregate data from Part A using a protocol amendment. Progression to Part B will be based on analysis of both immunogenicity and safety data gathered in Part A. Both immunogenicity and safety will be thoroughly assessed to select the vaccine and the dose(s) to be further evaluated in Part B. Safety data to be evaluated includes the package used by the SRC to assess individual dose levels and in addition any other safety observations that may be reported until the data cut off. Immunogenicity of all doses will be assessed. This ~~The~~ protocol amendment will include a summary of relevant safety and tolerability data collected in Part A. This protocol amendment will also include Part B specific inclusion/exclusion criteria, objectives/endpoints, a description of the planned statistical analyses, and descriptions of any added trial assessments and procedures. Part B ~~may~~ will use a randomized, placebo-controlled design in the likely target population (e.g., high risk populations such as elderly and/or immunocompromised populations). Part B may employ a surrogate marker as a measure of vaccine efficacy.	PEI feedback.
Section 1.1 (Table 1) ~~RBD of the S protein~~” for BNT162c1 was replaced with “A modified version of the S protein” for BNT162c2.	BioNTech decision based on non-clinical data.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 1.1 (Key inclusion criteria) & Section 5.1. WOCBP must agree to practice ~~one~~ two highly effective forms of contraception during the trial, starting after Visit 0 and continuously until 60 d after receiving the last immunization.	Correction of an inconsistency in protocol version 2.0.
Section 1 (Objectives and Endpoints) and Section 3 (Objectives and Endpoints/Exploratory Endpoint) • Cell-mediated immune (CMI) responses measured by Enzyme-Linked Immuno-Spot (ELISpot; CD4 and CD8 T-cell ELISpot) at baseline and at 42±4 d after the primary immunization. For BNT162a1, BNT162b1, BNT162b2 (P/B): • Cell-mediated immune (CMI) responses measured by Enzyme-Linked Immuno-Spot (ELISpot; CD4 and CD8 T-cell ELISpot) at baseline and at 29±3 d after the primary immunization. For BNT162c2 (SD): • Cell-mediated immune (CMI) responses measured by Enzyme-Linked Immuno-Spot (ELISpot; CD4 and CD8 T-cell ELISpot) at baseline and at 42±4 d 29±3 d after the primary immunization.	Correction of an inconsistency in protocol version 2.0.
Section 1.1 (Key exclusion criteria). Have a positive PCR-based test for ~~anti-~~SARS-CoV-2 within the 30 d prior to Visit 1.	Correction of an inconsistency in protocol version 2.0.
Section 1.1 (Key exclusion criteria) & Section 5.2. Exclusion criterion 26. Have had contact with persons diagnosed with COVID-19 or who tested positive for SARS-CoV-2 by any diagnostic test ~~antibodies~~ within the 30 d prior to Visit 0.	PEI feedback.
Section 1.2 (Schema) Part A has four cohorts (one per dose level), each with four planned groups (1A for BNT162a1, 1B for BNT162b1, 1C for BNT162b2, and 1D for BNT162c1) and two optional groups (1E, 1F, etc.). For details, see Table 1.	PEI feedback.
Section 2.1.1 (Overview of the disease). ~~"The World Health Organization (WHO) Situation Update Report dated April 8th, 2020 noted 1,353,361 confirmed cases with 79,235 deaths globally, including 720,219 confirmed cases with 57,639 deaths in the European region (WHO Situation Report Nr. 79).~~ "The WHO Situation Update Report dated April 15th, 2020 noted 1,914,916 confirmed cases with 123,010 deaths globally, including 977,596 confirmed cases with 84,607 deaths in the European region (WHO Situation Report Nr. 85)."	Data was updated.
Section 2.3.1 (Risk assessment). Due to their immune-modulatory effect, vaccines may cause systemic flu-like reactions such as temporary headache, fatigue, loss of appetite, myalgia, arthralgia, fever. Rarely, with certain prophylactic vaccines (e.g., as seen for vaccines using attenuated viruses) severe allergic reaction or a neurological side effects, such as a seizure, were seen. Although these rare side effects are a concern, the risk of a vaccine causing serious harm or death is considered to be extremely small, in particular for BNT162 vaccines, which are molecularly defined, highly purified and based on RNA, which naturally occurs and is metabolized in the human organism.	PEI feedback.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 2.3.1 (Risk assessment) text was added. Vaccine-related enhanced disease has been reported in the literature from non-clinical studies investigating different vaccine formulations tested to prevent various coronavirus-induced diseases. Such effects have not been documented so far for SARS-CoV-2. No data are currently available to exclude that BNT162 may cause enhanced disease in vaccinated subjects.	PEI feedback.
Section 2.3.1 (Risk assessment) text was updated. "Use the Subject Hotline to contact the trial site during their participation in the trial should they require guidance or should they experience any symptoms of illness. The reporting of any symptoms of illness, e.g., enhanced respiratory disease or flu-like symptoms, may trigger diagnostic measures at the discretion of the investigator."	PEI feedback.
Section 4.4 (End of trial definition (EoT)). A trial subject is considered to have completed the trial if they have completed all planned visits including the ~~Visit 6 (~~EoT Visit~~)~~, and the two follow-up visits ~~(Visits 7 and 8)~~.	PEI feedback triggering scheduling changes.
Section 4.4 (End of trial definition (EoT)). "The end-of-the-trial is defined as the date the last subject completed the ~~Visit 6 (~~EoT Visit~~)~~."	PEI feedback triggering scheduling changes.
Section 5.1 (Inclusion criteria) Inclusion criterion 8. "WOCBP must confirm that they practiced at least one highly effective form of contraception for the 14 d prior to Visit 0."	Correction of an inconsistency in protocol version 2.0.
Section 5.2 (Exclusion criteria) Exclusion criterion 11. "Have a positive PCR-based test for ~~anti~~ SARS-CoV-2 within the 30 d prior to Visit ~~0~~ 1."	Correction of an inconsistency in protocol version 2.0.
Section 6.6.1 (Dose limiting toxicity). "The same events will prompt IMP discontinuation for individual subjects as described in Section 6.6.4. Tasks connected to the discontinuation of IMP are described in Section 7.1."	PEI feedback.
Section 6.6.3 (Mitigation plans for specific AEs). "If subjects experience enhanced respiratory disease or progression of flu-like symptomatology, such as non-resolution of the symptoms after 7 d, symptom kinetics that are inconsistent with a relationship to RNA immunization, additional diagnostic measures should be considered and the Medical Monitor should be informed."	PEI feedback.
Section 6.6.4 (Safety stopping criteria). "See Section 6.6.1 for the list of events that must prompt discontinuation for the individual subjects. The SRC will review and evaluate the collected safety data periodically during the trial (see Section 10.1.5 for details). A decision to stop treatment for an individual subject or to terminate the trial may be taken if safety concerns are identified by the SRC. Suspected unexpected serious adverse reactions (SUSARs) will immediately be reviewed by the SRC. They will trigger a temporary stop of IMP administration to new subjects in the respective dose level cohort for that vaccine until the SRC	PEI feedback.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
recommendation to continue or to permanently stop IMP administration of new subjects in the respective dose level cohort for that vaccine. Guidance for discontinuation of trial treatment is provided in Section 7.1 For criteria for discontinuation of individual patients from IMP, see Section 7.1“	
Section 7.1 (Discontinuation of trial treatment) “Trial subjects permanently discontinued from IMP administration will complete all assessments planned for that visit and for the ~~Visit 6 (~~EoT Visit~~).~~ as listed in the SoA (Section 1.3).	PEI feedback triggering scheduling changes.
Section 8.2.1 (Physical examinations). “A brief (symptom directed) physical examination ~~will include, at a minimum, assessments of the skin, lungs, cardiovascular system, abdomen (liver), and lymph nodes~~.”	Correction of an inconsistency in protocol version 2.0.
Section 8.2.10 (SARS-CoV-2 testing). ~~PCR-based testing for SARS-CoV-2 as an eligibility criterion and testing for anti-SARS-CoV-2 antibodies as baseline reference for immunogenicity analysis will be performed at the times given in the SoA (Section 1.3).~~ SARS-CoV-2 testing will be performed at the time points provided in the SoA (Section 1.3). This include PCR-based testing for SARS-CoV-2 at Visit 0 as an elig bility criterion and blood draws for anti-SARS-CoV-2 antibody testing as baseline reference for immunogenicity analysis. If required, this reference will allow the discrimination between vaccinated and infected subjects. The anti-SARS-CoV-2 ant body testing will be performed with a commercially available antibody test. In case this commercial antibody test can, discriminate between vaccine-specific and infection-specific antibody responses (based on the antigens used), it will be used to test subjects who may have experienced enhanced respiratory disease or progression of flu-like symptomatology, such as non-resolution of the symptoms after 7 d, symptom kinetics that are inconsistent with a relationship to RNA immunization, as might be expected with a COVID-19 disease (see Section 6.6.3). In these cases, ad hoc anti-SARS-CoV-2 ant body testing will be performed to test for the development and presence of SARS-CoV-2-specific antibodies, ideally at 14 d and 28 d. This data will be used to evaluate the development and progression of an antibody response allowing the diagnosis of a manifest infection. In case this commercially available test cannot discriminate between vaccine-specific and infection-specific antibody responses, the same kind of analysis will be performed with a custom-made assay specifically developed by the CRO.	PEI feedback.
Section 8.3.1 (Adverse events of special interest) was updated. “~~Not applicable.~~ Enhanced respiratory disease or flu-like symptomatology not-resolved after 7 d or with symptom kinetics that are inconsistent with a relationship to RNA immunization will considered adverse events of special interest (AESI).”	PEI feedback.
Section 10.3.1 (Definition of AE and TEAE). “AEs with an onset date more than ~~21~~ 28 d after the last administration of IMP will be considered as treatment emergent only if assessed as related to IMP by the investigator.”	Correction of an inconsistency in protocol version 2.0.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 8.9 (Immunogenicity assessments). ~~Immune responses will be assessed at the times listed in the SoA (Section 1.3) using:~~ • a functional antibody titer, e.g., virus neutralization test (VNT). • an antibody binding assay, e.g., ELISA. • and/or equivalent assays dependent on availability by the time of trial conduct. • (for cell-mediated immune responses) ELISpot (CD4 and CD8 T-cell ELISpot). Immune responses will be assessed at the times listed in the SoA (Section 1.3) using: • a functional antibody titer, e.g., virus neutralization test (VNT). Seronegative is defined as titers below the starting dilution which corresponds to a titer of <1:10. Seroconversion after vaccination is defined as a 4-fold increase in titer for seronegative pre-vaccination sera: a titer >1:40. for seropositive pre-vaccination sera: a titer which is 4-fold higher than the measured pre-vaccination titer, e.g., titer rise from 1:20 to >1:80 after vaccination. • an antibody binding assay, e.g., ELISA. Seronegative is defined as titers below the starting dilution which corresponds to a titer of <1:100. Seroconversion after vaccination is defined as a 4-fold increase in titer for seronegative pre-vaccination sera: a titer of >1:400. for seropositive pre-vaccination sera: a titer which is 4-fold higher than the measured pre-vaccination titer, e.g., titer rise from 1:200 to >1:800 after vaccination. and/or • equivalent assays dependent on availability by the time of trial conduct. Cell-mediated immune (CMI) responses: • CMI assays, e.g., ELISpot. CMI analysis will include Th1-specific cytokines, e.g., IFN-gamma, TNF-alpha, IL-2, or IL12, and Th2-specific cytokines (e.g., IL4, IL-5, IL-10, IL-13) to analyze the induction of either balanced Th1/Th2 responses or of unbalanced Th1-dominant respectively Th2-dominant immune responses.	PEI feedback.
Section 10.4.2 (Contraception guidance). Women of childbearing potential (WOCBP) must practice ~~one~~ two highly effective forms of contraception during the trial, starting after Visit 0 and continuously until 60 d after receiving the last immunization. …….. The investigator or delegate should advise the subject how to achieve highly effective contraception. Use of ~~one~~ two of the following birth control methods may be considered as highly effective (trial subjects must use two of the listed methods)	Correction of an inconsistency in protocol version 2.0.
Section 10.1.5 (Committees - SRC). • Before progression to the next cohort, for each vaccine per cohort/dose level, assess the safety and tolerability data of the first ≥6 subjects (based on data collected pre-dose and post-dose up to and including Visit 2) and decide whether to approve initiation of the next cohort/dose level and to confirm the planned dose or define another dose for use. The data assessed by the SRC comprises 48 h data for 6 subjects including observation on site, phone interview (if available), vital signs, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome. data, decide whether to approve initiation of the next cohort/dose level and to confirm the planned dose or define another dose for use. The data assessed by the SRC is defined in Section **Error! Reference source not found.**	PEI feedback.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
• After completing its evaluation of the 48 h data for the first 6 subjects per group in cohort, the SRC may request a prolongation of the observation period to up to Day 7 data for later cohorts. • Before progression to Part B, review and evaluate at least the Day 21 data per vaccine to decide whether to progress to Part B, and if yes, define what doses will be given. The data assessed by the SRC comprises 48 h data for 6 subjects (including observation on site, phone interview (if available), vital signs, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome). data per vaccine to decide whether to progress to Part B, and if yes, define what doses will be given. The data assessed by the SRC is defined in Section **Error! Reference source not found.**.	
Section 10.3.1.9 (Documentation of particular situations). **„AEs of proven COVID-19 disease of moderate or severe intensity:** Any case of proven COVID-19 disease occurring during the observation period should be reported as an SAE, where the intensity of the respective AE is rated as "moderate" or "severe" (according to the criteria provided in Section 10.3.1.7). If none of the other SAE definitions are deemed suitable, then the SAE criterion of being a "medically important event" should be applied (according to the definitions provided in Section 10.3.1.4). An SAE form should be completed, including follow-up information, as detailed in Section 10.3.1.10 such that an SAE report and narrative can be prepared and distributed."	PEI feedback.

1.2 Protocol amendment no. 02

Amendment rationale

This amendment describes a dose adjustment for the vaccine BNT162c2 and the corrections of some inconsistencies and ambiguities.

This amendment will be issued after some of the planned trial subjects have already been enrolled into the trial. This change has no impact on the planned trial objectives or trial conduct.

Editorial changes are not listed.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Throughout the document, the term "COVID-~~2019~~" was harmonized to "COVID-19".	Harmonization – the protocol used COVID-2019 and COVID-19.
Section 1.1 (Trial Synopsis) "Table 1 - Summary of vaccine dose regimens" The planned doss for the BNT162c2 vaccine was reduced as follows: 1: (Starting dose): From 3 µg to 0.1 µg 2: From 10 µg to 0.3 µg 3: (De-escalation dose): From 1 µg to "Not planned" 4: From 30 µg to 1 µg	Non-clinical data suggesting a high potency, thereby allowing the use of a lower dose.
Section 1.1 (Trial Synopsis) "Trial design" – Part A For all cohorts, if the investigator considers necessary, the planned observation periods before proceeding to dose further subjects in the same group may be prolonged by 24 h. Dose de-escalation in the case of possible vaccine-related toxicities will be guided by the Safety Review Committee (SRC), as required.	Additional information added for clarification.
Section 1.1 (Trial, Synopsis) "Trial design" – Part A • If approved by the SRC, Part B will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects (including observation on site, phone interview, vital signs, TEAEs, local reactions, immunogenicity data, blood/clinical laboratory data, and brief physical examination outcome). Note: BNT162b1 and BNT162b2 have the same chemistry, BNT162a1 and BNT162c2 also have the same chemistry. Tolerability data obtained with one of the vaccine variants of each of these pairs may be potentially informative for the respective other one and should be taken in consideration by the SRC for recommendations of lower or interim doses. In the case that an individual experiences dose limiting toxicities or that the frequency or pattern of AEs within a sub-cohort gives cause for concern, the investigator may request by phone an ad hoc review by the SRC, at any time, before further doses of a given vaccine construct are administered. If approved by the SRC, Part B will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects (including observation on site, phone interview, vital signs, TEAEs, local reactions, immunogenicity data, blood/clinical laboratory data, and brief physical examination outcome).	Additional information added for clarification.
Section 1.1 (Trial Synopsis) Table "Trial treatments (BNT162 vaccines)" Part A dose finding: • For BNT162a1 ~~and BNT162c2~~: 1 µg, 3 µg, 10 µg, 30 µg (optionally/additionally doses <1 µg [de-escalation] or doses between 1 µg and 30 µg [intermediate doses]).	Non-clinical data suggesting a high potency, thereby allowing the use of a lower dose.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
• For BNT162b1 and BNT162b2: 1 µg, 10 µg, 30 µg, 100 µg (optionally/additionally doses <1 µg [de-escalation] or doses between 1 µg and 100 µg [intermediate doses]). • For BNT162c2: 0.1 µg, 0.3 µg, 1 µg (optionally/additionally doses between 0.1 µg and 1 µg [intermediate doses]).	
Section 1.1 (Trial Synopsis) Table "Trial treatments (BNT162 vaccines)" Dosage frequency: • One injection or two injections 21 d apart. Injection volumes will be between 0.05 mL ~~0.1 mL~~ and 1 mL.	Non-clinical data suggesting a high potency, thereby allowing the use of a lower dose.
Section 1.2 (Schema (graphical representation of the trial)) The figures depicting BNT162a1 and BNT162c2) was split into two figures and due to the changed doses inBNT162c2.	Non-clinical data suggesting a high potency, thereby allowing the use of a lower dose.
Section 1.3 (SoA) Table 2 - Footnote n i Excluding the de-escalation cohorts, only for the first 6 subjects per group. ……. ~~n Only for the first 6 subjects per group.~~	Clarification of an ambiguity regarding when wellbeing calls are planned.
Section 1.3 (SoA) Table 3 - Footnote o o Excluding the de-escalation cohorts, only ~~Only~~ for the first 6 subjects per group.	Clarification of an ambiguity regarding when wellbeing calls are planned.
Section 2.3.1 Risk Assessment • To date, there is very limited clinical experience with BNT162 vaccines in human subjects. Reactogenicity is anticipated and considered to contribute to the mode-of-action of inducing vaccine immune responses. Initial dose-ranging studies have suggested AE profiles consistent with previous usage of similar constructs in cancer patients, with AEs generally dividing into 2 groups: local injection site reactions and systemic flu-like illness. With BNT162 vaccines to date most reported AEs have been mild to moderate in intensity and no serious AEs have been reported. Fever of severe intensity has been reported. Most AEs can be managed with simple measures and resolve spontaneously.	Addition of preliminary data from the ongoing clinical trial.
Section 2.3.1 Risk Assessment ~~• Subject wellbeing questioning by telephone at 48±2 h after each immunization.~~ • Excluding the de-escalation cohorts, subject wellbeing questioning by telephone at 48±2 h after each immunization will be performed for the first 6 subjects per cohort (for P/B regimens only after the prime immunization). Additional subject wellbeing calls may be included at the discretion of the SRC. • In the case that an individual experiences dose limiting toxicities or that the frequency or pattern of AEs within a sub-cohort gives cause for concern, the investigator may request an ad hoc review by the SRC before further doses of a given vaccine construct are administered.	Clarification of an ambiguity regarding when wellbeing calls are planned. Addition of the option for wellbeing calls at the discretion of the SRC.
Section 2.3.1 Risk Assessment SRC may make recommendations on increasing observation periods and additional subject wellbeing calls may be included at the discretion of the SRC.	Additional information added for clarification.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 4.1 (Trial design) – Part A For all cohorts, if the investigator considers necessary, the planned observation periods before proceeding to dose further subjects in the same group may be prolonged by 24 h. Dose de-escalation in the case of possible vaccine-related toxicities will be guided by the Safety Review Committee (SRC), as required.	Additional information added for clarification.
Section 4.1 (Trial design) – Part A • If approved by the SRC, Part B will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects (including observation on site, phone interview, vital signs, TEAEs, local reactions, immunogenicity data, blood/clinical laboratory data, and brief physical examination outcome). Note: BNT162b1 and BNT162b2 have the same chemistry, BNT162a1 and BNT162c2 also have the same chemistry. Tolerability data obtained with one of the vaccine variants of each of these pairs may be potentially informative for the respective other one and should be taken in consideration by the SRC for recommendations of lower or interim doses. In the case that an individual experiences dose limiting toxicities or that the frequency or pattern of AEs within a sub-cohort gives cause for concern, the investigator may request by phone an ad hoc review by the SRC, at any time, before further doses of a given vaccine construct are administered. If approved by the SRC, Part B will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects (including observation on site, phone interview, vital signs, TEAEs, local reactions, immunogenicity data, blood/clinical laboratory data, and brief physical examination outcome).	Additional information added for clarification.
Section 4.3 (Justification for dose) Given that BioNTech proposes a rapid response scenario to a newly emerged pandemic outbreak, sufficient data is currently not available to experimentally validate the dose selection and initial starting dose. Therefore, BioNTech proposes a starting dose of 0.1 µg (for BNT162c2), 3 µg (for BNT162a1 ~~and BNT162c2~~) and 10 µg (for BNT162b1 and BNT162b2) in this trial based on non-clinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens).	Non-clinical data suggesting a high potency, thereby allowing the use of a lower dose.
Section 5.2.1 Exclusion criteria Part A (Criteria 7) WOCBP must agree to practice ~~two highly effective forms~~ a highly effective form of contraception during the trial, starting after Visit 0 and continuously until 60 d after receiving the last immunization.	Correction of an inconsistency with the ICF and to expand the eligible population.
Section 6.1 (IMP administered) Table “Trial treatments (BNT162 vaccines)” Part A dose finding: • For BNT162a1 ~~and BNT162c2~~: 1 µg, 3 µg, 10 µg, 30 µg (optionally/additionally doses <1 µg [de-escalation] or doses between 1 µg and 30 µg [intermediate doses]). • For BNT162b1 and BNT162b2: 1 µg, 10 µg, 30 µg, 100 µg (optionally/additionally doses <1 µg [de-escalation] or doses between 1 µg and 100 µg [intermediate doses]). • For BNT162c2: 0.1 µg, 0.3 µg, 1 µg (optionally/additionally doses between 0.1 µg and 1 µg [intermediate doses]).	Non-clinical data suggesting a high potency, thereby allowing the use of a lower dose.
Section 6.1 (IMP administered) Table “Trial treatments (BNT162 vaccines)” Dosage frequency: • One injection or two injections 21 d apart. Injection volumes will be between 0.05 mL ~~0.1 mL~~ and 1 mL.	Non-clinical data suggesting a high potency, thereby allowing the use of a lower dose.

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Section 6.6 (Dose modifications) The trial design allows for a flexible dosing which allows a better evaluation on the optimal dose range, i.e., the trial design includes the options: ~~• To replace the planned 10 µg, 30 µg and/or 100 µg doses with doses below the entry dose (3 µg or 10 µg). This is referred to as dose de-escalation.~~ • To replace or supplement the planned 1 µg, 3 µg, 10 µg, 30 µg and/or 100 µg dose levels with doses either below the planned starting doses of 3 µg or 10 µg or interim doses between the listed doses. • To adapt the planned escalation doses (0.3 µg, 1 µg, 10 µg, 30 µg, and 100 µg doses in Part A), whereby the highest dose will not exceed the highest planned dose for that vaccine. • To decrease the planned starting dose of one of the BNT162 vaccines based on observations made for a chemically related BNT162 vaccine already dosed in this trial.	Non-clinical data suggesting a high potency, thereby allowing the use of a lower dose.
Section 6.6.1 (Dose limiting toxicity) • Anaphylactic reaction considered related • Generalized urticaria considered related • Four trial subjects in that cohort with any severe unsolicited local event, if considered related and not manageable with simple measures (e.g., cooling, analgesia, nonsteroidal anti-inflammatory drugs [NSAIDs]) • Any systemic SAE within 7 days of vaccination considered related • Any fever >40.0°C (>104.0°F) within 7 days of vaccination considered related • Two trial subjects (at any dose level) with the same or similar severe (Grade 3) AE (including laboratory abnormalities) within 7 days of vaccination, considered related (for severity grading of adverse events see (see Section 10.3.1.7) ~~• Any systemic SAE considered related~~ • ~~Any severe non-SAE considered related~~	Harmonization with the relatedness categories given in Section 10.3.1
Section 8.2.7 Viral screening The screen will test for: Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis C antibodies, and HIV-1 and HIV-2 antibodies. For SARS-CoV-2 testing, see Section 8.2.10. Further viral and bacteria status data will be generated when using local PCR-testing to establish SARS-CoV-2 status via “point of care” devices at the trial sites. This data will not be recorded in the CRF and will not be part of data analysis of the trial. If the test results must be reported to relevant authorities, this notification will be done by the trial site. No further data will be generated if the PCR-testing takes place in the central laboratory.	Addition of sentence to enable usage of further local PCR-devices.
Section 8.2.9 (Subject wellbeing questioning) Cross-reference to the section “Assessment of Intensity“ inserted. Table 4 (Grading of local reactions to injectable product) was deleted.	Strategy change for the reporting of AEs (to enable cross-alignment with other planned clinical trials with BNT162 vaccine candidates)
Section 8.2.12 (Subject wellbeing questioning) (Excluding the de-escalation cohorts and after boost immunizations) Structured non-leading subject wel being questioning will be performed at the time given in the SoA (Section 1.3) for the first 6 subjects per cohort. Subject responses may trigger more in-	Clarification of an ambiguity regarding when wellbeing calls are planned.

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depth questioning on specific topics, and may trigger diagnostic measures (including ad hoc site visits) at the discretion of the investigator.	
Section 9.4.5 (Section 10.4.2 Contraception guidance) Additionally, the occurrence of clinically significant abnormal laboratory results within a trial subject will be analyzed using descriptive summary statistics for each parameter and visit by group. Abnormal laboratory results will be graded using the criteria given in US FDA Guidance for Industry 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials' (see Section 10.3.1.7).	Strategy change for the reporting of AEs (to enable cross-alignment with other planned clinical trials with BNT162 vaccine candidates)
Section 10.1.5 (Committees – SRC) • Throughout the trial, approval from the SRC will be required prior to resuming any dosing in a "stopped" cohort (see Section 6.6.1). The SRC may call for the opening of a lower dose level cohort. • SRC may make recommendations on increasing the length of the observation periods and additional subject wellbeing calls may be included at the discretion of the SRC.	Clarification of the SRC role.
Section 10.3.1.4 (Definition of SAE) • Results in persistent disability/incapacity<br~~The term disability means a substantial disruption of a person's ability conduct normal life functions.~~ This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.	Strategy change for the reporting of AEs (to enable cross-alignment with other planned clinical trials with BNT162 vaccine candidates)
Section 10.3.1.7 (Recording and Follow-Up of AE and/or SAE) Assessment of intensity<br~~The intensity of AEs or SAEs will be graded by the investigator. For further guidance on assessment assessments, see below:~~ • ~~Grade 1 - Mild; Signs and symptoms that can be easily tolerated. Symptoms can be ignored and disappear when the subject is distracted.~~ • ~~Grade 2 - Moderate; Symptoms cause discomfort but are tolerable; they cannot be ignored and affect concentration.~~ • ~~Grade 3 - Severe; Symptoms which affect usual daily activity.~~ Note: The grading scheme for protocol version 4.0 should only be adopted for subjects consented for inclusion in new cohorts that start enrolment after the protocol amendment has been approved and implemented (for any drug construct). All subjects in cohorts where first enrolment pre-dates the protocol amendment, should continue to use the grading scheme in protocol version 3.0, such that the same grading scheme is used for all subjects in any given cohort. The protocol version 3.0 grading scheme should continue to be used for subjects consented under protocol version 3.0, and that retrospective re-grading is not required. The intensity of AEs or SAEs will be graded by the investigator. For further guidance please refer to guideline "US FDA Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".For further guidance please refer to guideline "US FDA Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". Where specific guidance for an adverse event term is	Strategy change for the reporting of AEs (to enable cross-alignment with other planned clinical trials with BNT162 vaccine candidates)

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not provided, the following general approach should be followed:

FDA_Toxicity_Grading_2007

- Grade 1 - Mild; does not interfere with the subject's usual function.
- Grade 2 - Moderate; interferes to some extend with the subject's usual function.
- Grade 3 - Severe; interferes significantly with the subject's usual function.
- Grade 4 - Potentially Life threatening; life-threatening consequences, urgent intervention required.

Please also refer to the intensity tables given in the guideline for intensity of clinical and laboratory abnormalities to be reported as AEs:

- Guideline Section III.A for assessment of clinical abnormalities (local and systemic)

Local Reactions

Redness and swelling will be measured and recorded in centimeters and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 4.

Pain at the injection site will be assessed by the trial subject as absent, mild, moderate, or severe according the grading scale in Table 4.

Table 4: Local reaction grading scale

	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	2.5 cm to 5.0 cm	>5.0 cm to 10.0 cm	>10 cm	Necrosis or exfoliative dermatitis
Swelling	2.5 cm to 5.0 cm	>5.0 cm to 10.0 cm	>10 cm	Necrosis

Systemic events

Symptoms of vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5.

Table 5: Systemic event grading scale

	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Vomiting	1-2 times in 24 h	>2 times in 24 h	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 h	4 to 5 loose stools in 24 h	6 or more loose stools in 24 h	Emergency room visit or hospitalization for severe diarrhea

Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Fever

Fever is defined as an oral temperature of ≥38.0°C. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 6.

Table 6: Fever grading scale

	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever	38.0-38.4°C	38.5-38.9°C	39.0-40.0°C	>40.0°C

Laboratory abnormalities

Laboratory abnormalities will be graded according to the grading scheme given in Table 6.

Table 7: Laboratory abnormality grading scale

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Female) change from baseline value - g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hemoglobin (Male) change from baseline value – g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000

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WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
Chemistry	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen;
ULN = upper limit of normal; WBC = white blood cell.

Section 10.4.2 Contraception guidance

Women of childbearing potential (WOCBP) must practice ~~two highly effective forms~~ a highly effective form of contraception during the trial, starting after Visit 0 and continuously until 60 d after receiving the last immunization.

Men who are sexually active with a WOCBP and have not had a vasectomy must agree to practice a highly effective form of contraception with their female partner of childbearing potential during the trial, starting after Visit 0 and continuously until 60 d after receiving the last immunization.

Subjects with bilateral tubal occlusion, previous successful vasectomy or those who are truly abstinent or exclusively homosexual are deemed as being "not of reproductive potential".

The investigator or delegate should advise the subject how to achieve highly effective contraception. ~~Use of the~~ The following birth control methods may be considered as highly effective ~~(trials subjects must use two of the listed methods)~~:

- Intrauterine device. [a]
- Intrauterine hormone-releasing system. [a]

Correction of an inconsistency with the ICF and to expand the eligible population.

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• Combined estrogen and progestogen-based contraception: established use of oral, intravaginal, or transdermal hormonal methods of contraception. • Progesterone-based contraception: established use of oral, injected, or implanted a hormonal methods of contraception. • True abstinence or homosexuality. When the subjects are truly abstinent or homosexual, no second method of contraception is required. • Vasectomy (for a male subject or male partner of a female subject). [a] a) Contraception methods that in the context of this guidance are considered to have low user dependency.	

1.3 Protocol amendment no. 03

Amendment rationale

This amendment describes updates in response to PEI and IEC feedback on protocol version 4.0.

This amendment will be issued after some of the planned trial subjects have already been enrolled into the trial. This change has no impact on the planned trial objectives or trial conduct.

Editorial changes are not listed.

<table>
<tr><th>Changed text
(inserted text is blue/underlined; deleted text is red/struck out)</th><th>Rationale</th></tr>
<tr><td>Section 1.1 “Trial design” – Table 1 (Summary of vaccine dose regimens)

<table>
<tr><th rowspan="2">Vaccine</th><th rowspan="2">mRNA type</th><th>Vaccine encoded antigen</th><th>Vaccine IM dosing regimen</th><th colspan="5">Part A - Dose Groups & Dose (µg) (12 subjects per cohort)</th><th>Part B - Optional Expansion Cohorts</th></tr>
<tr><th></th><th></th><th>1
Starting dose</th><th>2</th><th>3
De-escalation dose</th><th>4</th><th>5*</th><th></th></tr>
<tr><td>BNT162a1</td><td>uRNA</td><td>RBD of he SARS-CoV-2 S protein</td><td>Prime: Day 1
Boost: Day 22</td><td>1A
3 µg</td><td>2A
10 µg</td><td>3A*
1 µg 0.1 µg</td><td>4A
30 µg</td><td>5A
0.3 µg</td><td>Doses to be selected based on Part A data</td></tr>
<tr><td>BNT162b1</td><td>modRNA</td><td>RBD of he S protein</td><td>Prime: Day 1
Boost: Day 22</td><td>1B
10 µg</td><td>2B
30 µg</td><td>3B
1 µg</td><td>4B
100 µg
60 µg*</td><td>5B
50 µg</td><td>As above</td></tr>
<tr><td>BNT162b2</td><td>modRNA</td><td>A modified version of he S protein</td><td>Prime: Day 1
Boost: Day 22</td><td>1C
10 µg</td><td>2C
30 µg</td><td>3C
1 µg</td><td>4C
100 µg</td><td></td><td>As above</td></tr>
<tr><td>BNT162c2</td><td>saRNA</td><td>A modified version of he S protein</td><td>Prime only: Day 1</td><td>1D
0.1 µg</td><td>2D
0 3 µg</td><td>Not planned</td><td>4D
1 µg</td><td></td><td>As above</td></tr>
</table>
* Dose to be defined/adapted by the Safety Review Committee (SRC).
IM = intramuscular; RBD = Receptor Binding Domain; S protein = SARS-CoV-2 Spike protein</td><td>Due to dose adjustments following IEC feedback and SRC requests.</td></tr>
<tr><td>Section 1.1 “Trial design” – Part A and Section 4.1 Overall design and Section 4.1 Overall design
Note: BNT162b1 and BNT162b2 have the same chemistry, BNT162a1 and BNT162c2 also have the same chemistry. Tolerability data obtained with one of the vaccine variants of each of these pairs may be potentially informative for the respective other one and should be taken in consideration by the SRC for recommendations of lower or interim doses.
Additional dose cohorts (e.g., Cohort 5) may be investigated at the discretion of the SRC, but will not exceed the pre-defined maximum dose (see Table 1).
Note: BNT162b1 and BNT162b2 are both non-modified uridine RNAs, while BNT162a1 and BNT162c2 are both nucleoside-modified pseudomethyl-uridine containing. This modification is known to impact the extent of innate immune activation at a given dose level, and thus potentially the extent of reactogenicity. Therefore, tolerability data obtained with one of the vaccine variants of</td><td>PEI & IEC feedback to amendment no. 2.</td></tr>
</table>

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each of these pairs may be potentially informative for the respective other one and should be taken in consideration by the SRC for recommendations of lower or interim doses.	
Section 1.1 "Trial design" – Part A In Cohort 1, the sentinel dosing/subject staggering process will be as follows: • One sentinel subject will be dosed on one day. • If the ……. • If the dosing in these 5 subjects was considered to be safe and well tolerated by the investigator based on 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48±2 h data from the sentinel subject): o The remaining 6 subjects in the group will be dosed. o If approved by the SRC, the next planned escalation dose (see Table 1) in Cohort 2 will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects including observation on site, phone interview, vital signs, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome. o If approved by the SRC, the planned de-escalation dose in Cohort 3 ~~(1 µg)~~ will be initiated. In Cohort 2, the subject staggering process will be as follows: • Two sentinel subjects will be dosed on one day. • If the ……. • If the dosing in these 4 subjects was considered to be safe and well tolerated by the investigator based 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48 h data from the sentinel subjects): o The remaining 6 subjects ……. o If approved by the SRC, … In Cohort 3, if possible, 12 subjects will be dosed with the planned ~~1 µg~~ dose on one day.	Due to dose adjustments following IEC feedback and SRC requests.
Section 1.1 "Trial treatments" and Section 6.1 "IMP administered" **Dosage levels:** See Table 1. The planned dose per vaccine candidate will not exceed the pre-defined maximum dose (see Table 1). ~~Part A dose finding:~~ ~~• For BNT162a1: 1 µg, 3 µg, 10 µg, 30 µg (optionally/additionally doses <1 µg [de-escalation] or doses between 1 µg and 30 µg [intermediate doses]).~~ ~~• For BNT162b1 and BNT162b2: 1 µg, 10 µg, 30 µg, 100 µg (optionally/additionally doses <1 µg [de-escalation] or doses between 1 µg and 100 µg [intermediate doses]).~~ ~~• For BNT162c2: 0.1 µg, 0.3 µg, 1 µg (optionally/additionally doses between 0.1 µg and 1 µg [intermediate doses]).~~	Due to dose adjustments following IEC feedback and SRC requests.
Section 1.2 Schema (graphical representation of the trial) The schema were updated to reflect the updated doses.	Due to dose adjustments following IEC feedback and SRC requests.
Section 1.3 - Table 2 (Schedule of trial procedures and assessments – BNT162a1, BNT162b1, and BNT162b2) A column for subject wellbeing questioning was inserted for 48 h after the boost immunization.	PEI feedback to amendment no. 2.

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Section 1.3 Schedule of activities Table 2 ~~i Excluding the de-escalation cohorts, only for the first 6 subjects per group (for P/B regimens only after the prime immunization).~~ i Only for the first 6 subjects per group.	PEI feedback to amendment no. 2.
Section 1.3 Schedule of activities) Table 3 ~~o Excluding the de-escalation cohorts, only for the first 6 subjects per group.~~ o Only for the first 6 subjects per group.	PEI feedback to amendment no. 2
Section 2.2 Trial rationale SARS-CoV-2 infections ……. BioNTech has developed a……. This trial will investigate the potential safety and immunogenicity of four prophylactic BNT162 vaccines against SARS-CoV-2, BNT162a1, BNT162b1, BNT162b2, and BNT162c2.The two variants of the BNT162b vaccines, BNT162b1 and BNT162b2, differ in the encoded antigen. The four prophylactic BNT162 vaccines against SARS-CoV-2 investigated in this trial BNT162-01 will also be investigated in clinical trials in the US and China. The status and preliminary results from all of these are trials are summarized in the following sections. **This trial (BNT162-01) - Preliminary results (status 22 May 2020)** For the vaccine candidate BNT162b1, 60 subjects have been dosed in 5 cohorts of 12 subjects each with doses of 1, 10, 30, 50 and 60 µg. The pattern of tolerability has been as anticipated and described in the protocol / informed consent form (ICF) with most subjects reporting flu-l ke symptoms and injection site reactions. Fever has been reported in approximately 25% of subjects. Onset of systemic symptoms may begin around 6 h but they more typically present 10 to 12 h post administration, with the fever usually starting 16 to 24 h post vaccination. All events resolve spontaneously or with simple medical management (e.g., cooling measures, antipyretics, reassurance), typically within 24 to 48 h of onset. Most adverse reactions that were reported in all dose groups were mild or moderate in severity. No serious adverse events (SAEs) have been reported within the post-vaccination observation period. A slight dose dependency for frequency and intensity of symptoms was observed between the 1 µg and 10 µg cohorts, but from 10 µg to 60 µg no clear dose dependency is apparent. On laboratory examination, a transitory depression of the lymphocyte counts and mild elevation of C-reactive protein (CRP) are seen, consistent with the expected mode of action of BNT162b1 effecting a reversible compartmentalization into lymphoid organs, with no associated clinical consequence seen. No subjects were withdrawn due to related AEs. Overall, the risk-benefit for this construct within the dose range explored remains unchanged. For the vaccine candidate BNT162a1, 6 subjects were exposure at a 3 µg dose. All subjects reported flu-l ke symptoms within 24 h of dosing, mostly of moderated intensity with fever in approximately 65% of subjects. One subject experienced vomiting and a second an episode of hypotension. A more marked elevation to CRP was noted, with a similar pattern of lymphocyte depression to that described above for the BNT162b1 vaccine candidate. All events resolved, however some subjects remaining symptomatic for a number of days. No SAEs have been reported and no subjects withdrew due to adverse events. The safety review committee resolved to explore a lower dose range subsequently. The first 6 subjects have been dosed at 0.3 µg and demonstrate a similar pattern of reactogenicity to that described for the BNT162b1 vaccine candidate, with almost exclusively mild effects reported to date. **US trial PF-07302048 - Preliminary results (status 22 May 2020)** This trial in the US will be conducted by Pfizer, Inc. (New York, US) and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany). The trial has been approved by the US regulatory authorities and trial conduct has started. The US trial PF-07302048 (NCT NCT04368728) is “a Phase I/II, placebo-controlled, randomized, observer-blind, dose-finding study to descr be the safety, tolerability, immunogenicity, and potential efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy adults.	Addition of current data from this and related trials at the request of the IEC.

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The trial PF-07302048 will evaluate the safety, tolerability, immunogenicity, and potential efficacy of up to 4 different SARS CoV 2 RNA vaccine candidates against COVID 19: As a 2-dose (separated by 21 or 60 days) or single-dose schedule At up to 3 different dose levels In 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age]) Dependent upon safety and/or immunogenicity data generated during the course of this trial, or the BNT162-01 clinical trial, it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses. The US trial consists of 3 stages. Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3; a final candidate/dose large-scale stage. The trial is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the trial sites, only the dispenser(s)/administrator(s) are unblinded. As of May 22, 2020 a total of 45 subjects have been enrolled in this trial, and received a first dose of the BNT162b1 vaccine candidate or placebo. Of these, 12 received 10 µg, 12 received 30 µg, 12 received 100 µg, and 9 received placebo. A degree of reactogenicity was see, with local and systemic reactions similar to those reported in the BNT162-01 trial. Reactogenicity was generally transient and of mild or moderate intensity. Severe reactogenicity events were only reported in the 100 µg dose level in at most one or two subjects. No grade 4 reactogenicity was reported, no stopping rules were met, and no serious adverse events (SAEs) were reported. The available reactogenicity data for the first 15 subjects administered a first dose of 100 µg of BNT162b1 (5 dosed 18 May 2020, 5 dosed 20 May 2020, 5 dosed 21 May 2020) has been evaluated by the trial independent review committee (IRC) in the context of all data now available after first doses of 10 µg and 30 µg. The results were considered to be consistent with dose related increases in local and systemic reactions. Based on the benefit-risk profile seen to date for BNT162b1, the IRC approved further trial progression as planned. Further evaluation of dosing will be based on continuing review of data from both the US trial PF-07302048 and BNT162-01 trial data, with particular attention to 50 µg and 60 µg doses. **Chinese trial - BNT162-03** This trial will be conducted by Shanghai Fosun Pharmaceutical Development, Inc. (Shanghai, China) and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany). The trial set-up is ongoing. Currently no IND has been submitted, therefore the trial has not been approved by the Chinese regulatory authorities and trial conduct has not started. This trial will be a phase I, randomized, placebo-controlled, observer-blind, safety and immunogenicity investigation of SARS-CoV-2 mRNA vaccine (BNT162b1) in healthy Chinese adults. After randomization, the trial for each subject will last for approximately 6 months or 12 months. Two doses of either SARS-CoV-2 vaccine (BNT162b1) or placebo will be given intramuscularly on Day 1 and on Day 22. After each age group completes the follow-up 28 days after boost vaccination (Day 50), periodical analysis will be conducted respectively. Subjects who are ≥18 years old and ≤55 years old will be enrolled in adult group, and healthy elderly people who are >55 years old will be enrolled in elderly group. Approximately 102 subjects from each age group enter into three dose escalating cohorts (10 µg, 30 µg and 100 µg) from low to high, with approximately 34 subjects at each dose level, including approximately 25 BNT162b1-treated subjects and approximately 9 placebo-treated subjects. There will be a sentinel group (2 subjects of 1 in BNT162b1 and 1 in placebo) in each cohort, the followed two sub-groups (32 subjects in total) in each cohort will be randomized (3:1) to inject BNT162b1 or placebo. If approved by the trial SRC after review of safety and tolerability data in the low dose cohort subjects, an escalated dose cohort may start. Alternatively, the SRC may recommend the start of a de-escalated dose cohort. After the 14-day safety observation post the boost vaccination of the first	

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subject in the first dose cohort of the adult group, the prime vaccination for sentinel subjects in the first dose cohort may start in the elderly group.	
Section 2.3.1 Risk assessment • As summarized in Section 2.2.1 and Section 2.2.2, With BNT162 vaccines to date most of the AEs reported AEs after immunization with BNT162 vaccine candidates have been mild to moderate in intensity and no ~~S~~serious AEs have been reported. Fever of severe intensity has been reported. Most AEs ~~were~~can be managed with simple measures and resolved spontaneously. • To date, there is very limited clinical experience with BNT162 vaccines in human subjects. Reactogenicity is anticipated and considered to contribute to the mode-of-action of inducing vaccine immune responses. Initial dose-ranging studies have suggested AE profiles consistent with previous usage of similar constructs in cancer patients, with AEs generally dividing into 2 groups: local injection site reactions and systemic flu-like illness. • As summarized in Section 2.2.1 and Section 2.2.2, to date most of the AEs reported after immunization with BNT162 vaccine candidates have been mild to moderate in intensity and no SAEs have been reported. Fever of severe intensity has been reported. Most AEs were managed with simple measures and resolved spontaneously. Whilst the general risk of effects potentially associated with the innate immune activation and transient secretion of associated cytokines are defined above based on the descr bed data, the dose response-relationship, and thus tolerability for this specific set of vaccine candidates will only be defined by the ongoing trials (this trial BNT162-01 and the US trial PF-07302048, see Section 2.2.2) and the planned Chinese trial (BNT162-03, see Section 2.2.3). • The mostly moderate flu-like AEs observed in all six of the first 6 subjects dosed at the 3 µg starting dose for BNT162a1 in the trial BNT162-01, combined with the vomiting and hypotension observed in one of the six subjects, led to a reduction of the starting dose from 3 µg to 0.3 µg for the next cohort to be treated with the same vaccine candidate. In this regard, since both the BNT162c2 and BNT162a1 vaccine candidates use the same type of nucleosides (i.e., pseudomethyl-uridine instead of uridine) that are known to define the extent of innate immune activation, the planned doses for the BNT162c2 vaccine candidate were also reduced (see Table 1). For example, the starting dose for BNT162c2 was reduced from 3 µg to 0.1 µg. The listed risks can be managed using routine symptom driven standard of care as described in Section 6.6.3. Treatment of these events is dependent on the discretion of the investigators.	Inclusion of current data from this and related trials at the request of the IEC.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 2.3.1 Risk assessment • ~~Excluding the de-escalation cohorts, subject wellbeing questioning by telephone at 48±2 h after each immunization will be performed for the first 6 subjects per cohort (for P/B regimens only after the prime immunization). Additional subject wellbeing calls may be included at the discretion of the SRC.~~ • Subject wellbeing questioning by telephone at 48±2 h after each immunization will be performed for the first 6 subjects per cohort.	PEI feedback to amendment no. 2
Section 4.3 Justification for dose Given that BioNTech proposes a rapid response scenario to a newly emerged pandemic outbreak, sufficient data is currently not available to experimentally validate the dose selection and initial starting dose. Therefore, BioNTech ~~proposes~~ proposed a starting dose of 0.1 µg (for BNT162c2), 3 µg (for BNT162a1) and 10 µg (for BNT162b1 and BNT162b2) in this trial based on non-clinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). Based on preliminary data from this trial, as explained below, the planned doses for the BNT162a1 and BNT162c2 vaccine candidates were reduced (see Table 1). The general safety and effectiveness of …. The BNT162 vaccines…. The doses…… Based on non-clinical data ……. As discussed in Section 2.3.1, to date, there is very limited clinical experience with BNT162 vaccines in human subjects. Reactogenicity is anticipated and considered to contribute to the mode-of-action of inducing vaccine immune responses. Initial dose-ranging studies have suggested AE profiles consistent with previous usage of similar constructs in cancer patients, with AEs generally dividing into 2 groups: local injection site reactions and systemic flu-like illness. As summarized in Section 2.2.1 and Section 2.2.2, to date most of the AEs reported after immunization with BNT162 vaccine candidates have been mild to moderate in intensity and no SAEs have been reported. Fever of severe intensity has been reported. Most AEs were managed with simple measures and resolved spontaneously. Based on the available ~~previous~~ clinical and non-clinical data experience, the sponsor expects the planned maximal doses (see Table 1) ~~of up to 100 µg~~ to be safe.	Inclusion of current data from this and related trials at the request of the IEC.
Section 6.6 Dose modifications • To replace or supplement the planned ~~1 µg, 3 µg, 10 µg, 30 µg and/or 100 µg dose levels with doses either below the planned starting doses of 3 µg or 10 µg or interim doses between the listed doses~~ dose levels with doses either below the planned starting doses or interim doses between the doses listed for that vaccine in Table 1. • To adapt the planned escalation doses ~~(0.3 µg, 1 µg, 10 µg, 30 µg and 100 µg doses in Part A)~~ for Part A, whereby the highest dose will not exceed the highest planned dose for that vaccine (see Table 1).	Due to dose adjustments following IEC feedback and SRC requests.
Section 6.6.1 Dose limiting toxicity • Two trial subjects (at any dose level) with the same or similar severe (Grade 3) AE (including clinically significant laboratory abnormalities) within 7 days of vaccination, considered related (for severity grading of adverse events see Section 10.3.1.7) Approval from the SRC will be required prior to any further dosing in the affected cohort. The SRC may call for the opening of a lower dose level cohort. The same events will prompt IMP discontinuation for individual subjects as described in Section 6.6.4. Tasks connected to the discontinuation of IMP are described in Section 7.1. The above guidance regulates how potential dose limiting toxicities may influence the decisions to further enroll trial subjects in any cohort. These decisions are taken by the SRC based on the 48 h safety data from the first 6 subjects of each cohort (see Section 4.1). Due to the staggered sentinel	PEI feedback to amendment no. 2.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
dosing design, subjects will have been followed for 4 d for the sentinel subjects when this SRC decision is made. The above guidance also regulates how potential dose limiting toxicities may influence the decisions to enroll subjects into the next cohort for that vaccine, i.e., to progress to the next cohort. These decisions are taken by the SRC based on the 48 h safety data from all 12 subjects of each cohort (see Section 4.1). Due to the staggered sentinel dosing design, subjects will have been followed for 6 d for the sentinel subjects when this SRC decision is made. The sum of the above events occurring at any time during the trial conduct (i.e., not just with 7 days of vaccination) will be used for the overall assessment of the candidate vaccine safety profile, i.e., to assess whether any of the observed side effects are possibly linked to vaccination.	
Section 8.2.7 Viral screening **8.2.7 Viral screening (for blood-borne viruses)** Viral screening for HIV 1 or 2, hepatitis B, hepatitis C will be performed using a commercially available kit at the times given in the SoA (Section 1.3). The screen will test for: Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis C antibodies, and HIV-1 and HIV-2 antibodies. For SARS-CoV-2 testing, see Section 8.2.10. ~~Further viral and bacterial status data will be generated when using local PCR-testing to establish SARS-CoV-2 status via "point of care" devices at the trial sites. This data will not be recorded in the CRF and will not be part of data analysis of the trial. If the test results must be reported to relevant authorities, this notification will be done by the trial site. No further data will be generated if the PCR-testing takes place in the central laboratory.~~	PEI feedback to amendment no. 2.
Section 8.2.10 SARS-CoV-2 testing SARS-CoV-2 testing will be performed at the time points provided in the SoA (Section 1.3). This includes PCR-based testing for SARS-CoV-2 at Visit 0 as an eligibility criterion and blood draws for anti-SARS-CoV-2 antibody testing as baseline reference for immunogenicity analysis. If required, this reference will allow the discrimination between vaccinated and infected subjects. The screen for SARS-CoV-2 can be performed by either a central laboratory or a "point of care" device at the trial site. • If a central laboratory is used: Only the SARS-CoV-2 status will be tested and no further data will be generated. • If a point of care device is used: The most commonly used devices come with pre-defined test panels that test for a range of pathogens and not just for SARS-CoV-2. Thus, inevitably and automatically, incidental data for pathogens other than SARS-CoV-2 will be generated when using such devices. Since this incidental data is not required by this trial, only the results for SARS-CoV-2 will be recorded in the CRF, analyzed, and reported as described in this protocol. If a test result for specific pathogen must be reported to relevant authorities, this notification will be done by the trial site.	PEI feedback to amendment no. 2.
Section 8.2.10 SARS-CoV-2 testing In these cases, ad hoc anti-SARS-CoV-2 ant body testing will be performed to test for the development and presence of SARS-CoV-2-specific antibodies, ideally at approximately 14 d and 28 d after immunization with the BNT162 candidate vaccine. This data will be used to evaluate the development and progression of an antibody response allowing the diagnosis of a manifest infection.	Clarification of an unclarity.
Section 8.2.12 Subject wellbeing questioning • ~~(Excluding the non-SRC requested de-escalation cohorts and after boost immunizations) Structured non-leading subject wellbeing questioning will be performed at the time given in the SoA (Section 1.3) for the first 6 subjects per cohort.~~ Subject responses may trigger more in-	PEI feedback to amendment no. 2.

<table>
<tr><th>Changed text
(inserted text is blue/underlined; deleted text is red/struck out)</th><th>Rationale</th></tr>
<tr><td>depth questioning on specific topics, and may trigger diagnostic measures (including ad hoc site visits) at the discretion of the investigator.
• Structured non-leading subject wellbeing questioning will be performed at the time given in the SoA (Section 1.3). Subject responses may trigger more in-depth questioning on specific topics, and may trigger diagnostic measures (including ad hoc site visits) at the discretion of the investigator.</td><td></td></tr>
<tr><td>Section 10.3.1.7 (Recording and Follow-Up of AE and/or SAE) Assessment of intensity

Table 4: Local reaction grading scale
<table>
<tr><th></th><th>Mild
(Grade 1)</th><th>Moderate
(Grade 2)</th><th>Severe
(Grade 3)</th><th>Potentially Life Threatening
(Grade 4)</th></tr>
<tr><td>Pain at the injection site</td><td>Does not interfere with activity</td><td>Interferes with activity</td><td>Prevents daily activity</td><td>Emergency room visit or hospitalization for severe pain</td></tr>
<tr><td>Tenderness</td><td>Mild discomfort to touch</td><td>Discomfort with movement</td><td>Significant discomfort at rest</td><td>Emergency room visit or hospitalization</td></tr>
<tr><td>Erythema / Redness [a]</td><td>2.5 cm to 5.0 cm</td><td>>5.0 cm to 10.0 cm</td><td>>10 cm</td><td>Necrosis or exfoliative dermatitis</td></tr>
<tr><td>Induration / Swelling [b]</td><td>2.5 cm to 5.0 cm</td><td>>5.0 cm to 10.0 cm</td><td>>10 cm</td><td>Necrosis</td></tr>
</table>
[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.</td><td>PEI feedback to amendment no. 2.</td></tr>
</table>

1.4 Protocol amendment no. 04

Amendment rationale

The changes planned by amendment 04 were discussed with the PEI on the basis of the submitted protocol version 6.0. Amendment 04 was revised in response to received feedback, to yield protocol version 7.0.

This amendment describes adaption of the protocol to:

- Allow the assessment of additional intermediate and low dose cohorts for BNT162b modRNA vaccine candidates to support identification of a suitable dose for Phase II/III evaluation.
- Allow the assessment of BNT162b1 modRNA vaccine candidate in elderly subjects, given its favorable safety, tolerability, and immunogenicity profile in younger adults to date and recently available non-human primate immunogenicity data for the BNT162b1 and other modRNA vaccine candidates.
- Plan the assessment of BNT162b2 modRNA vaccine candidate in elderly subjects.
- Allow the assessment of P/B cohorts for the BNT162c2 saRNA vaccine candidate.
- Allow revision of safety assessment & dose limiting toxicity criteria.
- Add additional for blood draws for explorative biomarker/immunogenicity research purposes.

Other changes are described below. Editorial changes are not listed.

This amendment will be issued after some of the planned trial subjects have already been enrolled into the trial.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 1.1 (Trial design) and Section 3 (Trial design) - Primary objective • The proportion of subjects with at least 1 unsolicited treatment emergent adverse event (TEAE): ○ For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): occurring up to 21±2 d after the prime immunization and 28±4 d after the boost immunization.	Addition of the testing of P/B regimen for BNT162c2.
Section 1.1 (Trial design) and Section 3 (Trial design) - Secondary objectives For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): • Functional antibody responses at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 28±4 d, 63±5 d, and 162±7 d after the boost immunization. • Fold increase in functional antibody titers 7±1 d and 21±2 d after primary immunization and at 21±2 d, 28±4 d, 63±5 d, and 162±7 d after the boost immunization. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 28±4 d, 63±5 d, and 162±7 d after the boost immunization. • For BNT162c2 (SD):	Addition of sampling for functional antibody responses.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
• Functional antibody responses at 7±1 d, 21±2 d, 29±3 d, 42±3 d, 84±5 d, and 183±7 d after the primary immunization. • Fold increase in functional antibody titers at 7±1 d, 21±2 d, 29±3 d, 42±3 d, 84±5 d, and 183±7 d after the primary immunization. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline at 7±1 d, 21±2 d, 29±3 d, 42±3 d, 84±5 d, and 183±7 d after the primary immunization.	
Section 1.1 (Trial design) and Section 3 (Trial design) - Exploratory objectives For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): • Antibody responses at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 29±3 d, 63±5 d, and 162±7 d after the boost immunization. • Fold increase in antibody titers at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 29±3 d, 63±5 d, and 162±7 d after the boost immunization. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers as compared to baseline at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 29±3 d, 63±5 d, and 162±7 d after the boost immunization. For BNT162c2 (SD): • Antibody responses at 7±1 d, 21±2 d, 29±3 d, 42±3 d, 84±5 d, and 183±7 d after the primary immunization. • Fold increase in antibody titers at 7±1 d, 21±2 d, 29±3 d, 42±3 d, 84±5 d, and 183±7 d after the primary immunization. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers as compared to baseline at 7±1 d, 21±2 d, 29±3 d, 42±3 d, 84±5 d, and 183±7 d after the primary immunization.	Addition of the testing of P/B regimen for BNT162c2. Addition of sampling for antibody responses.
Section 1.1 (Trial design) and Section 3 (Trial design) - Exploratory objectives For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): • Cell-mediated immune (CMI) responses measured by Enzyme-Linked Immuno-Spot (ELISpot) at baseline and at 29±3 d after the primary immunization.	Addition of the testing of P/B regimen for BNT162c2.
Section 1.1 (Trial design) and Section 3 (Trial design) Four different vaccines (BNT162a1, BNT162b1, BNT162b2, and BNT162c2) will be tested. ~~The trial has two parts: a dose-finding part (Part A) with four dose cohorts (treatment groups) for each vaccine and one pre-defined and one optional dose level for a de-escalation approach.~~ The trial has two parts: a dose-finding part (Part A) with three dose escalation cohorts (each with predefined dose levels) and two dose de-escalation cohorts (one pre-defined and one optional dose level) and, a second part (Part B) dedicated to recruit expansion cohorts with dose levels which are selected from data generated in Part A. The vaccines BNT162a1, BNT162b1, ~~and~~ BNT162b2, and BNT162c2 will be administered using a P/B regimen. The vaccine BNT162c2 will also be administered using a SD regimen. The chosen trial design reflects discussion and advice from the Paul-Ehrlich Institute (PEI) obtained in ~~two~~ scientific advice meetings held in February, March, and June 2020.	Addition of the testing of P/B regimen for BNT162c2. Rephrased for clarity.
Section 1.1 (Trial design) and Section 3 (Trial design) The first part of the trial (Part A) will follow a dose-escalation design. For some vaccines, a dose-de-escalation is also planned. … In Cohort 2, the subject staggering process will be as follows: • Two sentinel subjects will be dosed on one day.	Addition of the testing of P/B regimen for BNT162c2. Addition of additional cohorts for the testing of

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
• If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 4 further subjects will be dosed. … In Cohort 4, the subject staggering process will be as follows: • Two sentinel subjects will be dosed on one day. • If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 4 further subjects will be dosed. … ~~Additional dose cohorts~~ The optional dose de-escalation cohort (e.g., Cohort 5) may be investigated at the discretion of the SRC, but will not exceed the pre-defined maximum dose (see Table 1 and Table 2). For the BNT162b vaccines, protocol amendment 04 allows additional dose cohorts at the dose levels listed in Table 1. In these cohorts, since at doses lower than already tested, 12 subjects can be dosed with the planned dose on one day. For the BNT162b1 vaccine, protocol amendment 04 allows three additional cohorts in older adults at the dose levels listed in Table 2. In these cohorts, 12 subjects will be dosed using a sentinel dosing/subject staggering process as done for Cohort 4. For the BNT162b2 vaccine, additional cohorts in older adults will be added to allow the dosing of 12 subjects using a sentinel dosing/subject staggering process as done for Cohort 4. These additional cohorts will be activated using a dedicated protocol amendment including supportive immunogenicity and safety data in younger adults, before any older adults are dosed with BNT162b2. Note: BNT162b1, and BNT162b2 are ~~both~~ non-modified uridine RNAs, while BNT162a1 and BNT162c2 are both nucleoside-modified pseudomethyl-uridine containing. … ~~If approved by the SRC, Part B will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects (including observation on site, phone interview, vital signs, TEAEs, local reactions, immunogenicity data, blood/clinical laboratory data, and brief physical examination outcome).~~	BNT162b1 and later BNT162b2 vaccine candidates in older adults.
Section 1.1 (Trial design) and Section 3 (Trial design) - Table 1 Additional dose finding cohorts were added. Dose changes implemented in running cohorts were implemented. The dose for the originally planned BNT162b2 cohort 5C was reduced from 100 µg to 50 µg. Table 2 listing dosing regimens for older adult cohorts for BNT162b1 was added. Dose regimens were added for BNT162c2 for P/B dosing.	Modification of the planned dosing cohorts (see left for descriptions)
Section 1.1 and Section 3 - Table 1 ~~Details of Part B will be defined after evaluation of aggregate data from Part A using a protocol amendment.~~ ~~Progression to Part B will be based on analysis of both immunogenicity and safety data gathered in Part A. Both immunogenicity and safety will be thoroughly assessed to select the vaccine and the dose(s) to be further evaluated in Part B.~~ If approved by the SRC, Part B will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects (including observation on site, phone interview, vital signs, TEAEs, local reactions, immunogenicity data, blood/clinical laboratory data, and brief physical examination outcome). Details of Part B will be defined using a protocol amendment after thorough evaluation of immunogenicity and safety data from Part A for each vaccine candidate individually. Part B may be initiated for one or more vaccines while Part A is still ongoing, depending on the available data.	Update to improve clarity.
Section 1.1 (Trial duration)	

<table>
<tr><th>Changed text
(inserted text is blue/underlined; deleted text is red/struck out)</th><th>Rationale</th></tr>
<tr><td>In total, the planned trial duration is expected to be approximately 12 months. From screening visit (Visit 0) to the last visit (Visit 8 [BNT162c2; Visit 9 BNT162a1, BNT162b1, BNT162b2], and BNT162c2 (P/B)]), each trial subject will be in the trial for maximally 223 days. For logistical reasons, investigation of the different vaccines may not be able to start at the same time.</td><td></td></tr>
<tr><td>Section 1.1 (Population) and Section 4.1.2 (Planned number of trial subjects)
~~Healthy adults aged 18 to 55 years.~~
~~For each vaccine, in total up to 48 trial subjects (12 subjects for each of the 4 dose levels) will be required in Part A. If the decision is made to add a cohort to Part A, the total number of subjects per vaccine will increase to 60 subjects.~~
Healthy adults aged 18 to 55 years (Cohorts 1 to 7; younger adults) or aged 56 to 85 years (Cohorts 8 to 10; older adults). Subjects aged 56 to 85 years must be enrolled such that at least 6 subjects per cohort are aged 65 to 85 years (i.e., are elderly).
For each vaccine, 12 subjects are required for each of the cohorts planned in Part A. See Table 3 for the total number of subjects for each vaccine assuming all cohorts planned in Table 1 and Table 2 are performed.

Table 3: Overview of the total number of subjects for each vaccine in Part A
<table>
<tr><th>Vaccine / mRNA type</th><th>Vaccine dosing regimen</th><th>Maximum number of subjects (assuming all cohorts planned in Error! Reference source not found. are performed)</th></tr>
<tr><td>BNT162a1 / uRNA</td><td>Prime/Boost</td><td>60 (5 cohorts)</td></tr>
<tr><td>BNT162b1 / modRNA</td><td>Prime/Boost</td><td>120 (10 cohorts)</td></tr>
<tr><td>BNT162b2 / modRNA</td><td>Prime/Boost</td><td>120 (10 cohorts)</td></tr>
<tr><td>BNT162c2 / saRNA</td><td>Prime only</td><td>72 (6 cohorts)</td></tr>
<tr><td>BNT162c2 / saRNA</td><td>Prime/Boost</td><td>72 (6 cohorts)</td></tr>
</table></td><td>Addition of the testing of P/B regimen for BNT162c2.
Addition of cohorts for the assessment of additional intermediate and low dose cohorts for the BNT162b vaccines.
Addition of additional cohorts for the testing of BNT162b vaccine candidates in older adults.</td></tr>
<tr><td>Section 1.1 (Key inclusion criteria)
• ~~They must be aged 18 to 55 years, have a body mass index over 19 kg/m^2 and under 30~~ kg/m^2, and weigh at least 50 kg at Visit 0.
• For younger subject cohorts, volunteers must be aged 18 to 55 years, have a body mass index over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0
OR
For older adult cohorts, volunteers must be aged 56 to 85 years, have a body mass index over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0.
• They must be healthy, in the clinical judgment of the investigator, based on medical history, physical examination, 12-lead ECG, vital signs (systolic/diastolic blood pressure, pulse rate, body temperature, respiratory rate), and clinical laboratory tests (blood chemistry, hematology, and urine chemistry) at Visit 0.
Note: Healthy volunteers with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.</td><td>Addition of additional subject cohorts for the testing of BNT162b vaccine candidates in older adults.</td></tr>
<tr><td>Section 1.1 (Key exclusion criteria)
• Had any chronic use (more than ~~14~~ 21 continuous days) of any systemic medications including immunosuppressant’s or other immune-modifying drugs, within the 6 months prior to Visit 0 unless in the opinion of the investigator the medication would not prevent, limit, or confound the protocol-specified assessments or could compromise subject safety.
Note: Healthy participants with preexisting stable disease, defined as disease not requiring</td><td>Addition of additional subject cohorts for the testing of BNT162b vaccine</td></tr>
</table>

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significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. • Regular receipt of inhaled/nebulized corticosteroids. • …. • For older adults only: Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors: – Hypertension – Diabetes mellitus – Chronic pulmonary disease – Asthma – Chronic liver disease – Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2) – BMI ≥30 kg/m^2 – Anticipating the need for immunosuppressive treatment within the next 6 months – Resident in a long-term facility – Current vaping or smoking (occasional smoking is acceptable) – History of chronic smoking within the prior year	candidates in older adults.
Section 1.1 (Trial treatments) and Section 6.1 (IMP administered) Dosage frequency: One injection or two injections 21 d apart. Injection volumes will be up to 1.5 mL ~~between 0.05 mL and 1 mL~~.	Addition of volume flex bility due to the added additional cohorts for the BNT162b vaccine candidates.
Section 1.2 (Schema) The schema was updated to reflect: Addition of additional subject cohorts for the testing of BNT162b vaccine candidates in elderly. Addition of subject cohorts for the testing of BNT162c2 after P/B dosing.	Addition of additional subject cohorts.
Section 1.3 (Schedule of activities) **Table 3 (was 2)** The SoA was updated to reflect the added vaccine candidate BNT162c2 (P/B testing). Addition of blood draws explorative biomarker/immunogenicity research purposes and on Day 29 for immunogenicity. Addition of a blood draw for HLA based on EDTA-blood. Addition/modification of the below footnotes. f Clinical laboratory tests: (Chemistry) alkaline phosphatase, creatinine, ferritin, C-reactive protein, albumin, alanine aminotransferase, amylase, aspartate aminotransferase, gamma glutamyl transpeptidase, total bilirubin, blood urea nitrogen, glucose, lipase, sodium, potassium, calcium; (Hematology) hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count. Only in women who are not WOCBP: follicle stimulating hormone at Visit 0. …… [n] The listed blood draw days may be adapted if justified by the collected data. [o] For subjects who have given consent, one aliquot of the blood sample drawn for analysis of CMI may be used for human leukocyte antigen (HLA) typing to allow additional analysis of T	Update to reflect the addition of additional of blood draws. Update to reflect the addition of Visit 5 in Table 3 for BNT162c2 (SD).

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cell receptor repertoire and / or phenotypic characterization of T cells specific to vaccine-encoded antigens. [p] If HLA typing using the blood sample collected with Lithium Heparin is not conclusive, EDTA-blood will be drawn for HLA testing. **Table 4 (was 3)** The SoA was updated to reflect the added Visit 5 (Day 29), analog to as performed for vaccines investigated using P/B doing. Addition of a blood draw for HLA based on EDTA-blood. Deletion of one 100 mL blood draw for CMI testing (i.e., at Visit 6). Footnotes were re-sequenced. Addition/modification of the below footnotes. f Clinical laboratory tests: (Chemistry) alkaline phosphatase, creatinine, ferritin, C-reactive protein, albumin, alanine aminotransferase, amylase, aspartate aminotransferase, gamma glutamyl transpeptidase, total bilirubin, blood urea nitrogen, glucose, lipase, sodium, potassium, calcium; (Hematology) hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count. Only in women who are not WOCBP: follicle stimulating hormone at Visit 0. …… [l] The listed blood draw days may be adapted if justified by the collected data. [m] For subjects who have given consent, one aliquot of the blood sample drawn for analysis of CMI may be used for human leukocyte antigen (HLA) typing to allow additional analysis of T cell receptor repertoire and / or phenotypic characterization of T cells specific to vaccine-encoded antigens. … [p] If HLA typing using the blood sample collected with Lithium Heparin is not conclusive, EDTA-blood will be drawn for HLA testing.	
Section 2.2 (Trial rationale) ~~The four prophylactic BNT162 vaccines against SARS-CoV-2 investigated in this trial BNT162-01 will also be investigated in clinical trials in the US and China.~~ Some of the prophylactic BNT162 vaccines against SARS-CoV-2 investigated in this trial are under investigation (BNT162-02) or will be investigated in other clinical trials (BNT162-03). The status and preliminary results from all of these are trials are summarized in the following sections. The status and preliminary results from all of these are trials are summarized in the following sections. For the status of ongoing and planned clinical trials, see Table 5. **Table 5: Status of ongoing and planned clinical trials (as of June 22nd, 2020)** (Table was updated with June 22nd 2020 data)	Status update to provide transparency of ongoing data.
2.2.1 This trial (BNT162-01) - Preliminary results (status June 22nd, 2020) ~~**2.2.1 This trial (BNT162-01) - Preliminary results (status 22 May 2020)**~~ ~~For the vaccine candidate BNT162b1, 60 subjects have been dosed in 5 cohorts of 12 subjects each with doses of 1, 10, 30, 50 and 60 µg. The pattern of tolerability has been as anticipated and described in the protocol / informed consent form (ICF) with most subjects reporting flu-l ke symptoms and injection site reactions. Fever has been reported in approximately 25% of subjects. Onset of systemic symptoms may begin around 6 h but they more typically present 10 to 12 h post administration, with the fever usually starting 16 to 24 h post vaccination. All events resolve spontaneously or with simple medical management (e.g., cooling measures, antipyretics, reassurance), typically within 24 to 48 h of onset. Most adverse reactions that were reported in all dose groups were mild or moderate in severity. No serious adverse events (SAEs) have been~~	Status update to provide transparency of ongoing data.

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~~reported within the post vaccination observation period. A slight dose dependency for frequency and intensity of symptoms was observed between the 1 µg and 10 µg cohorts, but from 10 µg to 60 µg no clear dose dependency is apparent. On laboratory examination, a transitory depression of the lymphocyte counts and mild elevation of C-reactive protein (CRP) are seen, consistent with the expected mode of action of BNT162b1 effecting a reversible compartmentalization into lymphoid organs, with no associated clinical consequence seen. No subjects were withdrawn due to related AEs. Overall, the risk-benefit for this construct within the dose range explored remains unchanged.~~

~~For the vaccine candidate BNT162a1, 6 subjects were exposure at a 3 µg dose. All subjects reported flu-l ke symptoms within 24 h of dosing, mostly of moderated intensity with fever in approximately 65% of subjects. One subject experienced vomiting and a second an episode of hypotension. A more marked elevation to CRP was noted, with a similar pattern of lymphocyte depression to that described above for the BNT162b1 vaccine candidate. All events resolved, however some subjects remaining symptomatic for a number of days. No SAEs have been reported and no subjects withdrew due to adverse events. The safety review committee resolved to explore a lower dose range subsequently. The first 6 subjects have been dosed at 0.3 µg and demonstrate a similar pattern of reactogenicity to that described for the BNT162b1 vaccine candidate, with almost exclusively mild effects reported to date.~~

Summary of safety in trial BNT162-01 (up to June 22nd 2020)

In the trial BNT162-01, younger adults aged 18 to 55 years were dosed with one of four BNT162 vaccine candidates (BNT162a1, BNT162b1, BNT162b2, and BNT162c2). The most complete experience is available for the vaccine BNT162b1, which has been dosed in 5 cohorts of 12 subjects each (all subjects received active vaccine). Except for those in the highest dose cohort (60 µg), all subjects were dosed twice (i.e., prime and boost). The boost dose in the 60 µg dose cohort is pending.

Reactogenicity

Local reactions and systemic events are solicited from the subjects and recorded by them in a diary for 7 days following administration of the vaccine. Most subjects in all cohorts experienced the expected reactogenicity, typically starting within 24 h of dosing and resolving within 24 h. The specific, solicited local and systemic reaction are graded as described in Section 10.3.1.11 and are summarized below in Table 6 and Table 7.

Table 6: Number of adults aged 18 to 55 years with local symptoms (diary): BNT162b1

	Number of Subjects with Local Reactions (n=)								
	7d Post Prime				7d Post Boost			Total (both)	
	Subjects dosed prime	Any event	Any ≥ severe		Subjects dosed boost	Any event	Any ≥ severe	Any event	Any ≥ severe
BNT162b1	60	51	8		46	39	7	54	13
1 µg	12	6	0		11	7	2	7	2
10 µg	12	10	1		12	10	0	11	1
30 µg	12	11	4		12	11	2	12	5
50 µg	12	12	2		11	11	3	12	4
60 µg	12	12	1					12	1

Table 7: Number of adults aged 18 to 55 years with systemic symptoms (diary): BNT162b1

	Number of subjects with Systemic Reactions (n=)								
	7d Post Prime				7d Post Boost			Total (both)	
	Subjects dosed prime	Any event	Any ≥ severe		Subjects dosed boost	Any event	Any ≥ severe	Any event	Any ≥ severe

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BNT162b1	60	52	15		46	38	17		57	27
1 µg	12	9			12	7	2		11	2
10 µg	12	8	1		11	9	4		10	5
30 µg	12	11	3		12	11	6		12	6
50 µg	12	12	4		11	11	5		12	7
60 µg	12	12	7						12	7

In local reactions, most subjects reported injection site pain and tenderness, whilst reports of swelling / induration or erythema were scarce. The most common systemic reactions were headache and fatigue, experienced by most subjects. Grade 3 (severe intensity) local reactions were reported for pain, tenderness and swelling. Grade 3 (severe intensity) systemic reactions were fever, headache, myalgia, arthralgia, nausea, vomiting, chills, loss of appetite, malaise and fatigue.

Laboratory findings

A consistent pattern has been seen in the laboratory assessments with elevation of the C-reactive protein with concomitant reduction in the plasma lymphocyte count 24 h after vaccination. These changes are consistent with the know pharmacology of this technology, with the changes in lymphocytes known to represent a reversible compartmental shift from the vascular space to lymphoid organs. These observations have been self-limiting and without clinical consequence. There have been no other consistent findings on laboratory assessments.

Adverse events

Adverse events are collected throughout the trial and graded by the investigators on a 4-point scale (as per this protocol). Most subject report adverse events (Table 8), >90% of which are related to reactogenicity. 6 subjects had AEs rated as severe in intensity (Grade 3) covering 5 preferred terms: muscle tightness, headache, influenza like illness, injection site discomfort, pyrexia.

Table 8: Summary BNT162b1 TEAE (prime +/- boost) by number of subjects

BNT162b1	Subjects Dosed N =	Number of Subjects with (n=)					
		TEAEs	Mild AE	Moderate AE	Severe AE	SAE	Resolved AE
1 µg	12	11	10	7	2	0	11
10 µg	12	12	12	8	1	0	12
30 µg	12	12	12	9		0	12
50 µg	12	12	12	11	2	0	12
60 µg	12	12	12	10	1	0	12
Total	60	59	58	45	6	0	59

Summary

For vaccine BNT162b1, generally good tolerability was observed with no SAEs and no unexpected toxicities. To date, there is high acceptance by trial subjects with no withdrawals due to related AEs. Most reported AEs are signs and symptoms of reactogenicity, typical onset within first 24 h post immunization. All AEs / reactogenicity resolve spontaneously, mostly within 24 h. of onset and can be managed with simple measures (e.g., paracetamol). Laboratory assessments suggest a Th1 pattern of immune activation 24 h post dosing. Some dose dependency of tolerability has

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been observed, with 1 µg dose best tolerated. The possibly of a slight increase in reactogenicity following boost dose is noted, as is some inter-individual variability. Vaccine BNT162a1 showed a similar pattern of tolerability to BNT162b1, however reactogenicity was noted at a lower dose range. Most recently dosing has begun with vaccines BNT162b2 and BNT162c2. The early pattern of reactogenicity with the BNT162c2 candidate at doses <1 µg appears similar or less than that seen with vaccine BNT162b1 at the 1 µg dose. Early indications for tolerability of BNT162b2 at a 10 µg dose are very encouraging with only minimal local reactogenicity in initial reports.	
Section 2.2.2 US trial BNT162-02 - Preliminary results (status, June 22nd, 2020) **Section 2.2.2 (US trial BNT162-02 (PF-07302048) - Preliminary results (status 08 June 2020)** ~~This trial in the US will be conducted by Pfizer, Inc. (New York, US) and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany). The trial has been approved by the US regulatory authorities and trial conduct has started.~~ ~~The US trial PF-07302048 (NCT NCT04368728) is "a Phase I/II, placebo-controlled, randomized, observer-blind, dose finding study to descr be the safety, tolerability, immunogenicity, and potential efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy adults.~~ ~~The trial PF-07302048 will evaluate the safety, tolerability, immunogenicity, and potential efficacy of up to 4 different SARS-CoV-2 RNA vaccine candidates against COVID-19:~~ ~~As a 2-dose (separated by 21 or 60 days) or single-dose schedule~~ ~~At up to 3 different dose levels~~ ~~In 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age [stratified as ≤55 or >55 years of age])~~ ~~Dependent upon safety and/or immunogenicity data generated during the course of this trial, or the BNT162-01 clinical trial, it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.~~ ~~The US trial consists of 3 stages. Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3; a final candidate/dose large-scale stage.~~ ~~The trial is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the trial sites, only the dispenser(s)/administrator(s) are unblinded.~~ ~~As of May 22, 2020 a total of 45 subjects have been enrolled in this trial, and received a first dose of the BNT162b1 vaccine candidate or placebo. Of these, 12 received 10 µg, 12 received 30 µg, 12 received 100 µg, and 9 received placebo. A degree of reactogenicity was see, with local and systemic reactions similar to those reported in the BNT162-01 trial. Reactogenicity was generally transient and of mild or moderate intensity. Severe reactogenicity events were only reported in the 100 µg dose level in at most one or two subjects. No grade 4 reactogenicity was reported, no stopping rules were met, and no serious adverse events (SAEs) were reported.~~ ~~The available reactogenicity data for the first 15 subjects administered a first dose of 100 µg of BNT162b1 (5 dosed 18 May 2020, 5 dosed 20 May 2020, 5 dosed 21 May 2020) has been evaluated by the trial independent review committee (IRC) in the context of all data now available after first doses of 10 µg and 30 µg. The results were considered to be consistent with dose related increases in local and systemic reactions. Based on the benefit-risk profile seen to date for BNT162b1, the IRC approved further trial progression as planned. Further evaluation of dosing will be based on continuing review of data from both the US trial PF-07302048 and BNT162-01 trial data, with particular attention to 50 µg and 60 µg doses.~~ **Section 10.10.5 US trial BNT162-02 - Preliminary results (status, June 22nd, 2020)**	Status update to provide transparency of ongoing data.

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This trial in the US is conducted by Pfizer, Inc. (New York, US) and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany). The trial has been approved by the US regulatory authorities and trial conduct has started.

The US trial BNT162-02 (PF-07302048; NCT NCT04368728) is "a Phase I/II, placebo-controlled, randomized, observer-blind, dose-finding study to describe the safety, tolerability, immunogenicity, and potential efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy adults.

Summary of safety in BNT162-02 (status, June 22nd, 2020)

US Trial C4591001/BNT162-02 is a randomized and placebo-controlled trial, in which the trial subjects are randomized 4:1 to receive active vaccine or placebo. The available safety and tolerability data for younger adults aged 18 to 55 years (see Table 9) who have received dose 1 and dose 2 of BNT162b1 were broadly comparable to those in trial BNT162-01 and are briefly summarized below.

Preliminary safety and tolerability data in elderly (aged 65 to 85 years) after dosing with BNT162b1 are presented separately below and are summarized in **Figure 2 and Figure 3.**

Table 9: Number of adults aged 18 to 55 years dosed in BNT162-02 (status, June 22nd, 2020)

	BNT162b1		Placebo	
	Dose 1	Dose 2	Dose 1	Dose 2
18-55 years of age				
10 µg dose level	N=12	N=12	N=3	N=3
30 µg dose level	N=12	N=12	N=3	N=3
100 µg dose level	N=12	Not applicable	N=3	Not applicable

Overall, all dose levels exhibited a tolerability and safety profile consistent with modRNA-based vaccines, and a clear dose level response was observed after dose 1 and dose 2 in younger adults. Reactogenicity was generally higher after the second dose, but the symptoms resolved quickly over the course of a few days. The only reports of Grade ≥3 intensity (severe) were 1 case of fatigue in a subject in the 10 µg cohort and 1 case of chills in a single subject in the 30 µg cohort, both after their boost dose. Based on the tolerability profile observed with the 100 µg dose level after the first dose, an internal decision was made not to give a boost dose at 100 µg.

Summary of safety in elderly subjects (aged 65 to 85 years) in BNT162-02

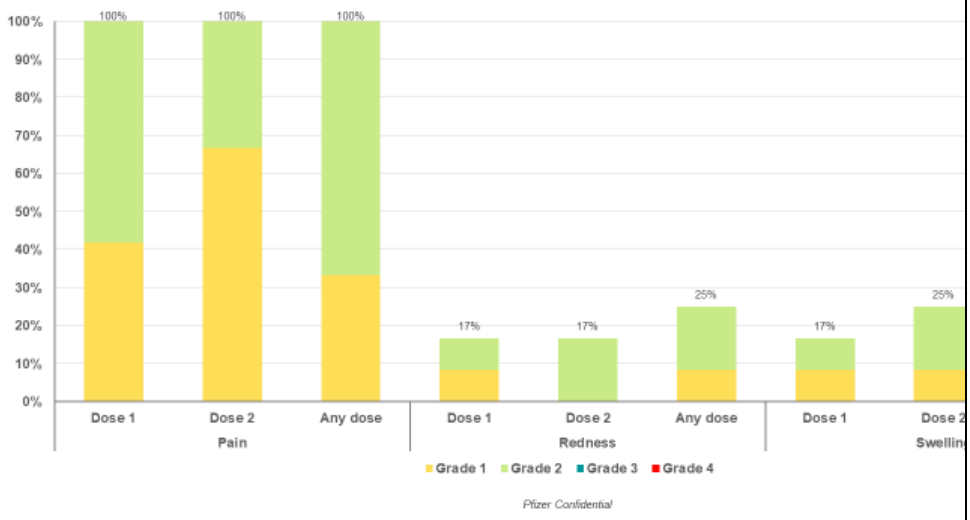
Preliminary safety and tolerability data after the first dose of 10 µg, 20 µg, and 30 µg in adults aged 65 to 85 years (see Table 10) after one dose of BNT162b1 are shown in Figure 2 and Figure 3.

Table 10 Number of adults aged 65 to 85 years dosed in BNT162-02 (status, June 22nd, 2020)

	BNT162b1		Placebo	
	Dose 1	Dose 2	Dose 1	Dose 2
65-85 years of age				
10 µg dose level	N=12	N=0	N=3	N=0
20 µg dose level	N=12	N=0	N=3	N=0
30 µg dose level	N=12	N=0	N=3	N=0

The first dose of BNT162b1 in this age group was generally well tolerated. One episode of severe muscle pain and erythematous rash occurred with mild fever occurred in an 81-year-old man on day 2 after receiving a 20 µg dose, consistent with varicella zoster (shingles). He was prescr bed Valacyclovir and this AE was reported as fully resolved within 7 days. The investigator reported this AE as not related to vaccine.

Part A



Part B

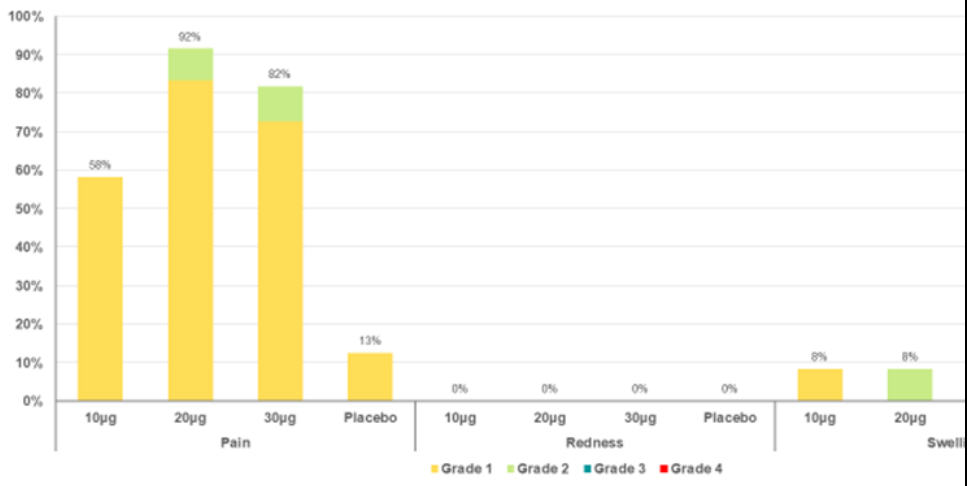


Figure 1: BNT162b1 - Local reactions in younger and elderly subjects

Panel A - Local reactions after doses 1 and 2 (i.e., prime and boost) of 30 µg BNT162b1 in younger subjects.

Panel B - Local reactions after dose 1 (i.e., prime) of 10, 20, and 30 µg BNT162b1 in elderly subjects.

Note: follow-up period for 10 µg and 30 µg groups: +2-4 days.

Part A (younger adults)

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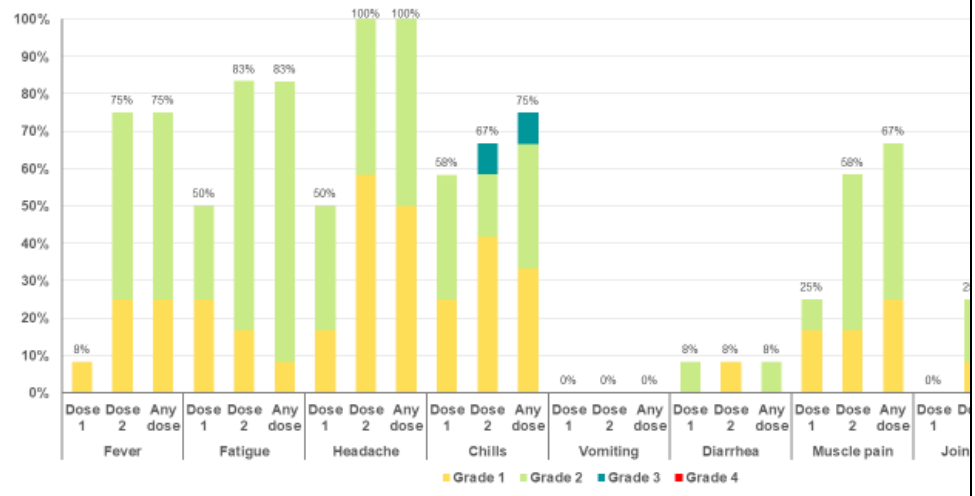

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Part B (Elderly)

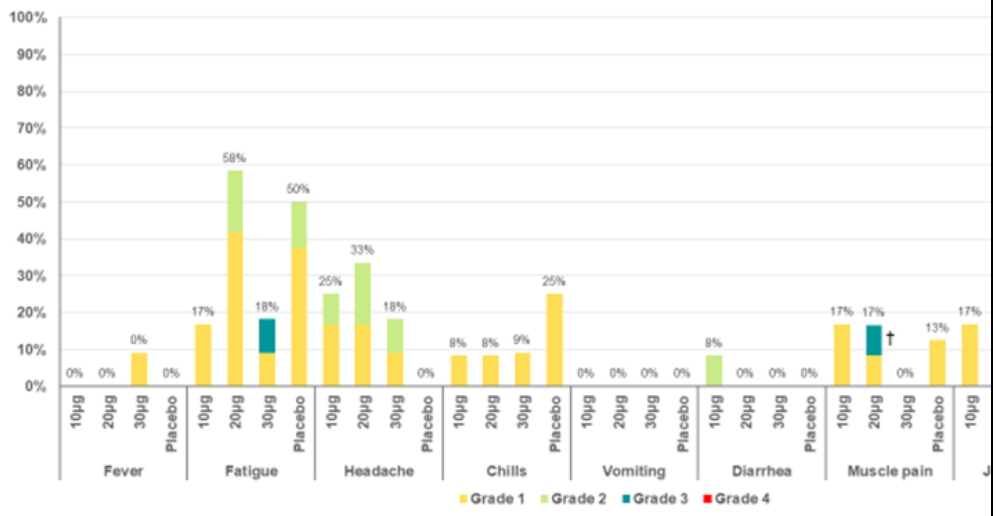

Figure 2: BNT162b1 - Systemic events in younger and elderly subjects

Panel A - Systemic events after doses 1 and 2 (i.e., prime and boost) of 30 µg BNT162b1 in younger subjects.
Panel B - Systemic events after dose 1 (i.e., prime) of 10, 20, and 30 µg BNT162b1 in elderly subjects.
Note: follow-up period for 10 µg and 30 µg groups: +2-4 days
† This is the participant that experienced Zoster which was the actual cause of the pain.

In general terms, the local tolerability of BNT162b1 in elderly subjects seems comparable to that recorded in younger adults. The pattern of systemic reactogenicity appears similar between the two age groups, poss bly with a lower overall incidence in the elderly subjects in comparison to the younger adults.

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Section 2.2.2 (Chinese trial - BNT162-03) ~~This trial will be conducted by Shanghai Fosun Pharmaceutical Development, Inc. (Shanghai, China) and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany). The trial set-up is ongoing. Currently no IND has been submitted, therefore the trial has not been approved by the Chinese regulatory authorities and trial conduct has not started.~~ ~~This trial will be a phase I, randomized, placebo-controlled, observer-blind, safety and immunogenicity investigation of SARS-CoV-2 mRNA vaccine (BNT162b1) in healthy Chinese adults.~~ ~~After randomization, the trial for each subject will last for approximately 6 months or 12 months. Two doses of either SARS-CoV-2 vaccine (BNT162b1) or placebo will be given intramuscularly on Day 1 and on Day 22. After each age group completes the follow-up 28 days after boost vaccination (Day 50), periodical analysis will be conducted respectively.~~ ~~Subjects who are ≥18 years old and ≤55 years old will be enrolled in adult group, and healthy elderly people who are >55 years old will be enrolled in elderly group. Approximately 102 subjects from each age group enter into three dose escalating cohorts (10 µg, 30 µg and 100 µg) from low to high, with approximately 34 subjects at each dose level, including approximately 25 BNT162b1-treated subjects and approximately 9 placebo-treated subjects. There will be a sentinel group (2 subjects of 1 in BNT162b1 and 1 in placebo) in each cohort, the followed two sub-groups (32 subjects in total) in each cohort will be randomized (3:1) to inject BNT162b1 or placebo.~~ ~~If approved by the trial SRC after review of safety and tolerability data in the low-dose cohort subjects, an escalated dose cohort may start. Alternatively, the SRC may recommend the start of a de-escalated dose cohort. After the 14-day safety observation post the boost vaccination of the first subject in the first dose cohort of the adult group, the prime vaccination for sentinel subjects in the first dose cohort may start in the elderly group.~~ The trial BNT162-03 will be conducted in healthy Chinese adults by Shanghai Fosun Pharmaceutical Development, Inc. (Shanghai, China) and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany). Currently the trial has not been approved and the concrete trial design is under discussion with the Chinese regulatory authorities to ensure alignment with the rapidly progressing overall clinical development and the adequacy of the Chinese trial for regional extension of the potential registrational data package.	Update reflecting the current preparation status.
Section 2.3.1 (Risk assessment) The risks linked to the trial-specific procedures and connected mitigations are as follows: • The volume of blood drawn will be kept to a minimum and will remain less than that drawn when donating blood (up to approximately 568~~358~~ mL blood will be drawn per subject over the complete trial, i.e., over approximately 7 months. … … ~~The mostly moderate flu-like AEs observed in all six of the first 6 subjects dosed at the 3 µg starting dose for BNT162a1 in the trial BNT162-01, combined with the vomiting and hypotension observed in one of the six subjects, led to a reduction of the starting dose from 3 µg to 0.3 µg for the next cohort to be treated with the same vaccine candidate. In this regard, since both the BNT162c2 and BNT162a1 vaccine candidates use the same type of nucleosides (i.e., pseudomethyl-uridine instead of uridine) that are known to define the extent of innate immune activation, the planned doses for the BNT162c2 vaccine candidate were also reduced (see Table 1). For example, the starting dose for BNT162c2 was reduced from 3 µg to 0.1 µg.~~ • The clinical experience with administration of the prime dose of BNT162b1 in 36 healthy elderly subjects aged 65 to 85 years in the US trial BNT162-02 is described in Section 2.2. The local tolerability of BNT162b1 in elderly subjects aged 56 seemed comparable to that recorded in younger subjects aged 18 to 55 years. The pattern of systemic reactogenicity appeared similar between the two age groups, possibly with a lower overall incidence in the elderly subjects in comparison to the younger subjects at equal doses. • The local tolerability of BNT162b1 in elderly subjects aged 56 seemed comparable to that recorded in younger subjects aged 18 to 55 years. The pattern of systemic reactogenicity	Update reflecting the added blood sampling and the available clinical data from the ongoing trials BNT162-01 and BNT162-02.

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appeared similar between the two age groups, possibly with a lower overall incidence in the elderly subjects in comparison to the younger subjects at equal doses.
• When assessing the risk for dosing of older subjects with BNT162 vaccine candidates, the follow information is relevant:
  • Preliminary data in subjects treated in the ongoing BNT162 trials backed by non-human primate (rhesus macaque) immunogenicity data have shown that BNT162b1 in the tested dose range is immunogenic.
  • There is risk that older adults may be under dosed with the vaccine doses chosen based on data for younger adults (as was observed for other vaccines) must be mitigated.
  • Preliminary data in elderly show a comparable to lower reactogenicity based on the observed local reactions and system events in similar doses (see the figures in Section 2.2.2). This observation may indicate a lower innate immune activatory capability of elderly, which in turn may mechanistically be associated with lower immunogenicity of dose levels that are immunogenic in the younger adults.
  • In this trial, the doses to be tested in older adults are within the range already shown to show acceptable tolerability in younger adults.
  • The planned starting dose with BNT162b1 for older subjects aged 55 to 85 years in this trial (10 µg) is 30% of the dose (30 µg) already shown to be acceptable in the subjects aged 65 to 85 years in the US trial BNT162-02.
  • This trial includes inclusion/exclusion criteria to exclude potential risk factors relevant for all adults, but additional criteria have been included to further protect the safety of enrolled older adults.
• The listed risks can be managed using routine symptom driven standard of care as described in Section 6.6.3. Treatment of these events is dependent on the discretion of the investigators.	

Section 5.1.1 (Inclusion criteria Part A) ~~4. They must be aged 18 to 55 years, have a body mass index over 19 kg/m2 and under 30 kg/m2, and weigh at least 50 kg at Visit 0.~~ 4. For younger subject cohorts, volunteers must be aged 18 to 55 years, have a body mass index over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0 OR For older adult cohorts, volunteers must be aged 56 to 85 years, have a body mass index over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0. 5. They must be healthy, in the clinical judgment of the investigator, based on medical history, physical examination, 12-lead ECG, vital signs (systolic/diastolic blood pressure, pulse rate, body temperature, respiratory rate), and clinical laboratory tests (blood chemistry, hematology, and urine chemistry) at Visit 0. Note: Healthy volunteers with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. … 7. WOCBP must agree to practice a highly effective form of contraception during the trial, starting after Visit 0 and continuously until 60 d after receiving the last immunization. WOCBP must agree to require their male partners to use condoms during sexual contact (unless male partners are sterilized or infertile).	Addition of additional subject cohorts for the testing of BNT162b vaccine candidates in older adults.
Section 5.2.1 (Exclusion criteria Part A) 6. Had any chronic use (more than ~~14~~ 21 continuous days) of any systemic medications including immunosuppressant's or other immune-modifying drugs, within the 6 months prior to Visit 0 unless in the opinion of the investigator the medication would not prevent, limit, or confound the protocol-specified assessments or could compromise subject safety. Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks	Addition of additional subject cohorts for the testing of BNT162b vaccine

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before enrollment, can be included. … 28. Regular receipt of inhaled/nebulized corticosteroids. 29. For older adults only: Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors: – Hypertension – Diabetes mellitus – Chronic pulmonary disease – Asthma – Chronic liver disease – Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2) – BMI ≥30 kg/m^2 – Anticipating the need for immunosuppressive treatment within the next 6 months – Resident in a long-term facility – Current vaping or smoking (occasional smoking is acceptable) – History of chronic smoking within the prior year	candidates in older adults.
Section 5.3 (Lifestyle considerations) For Cohorts 1, 2, 4, 7, and 8, the first 6 subjects dosed in each group will be required to remain at the site for approximately 24 h after the first immunization. The remaining trial subjects in these cohorts will be required to remain at the site for approximately 6 h after the first immunization. For cohorts ~~1, 2, and 4~~ with P/B dosing, all subjects dosed in each group will be required to remain at the site for approximately 6 h after the boost immunization.	
Section 6.3 (Measures to minimize bias: randomization and blinding) Not applicable for Part A. Details for Part B will be defined using a protocol amendment.	Update for clarification
Section 6.5 (Concomitant therapy) Paracetamol/acetaminophen at doses of ~~less than~~up to 4 g/day is permitted for use any time during the trial. Other concomitant medication may be considered on a case-by-case basis by the investigator, if required after consultation with the sponsor's Medical Monitor.	Update for clarification
Section 6.6 (Dose modifications) The trial design allows for a flexible dosing which allows a better evaluation on the optimal dose range. For details, see Section 4.1. ~~, i.e., the trial design includes the options:~~ ~~• To replace or supplement the planned dose levels with doses either below the planned starting doses or interim doses between the doses listed for that vaccine in Table 1.~~ ~~• To adapt the planned escalation doses for Part A, whereby the highest dose will not exceed the highest planned dose for that vaccine (see Table 1).~~ • ~~To decrease the planned starting dose of one of the BNT162 vaccines based on observations made for a chemically related BNT162 vaccine already dosed in this trial.~~ • ~~To add an additional cohort.~~	Update reflecting the addition of optional cohorts and doses to enable an optimal characterization of the dose-response and safety profile in support of the planned Phase II/III clinical trials and Part B of this trial.

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Section 6.6.1 (Dose limiting toxicity) During the time of enrollment into a given dose escalation cohort in Part A, if any of the following events occur, further dosing in that cohort will be stopped: • … • ~~Any possibly related~~ AEs within 7 days of vaccination assessed by the investigator to be potentially life-threatening (Grade 4) and that is possibly related, or for which there is no alternative, plausible, attributable cause. • Any systemic SAE within 7 days of vaccination that is assessed by the investigator as possibly ~~considered~~ related, or for which there is no alternative, plausible, attributable cause. • Any fever >40.0°C (>104.0°F) within 7 days of vaccination considered related • Two trial subjects (at any dose level) with the same or similar severe (Grade 3 or higher) AE (including clinically significant laboratory abnormalities) within 7 days of vaccination, considered related, or for which there is no alternative, plausible, attributable cause (for severity grading of adverse events see Section 10.3.1.7) For the cohorts with BNT162c2 P/B dosing, dosing will only start after SRC assessment of day 28 AE data (solicited and unsolicited) for the cohort testing BNT162c2 (SD). … The sum of the above events occurring at any time during the trial conduct (i.e., not just with 7 days of vaccination) will be used for the overall assessment of the candidate vaccine safety profile, i.e., to assess whether any of the observed side effects are possibly linked to vaccination. The assessment of dose limiting toxicity should be done consistently for all subjects treated with the **same treatment and dose.** **Part B** The to be tested doses for each vaccine in Part B will be chosen ~~by the SRC~~ after review of the safety, tolerability, and immunogenicity data from Part A for that vaccine.	Updated to provide additional guidance and clarification when handling dose limiting toxicity.
Section 8.2.9 (Assessment of local reactions) Local reactions after IM immunization will be assessed by the investigator at the times given in the SoA (Section 1.3). Local reactions will be graded using the criteria given in US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" for "Local Reaction to Injectable Products" (see the section "Assessment of intensity" in Section 10.3.1.10). This information will be used to validate the solicited assessment of local reactions in the patient diary and potentially support AE reporting.	Updated to provide additional guidance and clarification when assessing local reactions.
Section 8.2.10 (SARS-CoV-2 testing) SARS-CoV-2 testing (PCR-based and antibody-based) will be performed at the time points provided in the SoA (Section 1.3). This includes PCR-based testing for SARS-CoV-2 ~~at Visit 0~~ as an eligibility criterion and blood draws for anti-SARS-CoV-2 antibody testing as baseline reference for immunogenicity analysis.	Clarification of an ambiguity.
Section 8.2.13 (Assessment of systemic reactions) Systemic reactions after IM immunization will be assessed at the times given in the SoA (Section 1.3). Systemic reactions will be graded using the criteria given in US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" for "Systemic reaction grading scale" (see the section "Assessment of intensity" in Section 10.3.1.11).	Added to provide guidance when assessing systemic reactions.
Section 8.3.1 (Time period and frequency for collecting AE and SAE information All AEs and SAEs will be collected from the date of subject consent until discharge from the trial at Visit 8 (BNT162c2) [SD]) or Visit 9 (BNT162a1, BNT162b1, BNT162b2)., BNT162c2 [P/B]).	Update reflecting the addition of

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	additional cohorts.
Section 8.7 (Genetics) ~~Not applicable.~~ A blood sample (blood and / or isolated PBMCs) may be used for HLA typing of a subject to allow additional analysis, e.g., characterization of T cell receptor (TCR) repertoire and / or phenotypic characterization of antigen-specific T cells as further specified in Section 8.8 (Biomarkers). Further, an additional blood sample may also be used for profiling (e.g., by use of next-generation sequencing) of TCRs in peripheral blood after vaccination. Blood samples will only be used for genetic analysis if the trial subjects have provided informed consent for this genetic analysis.	Assessments added
Section 8.8 (Biomarkers) ~~Not applicable.~~ Up to 5 additional blood draws (with up to 200 mL in total) will be taken over the complete trial for explorative biomarker / immunogenicity research purposes. Research samples will be collected in order to investigate vaccine induced immune responses by use of, but not limited to, phenotypic or functional characterization of antigen-specific T cells (e.g., by flow cytometry-based phenotyping including multimer staining), analysis of TCR repertoire (e.g., by next generation sequencing) and multiplex-cytokine analysis. In addition, samples may be stored and analysis may be performed on biomarker variants thought to play a role in the mechanism of action of BNT162 to evaluate their association with observed clinical responses to BNT162. Furthermore, samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to BNT162. Samples for biomarker analysis will be retained for use for up to 5 years after the end of the trial.	Assessments added
Section 8.9 (Immunogenicity assessments) Immune responses will be assessed at the times listed in the SoA (Section 1.3) using: a functional antibody titer, e.g., virus neutralization test (VNT). Seronegative is defined as titers below the starting dilution which corresponds to a titer of <1:10. Seroconversion after vaccination is defined as a 4-fold increase in titer ○ for seronegative pre-vaccination sera: a titer ~~>~~≥1:40. ○ for seropositive pre-vaccination sera: a titer which is 4-fold higher than the measured pre-vaccination titer, e.g., titer rise from 1:20 to ~~>~~≥1:80 after vaccination. an antibody binding assay, e.g., ELISA. Seronegative is defined as titers below the starting dilution which corresponds to a titer of <1:100. Seroconversion after vaccination is defined as a 4-fold increase in titer ○ for seronegative pre-vaccination sera: a titer of ~~>~~≥1:400. ○ for seropositive pre-vaccination sera: a titer which is 4-fold higher than the measured pre-vaccination titer, e.g., titer rise from 1:200 to ~~>~~≥1:800 after vaccination. and/or equivalent assays dependent on availability by the time of trial conduct. Cell-mediated immune (CMI) responses: CMI assays, e.g., ELISpot, intracellular cytokine staining (ICS).	Assessments added

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MI analysis will include Th1-specific cytokines, (e.g., IFN-gamma, TNF-alpha, IL-2, or IL12) and Th2-specific cytokines (e.g., IL4, IL-5, IL-10, IL-13) to analyze the induction of either balanced Th1/Th2 responses, or of unbalanced Th1-dominant or Th2-dominant ~~respectively~~ or immune responses, respectively. Instructions on the sample collection, handling, and shipping will be provided in a Laboratory Manual. The methodology used for these assessments will be documented in the Biomarker Manual. Leftover blood after completion of the immunogenicity assessments may be used for additional analyses as described in Section 8.7 (Genetics) and/or Section 8.8 (Biomarkers).	
Section 8.10 (Blood collection) Up to approximately 568 mL blood will be drawn per subject over the complete trial, i.e., over approximately 7 months. Additional blood samples may be taken for safety assessments after AEs or SAEs. For enrolled subjects who have not completed the EoT visit (see the SoA in Section 1.3) before approval of Protocol Amendment 04, the optional additional blood draws added by protocol amendment 04 will only apply for subjects who give consent.	New section added to describe blood sampling.
Section 9.4.2 (Primary endpoints) Treatment-emergent AEs (TEAE) are defined in Section 10.3.1.1 and will be summarized using the Safety Set. In general, AEs will be analyzed by group (i.e., by type [BNT162a1, BNT162b1, BNT162b2, BNT162c2 SD, and BNT162c2 P/B] and dose level) and for each immunization, i.e., for: • Prime/boost regimens: Day 1-21 (pre-boost) ~~and (BNT162c2) Day 1-28~~ • Day 21(post-boost) - 28 • Single dose regimens: Day 1-28 • ~~(BNT162a1, BNT162b1, BNT162b2, BNT162c2) Day 1-21 (if applicable, Day 21 pre-boost)~~ • ~~(BNT162c2) Day 1-28~~ Additionally, AEs will be summarized for all dose levels combined for each type. • Any AE • Any AE excluding AEs based on solicited reporting via subject diaries • Related AE • Grade ≥3 AE • Related Grade ≥3 AE .. For each immunization, the number and percentage of subjects reporting at least one local reaction or systemic reaction (i.e., solicited data collected using subject diaries) will be summarized for each of the following types using the Safety Set: • Any local reactions or systemic reactions • RelatedAny local reactions or systemic reactions • ~~Grade ≥3 local reactions or systemic reactions~~ • ~~Related~~ Grade ≥3 local reactions or systemic reactions	Update to correct duplication. Update reflecting the addition of additional cohorts.
Section 9.4.5 (Other safety analyses) **ECG** ECG parameters to be summarized and assessed are given in Section 8.2.3. The scheduled time points for assessment are given in the SoA (see Section 1.3).	Clarification of an ambiguity

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ECGs will be judged by the investigator as clinically significant (yes/no). ~~The number and percentage of trial subjects with clinically significant ECG findings will be summarized by group for each visit.~~	
Section 10.1.5 (Committees - SRC) Key roles of the SRC are as follows: • Before progression to the next cohort, for each vaccine per cohort/dose level, • assess the data, decide whether to approve initiation of the next cohort/dose level and to confirm the planned dose or define another dose for use. The data assessed by the SRC is defined in Section 1.1. • After completing its evaluation of the 48 h data for the first 6 subjects per group in cohort, the SRC may request a prolongation of the observation period to up to Day 7 data for later cohorts or other similar adaptations to protect subject wellbeing.	Updated to reflect additional SRC tasks added by this protocol amendment.
Section 10.2 (Clinical laboratory tests) Follicle-stimulating hormone: ~~In women only.~~ Only in women who are not of childbearing potential.	Clarification of an ambiguity.
Section 10.3.1 (Definition of AE and TEAE • ~~An AE is any untoward medical occurrence in a trial subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.~~ • ~~NOTE: An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the IMP.~~ • An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. • Events after signing ICF and before IMP administration will be handled as AEs. • A TEAE is defined as any AE with an onset date on or after the first administration of IMP (if the AE was absent before the first administration of IMP) or worsened after the first administration of IMP (if the AE was present before the first administration of IMP). AEs with an onset date more than 28 d after the last administration of IMP will be considered as treatment emergent only if assessed as related to IMP by the investigator.	Alignment with the trial BNT162-02
Section 10.3.1.1 (Events meeting the AE definition) • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, and which are~~those~~ considered clinically significant in the medical and scientific judgment of the investigator, may be considered as AEs. • Only the diagnoses of clinically significant local and/or systemic reactogenicity e.g., injection site reactions need to be reported as AEs (generally, the individual signs and symptoms of local or systemic reactogenicity making up diagnostic AEs are already captured as solicited reactions). • New conditions or any worsening of a pre-existing condition detected or diagnosed after Visit 0.	Alignment with the trial BNT162-02
Section 10.3.1.7 (Recording and Follow-Up of AE and/or SAE) **Assessment of AE and/or SAE intensity**	Addition of guidance due to reporting changes

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~~Note: The grading scheme for protocol version 4.0 should only be adopted for subjects consented for inclusion in new cohorts that start enrolment after the protocol amendment has been approved and implemented (for any drug construct). All subjects in cohorts where first enrolment pre-dates the protocol amendment, should continue to use the grading scheme in protocol version 3.0, such that the same grading scheme is used for all subjects in any given cohort. The protocol version 3.0 grading scheme should continue to be used for subjects consented under protocol version 3.0, and that retrospective re-grading is not required.~~ The assessment of AE and/or SAE intensity should be done consistently for all subjects treated with the same treatment and dose. All subjects treated in completed cohorts, where the first treatment pre-dates approval of the protocol version 5.0 (i.e., including amendment 04), should continue to use the grading scheme in the earlier protocol version, such that the same grading scheme is used consistently for all subjects given the same treatment and dose. Where applicable, retrospective re-mapping of grading from 3-point to 4-point scale will be completed prior to database lock, with definitions for mild and moderate intensity events aligned and all events previously graded as severe intensity (on 3-point scale), queried to determine whether grade 3 (severe) or 4 (potentially life-threatening) should be applied. In case of doubt, the Medical Monitor should be consulted.	implemented to align BNT162-01 with the US trial BNT612-02.
Section 10.3.1.7 (Recording and follow-up of AE and/or SAE) The subsections “Local reactions”, “Systemic events”, “Fever”, and “Laboratory abnormalities” were moved to a new section, Section 10.3.1.11 (Assessments of intensity for solicited local and systemic reactions and laboratory abnormalities).	Adapted to avoid confusion between the assessment of AE/SAEs and the assessments of intensity for solicited local and systemic reactions and laboratory abnormalities.
Section 10.3.1.9 (Documentation of particular situations) **Abnormal laboratory results and vital signs values:** Not every laboratory or vital signs abnormality needs to be documented as AE. For clinically significant laboratory/vital signs abnormalities the following definitions and documentation rules apply: • If a laboratory/vital signs abnormal... • If a laboratory/vital signs… • If a laboratory/vital … If a laboratory/vital signs abnormality is not considered clinically significant by the investigator, then an AE does not need to be documented.	Addition of guidance due to reporting changes implemented to align BNT162-01 with the US trial BNT612-02.
Section 10.3.1.11 (Assessments of intensity for solicited local and systemic reactions and laboratory abnormalities) The subsections “Local reactions”, “Systemic events”, “Fever”, and “Laboratory abnormalities” were moved from section, Section 10.3.1.7 (Recording and follow-up of AE and/or SAE) to here without change.	Adapted to avoid confusion between the assessment of AE/SAEs and the assessments of intensity for solicited local and systemic reactions and

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	laboratory abnormalities.
Section 10.4.2 (Contraception guidance) ~~Women of childbearing potential (WOCBP)~~WOCBP must confirm that they practiced at least one highly effective form of contraception for the 14 d prior to Visit 0. WOCBP must practice a highly effective form of contraception during the trial, starting after Visit 0 and continuously until 60 d after receiving the last immunization. WOCBP must agree to require their male partners to use condoms during sexual contact (unless male partners are sterilized or infertile). Men who are sexually active with a WOCBP and have not had a vasectomy must agree to practice a highly effective form of contraception with their female partner of childbearing potential during the trial, starting after Visit 0 and continuously until 60 d after receiving the last immunization.	Clarification of an ambiguity.

1.5 Protocol amendment no. 05

Amendment rationale

Amendment 05 address feedback obtained from the PEI and the IEC on protocol version 7.0. Some changes were also implemented to align data collection and reporting in this trial with the data collection and reporting in the trials BNT162-02 and BNT162-04 (to facilitate later data merging).

The changes implemented are described below. Editorial changes are not listed.

This amendment will be issued after some of the planned trial subjects have already been enrolled into the trial.

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Section 1 and Section 4 (Objectives and endpoints) primary immunization. To describe the cellular immune responses. — For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): • Cell-mediated immune (CMI) responses measured by Enzyme-Linked Immuno-Spot (ELISpot) at baseline and at 29±3 d after the primary immunization. For BNT162c2 (SD): • CMI responses measured by ELISpot at baseline and at 29 ±3 d ~~42±4 d~~ after the primary immunization.	Alignment with other BNT162 trials
Section 1 (Trial design) and Section 4 (Overall Trial design) Four different vaccines (BNT162a1, BNT162b1, BNT162b2, and BNT162c2) will be tested. Note: Currently, dosing with this dose has been deferred. Dosing may be resumed if disease prevention data for the other vaccine candidates suggest the need for additional vaccine candidates. This trial has two parts. Part A is for dose ranging with dose escalation and de-escalation plus the evaluation of interim dose levels. It also includes dose ranging in older subjects. ~~The trial has two parts: a dose-finding part (Part A) with three dose escalation cohorts (each with predefined dose levels) and two dose de-escalation cohorts (one pre-defined and one optional dose level) and, a second part (~~Part B~~)~~ is dedicated to recruit expansion cohorts with dose levels which are selected from data generated in Part A.	PEI feedback & sponsor prioritization decision
Section 1 (Trial design) and Section 4 (Overall Trial design) **Part A** ~~The first part of the trial (Part A) will follow a dose-escalation design. For some vaccines, a dose-de-escalation is also planned.~~ Trial subjects with the first-in-human [FIH] immunization will be immunized using a sentinel…	Removal of duplication
Section 1 (Trial design) and Section 4 (Overall Trial design) In Cohort 1, the sentinel dosing/subject staggering process will be as follows: • One sentinel subject will be dosed on one day. • If the dosing in this subject was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 5 further subjects will be dosed (with intervals of at least 1 h between subjects). • If the dosing in these 5 subjects was considered to be safe and well tolerated by the investigator based on 48h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48±2 h data from the sentinel subject):	PEI feedback

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○ The remaining 6 subjects in the group will be dosed (with intervals of at least 30 min between subjects). ○ If approved by the SRC, the next planned escalation dose (see Table 1) ~~in Cohort 2~~ will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects including observation on site, short summary of phone interview (including statement about diary reports), vital signs, investigator reported local & systemic reactions, TEAEs, solicited local & systemic reactions ~~local reactions~~, blood/clinical laboratory data, and brief physical examination outcome. ○ If approved by the SRC, the planned de-escalation dose in Cohort 3 will be initiated.	
Section 1 (Trial design) and Section 4 (Overall Trial design) For any subsequent dose-escalation cohorts (to doses higher than the maximum already tested for a vaccine candidate), the sentinel/subject staggering process will be as follows: • Two sentinel subjects will be dosed on one day (with intervals of at least 30 min between subjects). • If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 4 further subjects will be dosed (with intervals of at least 30 min between subjects). • If the dosing in these 4 subjects was considered to be safe and well tolerated by the investigator based on 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48 h data from the sentinel subjects): ○ The remaining 6 subjects in the group will be dosed (with intervals of at least 30 min between subjects). ○ If approved by the SRC, the next planned escalation dose (see Table 1) will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects including observation on site, short summary of phone interview (including statement about diary reports), vital signs, investigator reported local and systemic reactions, TEAEs, solicited local & systemic reactions, blood/clinical laboratory data, and brief physical examination outcome. The maximum allowed dose for each vaccine candidate is defined in the Table 1. For the planned dose de-escalation cohorts, 12 subjects may be dosed on one day (with intervals of at least 30 min between subjects). The doses in these cohorts in younger adults must be lower than doses than doses that have shown acceptable tolerability in younger adults (based on the data from 12 subjects up until 48 h after the first dose). The same dose will not be administered twice, i.e., in two cohorts. For BNT162b1 and BNT162b2, administration of the planned 10 µg dose in older subjects (Cohort 8) may start once at least a 30 µg dose has shown acceptable tolerability in younger adults (based on the data from 12 subjects up until 48 h after the boost dose). The dose in Cohort 8 must also be confirmed by the SRC. In Cohort 8, 12 subjects will be dosed using a sentinel dosing/subject staggering (2-4-6) process with intervals of at least 1 h between the first 6 subjects and then at least 30 min intervals for the remaining 6 subjects. For BNT162b1 and BNT162b2, administration of the planned dose escalation cohorts in older adults (Cohorts 9 and 10), 12 subjects will be dosed using a sentinel dosing/subject staggering (2-4-6) process with intervals of at least 30 min between subjects. The doses planned in these cohorts will only be administered if the dose is confirmed by the SRC. For the unplanned dose de-escalation cohorts, i.e., where the SRC requests the use of a reduced dose for safety reasons, 12 subjects may be dosed on one day with intervals of at least 30 min between subjects (as for planned de-escalation cohorts). ~~In Cohort 2, the subject staggering process will be as follows:~~ ~~• Two sentinel subjects will be dosed on one day.~~ ~~• If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 4 further subjects will be dosed.~~ ~~• If the dosing in these 4 subjects was considered to be safe and well tolerated by the investigator based 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48 h data from the sentinel subjects):~~	PEI feedback

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- ~~The remaining 6 subjects in the group will be dosed.~~
- ~~If approved by the SRC, the next planned escalation dose (see Table 1) in Cohort 4 will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects (including observation on site, phone interview, vital signs, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome).~~

~~In Cohort 3, if possible, 12 subjects will be dosed with the planned dose on one day.~~

~~In Cohort 4, the subject staggering process will be as follows:~~

- ~~Two sentinel subjects will be dosed on one day.~~
- ~~If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 4 further subjects will be dosed.~~
- ~~If the dosing in these 4 subjects was considered to be safe and well tolerated by the investigator based 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48 h data from the sentinel subjects):~~
  - ~~The remaining 6 subjects in the group will be dosed.~~

~~Additional dose cohorts (e.g., Cohort 5) may be investigated at the discretion of the SRC, but will not exceed the pre-defined maximum dose (see Table 1).~~

~~For the BNT162b vaccines, protocol amendment 04 allows additional dose cohorts at the dose levels listed in Table 1. In these cohorts, since at doses lower than already tested, 12 subjects can be dosed with the planned dose on one day.~~

~~For the BNT162b1 vaccine, protocol amendment 04 allows three additional cohorts in older adults at the dose levels listed in Table 2. In these cohorts, 12 subjects will be dosed using a sentinel dosing/subject staggering process as done for Cohort 4.~~

~~For the BNT162b2 vaccine, additional cohorts in older adults will be added to allow the dosing of 12 subjects using a sentinel dosing/subject staggering process as done for Cohort 4. These additional cohorts will be activated using a dedicated protocol amendment including supportive immunogenicity and safety data in younger adults, before any older adults are dosed with BNT162b2.~~

Note: BNT162b1 and BNT162b2 are ~~non-~~modified uridine RNAs, while BNT162a1 and BNT162c2 are both nucleoside-modified pseudomethyl-uridine containing RNAs. RNA modification is known to impact the extent of innate immune activation at a given dose level, and thus potentially the extent of reactogenicity. Therefore, tolerability data obtained with one of the vaccine variants of each of these pairs may be potentially informative for the respective other one and should be taken in consideration by the SRC for recommendations of lower or interim doses.

Section 1 (Trial design) Table 1

PEI feedback

Table 1: Summary of vaccine dose regimens for younger adults aged 18 to 55 years in Part A

Vaccine / mRNA type	Vaccine encoded antigen	Vaccine IM dosing regimen	Part A - Cohort numbers & Dose (µg) (12 subjects per cohort)						
			1 Starting dose	2	3 De-escalation dose	4 ~~Maximum dose~~	5 Optional de-escalation dose	6	7
BNT162a1 / uRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	**1A** **3 µg** [b]	2A 0.6 µg [a]	3A 0.1 µg	4A [a] 2 µg [e]	5A 10.3 µg	6A 1 µg	
BNT162b1 / modRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	1B 10 µg	2B 30 µg	3B 1 µg	**4B** **60 µg** [d]	5B 50 µg	6B 3 µg	7B 20 µg
BNT162b2 / modRNA	Modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	1C 10 µg	2C 30 µg	3C 1 µg	**4C** [a] **60 µg** [d]	5C [a] 520 µg	6C [a] 3 µg	7C [a] 250 µg
BNT162c2 / saRNA	Modified version of the full length SARS-CoV-2 S protein	Prime only: Day 1	1D 0.1 µg	2D 0.3 µg	3D 0.1 µg to ≤3 µg [c]	4D 1 µg	5D [a] 0.6 µg	**6D** [a] **3 µg** [d]	
BNT162c2 / saRNA	Modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	1E 0.1 µg	2E [a] 0.3 µg	3E 0.1 µg to ≤3 µg [c]	4E [a] 1 µg	5E [a] 0.6 µg	**6E** [a] **3 µg** [d]	

[a] All dose escalation doses used must be judged acceptable by the Safety Review Committee (SRC) before use.
[b] Status 08 JUN 2020: This cohort was set on hold by the SRC after 6 subjects had been received their Day 1 dose, furthermore the SRC decided not to perform Day 22 dosing for these 6 subjects. Due to this hold, the starting dose is also the maximum dose.
[c] Specific doses to be defined, but in the range given. Already given doses will not be repeated.
[d] The planned maximum doses per vaccine candidate.
[e] Dosing with this vaccine variant has been put on hold. Dosing may be resumed if disease prevention data for the other vaccine candidates suggest the need for additional vaccine candidates.

IM = intramuscular; RBD = Receptor Binding Domain; S protein = SARS-CoV-2 spike protein: tbd = to be defined.

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Section 1 (Trial design) Table 2

Table 2: Summary of vaccine dose regimens for older adults aged 56 to 85 years in Part A

Vaccine / mRNA type	Vaccine encoded antigen	Vaccine IM dosing regimen	Part A - Cohort numbers & Dose (µg) (12 subjects per cohort)[a]		
			8 Older adults	9 Older adults	10 Older adults
BNT162b1 / modRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	8B 10~~3~~ µg	9B[a] 20~~10~~ µg	10B[a] 320 µg
BNT162b2 / modRNA[b]	Modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	8C 10~~3~~ µg	9C[a] 20~~10~~ µg	10C[a] 320 µg

[a] All dose escalation doses used must be judged acceptable by the Safety Review Committee (SRC) before use.
[b] ~~These cohorts will be activated using a dedicated protocol amendment before any older adults are dosed.~~

IM = intramuscular; RBD = Receptor Binding Domain; S protein = SARS-CoV-2 spike protein.

Note: The doses planned in this trial for older adults (i.e., adults aged between 55 and 85 years) reflect clinical data from the ongoing BNT162-01 and BNT162-02 trials with the vaccine candidates BNT162b1 and BNT162b2 in younger adults (aged between 18 and 55 years) and elderly (adults aged between 65 and 85 years). For details, see Section 2.2.

BNT162b1:

- BNT162b1 P/B doses of 1, 10, 30, and 50 µg showed acceptable tolerability in younger adults.
- Based on the tolerability profile after the prime dose at 60 µg (BNT162-01 trial) and 100 µg (BNT162-02 trial), the respective boost doses were not administered.
- BNT162b1 P/B doses of 10, 20, and 30 µg showed acceptable tolerability in elderly adults. This tolerability appears to be better than seen in younger adults at the same doses.

BT162b2:

- BNT162b2 P/B doses of 1, 10, and 30 µg showed acceptable tolerability in younger adults.
- BNT16b2 P/B doses of 10, 20, and 30 µg in elderly adults. This tolerability appears to be better than seen in younger adults at the same doses.

Based on the tolerability data summarized above, and the implemented safety measures (sentinel/staggered subject dosing, post-dose observations period, wel being questioning, etc.) as descr bed in the section Risk assessment, the planned doses in older subjects in this trial are expected to show acceptable tolerability.

Based on the available immunogenicity data after dosing with BNT162b1 and BNT162b2 in younger adults in the BNT162-02 trial (see the section US trial BNT162-02 - Preliminary results), the doses planned in this trial in older subjects are expected to show measurable immunogenicity.

Altogether, the doses planned in older subjects in this trial are considered adequate to support the trial objectives and to pose an acceptable risk to trial subjects.

PEI feedback

Section 1 (Trial design) and Section 4 (Overall Trial design)

Part B will only be started if approved using a substantial protocol amendment. ~~If approved by the SRC, Part B will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects (including observation on site, phone interview, vital signs, TEAEs, local reactions, immunogenicity data, blood/clinical laboratory data, and brief physical examination outcome).~~…

Part B will use a randomized, placebo-controlled design in the likely target population (e.g., higher risker populations such as ~~elderly and/or~~ immunocompromised populations). Part B may employ a surrogate marker as a measure of vaccine efficacy.

PEI feedback

Section 1 (Population) - Table 3

Table 3: Overview of the total number of subjects for each vaccine in Part A

Vaccine / mRNA type	Vaccine dosing regimen	Maximum number of subjects (assuming all cohorts planned in Table 1 are performed)
BNT162a1 / uRNA	Prime/Boost	~~60~~ 72 (~~5~~ 6 cohorts)
BNT162b1 / modRNA	Prime/Boost	120 (10 cohorts)
BNT162b2 / modRNA	Prime/Boost	120 (10 cohorts)
BNT162c2 / saRNA	Prime only	72 (6 cohorts)
BNT162c2 / saRNA	Prime/Boost	72 (6 cohorts)

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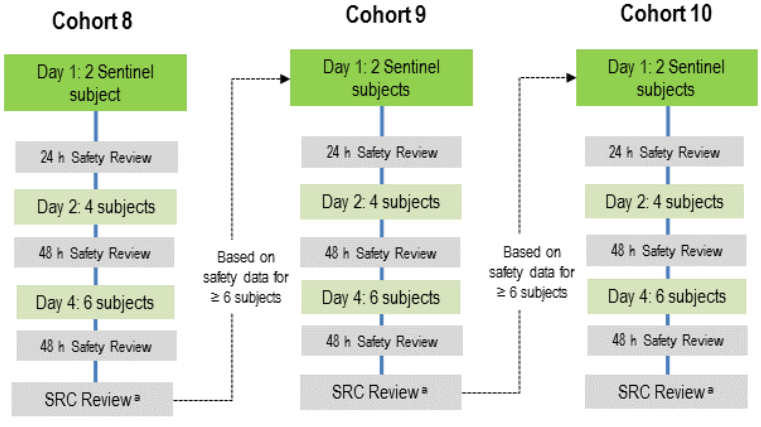
Section 1 (Key exclusion criteria) For older subjects: Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors: • Hypertension • Diabetes mellitus • Chronic pulmonary disease • Asthma • Chronic liver disease • Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2) • ~~BMI ≥30 kg/m^2~~ • …	IEC feedback
Section 1 (Trial treatments (BNT162 vaccines) - Dosage levels) and Section 6.1 (IMP administered) Part B expansion cohorts: The to be tested doses will be chosen ~~by the SRC~~ after review of the safety, tolerability, and immunogenicity data from Part A. Part B will only be started if approved using a substantial protocol amendment.	IEC feedback
Section 1.2 (Schema - Dose cohort schema for BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B)) a) The data assessed by the SRC for progressing comprises 48 h data for 6 subjects. b) If these cohorts use doses lower than already tested, 12 subjects may be dosed on one day in these cohorts and the cohorts may be conducted in parallel to each other / to any dose escalation cohorts. If they use doses higher than already tested, subjects will be dosed using a sentinel dosing/subject (2-4-6) staggering process. ~~For BNT162b1 and BNT162b2 only: Cohorts 5 to 7 are planned for dose finding (12 subjects can be dosed on one day in these cohorts) and Cohorts 8 to 10 for testing in older subjects will use sentinel dosing.~~ c) For the dose regimens, see Table 1 and Table 2.	PEI feedback
Section 1.2 (Schema - Dose cohort schema for BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B) - Cohorts with older adults)  Replaced with (where the column header “Cohort 8” was replaced with “Cohort 8 [d]”)	Clarification

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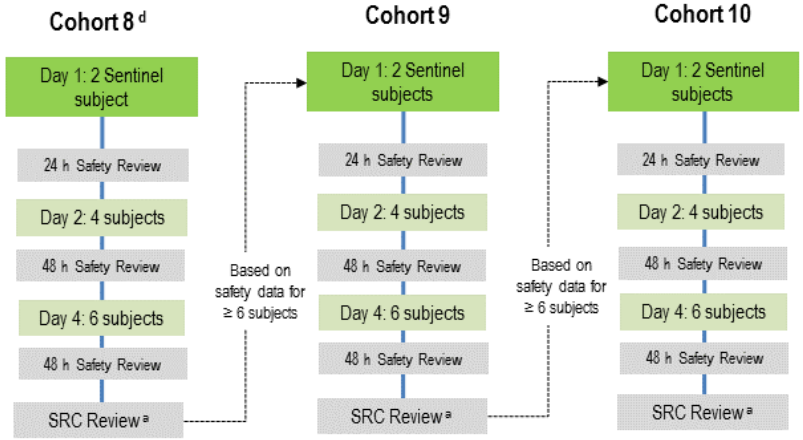
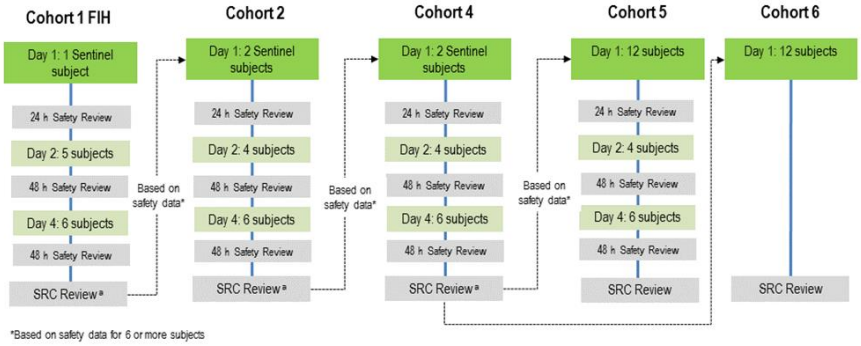
	
Section 1.2 (Schema - Dose cohort schema for BNT162c2 (SD)) a) The data assessed by the SRC for progressing comprises 48 h data for 6 subjects. b) If these cohorts use doses lower than already tested, 12 subjects may be dosed on one day in these cohorts and the cohorts may be conducted in parallel to each other / to any dose escalation cohorts. If they use doses higher than already tested, subjects will be dosed using a sentinel dosing/subject (2-4-6) staggering process. ~~For BNT162b1 and BNT162b2 only: Cohorts 5 to 7 are planned for dose finding (12 subjects can be dosed on one day in these cohorts) and Cohorts 8 to 10 for testing in older subjects will use sentinel dosing.~~ c) For the dose regimens, see Table 1 and Table 2. d) Administration of the planned 10 µg dose in Cohort 8 requires that at least a 30 µg dose has shown acceptable tolerability in younger adults. For the cohorts with BNT162c2 P/B dosing, dosing will only start after SRC assessment of day 28 AE data (solicited and unsolicited).	IEC feedback
Section 1.2 (Schema - Dose cohort schema for BNT162c2 (SD))  Replaced with (where the column headers “Cohort 5” and “Cohort 6” were switched)	PEI feedback

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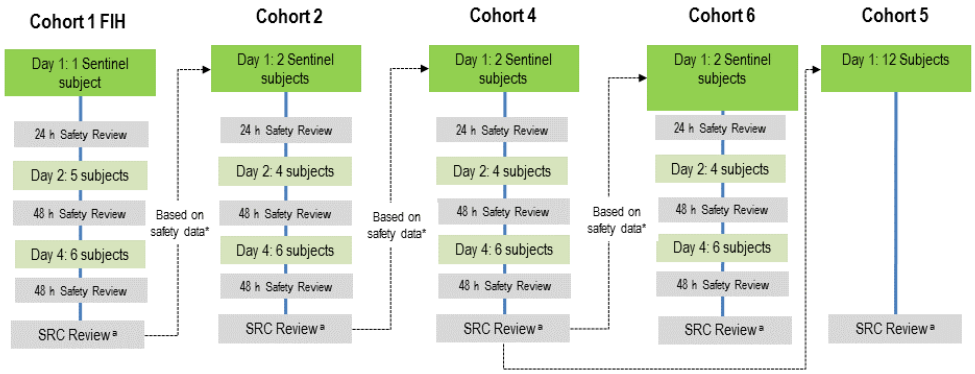
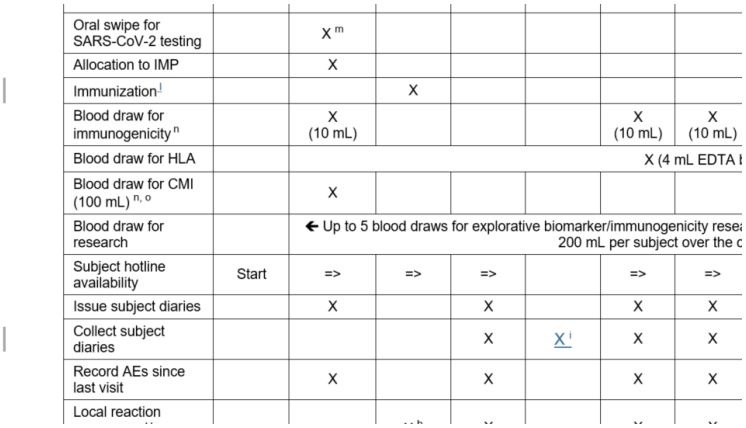
	
Section 1.3 (Schedule of activities - Table 4) 	Alignment with other trials
Section 1.3 (Schedule of activities - Table 4) h Flexibility for visit days: Visit 3 Day 8±1 d; Visit 4 Day 22±2 d; Visit 5 Day 29±3 d; Visit 6 Day 43±4 d; Visit 7 Day 50±4 d; Visit 8 Day 85±7 d; Visit 9 Day 184±9d. i Only for the first 6 subjects per group. Questioning on and documentation of AEs as well as systemic and local reactions, the latter in case of upcoming dose decision meetings. j Only IMP-related AEs. k Blood draw for anti-SARS-CoV-2 antibodies (samples will be stored until a test is commercially available). l For Cohorts 1 and 8, immunization with at least 1 h intervals between subjects for the first 6 subjects and then with of at least 30 min intervals for the remaining 6 subjects. For all other cohorts ~~Cohorts 2 and 4~~, immunization with at least 30 min intervals between subjects. m Oral swipe for SARS-CoV-2 testing either on Day -1 or at the Visit 1 on Day 1. n The listed blood draw days may be adapted if justified by the collected data. Leftover blood after completion of the immunogenicity assessments may be used for additional analyses as described in Section 8.7 (Genetics) and/or Section 8.8 (Biomarkers).	Clarification

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Section 1.3 (Schedule of activities - Table 5)	Alignment with other BNT162 trials

Blood draws for research		← Up to 5 blood draws for exploratory biomarker/immunogenicity research purposes will not exceed 200 mL per subject over the complete trial,					
Subject hotline availability	Start	=>	=>	=>		=>	=>
Issue subject diaries		X		X		X	X
Collect subject diaries				X	X [o]	X	X
Record AEs since last visit		X		X		X	X
Local reaction assessment/ systemic events			X [d]	X		X	X
Concomitant medication	X	X		X		X	X

Section 1.3 (Schedule of activities - Table 5) [k] For Cohort 1, immunization with at least 1 h intervals between subjects for the first 6 subjects and then with at least 30 min intervals for the remaining 6 subjects. For ~~Cohorts 2 and 4~~all other cohorts, immunization with 30 min intervals between subjects. [l] The listed blood draw days may be adapted if justified by the collected data. Leftover blood after completion of the immunogenicity assessments may be used for additional analyses as described in Section 8.7 (Genetics) and/or Section 8.8 (Biomarkers). [m] For subjects who have given consent, one aliquot of the blood sample drawn for analysis of CMI may be used for human leukocyte antigen typing to allow additional analysis of T cell receptor repertoire and / or phenotypic characterization of T cells specific to vaccine-encoded antigens. [n] Only IMP-related AEs. [o] Only for the first 6 subjects per group. Questioning on and documentation of AEs as well as systemic and local reactions, the latter in case of upcoming dose decision meetings. [p] If HLA typing using the blood sample collected with Lithium Heparin is not conclusive, EDTA-blood will be drawn for HLA testing.	Clarification

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Section 2.2 (Trial rationale - Table 6)	IEC feedback

Table 6: Status of ongoing and planned clinical trials (as of July 17th ~~June 22nd~~, 2020)

Trial number	Design	Current number dosed (subject age)
BNT162-01 (NCT04380701) Germany	Phase I/II, 2-part, dose escalation trial. Part A is open label and non-randomized. (All subjects receive active vaccine) Part B will be defined in a protocol amendment.	BNT162a1 (age 18-55 years): 0.1 µg 12 subjects prime / 12 boost 0.3 µg 12 subjects prime / 12 boost 3 µg 6 subjects prime (Further dosing with BNT162a1 has been deferred) BNT162b1 (age 18 to 55 years): 1 µg 12 subjects prime / 121 ~~1~~ boost 10 µg 12 subjects prime / 112 ~~2~~ boost 30 µg 12 subjects prime / 12 boost 50 µg 12 subjects prime / 11 boost 60 µg 12 subjects prime BNT162b2 (age 18 to 55 years): 1 µg 9 subjects prime 10 µg 12 subjects prime / 12 boost 20 µg 2 subjects prime 30 µg 12 subjects prime / 6 boost BNT162c2 (age 18 to 55 years): 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)

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Rationale

Section 2.2 (Trial rationale - Table 6)

IEC feedback

Trial number	Design	Current number dosed (subject age)
BNT162-02 / C4591001 (~~PF-07302048;~~ NCT NCT04368728) US	Phase I/II, placebo-controlled, randomized, observer-blind, dose-finding trial. (Subjects are randomized: 4 active vaccine to 1 placebo)	BNT162b1 (age 18 to 55 years): 10 µg 15 subjects prime / 15 boost 20 µg 15 subjects prime 30 µg 15 subjects prime / 15 boost 100 µg 15 subjects prime BNT162b1 (age 65 to 85 years): 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 years): 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 years): 10 µg 15 subjects prime 20 µg 15 subjects prime / 15 boost 30 µg 15 subjects prime / 15 boost
BNT162-03 China (NC to be obtained)	Phase I, randomized, placebo-controlled, observer-blind trial..	BNT162b1 (age 18 to 55 years): • Enrollment has not started. BNT162b1 (age >55 years): • 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.	BNT162a3 (age 18-55 years): Enrollment has not started. BNT162b3 (age 18 to 55 years): Enrollment has not started.

Section 2.2.1 (This trial (BNT162-01)

IEC feedback

Summary of immunogenicity in trial BNT162-01 (up to July 1st, 2020)

Two doses of BNT162b1 of 1, 10, 30 and 50 µg of BNT162b1 administered 21 d apart elicited antibody, and robust $CD4^+$ and $CD8^+$ T cell responses. All subjects exhibited strong antibody responses with RBD-binding IgG concentrations clearly above those observed in a COVID-19 convalescent human serum panel (HCS). Day 43 SARS-CoV-2 serum neutralizing geometric mean titers were in the range of 0.7-fold (1 µg) to 3.3-fold (50 µg) compared to those of HCS.

Preliminary data (at the time of preparation of this summary) from subjects with BNT162b2 suggest a robust induction by day 21 post first dose, of the production of antibodies conformational to complete CoV-2 spike protein, the antigen encoded by the RNA in this vaccine construct. The order of magnitude of response seems at least equivalent to that seen for anti-RBD antibodies with the b1 vaccine constructs.

Immunogenicity in for older adults receiving vaccine candidate BNT162b1 were not available at the time of preparation of this summary.

Summary of safety in trial BNT162-01 (up to July 1st 2020)

In the trial BNT162-01, younger adults aged 18 to 55 years were dosed with one of four BNT162 vaccine candidates (BNT162a1, BNT162b1, BNT162b2, and BNT162c2). The most complete experience is available for the vaccine BNT162b1, which has been dosed in 5 cohorts of 12 subjects each (all subjects received active vaccine). Except for those in the highest dose cohort (60 µg), all subjects were dosed twice (i.e., prime and boost).

Summary of safety - BNT162a1

BNT162a1 has been tested at doses of 0.1, 0.3, and 3 µg (starting dose level). In the first 6 subjects treated (sentinel and sub-group 2), the frequency and duration of systemic reactogenicity (predominantly of moderate intensity) led to a recommendation to de-escalate the dose. This was a precautionary measure by the trial SRC, although formal dose limiting toxicity criteria were not met. In the resultant 0.1 µg cohort minimal evidence of reactogenicity was found and a further cohort was treated at 0.3 µg BNT162a1. Across both these dose levels, most subjects reported only injection site reactions (pain and tenderness, almost exclusively of mild intensity) and no systemic reactions. No SAEs were reported. Currently, no further dosing with this vaccine candidate is planned. Dosing may be resumed if disease prevention data for the other vaccine candidates suggest the need for additional vaccine candidates.

Summary of safety BNT162c2

BNT162c2 has been tested at doses of 0.1, 0.3 and 1 µg. Minimal reactogenicity was reported with any local reactions (chiefly pain) being mild or moderate and present in 4, 7, and 11 subjects in each dose cohort respectively. Systemic reactions showed little dose dependency overall with 7, 7, and 8 subjects reporting any systemic reaction by respective dose cohort. 2 subjects each in the 0.3 and 1.0 µg cohorts reported severe local reactions. All reported events were self-limiting or simply managed. No SAEs were reported.

Summary of safety - BNT162b1

Reactogenicity - BNT162b1

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 graded as described in Section 10.3.1.11 and are summarized below in Table 7 and Table 8.

Table 7: BNT162b1 in younger adults - Number of subjects with local symptoms (diary)

	Number of subjects with local reactions (n=)							
	7 d Post Prime			7 d Post boost			Total (both)	
	Subjects dosed prime	Any event	Any ≥ severe	Subjects dosed boost	Any event	Any ≥ severe	Any event	Any ≥ severe
BNT162b1	60	51	8	46	39	7	54	13
1 µg	12	6	0	11	7	2	7	2
10 µg	12	10	1	12	10	0	11	1
30 µg	12	11	4	12	11	2	12	5
50 µg	12	12	2	11	11	3	12	4
60 µg	12	12	1				12	1

Table 8: BNT162b1 in younger adults - Number of subjects with systemic symptoms (diary)

	Number of subjects with systemic reactions (n=)							
	7 d Post Prime			7 d Post boost			Total (both)	
	Subjects dosed prime	Any event	Any ≥ severe	Subjects dosed boost	Any event	Any ≥ severe	Any event	Any ≥ severe

BNT162b1	60	52	15	46	38	17	57	27
1 µg	12	9	0	12	7	2	11	2
10 µg	12	8	1	11	9	4	10	5
30 µg	12	11	3	12	11	6	12	6
50 µg	12	12	4	11	11	5	12	7
60 µg	12	12	7				12	7

In local reactions, most subjects reported injection site pain and tenderness, whilst reports of swelling / induration or erythema were scarce. The most common systemic reactions were headache and fatigue, experienced by most subjects. Grade 3 (severe intensity) local reactions were reported for pain, tenderness and swelling. Grade 3 (severe intensity) systemic reactions were fever, headache, myalgia, arthralgia, nausea, vomiting, chills, loss of appetite, malaise, and fatigue.

Laboratory findings - BNT162b1

A consistent pattern has been seen in the laboratory assessments with elevation of the C-reactive protein with concomitant reduction in the plasma lymphocyte count 24 h after vaccination. These changes are consistent with the know pharmacology of this technology, with the changes in lymphocytes known to represent a reversible compartmental shift from the vascular space to lymphoid organs. These observations have been self-limiting and without clinical consequence. There have been no other consistent findings on laboratory assessments.

Adverse events - BNT162b1

Adverse events are collected throughout the trial and graded by the investigators on a 4-point scale (as per this protocol). Most subjects reported adverse events (see Table 9).

Table 9: BNT162b1 in younger adults - TEAE (prime +/- boost) by number of subjects

BNT162b1	Subjects dosed N =	Number of subjects with (n=)					
		TEAEs	Mild AE	Moderate AE	Severe AE	SAE	Resolved AE
1 µg	12	11	10	7	2	0	11
10 µg	12	12	12	8	1	0	12
30 µg	12	12	12	9	0	0	12
50 µg	12	12	12	11	2	0	12
60 µg	12	12	12	10	1	0	12
Total	60	59	58	45	6	0	59

AE = adverse events; n or N = number; SAE = Serious adverse event; TEAE = Treatment emergent adverse event.

Summary - BNT162b1

For BNT162b1, generally good tolerability was observed with no SAEs and no unexpected toxicities. To date, there is high acceptance by trial subjects with no withdrawals due to related AEs. Most reported AEs are signs and symptoms of reactogenicity, typical onset within first 24 h post immunization. All AEs / reactogenicity resolve spontaneously, mostly within 24 h. of onset and can be managed with simple measures (e.g., paracetamol). Laboratory assessments suggest a Th1 pattern of immune activation 24 h post dosing. Some dose dependency of tolerability has been observed, with 1 µg dose best tolerated. The poss bly of a slight increase in reactogenicity following boost dose is noted, as is some inter-individual variability.

Vaccine BNT162a1 showed a similar pattern of tolerability to BNT162b1, however reactogenicity was noted at a lower dose range. Most recently dosing has begun with vaccines BNT162b2 and BNT162c2. The early pattern of reactogenicity with the BNT162c2 candidate at doses <1 µg appears similar or less than that seen with vaccine BNT162b1 at the 1 µg dose. Early indications for tolerability of BNT162b2 at a 10 µg dose are very encouraging with only minimal local reactogenicity in initial reports.

Summary of safety - BNT162b2

Preliminary data are available from subjects treated with BNT162b2 with not all subjects arriving at the visits where tolerability reports are collected ahead of this data cutoff. Data below are therefore preliminary and incomplete and should be interpreted with caution.

Reactogenicity - BNT162b2

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 graded as described in Section 10.3.1.11 and are summarized below in Table 10 and Table 11 respectively.

Table 10: 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 11: 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 the three Grade 3 (severe intensity) systemic reactions was a report of headache, myalgia and malaise, each on one day of recording.

Adverse events & Laboratory findings - BNT162b2

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 collected throughout the trial and graded by the investigators on a 4-point scale (as per this protocol). Most subject report adverse events, >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.

Summary - BNT162b2

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.

~~In the trial BNT162-01, younger adults aged 18 to 55 years were dosed with one of four BNT162 vaccine candidates (BNT162a1, BNT162b1, BNT162b2, and BNT162c2). The most complete experience is available for the vaccine BNT162b1, which has been dosed in 5 cohorts of 12 subjects each (all subjects received active vaccine). Except for those in the highest dose cohort (60 µg), all subjects were dosed twice (i.e., prime and boost). The boost dose in the 60 µg dose cohort is pending.~~

~~ReactogenicityLocal reactions and systemic events are solicited from the subjects and recorded by them in a diary for 7 days following administration of the vaccine. Most subjects in all cohorts~~

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~~experienced the expected reactogenicity, typically starting within 24 h of dosing and resolving within 24 h. The specific, solicited local and systemic reaction are graded as described in Section **Error! Reference source not found.** and are summarized below in Table 1 and Table 2.~~

~~Table 1: Number of adults aged 18 to 55 years with local symptoms (diary): BNT162b1~~

~~-~~	~~Number of Subjects with Local Reactions (n=)~~								
~~-~~	~~7 d Post Prime~~			~~7 d Post Boost~~			~~Total (both)~~	
	~~Subjects dosed prime~~	~~Any event~~	~~Any ≥ severe~~	~~Subjects dosed boost~~	~~Any event~~	~~Any ≥ severe~~	~~Any event~~	~~Any ≥ severe~~
~~BNT162b1~~	~~60~~	~~51~~	~~8~~	~~46~~	~~39~~	~~7~~	~~54~~	~~13~~
~~1 µg~~	~~12~~	~~6~~	~~0~~	~~11~~	~~7~~	~~2~~	~~7~~	~~2~~
~~10 µg~~	~~12~~	~~10~~	~~1~~	~~12~~	~~10~~	~~0~~	~~11~~	~~1~~
~~30 µg~~	~~12~~	~~11~~	~~4~~	~~12~~	~~11~~	~~2~~	~~12~~	~~5~~
~~50 µg~~	~~12~~	~~12~~	~~2~~	~~11~~	~~11~~	~~3~~	~~12~~	~~4~~
~~60 µg~~	~~12~~	~~12~~	~~1~~				~~12~~	~~1~~

~~Table 2: Number of adults aged 18 to 55 years with systemic symptoms (diary): BNT162b1~~

~~-~~	~~Number of subjects with Systemic Reactions (n=)~~							
~~-~~	~~7 d Post Prime~~			~~7 d Post Boost~~			~~Total (both)~~	
	~~Subjects dosed prime~~	~~Any event~~	~~Any ≥ severe~~	~~Subjects dosed boost~~	~~Any event~~	~~Any ≥ severe~~	~~Any event~~	~~Any ≥ severe~~
~~BNT162b1~~	~~60~~	~~52~~	~~15~~	~~46~~	~~38~~	~~17~~	~~57~~	~~27~~
~~1 µg~~	~~12~~	~~9~~		~~12~~	~~7~~	~~2~~	~~11~~	~~2~~
~~10 µg~~	~~12~~	~~8~~	~~1~~	~~11~~	~~9~~	~~4~~	~~10~~	~~5~~
~~30 µg~~	~~12~~	~~11~~	~~3~~	~~12~~	~~11~~	~~6~~	~~12~~	~~6~~
~~50 µg~~	~~12~~	~~12~~	~~4~~	~~11~~	~~11~~	~~5~~	~~12~~	~~7~~
~~60 µg~~	~~12~~	~~12~~	~~7~~				~~12~~	~~7~~

~~In local reactions, most subjects reported injection site pain and tenderness, whilst reports of swelling / induration or erythema were scarce. The most common systemic reactions were headache and fatigue, experienced by most subjects. Grade 3 (severe intensity) local reactions were reported for pain, tenderness and swelling. Grade 3 (severe intensity) systemic reactions were fever, headache, myalgia, arthralgia, nausea, vomiting, chills, loss of appetite, malaise and fatigue.~~

~~*Laboratory findings*~~

~~A consistent pattern has been seen in the laboratory assessments with elevation of the C-reactive protein with concomitant reduction in the plasma lymphocyte count 24 h after vaccination. These changes are consistent with the know pharmacology of this technology, with the changes in lymphocytes known to represent a reversible compartmental shift from the vascular space to lymphoid organs. These observations have been self-limiting and without clinical consequence. There have been no other consistent findings on laboratory assessments.~~

~~*Adverse events*~~

~~Adverse events are collected throughout the trial and graded by the investigators on a 4-point scale (as per this protocol). Most subject report adverse events (Table 3), >90% of which are related to reactogenicity. 6 subjects had AEs rated as severe in intensity (Grade 3) covering 5 preferred terms: muscle tightness, headache, influenza like illness, injection site discomfort, pyrexia.~~

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~~**Table 3: Summary BNT162b1 TEAE (prime +/ boost) by number of subjects**~~

~~BNT162b1~~	~~Subjects Dosed N =~~	~~Number of Subjects with (n=)~~					
		~~TEAEs~~	~~Mild AE~~	~~Moderate AE~~	~~Severe AE~~	~~SAE~~	~~Resolved AE~~
~~1 µg~~	~~12~~	~~11~~	~~10~~	~~7~~	~~2~~	~~0~~	~~11~~
~~10 µg~~	~~12~~	~~12~~	~~12~~	~~8~~	~~1~~	~~0~~	~~12~~
~~30 µg~~	~~12~~	~~12~~	~~12~~	~~9~~		~~0~~	~~12~~
~~50 µg~~	~~12~~	~~12~~	~~12~~	~~11~~	~~2~~	~~0~~	~~12~~
~~60 µg~~	~~12~~	~~12~~	~~12~~	~~10~~	~~1~~	~~0~~	~~12~~
~~Total~~	~~60~~	~~59~~	~~58~~	~~45~~	~~6~~	~~0~~	~~59~~

~~*Summary*~~

~~For vaccine BNT162b1, generally good tolerability was observed with no SAEs and no unexpected toxicities. To date, there is high acceptance by trial subjects with no withdrawals due to related AEs. Most reported AEs are signs and symptoms of reactogenicity, typical onset within first 24 h post immunization. All AEs / reactogenicity resolve spontaneously, mostly within 24 h. of onset and can be managed with simple measures (e.g., paracetamol). Laboratory assessments suggest a Th1 pattern of immune activation 24 h post dosing. Some dose dependency of tolerability has been observed, with 1 µg dose best tolerated. The poss bly of a slight increase in reactogenicity following boost dose is noted, as is some inter individual variability.~~

~~Vaccine BNT162a1 showed a similar pattern of tolerability to BNT162b1, however reactogenicity was noted at a lower dose range. Most recently dosing has begun with vaccines BNT162b2 and BNT162c2. The early pattern of reactogenicity with the BNT162c2 candidate at doses <1 µg appears similar or less than that seen with vaccine BNT162b1 at the 1 µg dose. Early indications for tolerability of BNT162b2 at a 10 µg dose are very encouraging with only minimal local reactogenicity in initial reports.~~

Section 2.2.2 (US trial BNT162-02

IEC feedback

The trial BNT162-02 (Pfizer trial code C4591001; NCT 04368728) is a Phase I/II, placebo-controlled, randomized, observer-blind, dose-finding study to describe the safety, tolerability, immunogenicity, and potential efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy adults, in which the subjects are randomized 4:1 to receive active vaccine or placebo (Mulligan et al. 2020).

Summary of Immunogenicity in BNT162-02 (status, July 1st, 2020)

For vaccine candidate BNT162b1, RBD-binding IgG concentrations and SARS-CoV-2 neutralizing titers were assessed in younger adults (aged 18 to 55 years). By 7 d after the second dose (for the 10 µg and 30 µg dose levels) RBD-binding IgG geometric mean concentrations had increased to 4,813-27,872 U/mL. In comparison, a panel of 19 convalescent sera drawn at least 14 d after PCR-confirmed diagnosis from 38 patients 18 to 83 years of age had an RBD-binding IgG GMC of 602 U/mL.

For all doses, modest increases in SARS-CoV-2 neutralizing geometric mean titers (GMTs) were observed 21 d after Dose 1 (Figure 4b). Substantially greater serum neutralizing GMTs were achieved 7 d after the second 10 µg or 30 µg dose, reaching 168-267, compared to 94 for the convalescent serum panel. The kinetics and durability of neutralizing titers are being monitored.

Immunogenicity in for older adults receiving vaccine candidate BNT162b1 and any subjects receiving vaccine candidate BNT162b2 were not available at the time of preparation of this summary.

Summary of safety in younger adults (aged 18 to 55 years) BNT162-02 (status, July 1st, 2020)

The available safety and tolerability data for younger adults who have received dose 1 and dose 2 of BNT162b1 were broadly comparable to those in trial BNT162-01 and are briefly summarized below.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Overall, all dose levels exhibited a tolerability and safety profile consistent with modRNA-based vaccines, and a clear dose level response was observed after dose 1 and dose 2 in younger adults. Reactogenicity generally seemed slightly higher after the second dose, but the symptoms resolved quickly over the course of a few days. The only reports of Grade ≥3 intensity (severe) were 1 case of fatigue in a subject in the 10 µg cohort and 1 case of chills in a single subject in the 30 µg cohort, both after their boost dose. Based on the tolerability profile observed with the 100 µg dose level after the first dose, an internal decision was made not to give a boost dose at 100 µg. Overall, BNT162b1 and BNT162b2 P/B doses of 10, 20, and 30 µg showed acceptable tolerability in elderly adults. This tolerability appears to be better than seen in younger adults at the same doses. *BNT162b1 - Summary of safety in elderly adults (aged 65 to 85 years) in BNT162-02 (cut-off 01-JUL-2020)* Data for vaccine candidate BNT162b1 in elderly adults are available for all dose levels (10, 20, and 30 µg) post-dose 1, with partial data for 10 µg post-dose 2 (2 to 3 d of follow-up post-dose 2 at the time of this data cut 01-JUL-2020). *Local reactions - BNT162b1* As shown in Figure 2, 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, 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. **Figure 2: BNT162b1 in elderly adults: Local reactions after doses 1 and 2 in trial BNT162-02** *Systemic reactions - BNT162b1* As shown in Figure 3, the most frequent prompted systemic reactions were fatigue and headache. Some apparent variability between dose levels is noted, but no consistent pattern of dose dependency seen. The partial data from the 10 µg group post-dose 2 (boost) suggests an increased frequency and/or severity post-boost. The majority of systemic reactions were mild or moderate, arose within the first 1 to 2 d after vaccination, and were short-lived. Two severe reactions were reported, for one participant each: severe muscle pain and severe fatigue, post-dose 1 at 20 µg and 30 µg, respectively. The former was pain related to onset of herpes zoster (see Adverse events). 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. **Figure 3: BNT162b1 in elderly adults: Systemic reactions in trial BNT162-02** *Adverse events & laboratory assessments - BNT162b1* For elderly adults who were vaccinated with BNT162b1, one severe AE was reported for a participant 2 d post-dose 2 of 20 µg. This subject experienced herpes zoster, which was considered unrelated to the study vaccine by the investigator. No SAEs were reported. No change in routine clinical laboratory values or abnormalities was observed for the majority of participants after the first dose of BNT162b1. As in the younger adult age group, most laboratory changes were decreases in lymphocyte count post-dose 1. One Grade 3 decrease in lymphocyte count was reported for 1 participant at the 30 µg dose level. One Grade 4 decrease in lymphocyte count was reported for 1 participant at the 10 µg dose level. Decreases in lymphocytes after the first dose were transient and returned to normal 6 to 8 d after vaccination. **BNT162b2 - Summary of safety in elderly adults (aged 65 to 85 years) in BNT162-02 (cut-off 01-JUL-2020)** Data for vaccine candidate BNT162b2 in elderly are available for 20 µg and 30 µg dose levels post-dose 1, with partial data for 10 µg post-dose 1 (1 to 3 d of follow-up post-dose 1 at the time of this data cut 01-Jul-2020).	

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Local reactions - BNT162b2

As shown in Figure 4, pain at the injection site was the most frequent prompted local reaction, increasing in frequency with increasing dose level. All prompted local reactions were mild in severity.

Figure 4: BNT162b2 in elderly adults: Local reactions after Dose 1 in trial BNT162-02

Systemic reactions - BNT162b2

*As shown in Figure 5, the most frequent prompted systemic reactions in subjects receiving BNT162b2 were fatigue and heada*che and fatigue in the placebo group. Systemic reactions were generally infrequent and did not appear to be dose dependent. Systemic reactions were mild or moderate, arose within the first 1 to 2 d after vaccination, and were short-lived.

Figure 5: BNT162b2 in elderly adults: Systemic events after Dose 1 in trial BNT162-02

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 vaccinated with BNT162b2. No change in routine clinical laboratory values or abnormalities were observed for the majority of participants after the first dose of BNT162b2. Two participants 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 vaccination.

~~This trial in the US is conducted by Pfizer, Inc. (New York, US) and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany). The trial has been approved by the US regulatory authorities and trial conduct has started.~~

~~The US trial BNT162-02 (PF-07302048; NCT NCT04368728) is "a Phase I/II, placebo-controlled, randomized, observer-blind, dose-finding study to describe the safety, tolerability, immunogenicity, and potential efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy adults.~~

~~Summary of safety in BNT162-02 (status, June 22nd, 2020)~~

~~US Trial C4591001/BNT162-02 is a randomized and placebo-controlled trial, in which the trial subjects are randomized 4:1 to receive active vaccine or placebo. The available safety and tolerability data for younger adults aged 18 to 55 years (see Table 10) who have received dose 1 and dose 2 of BNT162b1 were broadly comparable to those in trial BNT162-01 and are briefly summarized below.~~

~~Preliminary safety and tolerability data in elderly (aged 65 to 85 years) after dosing with BNT162b1 are presented separately below and are summarized in Figure 2 and Figure 3.~~

~~**Table 4: Number of adults aged 18 to 55 years dosed in BNT162 02 (status, June 22nd, 2020)**~~

	~~BNT162b1~~		~~Placebo~~	
	~~Dose 1~~	~~Dose 2~~	~~Dose 1~~	~~Dose 2~~
~~18 55 years of age~~				
~~10 µg dose level~~	~~N=12~~	~~N=12~~	~~N=3~~	~~N=3~~
~~30 µg dose level~~	~~N=12~~	~~N=12~~	~~N=3~~	~~N=3~~
~~100 µg dose level~~	~~N=12~~	~~Not applicable~~	~~N=3~~	~~Not applicable~~

~~Overall, all dose levels exhibited a tolerability and safety profile consistent with modRNA-based vaccines, and a clear dose level response was observed after dose 1 and dose 2 in younger adults. Reactogenicity was generally higher after the second dose, but the symptoms resolved quickly over the course of a few days. The only reports of Grade ≥3 intensity (severe) were 1 case of fatigue in a subject in the 10 µg cohort and 1 case of chills in a single subject in the 30 µg cohort, both after their boost dose. Based on the tolerability profile observed with the 100 µg dose level after the first dose, an internal decision was made not to give a boost dose at 100 µg.~~

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~~Summary of safety in elderly subjects (aged 65 to 85 years) in BNT162-02~~

~~Preliminary safety and tolerability data after the first dose of 10 µg, 20 µg, and 30 µg in adults aged 65 to 85 years (see Table 11) after one dose of BNT162b1 are shown in Figure 2 and Figure 3.~~

~~Table 11: Number of adults aged 65 to 85 years dosed in BNT162-02 (status, June 22nd, 2020)~~

	~~BNT162b1~~		~~Placebo~~	
	~~Dose 1~~	~~Dose 2~~	~~Dose 1~~	~~Dose 2~~
~~65-85 years of age~~				
~~10 µg dose level~~	~~N=12~~	~~N=0~~	~~N=3~~	~~N=0~~
~~20 µg dose level~~	~~N=12~~	~~N=0~~	~~N=3~~	~~N=0~~
~~30 µg dose level~~	~~N=12~~	~~N=0~~	~~N=3~~	~~N=0~~

~~The first dose of BNT162b1 in this age group was generally well tolerated. One episode of severe muscle pain and erythematous rash occurred with mild fever occurred in an 81-year-old man on day 2 after receiving a 20 µg dose, consistent with varicella zoster (shingles). He was prescribed Valacyclovir and this AE was reported as fully resolved within 7 d. The investigator reported this AE as not related to vaccine.~~

~~**Part A**~~

~~**Part B**~~

~~Figure 2: BNT162b1 - Local reactions in younger and elderly subjects~~

~~Panel A - Local reactions after doses 1 and 2 (i.e., prime and boost) of 30 µg BNT162b1 in younger subjects.~~

~~Panel B - Local reactions after dose 1 (i.e., prime) of 10, 20, and 30 µg BNT162b1 in elderly subjects.~~

~~Note: follow-up period for 10 µg and 30 µg groups: +2-4 days.~~

~~Part A (younger adults)~~

~~Part B (Elderly)~~

~~Figure 3: BNT162b1 - Systemic events in younger and elderly subjects Panel A - Systemic events after doses 1 and 2 (i.e., prime and boost) of 30 µg BNT162b1 in younger subjects.~~

~~Panel B - Systemic events after dose 1 (i.e., prime) of 10, 20, and 30 µg BNT162b1 in elderly subjects.~~

~~Note: follow-up period for 10 µg and 30 µg groups: +2-4 days.~~

~~‡ This is the participant that experienced Zoster which was the actual cause of the pain.~~

~~In general terms, the local tolerability of BNT162b1 in elderly subjects seems comparable to that recorded in younger adults. The pattern of systemic reactogenicity appears similar between the two age groups, possibly with a lower overall incidence in the elderly subjects in comparison to the younger adults.~~

Section 2.3.1 (Risk assessment)

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

- The volume of blood drawn will be kept to a minimum and will remain less than that drawn when donating blood (up to approximately ~~568~~ 582 mL blood will be drawn per subject over the complete trial, i.e., over approximately 7 months).
- All trial-specific procedures will be performed by qualified trial site personnel.
- Immunization will be done by a physician.
- Human experience with BNT162 vaccines was not available ~~have not been administered to humans~~ prior to this trial. However, clinical data was available for RNAs formulated with related

Error correction and updating

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but not identical liposomal compositions or non-formulated RNAs and can support risk assessment of the BNT162 vaccines.	
Section 2.2.3 (Chinese trial - BNT162-03) The trial BNT162-03 will be conducted in healthy Chinese adults by Shanghai Fosun Pharmaceutical Development, Inc. (Shanghai, China) and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany). 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 years (younger adults) and >55 years (older adults). Currently the trial has been approved by the Chinese regulatory authorities and trial set up is ongoing. ~~Currently the trial has not been approved and the concrete trial design is under discussion with the Chinese regulatory authorities to ensure alignment with the rapidly progressing overall clinical development and the adequacy of the Chinese trial for regional extension of the potential registrational data package.~~	Updating
Section 2.2.4 (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. Currently trial approval has been requested and trial set up is ongoing.	Updating
Section 2.3.1 (Risk assessment) • The volume of blood drawn will be kept to a minimum and will remain less than that drawn when donating blood (up to approximately ~~568~~ 582 mL blood will be drawn per subject over the complete trial, i.e., over approximately 7 months). • … • Human experience with BNT162 vaccines was not available prior to this trial. However, clinical data was available for RNAs formulated with related but not identical liposomal compositions or non-formulated RNAs and can support risk assessment of the BNT162 vaccines. • ~~BNT162 vaccines have not been administered to humans prior to this trial. However, clinical data is available for RNAs formulated with related but not identical liposomal compositions or non-formulated RNAs and can support risk assessment of the BNT162 vaccines.~~	Updating and correction of an error

Section 2.3.1 (Risk assessment) • Whilst the general risk of effects potentially associated with the innate immune activation and transient secretion of associated cytokines are defined above based on the descr bed data, the dose response-relationship, and thus tolerability for this specific set of vaccine candidates will only be defined by the ongoing trials (this trial BNT162-01 and the US trial BNT162-02, see Section **Error! Reference source not found.**) and the planned Chinese trial (BNT162-0 3, see Section **Error! Reference source not found.**). ~~The clinical experience with administration of the prime dose of BNT162b1 in 36 healthy elderly subjects aged 65 to 85 years in the US trial BNT162-02 is described in Section **Error! R eference source not found.**. The local tolerability of BNT162b1 in elderly subjects aged 56 seemed comparable to that recorded in younger subjects aged 18 to 55 years. The pattern of systemic reactogenicity appeared similar between the two age groups, possibly with a lower overall incidence in the elderly subjects in comparison to the younger subjects at equal doses.~~ ~~The local tolerability of BNT162b1 in elderly subjects aged 56 seemed comparable to that recorded in younger subjects aged 18 to 55 years. The pattern of systemic reactogenicity appeared similar between the two age groups, possibly with a lower overall incidence in the elderly subjects in comparison to the younger subjects at equal doses.~~ The clinical experience after P/B dosing with BNT162b1 at 10, 20, and 30 µg and single doses of BNT162b2 at 10, 20, and 30 µg, in healthy elderly adults aged 65 to 85 years in the US trial BNT162-02 is described in Section 2.2.2. The local tolerability of BNT162b1 and BNT162b2 in elderly adults seemed comparable to that recorded in younger adults aged 18 to 55 years. L kewise, the pattern of systemic reactogenicity appeared similar between the two age groups, possibly with a lower overall incidence in the elderly adults in comparison to the younger adults at equal doses (for details, see Section 2.2.2). Preliminary data in elderly adults, show lower antibody responses in older adults than in younger adults (for details, see Section 2.2.2). The investigation of higher dose range in older adults in this trial is therefore required to support the Phase III program planned to support marketing approval. • When assessing the risk for dosing of older subjects with BNT162 vaccine candidates, the follow information is relevant: – Preliminary data in subjects treated in the ongoing BNT162 trials backed by non-human primate (rhesus macaque) immunogenicity data have shown that BNT162b1 in the tested dose range is immunogenic. – There is risk that older adults may be under dosed with the vaccine doses chosen based on data for younger adults (as was observed for other vaccines) must be mitigated. – Preliminary data in elderly show a comparable to lower reactogenicity based on the observed local reactions and system events in similar doses (see the figures in Section **Error! Reference source not found.**). This observation may indicate a lower i nnate immune activatory capability of elderly, which in turn may mechanistically be associated with lower immunogenicity of dose levels that are immunogenic in the younger adults. – ~~In this trial, the doses to be tested in older adults are within the range already shown to show acceptable tolerability in younger adults.~~ – ~~The planned starting dose with BNT162b1 for older subjects aged 55 to 85 years in this trial (10 µg) is 30% of the dose (30 µg) already shown to be acceptable in the subjects aged 65 to 85 years in the US trial BNT162-02.~~ – In this trial, the P/B BNT162b1 and BNT162b2 doses planned in older adults (10, 20, and 30 µg) are within the range already shown to show acceptable tolerability in younger adults and in elderly adults in the BNT162-02 trial (for details, see Section 2.2.2). This tolerability in elderly adults appears to be better than seen in younger adults at the same doses. – Although using doses already found to show acceptable tolerability in younger adults and an even better tolerability in elderly adults, this trial implements numerous safety measures (e.g., sentinel dosing/staggering of subjects, on-site observation periods after each immunization, wellbeing questioning, frequent on-site visits after immunization).	Updating and correction of an error

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– This trial includes inclusion/exclusion criteria to exclude potential risk factors relevant for all adults, but additional criteria have been included to further protect the safety of enrolled older adults. • The listed risks can be managed using routine symptom driven standard of care as described in Section 6.6.3. Treatment of these events is dependent on the discretion of the investigators. • ~~Since this trial will involve the first immunization of humans with the BNT162 vaccines, the trial subjects in Cohorts 1, 2 and 4 will be immunized using a sentinel dosing/staggering of subjects (EMA 2017 guidance "Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products").~~ • Since this trial involves the first immunization of humans with the BNT162 vaccines, in the FIH cohorts and all dose escalation cohorts use a sentinel dosing/staggering of subjects (EMA 2017 guidance "Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products").	
Section 2.3.1 (Risk assessment) • After each assessment, the SRC may request a prolongation of the observation periods to up to Day 7 for later cohorts. Experience in this ongoing trial and in the ongoing BNT162-02 trial, has confirmed the adequacy of the implemented observations periods. • The expanded SRC will review and evaluate at least the Day 21 data per vaccine to ~~decide whether to progress to Part B, and if yes, define~~confirm what doses will be given in Part B. • The SRC may make recommendations on increasing observation periods and additional subject wellbeing calls may be included at the discretion of the SRC. • To ensure trial subject safety during the trial, their safety will be monitored from Visit 0 (screening) until approximately 6 months after the last immunization.	Updating and correction of an error
Section 2.3.1 (Risk assessment)	Updating and correction of an error
Section 4.3 (Justification for dose) Based on the available clinical and non-clinical data experience, the sponsor expects the planned maximal doses (see Table 1) to be safe. The doses planned in this trial for older adults (i.e., adults aged between 55 and 85 years) reflect clinical data from the ongoing BNT162-01 and BNT162-02 trials with the vaccine candidates BNT162b1 and BNT162b2 in younger adults and elderly (adults aged between 65 and 85 years). After P/B dosing, these doses (10, 20, and 30 µg) showed acceptable tolerability in younger adults and in elderly adults. For details, see Section 2.2.2. Taken together, the planned starting doses in this trial with healthy subjects are considered to be safe, but still sufficient to induce an antiviral immune response.	IEC feedback
Section 5.2.1 (Exclusion criteria Part A) For older subjects: Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors: • … • Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)	IEC feedback

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~~• BMI ≥30 kg/m^2~~ • ….	
Section 5.3 (Lifestyle considerations) Strenuous physical activity will not be allowed on visit days. When at the trial site, trial subjects will not be allowed to smoke or to drink alcohol. For Cohort 1 and any subsequent dose-escalation cohort (in younger adults or older adults), the first 6 subjects dosed in each group will be required to remain at the site for approximately 24 h after the first immunization. The remaining trial subjects in these cohorts will be required to remain at the site for approximately 6 h after the first immunization. For any dose de-escalation or dose-refinement cohorts, i.e., cohorts with doses lower than previously tested and found to be acceptable, trial subjects will be required to remain at the site for approximately 6 h after the first immunization. For all cohorts with P/B dosing (irrespective of whether dose escalation, dose de-escalation, or dose-refinement cohorts), all trial subjects will be required to remain at the site for approximately 6 h after the boost immunization. ~~For Cohorts 1, 2, 4, 7, and 8, the first 6 subjects dosed in each group will be required to remain at the site for approximately 24 h after the first immunization. The remaining trial subjects in these cohorts will be required to remain at the site for approximately 6 h after the first immunization.~~ ~~For cohorts with P/B dosing, all subjects dosed in each group will be required to remain at the site for approximately 6 h after the boost immunization.~~ ~~For Cohort 3, subjects will be required to remain at the site for approximately 6 h after immunization.~~	Updated for clarity
Section 6.6 (Dose modifications) The decision to make dose adaptions or~~,~~ to initiate ~~add~~ a cohort, or to progress to Part B for each vaccine will be made by the SRC (for details, see Section 10.1.5). Dose de-escalation and escalation rules have been defined in this protocol (see Section 6.6.2).	IEC feedback
Section 6.6.1 (Dose limiting toxicity) During the time of enrollment into a given dose escalation cohort in Part A, if any of the following events occur, it will be considered an individual dose limiting toxicity and further dosing in that cohort will be stopped: • Anaphylactic reaction considered related • Generalized urticaria considered related • … • Any fever >40.0°C (>104.0°F) within 7 days of vaccination considered related and confirmed by an investigator or medically qualified person. … The assessment of dose limiting toxicity should be done consistently for all subjects treated with the same treatment and dose. In addition to data entry in the CRF, DLTs will be reported within 24 h via SAE Report Form as described in Section 10.3.1.10 and forwarded to the safety contacts listed in the same section.	Clarification and alignment with other BNT162 trials
Section 6.6.2 (Dose modification guidance/rules) The trial design also allows for: • The selection of which BNT162 vaccine(s) dose regimens and posologies that will be investigated in Part B following a substantial protocol amendment. **Part A** See Section 10.1.5 for the data set upon which SRC decisions described below for Part A are made. ~~**Part A**~~ • The decision to test reduced or intermediate doses will be made for each vaccine independently	IEC feedback

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• … **Part B** The to be tested doses for each vaccine in Part B will be chosen after review of the safety, tolerability, and immunogenicity data from Part A for that vaccine. Relevant safety and tolerability data collected in Part A will be included in the protocol amendment planned to define details of Part B and / or the BNT162 IB.	
Section 8.2.8 (Subject diaries) Trial subjects will be given subject diaries at Visit 1 and be asked to record any ~~AEs~~ reactions between visits, solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) and solicited systemic ~~AEs~~ reactions (nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever [i.e., ≥38°C]).	Alignment with other BNT162 trials
Section 8.2.9 (Assessment of local reactions) Local reactions after IM immunization will be assessed by the investigator at the times given in the SoA (Section 1.3). This information will be used to validate the solicited assessment of local reactions in the patient diary and potentially support AE reporting. Local reactions (both investigator assessed and solicited in the subject diaries) will be graded using ~~the~~ criteria based on the guidance given in US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" for "Local Reaction to Injectable Products" (see the section "Assessment of intensity" in Section 10.3.1.11). ~~This information will be used to validate the solicited assessment of local reactions in the patient diary and potentially support AE reporting.~~	Clarification
Section 8.2.13 (Assessment of systemic reactions) Systemic reactions after IM immunization will be assessed via daily solicited reports in the subject diaries and at the times given in the SoA (Section 1.3). Systemic reactions will be graded using ~~the~~ criteria based on the guidance given in US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" for "Systemic reaction grading scale" (see the section "Assessment of intensity" in Section 10.3.1.11).	Clarification
Section 8.7 (Genetics) A blood sample (blood and / or isolated PBMCs) may be used for HLA typing of a subject to allow additional analysis, e.g., characterization of T cell receptor (TCR) repertoire and/or phenotypic characterization of antigen-specific T cells as further specified in Section 8.8 (Biomarkers). Data generated with these additional analyses may provide information about the HLA dependency of immune response (e.g., if distinct HLA types have stronger / better immune response towards SARS-CoV-2). … Leftover blood after completion of the immunogenicity assessments may be used for the genetic analyses as described here.	IEC feedback and clarification
Section 8.8 (Biomarkers) Samples for biomarker analysis will be retained for use for up to 5 years after the end of the trial. The tube with the sample will be labeled with a number (optionally also with a bar code) to keep the subject's identity confidential; the tube label will not include information that could be used to identify the subject. Results of the blood analyses will be linked to the clinical information collected during the trial using this specific number. The analysis will only be carried out on the basis of the label data and samples. Biomarker samples and all data generated using the samples, will be handled in accordance with applicable laws and regulations; this includes requirements applicable for data protection, for sample shipment outside Germany, and a potential withdrawal of consent.	IEC feedback

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Blood samples will only be used for biomarker analysis if the trial subjects have provided informed consent for this biomarker analysis.	
Section 8.9 (Immunogenicity assessments) • an antibody binding assay, e.g., and assays to characterize antibodies (e.g., affinity, IgG subclass), e.g., ELISA. … … Blood samples will only be used for additional analyses if the trial subjects have provided informed consent for these additional analyses.	Clarification
Section 8.10 (Blood collection) Up to approximately ~~568~~ 582 mL blood will be drawn per subject over the complete trial, i.e., over approximately 7 months.	Error correction
Section 9.4.2 (Primary endpoints) P/B regimens: • Day 1-21 (pre-boost) • Day 1 to 7 • Day 21 (post-boost) - 28 • Day 21 (post-boost) to 50 SD regimens: • Day 1-28 … Local reactions and systemic reactions will be graded using ~~the~~ criteria based on the guidance given in US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (see Section 10.3.1.11). … The analysis of local and systemic reactions will be repeated with a reduced set of terms (called the "comparability analysis"), to facilitate l ke-for-like comparisons between different trials in the clinical development program for BNT162 vaccines.	Corrections of an omission and alignment with other BNT162 trials
Section 9.4.5 (Other safety analyses - Clinical laboratory parameters) Abnormal laboratory results will be graded using ~~the~~ criteria based on the guidance given in US FDA Guidance for Industry 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials' (see Section 10.3.1.11).	Clarification
Section 10.1.5 (Committees - SRC) • ~~Before progression to Part B, review and evaluate both safety and immunogenicity data per vaccine to decide whether to progress to Part B, and if yes, define what doses will be given. The data assessed by the SRC is defined in Section 1.1.~~	IEC feedback
Section 10.3.1 (Definition of AE and TEAE) • An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding that is clinically significant), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.	Alignment with other BNT162 trials

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 10.3.1.1 (Events meeting the AE definition) • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, and which are considered clinically significant in the medical and scientific judgment of the investigator, may be considered as AEs. • Reactogenicity need only be reported as an AE if doing so provides clinically significant information not available elsewhere (such as the solicited reactions listings), e.g., severe reactogenicity lasting longer than the period of solicitation of symptoms in the subject diary. Diagnostic AEs for local and/or systemic reactogenicity, e.g., "injection site reaction" or "flu-like illness", should generally be preferred over AEs reporting of individual signs and symptoms. ~~Only the diagnoses of clinically significant local and/or systemic reactogenicity e.g., injection site reactions need to be reported as AEs (generally, the individual signs and symptoms of local or systemic reactogenicity making up diagnostic AEs are already captured as solicited reactions).~~	Alignment with other BNT162 trials
Section 10.3.1.7 (Recording and Follow-Up of AE and/or SAE - Assessment of AE and/or SAE intensity) The intensity of AEs or SAEs will be graded by the investigator. For further guidance on grading of solicited reactions, please refer to guideline "US FDA Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". Where specific guidance for an adverse event term is not provided, the following general approach should be followed:	Alignment with other BNT162 trials
Section 10.3.1.10 (Reporting of SAEs) All SAEs or DLTs (even if non-serious) which occur in a trial subject during the observation period, whether considered to be associated with trial medication or not, must be reported by the investigator to the sponsor within 24 h following knowledge of the event.	Alignment with other BNT162 trials
Section 10.3.1.11 (Assessments of intensity for solicited local and systemic reactions and laboratory abnormalities - Fever) If a fever of ≥39.0°C is recorded by a subject during the 7-day post-vaccination diary period, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as >40.0°C for recording the trial database. If a participant experiences a confirmed fever >40.0°C, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.	Alignment with other BNT162 trials
Section 10.10 (Protocol amendments) Changes made to the protocol using the protocol amendments are descr bed in detail in the document Protocol Amendment History which is available upon request. This Protocol Amendment History is filed together with the protocol in the trial master file. (The entire Protocol amendments section was made into this standalone Protocol Amendment History) **10.10.5 Protocol amendment no. 05** **Amendment rationale** Amendment 05 address feedback obtained from the PEI and the IEC on protocol version 7.0. Some changes were also implemented to align data collection and reporting in this trial with the data collection and reporting in other trials with BNT162 vaccines candidates (to facilitate data merging). This amendment will be issued after some of the planned trial subjects have already been enrolled into the trial.	Eliminate protocol amendment section taking 30% of the entire protocol length.

1.6 Protocol amendment no. 06

Amendment rationale

Protocol amendment 6.0 implemented three additional cohorts (Cohorts 11, 12, and 13) comprising up to additional 150 trial subjects aged from 18 to 85 years receiving BNT162b2 only.

BNT162b2 has entered a Phase II/III evaluation of efficacy, with the intent to support an application for marketing authorization. The dosing regimen under investigation is two 30 µg BNT162b2 doses given ~21 d apart.

The expansion cohorts implemented by this amendment are intended to provide a more in depth characterization of the adaptive immune responses induced by BNT162b2, associated vaccine safety, and the impact of factors such as subject disposition and dosing posology on humoral and cell-mediated immunity. These cohorts will extend the safety data of BNT162b2 to a broader trial population and thus closer to the vaccine target population.

Moreover, each of these cohorts will add to a more differentiated understanding of the BNT162b2-induced adaptive immune response composed of antigen-specific antibodies, CD4 and CD8 T-cells, with a view to developing insights into the mechanisms by which immunity to SARS-CoV-2 may be induced and factors driving any variability in response. Alternative treatment approaches for difficult to treat or high risk subjects may be determined. In each of these dose cohorts, a broader characterization of T-cell and antibody responses and their inter-individual variation will be performed. This will include the characterization of the dependency of adaptive immune responses on factors such as age and gender.

For further background on the scientific rationale for the expansion cohorts, see Section 4.2 of the protocol.

The planned dose of BNT162b2, two 30 µg BNT162b2 doses given ~21 d apart, the same regime that has already been tested in the dose escalation phase of this trial and in almost 17,000 adult subjects, including those with acute and chronic illnesses, in the ongoing global Phase I/II/III trial BNT162-02/C4591001 (ClinicalTrials.gov NCT: 04368728).

The three expansion cohorts are as follows:

- Cohort 11: Alternative posology cohort with 30 healthy adults who will receive BNT162b2 using one 3 µg prime dose and one 30 µg boost dose of BNT162b2 given approximately 21 d apart (P/B regimen).
- Cohort 12: Adaptive immune response cohort (including safety and long term immune response) with 90 healthy adults who will receive of two 30 µg BNT162b2 doses given approximately 21 d apart (P/B regimen).
- Cohort 13: Population expansion cohort (including safety and long term immune response) with 30 immunocompromised adults who will receive of two 30 µg BNT162b2 doses given approximately 21 d apart (P/B regimen).

This amendment also addresses feedback obtained from the PEI and the IEC on protocol version 8.0.

This amendment also introduces logistical simplifications, i.e., except for Cohorts 1 and 8, the minimum interval between dosed trial subjects has been reduced from 30 min to 15 min for the prime and boost doses in the still to be completed Cohorts 2 to 10 (inclusive). Also, the minimum interval has been set to at least 5 min for the prime and boost doses in Cohorts 11 and 12, and to 15 min (prime) and 5 min (boost for Cohort 13. This simplification/design is considered justified:

- Because all FIH cohorts for the different BNT162 vaccine variants have been completed.
- Due to the extensive experience and exposure already achieved with BNT162 vaccine candidates, including that almost 17,000 trial subjects have been dosed at least once with BNT162b2 (see Table 9 in the protocol).

Further changes were implemented to align data collection and reporting in this trial with the data collection and reporting in other trials with BNT162 vaccines candidates (to facilitate data merging).

This amendment will be issued after some of the planned trial subjects have already been enrolled into the trial.

<table>
<tr><th>Changed text
(inserted text is blue/underlined; deleted text is red/struck out)</th><th>Rationale</th></tr>
<tr><td>Title page

CLINICAL TRIAL PROTOCOL
INCLUDING AMENDMENTS NOS. 01 TO 0506

BNT162-01

<table>
<tr><td>Version:</td><td>8.09.0</td><td>Date:</td><td>21 Jul 05 OCT 2020</td></tr>
<tr><td>Sponsor:</td><td colspan="3">BioNTech RNA Pharmaceuticals GmbH</td></tr>
</table>

<table>
<tr><td>Trial title:</td><td>A multi-site, Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy and immunocompromised adults</td></tr>
<tr><td>Brief title:</td><td>A multi-site Phase I/II trial investigating the safety and effects of four BNT162 vaccines against COVID-19 in healthy and immunocompromised adults</td></tr>
<tr><td>Trial phase:</td><td>Phase I/II</td></tr>
<tr><td>Indication:</td><td>Protection against COVID-19</td></tr>
<tr><td>Product:</td><td>BNT162: SARS-CoV-2 - RNA lipid nanoparticle (RNA-LNP) vaccines utilizing different RNA formats, i.e., non-modified uridine containing messenger RNA (uRNA, called BNT162a1), nucleoside modified messenger RNA (modRNA, two variants, called, BNT162b1 and, BNT162b2), self-amplifying messenger RNA (saRNA, calledand BNT162c2,)</td></tr>
<tr><td>Coordinating and Principal investigator:</td><td>Dr. Dr. med. Armin Schultz, CRS Clinical Research Services Mannheim GmbH, Germany (tel.: +49 621 15045 165)</td></tr>
<tr><td>Trial sites:</td><td>CRO sMultiple sites ites in Berlin and Mannheim,in Germany. For further details of the study sites and site personnel, see the Trial Master File (TMF).</td></tr>
<tr><td>Contract research organization (CRO):</td><td>CRS Clinical Research Services Mannheim GmbH, Germany</td></tr>
<tr><td>Sponsor's responsible person:</td><td>Özlem Türeci, MD, Chief Medical Officer, BioNTech SE</td></tr>
<tr><td>Sponsor:</td><td>BioNTech RNA Pharmaceuticals GmbH, An der Goldgrube 12, 55131 Mainz, Germany</td></tr>
<tr><td>Regulatory identifiers:</td><td>EudraCT no.: 2020-001038-36; ClinicalTrials.gov NCT: 04380701; WHO UTN: U1111-1249-4220</td></tr>
<tr><td>Medical Monitor:</td><td>The sponsor's Medical Monitor name and contact information will be provided separately</td></tr>
</table>
</td><td>Update to reflect the added expansion cohorts, to indicate that that Dr. Schultz is also the coordinating investigator (as well as being the principal investigator at one site), to reflect the increased number of trial sites, and to add the clinicaltrials.gov NCT.</td></tr>
<tr><td>Section 1.1 Trial synopsis
A multi-site, Phase I/II, 2-part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy and immunocompromised adults</td><td>Update to reflect the added expansion cohorts.</td></tr>
</table>

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 1.1 Trial synopsis and Section 3 Objectives and endpoints **Objectives** / **Endpoints** [a] **Primary objective** (All cohorts) To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after single dose (SD; prime only) or prime/boost (P/B) immunization. • Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7~~±1~~ d after each immunization~~.~~ (trial days 8 and 29). • Solicited systemic reactions (nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever) recorded up to 7~~±1~~ d after each immunization~~.~~ (trial days 8 and 29). • The proportion of subjects with at least 1 unsolicited treatment~~-~~emergent adverse event (TEAE): o For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): occurring up to 21~~±2~~ d after the prime immunization (trial day 22) and 28~~±4~~ d after the boost immunization~~.~~ (trial day 50). o For BNT162c2 (SD): The proportion of subjects with at least 1 unsolicited TEAE occurring up to 28~~±4~~ d after the immunization~~.~~ (trial day 29).	Update to reduce duplication, to make the relationship to trials days clearer (but otherwsie without making content changes), and to emphasize that the objective apply to all cohorts including the added expansion cohorts.
Section 1.1 Trial synopsis and Section 3 Objectives and endpoints **Secondary objectives** (All cohorts) To describe the immune response in healthy adults after SD or P/B immunization measured by a functional antibody titer, e.g., virus neutralization test (VNT) or an equivalent assay available by the time of trial conduct. For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): ~~Functional antibody responses~~As compared to baseline at 7~~±1 d~~ and 21~~±2~~ d after primary immunization (trial days 8 and 22) and at 7, 14 [b], 21~~±2 d~~, 28~~±4 d~~, 63~~±5 d~~, and 162~~±7~~ d after the boost immunization~~.~~ (trial days 5 to 9): • Functional antibody responses (titers). • ~~Fold increase in functional antibody titers 7±1 d and 21±2 d after primary immunization and at 21±2 d, 28±4 d, 63±5 d, and 162±7 d after the boost immunization.~~ • ~~Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 28±4 d, 63±5 d, and 162±7 d after the boost immunization.~~ ~~For BNT162c2 (SD):~~ • ~~Functional antibody responses at 7±1 d, 21±2 d, 29±3 d, 42±3 d, 84±5 d, and 183±7 d after the primary immunization.~~ • ~~Fold increase in functional antibody titers at 7±1 d, 21±2 d, 29±3 d, 42±3 d, 84±5 d, and 183±7 d after the primary immunization~~. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline. For BNT162c2 (SD): As compared to baseline at 7~~±1 d~~, 21~~±2 d, 29±3 d~~, 28, 42~~±3 d~~, 84~~±5 d~~, and 183~~±7~~ d after the primary immunization (trial days 8 to 184): • Functional antibody responses (titers). • Fold increase in functional antibody titers • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline.	Update to reduce duplication, to make the relationship to trials days clearer (but otherwsie without making content changes), and to emphasize that the objective apply to all cohorts including the added expansion cohorts.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 1.1 Trial synopsis and Section 3 Objectives and endpoints	Update to clarify that the endpoint assessments outputs may be concentrations or titers, to reduce duplication, to make the relationship to trials days clearer (but otherwsie without making content changes), to emphasize that the objective apply to all cohorts including the added expansion cohorts.

Exploratory objectives	
(All cohorts) To describe the immune response in healthy adults after SD or P/B immunization measured by an antibody binding assay, e.g., enzyme-linked immunosorbent assay (ELISA) or an equivalent assay available by the time of trial conduct.	For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B~~):~~) ~~Antibody responses~~As compared to baseline at 7~~±1 d~~ and 21 ~~±2~~ d after primary immunization (trial days 8 and 22) and at 7, 14 [b], 21~~±2 d, 29±3 d~~, 28, 63~~±5 d~~, and 162~~±7~~ d after the boost immunization. (trial days 8 to 184). • Antibody responses measured (concentrations/titers). • Fold increase in antibody ~~titers at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 29±3 d, 63±5 d, and 162±7 d after the boost immunization.~~(concentrations/titers). • Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody ~~titers as compared to baseline at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 29±3 d, 63±5 d, and 162±7 d after the boost immunization~~concentrations/titers. For BNT162c2 (SD) As compared to baseline at 7, 21, 28, 42, 84, and 183 d after the primary immunization (trial days 8 to 184): • Antibody responses ~~at 7±1 d, 21±2 d, 29±3 d, 42±3 d, 84±5 d, and 183±7 d after the primary immunization.~~measured (concentrations). • Fold increase in antibody ~~titers at 7±1 d, 21±2 d, 29±3 d, 42±3 d, 84±5 d, and 183±7 d after the primary immunization.~~(concentrations). • Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody ~~titers as compared to baseline at 7±1 d, 21±2 d, 29±3 d, 42±3 d, 84±5 d, and 183±7 d after the primary immunization~~concentrations.

<table>
<tr><th>Changed text
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<tr><td>Section 1.1 Trial synopsis and Section 3 Objectives and endpoints

<table>
<tr><td>Additional exploratory objectives
(Only for the Expansion cohorts [Cohorts 11 to 13])
To further characterize the long term adaptive immune response after P/B immunization with 30 µg BNT162b2.</td><td>As compared to baseline at 7 and 21 d after primary immunization (trial days 8 and 22) and at 7, 14 [b], 21, 28, 63, and 162, 343, 525, and 708 d after the boost immunization (trial days 8 to 730).
• Functional antibody titers measured (e.g.) using VNT.
o Measured cross-neutralization of viruses from other coronavirus families.
• Further assays for:
o Antibody-dependent cellular cytotoxicity (ADCC)
o Antibody induced phagocytosis.
o Immune cell degranulation.
o Activation of immune cells such as lymphocytes and granulocytes.
o Antibody mediated uptake and formation of immune complexes.</td></tr>
<tr><td>Additional exploratory objectives only for the Expansion cohorts [Cohorts 11 to 13])
To further characterize the long term adaptive immune response after P/B immunization with 30 µg BNT162b2.</td><td>As compared to baseline at 364, 546, and 729 d after the primary immunization (trial days 365 to 730):
• Functional antibody titers measured (e.g.) using VNT.
o Antibody responses measured (titers).
o Fold increase in antibody titers.
o Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers.
• Functional antibody binding concentrations measured (e.g.) using ELISA.
o Antibody responses measured.
o Fold increase in antibody titers.
o Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers.
• CMI responses measured (e.g.) using ELISpot and ICS.</td></tr>
</table>
</td><td>Update to reflect the added expansion cohorts.</td></tr>
<tr><td>Section 1.1 Trial synopsis and Section 3 Objectives and endpoints

<table>
<tr><th>Objectives</th><th>Endpoints [a]</th></tr>
<tr><td>(Only for the Expansion cohorts [Cohorts 11 to 13])
To further characterize the adaptive immune response: Assessment of cell-mediated immunity</td><td>• Further characterization of vaccine and SARS-CoV-2 specific antigen-specific CD4 and CD8 T-cells, e.g., using ELISpot, ICS.
• Functional characterization of T-cells (e.g. antigen dependent cytokine secretion, activation, proliferation, cytotoxicity, determination of human leukocyte antigen [HLA] restriction).
• Cellular and molecular phenotyping of immune cells using e.g., immunophenotypic characterization of T-cells to define reactive T-cell subsets.
• Bulk or single cell T-cell receptor (TCR) and transcriptome sequencing, quantitative polymerase chain reaction (qt-PCR) studies to profile and characterize and track TCRs and quantify the number of antigen-specific T-cells.</td></tr>
</table>
a) The given days are approximate; the respective schedule of activities defines assessment windows.
b) Only cohorts starting prime dosing after approval of amendment 09.

The additional exploratory objectives apply for subjects included in the expansion cohorts in addition to all primary, secondary, and exploratory endpoints defined for other trial subjects.</td><td>Update to reflect the added expansion cohorts.</td></tr>
</table>

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 1.1 Trial synopsis and Section 4.1 Overall design ~~Four different vaccines (BNT162a1, BNT162b1, BNT162b2, and BNT162c2) will be tested. Note: Currently, dosing with this dose has been deferred. Dosing may be resumed if disease prevention data for the other vaccine candidates suggest the need for additional vaccine candidates. This trial has two parts. Part A is for dose ranging with dose escalation and de-escalation plus the evaluation of interim dose levels. It also includes dose ranging in older subjects. Part B is dedicated to recruit expansion cohorts with dose levels which are selected from data generated in Part A.~~ This trial has two parts. Part A and Part B. Due to changes in the overall clinical development plan, Part B will no longer be conducted. The objective originally described for Part B have been implemented in the ongoing development via a pivotal Phase I/II/III trial BNT162-02/C4591001 (ClinicalTrials.gov NCT: 04368728). Part A is for dose ranging of four different vaccines (BNT162a1, BNT162b1, BNT162b2, and BNT162c2) will be undertaken with dose escalation and de-escalation plus the evaluation of interim dose levels. It also includes dose ranging in older subjects.	Update to reflect the added expansion cohorts.
Section 1.1 Trial synopsis and Section 4.1 Overall design BNT162b2, for which the dose regimen has been determined in the dose ranging in Part A of this trial, has now entered efficacy evaluation in the ongoing development via a pivotal Phase I/II/III trial BNT162-02/C4591001 (ClinicalTrials.gov NCT: 04368728). Therefore, for BNT162b2, amendment 09 of this trial introduces expansion cohorts designed to expand the existing safety profiling to a broader population and to enable detailed characterization of the adaptive immune responses, including determine factors that impact them. These cohorts will involve healthy and immunocompromised populations treated according to the selected dosing posology and exploring an alternative posology. The chosen trial design reflects discussion and advice from the Paul-Ehrlich Institute (PEI) obtained in scientific advice meetings held in February, March, and June 2020 in response to a fast-changing situation.	Update to reflect the added expansion cohorts.
Section 1.1 Trial synopsis and Section 4.1 Overall design ***Part A*** The first part of the trial (Part A) will follow a dose escalation design. Discretionary dose de-escalation and refinement is also planned. Part A will consist of a screening/treatment phase and a follow-up phase. Dose ranging cohorts: Trial subjects with the first-in-human [FIH] immunization will be immunized using a sentinel…	Update to introduce the screening, treatment, and follow-up phases.

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Section 1.1 Trial synopsis and Section 4.1 Overall design For any subsequent dose escalation cohorts (to doses higher than the maximum already tested for a vaccine candidate), the sentinel/subject staggering process will be as follows: • Two sentinel subjects will be dosed on one day (with intervals of at least 30 min between subjects). • If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 4 further subjects will be dosed (with intervals of at least ~~30~~ 15 min between subjects). • If the dosing in these 4 subjects was considered to be safe and well tolerated by the investigator based on 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48 h data from the sentinel subjects): ○ The remaining 6 subjects in the group will be dosed (with intervals of at least ~~30~~ 15 min between subjects). ○ … The maximum allowed dose for each vaccine candidate is defined in the Table 1. For the planned dose de-escalation cohorts, 12 subjects may be dosed on one day (with intervals of at least ~~30~~ 15 min between subjects). The doses in these cohorts in younger adults must be lower than doses than doses that have shown acceptable tolerability in younger adults (based on the data from 12 subjects up until 48 h after the first dose). The same dose will not be administered twice, i.e., in two cohorts.	Reduction of intervals between subjects for logistical reasons (given the now available clinical experience with BNT162b2 immunization)
Section 1.1 Trial synopsis and Section 4.1 Overall design For BNT162b1 and BNT162b2, administration of the planned dose escalation cohorts in older adults (Cohorts 9 and 10), 12 subjects will be dosed using a sentinel dosing/subject staggering (2-4-6) process with intervals of at least 30 min between subjects. The doses planned in these cohorts will only be administered if the dose is confirmed by the SRC. The doses planned for Cohorts 8 to 10 are defined in Table 2. For the unplanned dose de-escalation cohorts, i.e., where the SRC requests the use of a reduced dose for safety reasons, 12 subjects may be dosed on one day with intervals of at least ~~30~~ 15 min between subjects (as for planned de-escalation cohorts). Note: BNT162b1 and BNT162b2 are nucleoside modified uridine RNAs, while BNT162a1 and BNT162c2 are both ~~nucleoside~~non-modified ~~pseudomethyl~~ uridine containing RNAs. RNA modification is known to impact the extent of innate immune activation at a given dose level, and thus potentially the extent of reactogenicity. Therefore, tolerability data obtained with one of the vaccine variants of each of these pairs may be potentially informative for the respective other one and should be taken in consideration by the SRC for recommendations of lower or interim doses.	Reduction of intervals between subjects for logistical reasons (given the now available clinical experience with BNT162b2 immunization). Correction of an error.

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Section 1.1 Trial synopsis and Section 4.1 Overall design Expansion cohorts: Protocol amendment 6.0 implemented three additional cohorts (Cohorts 11, 12, and 13) comprising additional 150 trial subjects aged from 18 to 85 years receiving BNT162b2 only. BNT162b2 has entered a Phase II/III evaluation of immunogenicity and efficacy, with the intent to support an application for marketing authorization. The dosing regimen under investigation is two 30 µg BNT162b2 doses given ~21 d apart. The expansion cohorts are intended to provide a more in depth characterization of the adaptive immune responses induced by BNT162b2, associated vaccine safety, and the impact of factors such as subject disposition and dosing posology on humoral and cell-mediated immunity. These cohorts will extend the safety data from Part A for of BNT162b2 to a broader trial population and thus closer to the vaccine target population. Moreover, each vaccine candidate individually. Part Bof these cohorts will add to a more differentiated understanding of the BNT162b2-induced adaptive immune response composed of antigen-specific antibodies, CD4 and CD8 T-cells, with a view to developing insights into the mechanisms by which immunity to SARS-CoV-2 may be initiatedinduced and factors driving any variability in response. Alternative treatment approaches for one difficult to treat or more vaccines while Part A is still ongoing, depending on the available data. high risk subjects may be determined. In each of these dose cohorts, a broader characterization of T-cell and antibody responses and their inter-individual variation will be performed. This will include the characterization of the dependency of adaptive immune responses on factors such as age, HLA haplotype, body mass index (BMI) and gender. The planned dose of BNT162b2, two 30 µg BNT162b2 doses given 21 d apart, is the same regimen that has already been tested in the dose escalation phase of this trial and in almost 17,000 adult subjects, including those with acute and chronic illnesses, in the ongoing global Phase I/II/III trial BNT162-02/C4591001 (ClinicalTrials.gov NCT: 04368728). As such, all trial subjects in the three expansion cohorts can be treated in parallel. For Cohort 13, the interval between prime immunizations will be at least 15 min. For prime immunization in Cohorts 11 and 12 and for all cohorts after the boost immunization, the interval will be at least 5 min. The three expansion cohorts (with comparable numbers of male and female subjects for each of the defined age groups, see the section Population below) are as follows: • Cohort 11: Alternative posology cohort with 30 healthy adults who will receive BNT162b2 using one 3 µg prime dose and one 30 µg boost dose of BNT162b2 given approximately 21 d apart (P/B regimen). • Cohort 12: Adaptive immune response cohort (including safety and long term immune response) with 90 healthy adults who will receive two 30 µg BNT162b2 doses given approximately 21 d apart (P/B regimen). • Cohort 13: Population expansion cohort (including safety and long term immune response) with 30 immunocompromised adults who will receive of two 30 µg BNT162b2 doses given approximately 21 d apart (P/B regimen). For the scientific rational for the expansion cohorts, see Section 4.2. All trial site visits for subjects in the expansion cohorts will be conducted on an outpatient basis, with the clinical judgment of the investigator determining whether a period of observation beyond that required for completion of study procedures is required, on a case by case basis. Standard measures to avoid cross-contamination of immunocompromised individuals with high risk pathogens should be followed for 24 months after the primary immunization.	Update to reflect the added expansion cohorts.

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Section 1.1 Trial synopsis and Section 4.1 Overall design ***Part B*** ~~Part B will only be started if approved using a substantial protocol amendment.~~ ~~Details of Part B will be defined using a protocol amendment after thorough evaluation of immunogenicity and safety data from Part A for each vaccine candidate individually. Part B may be initiated for one or more vaccines while Part A is still ongoing, depending on the available data.~~ ~~Safety data to be evaluated includes the package used by the SRC to assess individual dose levels and in addition any other safety observations that may be reported until the data cut off. Immunogenicity of all doses will be thoroughly assessed.~~ ~~The protocol amendment will include a summary of relevant safety and tolerability data collected in Part A. This protocol amendment will also include Part B specific inclusion/exclusion criteria, objectives/endpoints, a description of the planned statistical analyses, and descriptions of any added trial assessments and procedures.~~ ~~Part B will use a randomized, placebo-controlled design in the likely target population (e.g., higher risk populations such as immunocompromised populations). Part B may employ a surrogate marker as a measure of vaccine efficacy.~~ Due to changes in the overall clinical development plan, Part B will no longer be conducted.	Update to reflect the deletion of Part B. The objectives originally described for Part B have been implemented in the ongoing development via a pivotal Phase I/II/III trial (BNT162-02 / C4591001).
Section 1.1 Trial synopsis and Section 4.1 Overall design **Table 1: ~~Summary of~~Dose ranging: vaccine dose regimens for younger adults aged 18 to 55 years in Part A (Cohorts 1 to 7)** **Part A – Cohort numbers & Dose (µg) (12 subjects per cohort)** **Vaccine / mRNA type** | **Vaccine-encoded antigen** | **Vaccine IM dosing regimen** | **1 Starting dose** | **2** | **3 De-escalation dose** | **4** | **5 Optional de-escalation dose** | **6** | **7** BNT162a1 / uRNA | RBD of the SARS-CoV-2 S protein | Prime: Day 1 Boost: Day 22 | **1A 3 µg** [b] | 2A 0.6 µg [a] | 3A 0.1 µg | 4A [a] 2 µg [e] | 5A 0.3 µg | 6A 1 µg | BNT162b1 / modRNA | RBD of the SARS-CoV-2 S protein | Prime: Day 1 Boost: Day 22 | 1B 10 µg | 2B 30 µg | 3B 1 µg | **4B 60 µg** [d] | 5B 50 µg | 6B 3 µg | 7B 20 µg BNT162b2 / modRNA | Modified version of the full length SARS-CoV-2 S protein | Prime: Day 1 Boost: Day 22 | 1C 10 µg | 2C 30 µg | 3C 1 µg | **4C** [a] **60 µg** [d] | 5C [a] 20 µg | 6C [a] 3 µg | 7C [a] 50 µg BNT162c2 / saRNA | Modified version of the full length SARS-CoV-2 S protein | Prime only: Day 1 | 1D 0.1 µg | 2D 0.3 µg | 3D 0.1 µg to <3 µg [c] | 4D 1 µg | 5D [a] 0.6 µg | **6D** [a] **3 µg** [d] | BNT162c2 / saRNA | Modified version of the full length SARS-CoV-2 S protein | Prime: Day 1 Boost: Day 22 | 1E 0.1 µg | 2E [a] 0.3 µg | 3E ~~0~~.1 µg ~~to ≤3 µg~~ [c] | **4E** [a] 1~~3~~ **µg** | 5E [a] 0.6 µg | 6E [a] ~~3~~5-10 µg [d] | 7E 5-10 µg [a] All dose escalation doses used must be judged acceptable by the Safety Review Committee (SRC) before use. [b] Status 08 JUN 2020: This cohort was set on hold by the SRC after 6 subjects had been received their Day 1 dose, furthermore the SRC decided not to perform Day 22 dosing for these 6 subjects. Due to this hold, the starting dose is also the maximum dose. [c] Specific doses to be defined, but in the range given. Already given doses will not be repeated. [d] The planned maximum doses per vaccine candidate. [e] Dosing with this vaccine variant has been put on hold. Dosing may be resumed if disease prevention data for the other vaccine candidates suggest the need for additional vaccine candidates. IM = intramuscular; RBD = Receptor Binding Domain; S protein = SARS-CoV-2 spike protein; tbd = to be defined. Note: Currently, dosing with BNT162a1 has been deferred. Dosing may be resumed if disease prevention data for the other vaccine candidates suggest the need for additional vaccine candidates.	Updated to reflect implemented doses changes and the terminology „dose ranging“.

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Section 1.1 Trial synopsis and Section 4.1 Overall design **Table 2: ~~Summary of~~Dose ranging: vaccine dose regimens for older adults aged 56 to 85 years in Part A (Cohorts 8 to 10)**	Updated to reflect implemented doses changes and the terminology „dose ranging“. Update correct typos, to reflect deletion of Section 2.2, and to align the tolerabiliyt across sections.

Vaccine / mRNA type	Vaccine-encoded antigen	Vaccine IM dosing regimen	Part A – Cohort numbers & Dose (µg) (12 subjects per cohort)[a]		
			8 Older adults	9 Older adults	10 Older adults
BNT162b1 / modRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	8B 10 µg	9B[a] 20 µg	10B[a] 30 µg
BNT162b2 / modRNA	Modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	8C 10 µg	9C[a] 20 µg	10C[a] 30 µg

[a] All dose escalation doses used must be judged acceptable by the Safety Review Committee (SRC) before use.
IM = intramuscular; RBD = Receptor Binding Domain; S protein = SARS-CoV-2 spike protein.

Note: The doses planned in this trial for older adults (i.e., adults aged between 55 and 85 years) reflect clinical data from the ongoing BNT162-01 and BNT162-02 trials with the vaccine candidates BNT162b1 and BNT162b2 in younger adults (aged between 18 and 55 years) and elderly (adults aged between 65 and 85 years). For details, see ~~Section~~ the BNT162 IB.

BNT162b1:

- BNT162b1 P/B doses of 1, 10, 30, and 50 µg showed acceptable tolerability in younger adults.
- Based on the tolerability profile after the prime dose at 60 µg (BNT162-01 trial) and 100 µg (BNT162-02 trial), the respective boost doses were not administered.
- BNT162b1 P/B doses of 10, 20, and 30 µg showed acceptable tolerability in elderly adults. This tolerability appears to be better than seen in younger adults at the same doses.

~~BT162b2~~BNT162b2:

- BNT162b2 P/B doses of 1, 10, and 30 µg showed acceptable tolerability in younger adults.
- ~~BNT16b2~~BNT162b2 P/B doses of 10, 20, and 30 µg showed acceptable tolerability in elderly adults. This tolerability appears to be better than seen in younger adults at the same doses.

Based on the tolerability data summarized above, and the implemented safety measures (sentinel/staggered subject dosing, post-dose observations period, wellbeing questioning, etc.) as described in the section Risk assessment, the planned doses in older subjects in this trial are expected to show acceptable tolerability.
Based on the available immunogenicity data after dosing with BNT162b1 and BNT162b2 in younger adults in the BNT162-02 trial (see the ~~section~~),BNT162 IB), the doses planned in this trial in older subjects are expected to show lower but measurable immunogenicity than in younger adults.
Altogether, the doses planned in older subjects in this trial are considered adequate to support the trial objectives and to pose an acceptable risk to trial subjects.

Section 1.1 Trial synopsis and Section 4.1 Overall design **Table 3: Expansion cohorts for BNT162b2 (age 18 to 85 years) in Part A (Cohorts 11 to 13)**	Update to reflect the added expansion cohorts.

Vaccine / mRNA type	Vaccine-encoded antigen	Vaccine IM dosing regimen	Part A –– Cohort numbers & Dose (µg) (number subjects per cohort)		
			11C (N = 30) Healthy adults (Alternative posology)	12C (N = 90) Healthy adults (Adaptive immune response cohort)	13C (N = 30) Immunocompromised but otherwise healthy adults (Population expansion cohort)
BNT162b2 / modRNA	Modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	3 µg 30 µg	30 µg 30 µg	30 µg 30 µg

S protein = SARS-CoV-2 spike protein.

Section 1.1 Trial synopsis **Trial duration** ~~In total, the planned trial duration is expected to be approximately 12 months. From screening visit (Visit 0) to the last visit (Visit 8 [BNT162c2 [SD]; Visit 9 BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B)]), each trial subject will be in the trial for maximally 223 d.~~ In total, the planned trial duration (i.e., the sum of the screening, treatment, and follow-up phases) for subjects is expected to be approximately 214 d for Cohorts 1 to 10 and 738 d Cohorts 11 to 13. For logistical reasons, investigation of the different vaccines may not be able to start at the same time.	Update to reflect the added expansion cohorts.

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Section 1.1 Trial synopsis **Population** ~~Healthy adults aged 18 to 55 years (Cohorts 1 to 7; younger adults) or aged 56 to 85 years (Cohorts 8 to 10; older adults). Subjects aged 56 to 85 years must be enrolled such that at least 6 subjects per cohort are aged 65 to 85 years (i.e., are elderly).~~ ~~For each vaccine, 12 subjects are required for each of the cohorts planned in Part A. See Table 3 for the total number of subjects for each vaccine assuming all cohorts planned in Table 1 and Table 2 are performed.~~ ~~The planned number of trial subjects in Part B will be calculated based on the data from Part A and defined in a protocol amendment.~~ Dose ranging Cohorts (Cohorts 1 to 10) • Healthy adults aged 18 to 55 years (Cohorts 1 to 7; younger adults) or aged 56 to 85 years (Cohorts 8 to 10; older adults). Subjects aged 56 to 85 years must be enrolled such that at least 6 subjects per cohort are aged 65 to 85 years (i.e., are elderly). For each vaccine, 12 subjects are required for each of the dose ranging cohorts. Expansion cohorts (Cohorts 11 to 13) • Cohort 11 - Alternative posology cohort: 30 healthy adults aged 18 to 85 years with comparable numbers of male and female subjects for each of the following age groups: 18 to 55 years, 56 to 85 years (15 per age group). • Cohort 12 - Adaptive immune response cohort: 90 healthy adults, with comparable numbers of male and female subjects for each of the following age groups: 18 to 55 years, 56 to 65 years, and 65 to 85 years (30 per age group). • Cohort 13 - Population expansion cohort: 30 immunocompromised adults aged 18 to 85 years with comparable numbers of male and female subjects for each of the following age groups: 18 to 55 years, 56 to 85 years (15 per age group). Table 3: Overview of the total number of subjects for each vaccine in Part A **Vaccine / mRNA type** | **Vaccine dosing regimen** | **Maximum number of subjects (assuming all cohorts planned in Table 1 are performed)** BNT162a1 / uRNA | Prime/Boost | 72 (6 cohorts) BNT162b1 / modRNA | Prime/Boost | 120 (10 cohorts) BNT162b2 / modRNA | Prime/Boost | 270 ~~120~~ (13 ~~10~~ cohorts) BNT162c2 / saRNA | Prime only | 72 (6 cohorts) BNT162c2 / saRNA | Prime/Boost | 84 ~~72~~ (7 ~~6~~ cohorts)	Update to reflect the added expansion cohorts. Correction of an error.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 1.1 Trial synopsis and Section 5.1.1 **Key inclusion criteria** Volunteers are only elig ble to be enrolled in the trial if they meet the following criteria: • For younger adult cohorts, volunteers must be aged 18 to 55 years, have a BMI over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0. OR For older adult cohorts, volunteers must be aged 56 to 85 years, have a BMI over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0. OR For the immunocompromised adult cohort (Cohort 13), volunteers must be aged 18 to 85 years, have a BMI over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0. They must be healthy, in the clinical judgment of the investigator, based on medical history, physical examination, 12-lead ECG, vital signs (systolic/diastolic blood pressure, pulse rate, body temperature, respiratory rate), and clinical laboratory tests (blood chemistry, hematology, and urine chemistry) at Visit 0. Note: Healthy volunteers with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. OR For the immunocompromised cohort (Cohort 13); volunteers who have previously received solid organ transplant, or peripheral blood stem cell transplantation ≥6 months after transplantation, or individuals with human immunodeficiency virus (HIV) infection with a CD4+ T-cell count of ≥200 x 106 /L. Individuals with lower T-cell counts will be excluded from the trial on the basis that this represents a significant medical complication. In the clinical judgment of the investigator, volunteers must be immunocompromised but otherwise healthy. After consultation with the Medical Monitor, this may include individuals receiving immunosuppressant therapy due to another confounding disease at least 2 wks prior to enrollment and/or at least 6 wks following immunization with BNT162b2, and/or individuals with immunosuppressive treatment of an autoimmune disease if the disease is stable.	Update to reflect the added expansion cohort with immuno-compromised subjects.

Section 1.1 Trial synopsis **Key exclusion criteria** Volunteers are excluded from the trial if they present any of the following criteria: • Have had any acute illness… • Have a known allergy, hypersensitivity, … • Had any medical condition or any major surgery (e.g., requiring general anesthesia) within the past 5 years which, in the opinion of the investigator, could compromise their wellbeing if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments. See the inclusion criteria for non-excluded medical conditions for Cohort 13. • Have any surgery planned during the trial, … • Had any chronic use (more than 21 continuous days) of any systemic medications, including immunosuppressants or other immune-modifying drugs (except for Cohort 13), within the 6 … • Regular receipt of inhaled/nebulized corticosteroids (except for cohort 13). • Had any vaccination within the 28 d prior to Visit 0. • Had administration of any immunoglobulins and/or any blood products within the … • Had administration of another IMP including vaccines within 60 d or 5 half-lives … • Have a known history or a positive test offor any of HIV 1 or 2, Hepatitis B, or Hepatitis C, or (except for Cohort 13) HIV 1 or 2 within the 30 d prior to Visit 0. • Have a positive PCR-based test for SARS-CoV-2 within the 30 d prior to Visit 1. • Previously participated in an investigational trial involving lipid nanoparticles. • Have a history (within the past 5 years) of substance abuse or known medical… • Have a history of hypersensitivity or serious reactions to previous vaccinations. • Have a history of Guillain-Barré syndrome within 6 wks following a previous vaccination. • Have a history of narcolepsy. • (Except for Cohort 13) Have a history of or suspected immunosuppressive condition, acquired or congenital, as determined by medical history and/or physical examination at Visit 0. • Have symptoms of the coronavirus disease 2019 (COVID-19), e.g., respiratory symptoms, … • Have had contact with persons diagnosed with COVID-19 or who tested positive… • Are soldiers, ~~subjects~~volunteers in detention, CRO or sponsor staff or their family members. • For older ~~subjects~~volunteers and for Cohort 13: Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors: ○ Hypertension ○ Diabetes mellitus ○ Chronic obstructive pulmonary disease ○ Asthma ○ Chronic liver disease ○ Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2) ○ ~~Anticipating the need for immunosuppressive treatment within the next 6 months~~ ○ Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies. ○ Sickle cell disease ○ Cancer (except for cohort 13) ○ Are immune compromised due to stem cell or organ-transplantation with significant medical complications such as acute or chronic graft rejection or graft versus host disease requiring intensive immunosuppressive treatment within the next 6 months, transplant failure or infectious complications or other conditions that would be considered a contraindication for vaccination. ○ Are immune compromised due to HIV infection with a $CD4^+$ count of < 200 x 10^6 /L at screening or significant medical complications such as opportunistic infections, malignant complications (e.g., lymphoma, Kaposi sarcoma), other organ manifestations consistent	Update to reflect the added expansion cohort with immuno-compromised subjects.

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with advanced acquired immunodeficiency syndrome (AIDS) or other conditions that would be considered a contraindication for vaccination. ○ Resident in a long-term facility. ○ Current vaping or smoking (occasional smoking is acceptable). ○ History of chronic smoking within the prior year.	

Section 5.2.1 **Key exclusion criteria** Volunteers are excluded from the trial if they present any of the following criteria: 1. Have had any acute illness… 2. Have a known allergy, hypersensitivity, … 3. Had any medical condition or any major surgery (e.g., requiring general anesthesia) within the past 5 years which, in the opinion of the investigator, could compromise their wellbeing if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments. See the inclusion criteria for non-excluded medical conditions for Cohort 13. 4. Have any surgery planned during the trial, … 5. Had any chronic use (more than 21 continuous days) of any systemic medications, including immunosuppressants or other immune-modifying drugs (except for Cohort 13), within the 6 … 6. Regular receipt of inhaled/nebulized corticosteroids (except for cohort 13). 7. Had any vaccination within the 28 d prior to Visit 0. 8. Had administration of any immunoglobulins and/or any blood products within the … 9. Had administration of another IMP including vaccines within 60 d or 5 half-lives … 10. Have a known history or a positive test offor any of HIV 1 or 2, Hepatitis B, or Hepatitis C, or (except for Cohort 13) HIV 1 or 2 within the 30 d prior to Visit 0. 11. Have a positive PCR-based test for SARS-CoV-2 within the 30 d prior to Visit 1. 12. Previously participated in an investigational trial involving lipid nanoparticles. 13. Have a history (within the past 5 years) of substance abuse or known medical… 14. Have a history of hypersensitivity or serious reactions to previous vaccinations. 15. Have a history of Guillain-Barré syndrome within 6 wks following a previous vaccination. 16. Have a history of narcolepsy. 17. (Except for Cohort 13) Have a history of or suspected immunosuppressive condition, acquired or congenital, as determined by medical history and/or physical examination at Visit 0. 18. Have symptoms of the coronavirus disease 2019 (COVID-19), e.g., respiratory symptoms, … ... … 26. Have had contact with persons diagnosed with COVID-19 or who tested positive… 27. Are soldiers, ~~subjects~~volunteers in detention, CRO or sponsor staff or their family members. 28. Regular receipt of inhaled/nebulized corticosteroids. 29. For older ~~subjects~~volunteers and for Cohort 13 only: Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors: ○ Hypertension ○ Diabetes mellitus ○ Chronic obstructive pulmonary disease ○ Asthma ○ Chronic liver disease ○ Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2) ○ ~~Anticipating the need for immunosuppressive treatment within the next 6 months~~ ○ Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies. ○ Sickle cell disease ○ Cancer (except for cohort 13) ○ Are immune compromised due to stem cell or organ-transplantation with significant medical complications such as acute or chronic graft rejection or graft versus host disease	Update to reflect the added expansion cohort with immuno-compromised subjects.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
requiring intensive immunosuppressive treatment within the next 6 months, transplant failure or infectious complications or other conditions that would be considered a contraindication for vaccination. ○ Are immune compromised due to HIV infection with a $CD4^+$ count of < 200 x 10^6 /L at screening or significant medical complications such as opportunistic infections, malignant complications (e.g., lymphoma, Kaposi sarcoma), other organ manifestations consistent with advanced acquired immunodeficiency syndrome (AIDS) or other conditions that would be considered a contraindication for vaccination. ○ Resident in a long-term facility. ○ Current vaping or smoking (occasional smoking is acceptable). ○ History of chronic smoking within the prior year.	
Section 1.1 Trial synopsis and Section 6.1 IMP administered **Trial treatments** **Dosage levels:** See **Error! Reference source not found.**. The planned dose per vaccine candidate will not exceed the pre-defined maximum doses (see **Error! Reference source not found.**). ~~Part B expansion cohorts:~~ ~~The to-be-tested doses will be chosen after review of the safety, tolerability, and immunogenicity data from Part A. Part B will only be started if approved using a substantial protocol amendment.~~	Update to reflect the deletion of Part B.
Section 1.1 Trial synopsis and Section 5.2.1 **Statistics** ~~The statistical analysis will be performed once all subjects have been enrolled and completed all visits according to the SoA (Section 1.3).~~ ~~No formal interim statistical analysis will be performed. However, the statistical analysis may be performed in the following sequence separately for each type: once all subjects in the respective group have been followed-up for at least 21 d and once all subjects have discontinued the trial, respectively.~~ The final analysis will be performed once all subjects have completed the End of Treatment (EoT visit; Visit 7). An analysis update will be performed once all subjects will have completed the last planned visit. No formal interim statistical analysis will be performed. However, preliminary analyses based on all data collected until a pre-defined data cut-off date (snapshot analyses) may be performed for each cohort once subjects within a cohort will have been followed up for at least 7 d following each dose. ~~The planned protocol amendment will include a description of the planned statistical analyses planned for Part B.~~	Update to reflect the deletion of Part B. Update to reflect the addition of expansion cohorts.

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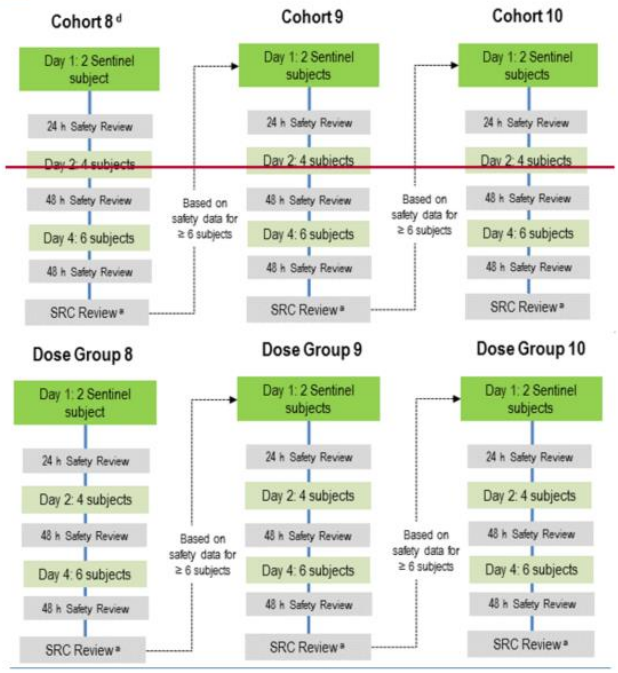
Section 1.1 Trial synopsis **Schema** *Cohorts 8 to 10 with older adults*  a) The data assessed by the SRC for progressing comprises 48 h data for 6 subjects. b) Subjects will be dosed using a sentinel dosing/subject (2-4-6) staggering process unless the planned dose is the same or lower than previously found to show acceptable tolerability (in which case, all subjects may be dosed on one day). c) For the dose regimens, see Table 1 and Table 2.	Update to reflect the addition of expansion cohorts and the dose ranging terminology.

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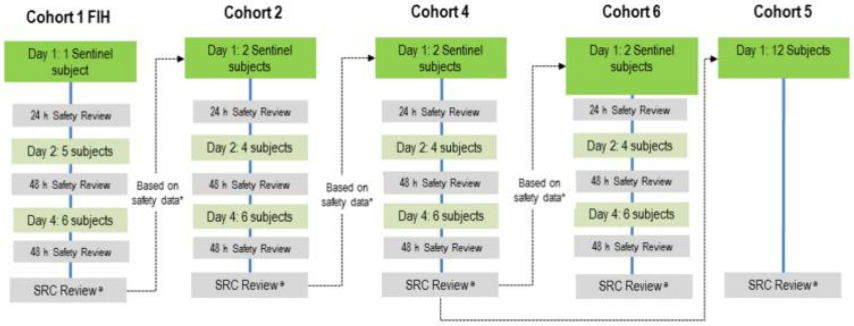
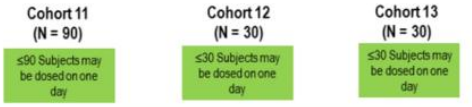
Section 1.1 Trial synopsis **Schema** **Dose ranging cohort schema for BNT162c2 (SD) [b]**  a) The data assessed by the SRC for progressing comprises 48 h data for 6 subjects. b) For the dose regimens, see Table 1. **Expansion cohorts - Cohorts 11 to 13 [a]**  a) For the dose regimens, see Table 3. **Figure 1: Graphical depiction of the dose-finding process in Part A** FIH = First-in-humans; h = hour(s); SRC = Safety Review Committee.	Update to reflect the addition of expansion cohorts.
Section 1.1 Trial synopsis - Table 5 	Procedure / Assessment	Visit 0	Visit 1 Pre-dose	Visit 1 (Post-) dDosing & Post-dose	Visit 2 at 24±2h	Phone call at 48±2h	Visit 3	Visit 4 Pre-dose	Visit 4 Dosing & Post-dose	Phone call at 48±2h	Visit 5 ~7 d from Visit 4	Visit 5a	Visit 6 ~21 d from Visit 4	Visit 7 ~28 d from Visit 4 (EoT Visit)	Visit 8 ~63 d from Visit 4 (FU Visit)	Visit 9 ~162 d from Visit 4 (FU Visit)
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Day [h]	-30 to 0	1	1	2		8	22	22		29	36 [q]	43	50 [r]	85	184
Days to last dose [h]		0	0			7	21	0		7	14	21	28	63	162
Blood draw for clinical laboratory (15 mL) [f]	X ~~(15 mL)~~	X ~~(15 mL)~~		X ~~(15 mL)~~		X ~~(15 mL)~~				X ~~(15 mL)~~			X ~~(15 mL)~~		
Blood draw for viral screening [g]	X (5 mL)														
Blood draw for SARS-CoV-2 testing [k]	X (2.6 mL)														
Oral swipe for SARS-CoV-2 testing		X [m]													
Allocation to IMP		X													
Immunization [i]			X [r]					X							
Blood draw for immunogenicity (10 mL) [n]		X ~~(10 mL)~~				X ~~(10 mL)~~	X ~~(10 mL)~~			X ~~(10 mL)~~	X	X ~~(10 mL)~~	X ~~(10 mL)~~	X ~~(10 mL)~~	X ~~(10 mL)~~
Blood draw for HLA			X (4 mL EDTA-blood) [p]												
Blood draw for CMI (100 mL) [n, o]		X								X					
~~Blood draw for research~~			~~← Up to 5 blood draws for explorative biomarker/immunogenicity research purposes. Blood draw volumes may vary. The total blood volume drawn will not exceed 200 mL per subject over the complete trial, i.e., over approximately 7 months. →~~												
Blood draw for research												X (≤100 mL)		X (≤50 mL)	X (≤50 mL)		Update to reflect the addition of expansion cohorts.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 1.1 Trial synopsis - Table 5 transpeptidase, total bilirubin, blood urea nitrogen, glucose, lipase, sodium, potassium, calcium; (Hematology) hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count. Only in women who are not WOCBP (to confirm postmenopausal status): follicle stimulating hormone at Visit 0. g Viral screening for human immunodeficiency virus (HIV) 1 or 2, hepatitis B, hepatitis C. h Flexibility for visit days: Visit 3 Day 8±1 d; Visit 4 Day 22±2 d; Visit 5 Day 29±3 d; Visit 6 Day 43±4 d; Visit 7 Day 50±4 d; Visit 8 Day 85±7 d; Visit 9 Day 184±9d. i Only for the first 6 subjects per group. Questioning on and documentation of AEs as well as systemic and local reactions, the latter in case of upcoming dose decision meetings. j Only IMP-related AEs and any SAEs. k Blood draw for anti-SARS-CoV-2 antibodies (samples will be stored until a test is commercially available). l For Cohorts 1 and 8, immunization with at least 1 h intervals between subjects for the first 6 subjects and then with of at least 30 min intervals for the remaining 6 subject. For all other cohorts, immunization with at least ~~30~~ 15 min intervals between subjects and for the boost injections. m Oral swipe for SARS-CoV-2 testing either on Day -1 or at the Visit 1 on Day 1. n The listed blood draw days may be adapted if justified by the collected data. Leftover blood after completion of the immunogenicity assessments may be used for additional analyses as described in Section 8.7 (Genetics) and/or Section 8.8 (Biomarkers). o For subjects who have given consent, one aliquot of the blood sample drawn for analysis of CMI may be used for HLA typing to allow additional analysis of T-cell receptor repertoire and / or phenotypic characterization of T-cells specific to vaccine-encoded antigens. p If HLA typing using the blood sample collected with Lithium Heparin is not conclusive, EDTA-blood will be drawn for HLA testing. q Only cohorts starting prime dosing after approval of protocol amendment 06. r When entering the follow-up phase, i.e., after completing the EoT visit, subjects are allowed to participate in other clinical trials not investigating COVID-19 vaccines or treatments. Notes: If the boost dose is not administered or if trial subjects permanently discontinued from IMP administration, subjects will complete all assessments planned for that visit and for the EoT Visit as listed in the SoA. The additional Visit 5a added by protocol amendment 06 will only apply for subjects who give consent.	Update to reflect the addition of expansion cohorts.
Section 1.1 Trial synopsis - Table 6 **Procedure/Assessment** | **Visit 0** | **Visit 1 Pre-dose** | **Visit 1 Dosing & Post-dose** | **Visit 2 at 24±2h** | **Phone call at 48±2 h** | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6 (EoT Visit)** | **Visit 7 (FU Visit)** | **Visit 8 (FU Visit)** **Day** [a] | **-30 to 0** | **1** | **1** | **2** | | **8** | **22** | **29** | **43** [q] | **85** | **184** Blood draw for HLA testing [p] | | X (4 mL EDTA-blood) | | | | | | | | | | Blood draw for CMI testing (100 mL) [l, m] | | X | | | | | | X | | | | ~~Blood draws for research~~ | | ← ~~Up to 5 blood draws for explorative biomarker/immunogenicity research purposes. Blood draw volumes may vary. The total blood volume drawn will not exceed 200 mL per subject over the complete trial, i.e., over approximately 7 months.~~ → | | | | | | | | | | Blood draws for research | | | | | | | | | X (≤100 mL) | X (≤50 mL) | X (≤50 mL) Subject hotline availability | Start | => | => | => | | => | => | => | => | => | End Issue subject diaries | | X | | X | | X | X | X | | | | Collect subject diaries | | | | X | X [o] | X | X | X | X | | | Record AEs since last visit | | X | | X | | X | X | X | X | X [n] | X [n] Local reaction assessment/ systemic events | | | X [d] | X | | X | X | X | | | | Concomitant medication | X | X | | X | | X | X | X | X | | | Subject wellbeing questioning | | | | | X [o] | | | | | | | a Flexibility for visit days: Visit 3 Day 8±1 d; Visit 4 Day 22±2 d; Visit 5 Day 29±3 d; Visit 6 Day 43±4 d; Visit 7 Day 85±7 d; Visit 8 Day 184±9d. b Brief (symptom-directed) physical examination; no height measurement. c Vital signs: systolic/diastolic blood pressure, pulse rate, respiratory rate, and body temperature; body weight only Visit 0. d At 1, 3, and 6 h (±15 min) after immunization. e Urine screening for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cocaine, cannabinoids, opiates, methadone, methamphetamines, phencyclidine, tricyclic antidepressants). f Dipstick urine analysis: glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrite, and leukocytes. Microscopic urinalysis: if warranted by dipstick results, urine sediment will be microscopically examined for the presence of red blood cells, white blood cells, casts, crystals, epithelial cells, and bacteria. g Clinical laboratory tests: (Chemistry) alkaline phosphatase, creatinine, ferritin, C-reactive protein, albumin, alanine aminotransferase, amylase, aspartate aminotransferase, gamma glutamyl transpeptidase, total bilirubin, blood urea nitrogen, glucose, lipase, sodium, potassium, calcium; (Hematology) hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count. Only in women who are not WOCBP (to confirm postmenopausal status): follicle stimulating hormone at Visit 0. h Viral screening for human immunodeficiency virus (HIV) 1 or 2, hepatitis B, hepatitis C. i Blood draw for anti-SARS-CoV-2 antibodies. j Oral swipe for SARS-CoV-2 testing either on Day -1 or at the Visit 1 on Day 1. k For Cohort 1, immunization with at least 1 h intervals between subjects for the first 6 subjects and then with at least 30 min intervals for the remaining 6 subjects. For all other cohorts, immunization with ~~30~~ 15 min intervals between subjects. l The listed blood draw days may be adapted if justified by the collected data. Leftover blood after completion of the immunogenicity assessments may be used for additional analyses as described in Section 8.7 (Genetics) and/or Section 8.8 (Biomarkers). m For subjects who have given consent, one aliquot of the blood sample drawn for analysis of CMI may be used for human leukocyte antigen typing to allow additional analysis of T-cell receptor repertoire and / or phenotypic characterization of T-cells specific to vaccine-encoded antigens. n Only IMP-related AEs and any SAEs. o Only for the first 6 subjects per group. Questioning on and documentation of AEs as well as systemic and local reactions, the latter in case of upcoming dose decision meetings. p If HLA typing using the blood sample collected with Lithium Heparin is not conclusive, EDTA-blood will be drawn for HLA testing. q When entering the follow-up phase, i.e., after completing the EoT visit, subjects are allowed to participate in other clinical trials not investigating COVID-19 vaccines or treatments.	Update to reflect the addition of expansion cohorts.
Section 1.1 Trial synopsis - Table 7 Addition of Table 7.	Update to reflect the addition of expansion cohorts.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section - Trial-specific abbreviations/terms Elderly (adults) — As defined in ICH E7, individuals aged 65 years or older Older (adults) — Defined in this document to be individuals aged 56 to 85 years VNT — Virus neutralization test Younger (adults) — Defined in this document to be individuals aged 18 to 55 years	Clarification
Section 2.2 Trial rationale Some of the prophylactic BNT162 vaccines against SARS-CoV-2 investigated in this trial are under investigation ~~(BNT162-02) or will be investigated~~ in other ~~clinical~~ongoing trials (see Table 4 ~~BNT162-03~~). The status and preliminary results from all of these are trials are summarized in the following sections. Table 8 (Status of ongoing and planned clinical trials) was updated to reflect the status on 24 SEP 2020.	Update to reflect the current status.
Section 2.2.1 This trial (BNT162-01) - Preliminary results Given the rapidly changing situation, this section deleted and crossreferences inserted to the current BNT162 IB which contains the current reference safety information.	
Section 2.2.2 US trial BNT162-02 - Preliminary results Given the rapidly changing situation, this section deleted and crossreferences inserted to the current BNT162 IB which contains the current reference safety information.	
Section 2.2.3 Chinese trial - BNT162-03 Given the rapidly changing situation, this section deleted and crossreferences inserted to the current BNT162 IB which contains the current reference safety information.	
Section 2.2.4 BNT162-04 for BNT162b3 Given the rapidly changing situation, this section deleted and crossreferences inserted to the current BNT162 IB which contains the current refrence safety information.	

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Section 2.3.1 Risk assessment The risks linked to the trial-specific procedures and connected mitigations are as follows: • The volume of blood drawn will be kept to a minimum and will remain less than that drawn when donating blood ~~(up to approximately 582 mL blood will be drawn per subject over the complete trial, i.e., over approximately 7 months)~~: ○ For subjects in Cohorts 1 to 10, up to approximately 592 mL blood will be drawn per subject over the complete trial, i.e., over approximately 223 d. ○ For subjects in Cohorts 11 to 13, up to approximately 1022 mL blood will be drawn per subject over the complete trial, i.e., over approximately 760 d. • All trial-specific procedures will be performed by qualified trial site personnel.	Update to reflect the addition of expansion cohorts. Update to reflect the addition of Visit 5a for still to be started cohorts.
Section 2.3.1 Risk assessment • Due to the IM route the risk of systemic reactions is considered low. • ~~An IM vaccine based on modRNA encapsulated into a related but not identical vaccination has reported mostly mild to moderate, mostly local solicited AEs (mostly injection site pain) of 1-3 d duration that resolved without intervention. Fever was the only systemic solicited AE (Feldman et al. 2019).~~ • As with other vaccines, and with single stranded RNA being an innate immune sensor-agonist, BNT162 vaccine administration may cause temporary headache, fatigue or loss of appetite. Rarely, with certain prophylactic vaccines (e.g., as seen for vaccines using attenuated viruses) severe allergic reactions or neurological side effects, such as seizures, were seen. Although these rare side effects are a concern, the risk of a vaccine causing serious harm or death is considered to be extremely small, in particular for BNT162 vaccines, which are molecularly defined, highly purified, subunit vaccines. • The available non-clinical data of BNT162a, BNT162b, and BNT162c suggest a favorable safety profile with events that are mild and mostly related to the mode-of-action and the RNA-intrinsic stimulation of innate immune sensors. • Based on the available clinical and non-clinical data on the individual components (uRNA, modRNA, saRNA, the specific LNP formulation), that are combined within the BNT162 products, a favorable safety profile of BNT162 products is expected with mild and localized effects (see the BNT162 IB for details on these trials). ○ ~~IV administration to cancer patients of uRNA in a different liposomal formulation (i.e., uRNA-LPX) had a favorable safety profile. In these trials, systemic exposure at doses up to 400 µg to uRNA-LPX IV was tolerated. In line with the transient secret on of a distinct range of cytokines observed in these patients, the AE profile was found to be dominated by mild to moderate flu-like symptoms, e.g., pyrexia and chills. These immune modulation-related AEs started within 2-6 h after IV injection, resolved within 24 h.~~ ○ ~~Non-formulated uRNA administered in oncological trials intradermally or injected into inguinal lymph nodes was tolerated with only occasional and mild local reactions. Systemic reactions after local application were not observed.~~ ○ ~~Non-formulated modRNA administered in buffer into tumor lesions of cancer patients was tolerated with occasional mild local reactions. Systemic reactions after local application were not observed.~~	Update to reflect the now available clinical experience with BNT162 vaccine immunization.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 2.3.1 Risk assessment To date, ~~there is limited~~ based on available clinical experience with BNT162 vaccines in human subjects ~~(see Section 2.2)~~. ~~• Reactogenicity is anticipated and considered to contribute to the mode of action of inducing vaccine immune responses. Initial dose ranging studies have suggested AE profiles consistent with previous usage of similar constructs in cancer patients, with AEs generally dividing into 2 groups: local injection site reactions and systemic flu like illness.~~ ~~• As summarized in Section 2.2.1 and Section 2.2.2, to date most of the AEs reported after immunization with BNT162 vaccine candidates in the ongoing trials have been mild to moderate in intensity and no SAEs have been reported. Fever of severe intensity has been reported. Most AEs were managed with simple measures and resolved spontaneously.~~ • Generally, good tolerability was observed. Overall, many of the reported TEAEs appear to be similar to reactogenicity events anticipated for IM-administered vaccines, typically with an onset within first 24 h post immunization. All events / 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. Most TEAEs were managed with simple measures and resolved spontaneously. • The adverse reactions (AEs for which there is a reason to conclude that the vaccine caused the events) identified for BNT162 vaccines at this time are: injection site pain, fever, fatigue, headache, chills, and muscle pain. • Whilst the general risk of effects potentially associated with the innate immune activation and transient secretion of associated cytokines are defined above based on the described data, the dose response-relationship, and thus the tolerability for this specific set of vaccine candidates will only be defined by the ongoing trials (this trial BNT162-01, and the US trial BNT162-02, and the planned Chinese trial BNT162-03 (see ~~Section 2.2~~ the BNT162 IB). • The clinical experience after P/B dosing with BNT162b1 at 10, 20, and 30 µg and single doses of BNT162b2 at 10, 20, and 30 µg, in healthy elderly adults aged 65 to 85 years in the US trial BNT162-02 is described in ~~Section 2.2.2~~ the BNT162 IB. • The local tolerability of BNT162b1 and BNT162b2 in elderly adults seemed comparable to that recorded in younger adults aged 18 to 55 years. Likewise, the pattern of systemic reactogenicity appeared similar between the two age groups, possibly with a lower overall incidence in the elderly adults in comparison to the younger adults at equal doses (for details, see ~~Section 2.2.2~~ the BNT162 IB). • Preliminary data in elderly adults, show lower but measurable antibody responses in older adults than in younger adults (for details, see ~~Section 2.2.2~~ the BNT162 IB). The investigation of higher dose range in older adults in this trial ~~is~~ may therefore be required to support the Phase III program planned to support marketing approval.	Update to reflect the now available clinical experience with BNT162 vaccine immunization.
Section 2.3.1 Risk assessment When assessing the risk for dosing of older subjects with BNT162 vaccine candidates in this trial, the follow information is relevant: • Preliminary data in subjects treated in the ongoing BNT162 trials backed by non-human .. • The risk that older adults may be under dosed with the vaccine doses chosen based on … • Preliminary data in elderly show a comparable to lower reactogenicity based on the ... • In this trial, the P/B BNT162b1 and BNT162b2 doses planned in older adults (10, 20, and 30 µg) are within the range already shown to show acceptable tolerability in younger adults and in elderly adults in thethis trial and/or BNT162-02 trial (for details, see ~~Section 2.2.2~~ the BNT162 IB). This tolerability in elderly adults appears to be better than seen in younger adults at the same doses.	Update to reflect the deletion of Part B.

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Section 2.3.1 Risk assessment To further ensure trial subject safety during dose ranging cohorts, the trial protocol foresees that: • On -site observation periods after each immunization (i.e., 24 h for the first 6 subjects…	Update to reflect the addition of expansion cohorts.
Section 2.3.1 Risk assessment • After each assessment, the SRC may request a prolongation of the observation periods to up to Day 7 for later cohorts. Experience in this ongoing trial and in the ongoing BNT162-02 trial, has confirmed the adequacy of the implemented observations periods. • ~~The expanded SRC will review and evaluate at least the Day 21 data per vaccine to confirm what doses will be given in Part B.~~ • The SRC may make recommendations on increasing observation periods and … • To ensure trial subject safety during the trial, their safety will be monitored from … For the expansion cohorts: • Due to the extensive experience and exposure already achieved with BNT162b2 at 30 µg in the ongoing global Phase II/III trial (from which frequent, rolling safety data submissions to health authorities are being made) the measures implemented for dose ranging cohorts are deemed unnecessary for the expansion cohorts (by 24 SEP 2020, almost 17,000 trial subjects have been dosed at least once with BNT162b2, see Table 9). • Immunocompromised individuals are considered at increased risk from infection with SARS-CoV-2 and of infections in general. Risk minimization measures already in place for the protection of all subjects in this trial are also considered sufficient to protect this increased risk group, who are generally regarded as ambulatory in nature. Care should however be taken to avoid unnecessary extension of on site time and site visits for these subjects, to minimize their risk of exposure to high risk pathogens.	Update to reflect the addition of expansion cohorts.
Section 4.1.2 Planned number of trial subjects ~~**In Part A**~~ ~~For each vaccine, 12 subjects are required for each of the cohorts planned in Part A. See Table 3 for the total number of subjects for each vaccine assuming all cohorts planned in Table 1 and Table 2 are performed.~~ ~~**In Part B**~~ ~~The planned number of trial subjects in Part B will be calculated based on the data from Part A and defined in a protocol amendment.~~ See Table 4.	Update to reflect the addition of expansion cohorts.

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Section 4.2 Scientific rationale for the trial design Trial subjects in Cohort 1 (with the FIH immunization), will be immunized using a sentinel dosing/staggering of subjects (EMA 2017 guidance “Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products”). ~~Part B of the trial will follow after evaluation of the Part A. Part B will be used to define the optimal final dose with respect to safety and immunogenicity for further evaluations in Phase III trials. Part B will also investigate vaccine administration in vulnerable populations (e.g., elderly, immunocompromised populations, and other fragile populations, and/or indicated populations.~~ The expansion cohorts (Cohorts 11 to 13) are designed to be complementary to the ongoing global Phase I/II/III trial BNT162-02/C4591001 (ClinicalTrials.gov NCT: 04368728), to demonstrate clinical efficacy and safety for two 30 µg BNT162b2 doses given ~21 d apart, which will enroll over 40’000 subjects. The Phase I/II/III trial does not include the detailed immunogenicity assessments needed to better understand the mode-of-action of the vaccine and approaches for potential improvements, e.g., in defined populations (by age, gender, immunocompromised status, certain ethnicity-associated HLA, etc.). This trial will therefore include such immunogenicity assessments, including detailed characterization of immune responses to BNT162b2 in respect of binding antibodies, neutralizing antibodies, and cell-mediated immunity, including evaluation of CD4 and CD8 T-cell responses. Cohort 11 aims to determine whether a lower prime dose may further improve vaccine tolerability (reactogenicity), without compromising immunogenicity whilst exploring whether this alternative posology promotes a more favorable pattern of composite immune response modulation. A lower prime dose may further improve reactogenicity and may modulate the pattern of the composite immune response towards a more pronounced B cell response. This alternative posology, if proven effective, could support future ring-vaccination strategies and substantial dose efficiencies. The latter could be important during the scale-up phase at the beginning of a pandemic. It has previously been demonstrated for non-RNA vaccines that an asymmetric prime-boost strategy does not adversely impact the resulting immunogenicity. The use of a lower prime dose may enable optimization of the initial CMI response, when it is most beneficial for acute patient protection, without compromising the overall humoral response. This cohort will include long term monitoring of the immune response and immune-defense. Cohort 12 is intended to complement the ongoing Phase II/III evaluation of efficacy by including assessment of the immune mechanisms induced by this unique class of vaccine. The data from this cohort addresses the expected dynamic range of inter-individual variability and could provide insights into treatment success factors and/or development strategies for future vaccine candidate design/selection for the current pandemic and future COVID-19 outbreaks. This cohort will include long term monitoring of the immune response and immune-defense. Cohort 13 will comprise immunocompromised adults, a population that has a particular risk in the current pandemic for contracting COVID-19 and for severe complications. The reactogenicity but also the immune response to BNT162b2 may be dampened in immunocompromised individuals. This cohort will show whether the immune response is indeed compromised and if yes to which extent and in which of its components and thus allow rational approaches to also serve this population of subjects. It is crucial that the priority vaccination of high risk populations is supported by data demonstrating that vaccination will be well tolerated and clinically beneficial. BNT162b2 was selected for Phase II/III evaluation of efficacy, in part, due to its superior performance in elderly subjects, who typically demonstrate lower reactogenicity than younger subjects, but also lower levels of immunogenicity than younger subjects. The objective of Cohort 13 is to characterize the immune responses in a population with both the age-related lower immunogenicity and the lower immunogenicity linked to being immunocompromised. This knowledge could help guide future treatment optimization strategies. This cohort will include long term monitoring of the immune response and immune-defense. Part B of the trial will no longer be conducted due to changes in the global clinical development plan in a rapidly evolving situation.	Update to reflect the addition of expansion cohorts.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 4.3 Justification for dose The doses planned in this trial were discussed with the PEI in a Scientific Advice Meeting on February 6th, 2020. At this meeting, the PEI supported the high-level design of this trial, conditional to dose exploration and, if appropriate, re-consideration of the dose regimens for Part B. This protocol reflects this advice. ~~Based on non-clinical data of the RNA components (uRNA, modRNA, saRNA), with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this trial, the sponsor expects that doses in the 1 to 5 µg range will be immunogenic and induce neutralizing antibodies. We further expect that 3 to 10 fold higher doses will be required to elicit a stronger antibody response.~~ As discussed in Section 2.3.1, to date, there is very limited clinical experience with BNT162 vaccines in human subjects. Reactogenicity is anticipated and considered to contribute to the mode-of-action of inducing vaccine immune responses. Initial dose ranging studies have suggested AE profiles consistent with previous usage of similar constructs in cancer patients, with AEs generally dividing into 2 groups: local injection site reactions and systemic flu-like illness. As summarized in ~~Section 2.2.1 and Section 2.2.2~~ the BNT162 IB, to date most of the AEs reported after immunization with BNT162 vaccine candidates have been mild to moderate in intensity and no SAEs have been reported. Fever of severe intensity has been reported. Most AEs were managed with simple measures and resolved spontaneously. Based on the available clinical and non-clinical data experience, the sponsor expects the planned maximal doses (see Table 1) to be safe. The doses planned in this trial for older adults (i.e., adults aged between 55 and 85 years) reflect clinical data from the ongoing BNT162-01 and BNT162-02 trials with the vaccine candidates BNT162b1 and BNT162b2 in younger adults and elderly (adults aged between 65 and 85 years). After P/B dosing, these doses (10, 20, and 30 µg) showed acceptable tolerability in younger adults and in elderly adults. For details, see ~~Section 2.2.2~~ the BNT162 IB. The dosing regimen planned in this trial for the expansion cohorts (Cohort 12 and 13), two 30 µg BNT162b2 doses given ~21 d apart (P/B regimen), is the dosing regimen currently being tested in the ongoing global Phase II/III trial BNT162-02. Status 24 SEP 2020, almost 17,000 trial subjects have been dosed with 30 µg BNT162b2 P/B. Cohort 12 will explore an alternative posology with low dose prime (3 µg) and standard dose boost (30 µg) as described elsewhere. Taken together, the planned starting doses in this trial ~~with healthy subjects~~ are considered to be safe, but still sufficient to induce an antiviral immune response.	Update to reflect the addition of expansion cohorts.
Section 4.4 End of treatment (EoT) and end of trial definition ~~A trial subject is considered to have completed the trial if they have completed all planned visits including the EoT Visit, and the two follow-up visits as listed in the SoA (see Section 1.3).~~ ~~The EoT is defined as the date the last subject completed the EoT Visit.~~ A trial subject is considered to have completed the trial if they have completed all planned visits as listed in the SoA, including all follow-up visits (see Section 1.3). The EoT is defined as the date the last subject completed the EoT Visit (for BNT162c2 given SD Visit 6, for all cohorts with P/B dosing Visit 7). The end of trial is defined as the date when the last subject completed the last planned visit given in the SoA (see Section 1.3).	Clarification given the addition of expansion cohorts.
Section 5.1.2 Inclusion criteria Part B This entire section was deleted.	Update to reflect the deletion of Part B.

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Section 5.3 Lifestyle considerations Strenuous physical activity will not be allowed on visit days. When at the trial site, trial subjects will not be allowed to smoke or to drink alcohol. Trial subjects will be required to practice social distancing and to follow good practices to reduce their chances of being infected or spreading COVID-19, e.g., as described in the WHO guidance "Protection measures for persons who are in or have recently visited (past 14 days) areas where COVID-19 is spreading" or regional equivalents. Trial subjects will be warned to avoid contact with persons tested positive for SARS-CoV-2 antibodies or those who have an increased risk for infection. *Dose ranging (Cohorts 1 to 10)* For Cohort 1 and any subsequent dose-escalation cohort (in younger adults or older adults), the first 6 subjects dosed in each group will be required to remain at the site for approximately 24 h after the first immunization. The remaining trial subjects in these cohorts will be required to remain at the site for approximately 6 h after the first immunization. For any dose de-escalation or dose-refinement cohorts, i.e., cohorts with doses lower than previously tested and found to be acceptable, trial subjects will be required to remain at the site for approximately 6 h after the first immunization. For all cohorts with P/B dosing (irrespective of whether dose escalation, dose de-escalation, or dose-refinement cohorts), all trial subjects will be required to remain at the site for approximately 6 h after the boost immunization. Trial subjects will be warned to avoid contact with persons tested positive for SARS-CoV-2 antibodies or those who have an increased risk for infection. *Expansion for BNT162b2 (Cohorts 11 to 13)* For Cohorts 11 to 13, all trial subjects will not be required to remain at the site beyond the time required for all trial-visit-related procedures to be completed. Care should be taken with Cohort 13 subjects (immunocompromised) to minimize duration of site visits. ~~Trial subjects will be warned to avoid contact with persons tested positive for SARS-CoV-2 antibodies or those who have an increased risk for infection.~~ ~~Trial subjects will be required to practice social distancing and to follow good practices to reduce their chances of being infected or spreading COVID-19, e.g., as described in the WHO guidance "Protection measures for persons who are in or have recently visited (past 14 days) areas where COVID-19 is spreading" or regional equivalents.~~	Update to reflect the addition of expansion cohorts.
Section 6.3 Measures to minimize bias: randomization and blinding Not applicable for Part A. ~~Details for Part B will be defined using a protocol amendment.~~	Update to reflect the deletion of Part B.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 6.5 Concomitant therapy Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest) that the trial subject receives during the trial, i.e., starting after Visit 0 and until ~~Visit 8 (BNT162c2) or Visit 9 (BNT162a1, BNT162b1, BNT162b2)~~ the EoT Visit, must be recorded along with the: • Reason for use • Dates of administration including start and end dates • Dosage information including dose and frequency The sponsor's Medical Monitor should be contacted if there are any questions r… Trial subjects must abstain from taking prescription or non-prescription drugs …. Trial subjects are required to agree to not be vaccinated during the trial, starting after Visit 0 … Nonsteroidal anti-inflammatory drugs (NSAIDs), e.g., p~~P~~aracetamol/acetaminophen at doses of up to 4 g/day is permitted for use any time during the trial. Other concomitant medication may be considered on a case by case basis by the investigator, if required after consultation with the sponsor's Medical Monitor.	Simplification and alignment with Section 6.6.1 (Dose limiting tolerability).
Section 6.6.1 Dose limiting toxicity *Applicable to dose ranging cohorts only* During the time of enrollment into a given dose escalation cohort in Part A, if any of the following events occur, it will be considered an individual dose limiting toxicity and further dosing in that cohort will be stopped: • Anaphylactic reaction considered related. • Generalized urticaria considered related. • Four trial subjects in that cohort with any severe unsolicited local event, if … • AEs within 7 d of vaccination assessed by the investigator to be potentially … • Any systemic SAE within 7 d of vaccination that is assessed by the investigator… • Any fever >40.0°C (>104.0°F) within 7 d of vaccination considered related and confirmed by an investigator or medically qualified person. • Two trial subjects (at any dose level) with the same or similar severe (Grade 3 or higher) AE or reactogenicity (including clinically significant laboratory abnormalities) within 7 d of vaccination, considered related, or for which there is no alternative, plausible, attributable cause (for severity grading of AEs see Section 10.3.1.7).	Update to reflect the addition of expansion cohorts.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 6.6.2 Dose modification guidance/rules ~~The trial design also allows for:~~ ~~• The selection of which BNT162 vaccine(s) dose regimens and posologies that will be investigated in Part B following a substantial protocol amendment.~~ **Part A** See Section 10.1.5 for the data set upon which SRC decisions described below for Part A are made. • The decision to test reduced or intermediate doses will be made for each vaccine independently. • Any proposal to alter the planned escalation dose, or to test an additional de-escalation dose, must be approved by the SRC. Dose escalation: • Dose escalation will only continue if the previous dose was considered safe and well tolerated by the SRC. • Any proposal to alter the planned escalation doses must be approved by the SRC. ~~Part B~~ ~~The to be tested doses for each vaccine in Part B will be chosen after review of the safety, tolerability, and immunogenicity data from Part A for that vaccine.~~ ~~Relevant safety and tolerability data collected in Part A will be included in the protocol amendment planned to define details of Part B and / and / or the BNT162 IB.~~	Update to reflect deletion of Part B.
Section 7.1 Discontinuation of trial treatment In rare instances, it may be necessary for a trial subject to permanently discontinue IMP administration (i.e., to not receive the boost dose for groups with P/B regimens). If IMP administration is definitively discontinued, the trial subject will remain in the trial to be evaluated for safety. For cohorts with P/B dosing, if the boost dose is not administered, subjects should still complete all assessments planned in the SoA (Section 1.3). IMP administration must be stopped if dose limiting toxicities described in Section 6.6.1 are observed. If any of the above are observed, an unscheduled safety analysis by the SRC will be required. Trial subjects who tolerated initial vaccinations will be allowed to receive a second vaccination during this time. Trial subjects permanently discontinued from IMP administration will complete all assessments planned for that visit and for the EoT Visit as listed in the SoA (Section 1.3). In the event of discontinuation of trial treatment, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of trial treatment or also from trial procedures, post-treatment follow-up, and/or future collection of additional information. Trial subjects permanently discontinued from IMP administration will complete all assessments planned for that visit and for the EoT Visit as listed in the SoA (Section 1.3).	Update for clarification.
Section 7.1.1 Temporary discontinuation Not applicable. For the Cohorts 11 to 13 (inclusive), temporary delays to the boost doses due to intercurrent illness (i.e., immunization with the boost dose within 1 wk of the scheduled day) are allowed.	Update for clarification.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 7.2 Trial subject discontinuation/withdrawal from the trial If possible, permanently discontinued trial subjects will: • Complete all assessments planned for that visit and for the EoT Visit ~~Visit 6~~, if discontinued on a visit day. • Complete all assessments planned for the EoT Visit ~~Visit 6~~, if not discontinued on a visit day.	Update to reflect the addition of expansion cohorts.
Section 8.3.1 Time period and frequency for collecting AE and SAE information ~~All AEs and SAEs will be collected from the date of subject consent until discharge from the trial at Visit 8 (BNT162c2 [SD]) or Visit 9 (BNT162a1, BNT162b1, BNT162b2, BNT162c2 [P/B]).~~ ~~All SAEs (initial and follow-up reports) will be recorded and reported to the sponsor or designee within 24 h after becoming aware of the event, as indicated in Section 10.3.1.10.~~ For Cohorts 1 to 10, all AEs and SAEs will be collected from the date of subject consent until discharge from the trial only IMP-related AEs and any SAEs will be collected. For Cohorts 11 to 13, all AEs and SAEs will be collected from the date of subject consent until Visit 7. Thereafter, at Visits 8 and 9 only IMP-related AEs and any SAEs will be collected. At Visits 10, 11, and 12, only any SAEs will be collected.	Update to reflect the addition of expansion cohorts.
Section 8.3.3 Follow-up of AEs and SAEs All ongoing AEs/SAEs will be followed until resolution, considered by the investigator to be stable or chronic (resolved with sequelae), the trial subject is lost to follow-up or the trial subject withdraws consent. If no final status is reached by the time of ~~Visit 8 (BNT162c2) or Visit 9 (BNT162a1, BNT162b1, BNT162b2)~~ discharge from the trial, the investigator must confirm the unavailability of a final status.	Update to reflect the addition of expansion cohorts.
Section 8.7 Genetics For Cohorts 1 to 10, a ~~A~~ blood sample (blood and / or isolated PBMCs) may be used for HLA typing of a subject to allow additional analysis, e.g., characterization of TCR repertoire and/or phenotypic characterization of antigen-specific T-cells as further specified in Section 8.8 (Biomarkers). Data generated with these additional analyses may provide information about the HLA dependency of immune response (e.g., if distinct HLA types have stronger / better immune response towards SARS-CoV-2). For Cohorts 11 to 13, a blood sample (blood and / or isolated PBMCs) will be used for HLA typing of a subject to allow additional analysis. HLA analysis will be conducted in all subjects in the Cohorts 11 to 13.	Update to reflect the addition of expansion cohorts.
Section 8.8 Biomarkers (CMI responses, explorative biomarker, immunogenicity research purposes) ~~Up to 5 additional blood draws (with up to 200 mL in total) will be taken over the complete trial for explorative biomarker/immunogenicity research purposes.~~ Three additional blood draws (with up to 200 mL in total) will be taken at the times listed in the SoA (Section 1.3) for explorative biomarker/immunogenicity research purposes, these will be in addition to standard trial assessments in selected dose ranging cohorts, and as core elements of the assessments of the expansion cohorts.	Update to fix the previously flexible blood sampling without altering the total volume of blood drawn.

Section 8.9 Immunogenicity assessments ~~Immune responses will be assessed at the times listed in the SoA (Section 1.3) using:~~ ~~a functional antibody titer, e.g., virus neutralization test (VNT).~~ ~~Sero negative is defined as titers below the starting dilution which corresponds to a titer of <1:10.~~ ~~Seroconversion after vaccination is defined as a 4-fold increase in titer~~ ~~o for seronegative pre-vaccination sera: a titer ≥1:40.~~ ~~o for seropositive pre-vaccination sera: a titer which is 4-fold higher than the measured pre-vaccination titer, e.g., titer rise from 1:20 to ≥1:80 after vaccination.~~ ~~an ant body binding assay, e.g., and assays to characterize antibodies (e.g., affinity, IgG subclass), e.g., ELISA.~~ ~~Sero negative is defined as titers below the starting dilution which corresponds to a titer of <1:100.~~ ~~Seroconversion after vaccination is defined as a 4-fold increase in titer~~ ~~o for seronegative pre-vaccination sera: a titer of ≥1:400.~~ ~~o for seropositive pre-vaccination sera: a titer which is 4-fold higher than the measured pre-vaccination titer, e.g., titer rise from 1:200 to ≥1:800 after vaccination.~~ ~~and/or~~ ~~equivalent assays dependent on availability by the time of trial conduct.~~ ~~Cell-mediated immune (CMI) responses:~~ ~~CMI assays, e.g., ELISpot, intracellular cytokine staining (ICS).~~ ~~CMI analysis will include Th1-specific cytokines (e.g., IFN-gamma, TNF-alpha, IL-2, or IL12) and Th2-specific cytokines (e.g., IL4, IL-5, IL-10, IL-13) to analyze the induction of either balanced Th1/Th2 responses, or of unbalanced Th1-dominant or Th2-dominant immune responses, respectively.~~ Immune responses as laid down in the trial objectives will be assessed at the times listed in the SoA (Section 1.3) using: 1) A functional antibody titer determined, e.g., via VNT or an equivalent assay. • Sero negative is defined as titers below the starting dilution (i.e., below the LOD [limit of detection] of the assay). • Seroconversion after immunization is defined as a 4-fold increase in titer. o for seronegative pre-immunization sera: a titer ≥ 4-times the LOD. o for seropositive pre-immunization sera: a titer which is 4-fold higher than the measured pre-immunization titer. 2) An antibody binding assay, e.g., ELISA or an equivalent assay. • Seroconversion after immunization is defined as a 4-fold increase in titer/antibody concentration. 3) CMI/responses mediated by immune cells such as CD4 and CD8 T-cells and their functional phenotypic subset by, e.g., ELISpot, ICS, multimer analyses, cytokine secretion assays, flow cytometry and other tests. CMI analysis will include among others CD4 and CD8 T-cells, Th1-specific cytokines (e.g., IFN-gamma, TNF-alpha, IL-2, or IL-12) and Th2-specific cytokines (e.g., IL-4, IL-5, IL-10, IL-13) to analyze the induction of either balanced Th1/Th2 responses, or of unbalanced Th1-dominant or Th2-dominant immune responses, respectively. Additional exploratory analyses of IMP-induced antibody responses with selected samples may include: • Assessing neutralization activity against variant spike proteins from other SARS-CoV-2 strains or other coronavirus families.	Update to reflect the addition of expansion cohorts and for clarification.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
• Antibody affinity, isotype and subclass analysis / functional assessment of antibodies, e.g., ADCC, antibody induced phagocytosis, immune cell degranulation, activation of immune cells such as lymphocytes and granulocytes. • Mechanisms that are potentially associated with antibody-dependent enhancement (ADE), e.g., ant body mediated uptake of (pseudo)-virus-particles into cells, formation of immune complexes. Additional exploratory analyses of vaccine-induced CMI (including non-T-cell based) responses with selected samples may include: • Analysis of immune activation, proliferation, cytotoxicity and cellular, molecular of immune cells subsets. • Bulk or single cell TCR and transcriptome sequencing, qt-PCR studies to profile and characterize, and track TCRs and to quantify the number of antigen-specific T-cells. • Analyses of polymorphism in immune response genes. Correlations will be descr bed – in particular for Cohorts 11 to 13 – between these immune responses and different subject disposition / characterization parameters such as age, gender, HLA, in relation to each other with further exploration as scientifically determined. Instructions on the sample collection, handling, and shipping will be provided in a Laboratory Manual. The methodology used for these assessments will be documented in the Biomarker Manual.	

<table>
<tr><th>Changed text
(inserted text is blue/underlined; deleted text is red/struck out)</th><th>Rationale</th></tr>
<tr><td>Section 8.10 Blood collection

For subjects in Cohorts 1 to 10, up ~~Up~~ to approximately ~~582~~ 592 mL blood will be drawn per subject over the complete trial, i.e., over approximately ~~7 months~~ 223 d.
For subjects in Cohorts 11 to 13, up to approximately 1022 mL blood will be drawn per subject over the complete trial, i.e., over approximately 760 d.</td><td>Update to reflect the addition of expansion cohorts and addition of blood draw at the added Visit (5a).</td></tr>
<tr><td>Section 9.2 Sample size determination

For the expansion cohorts the probability to observe a particular TEAE with incidence of 5% at least once in 30 and 90 subjects per group, respectively, is 78.5% and 99.0% respectively (see Table 10).

Table 10: Probability to observe a particular TEAE at least once
<table><tr><th>Number of subjects</th><th>TEAE incidence</th><th>Probability to observe a particular TEAE at least once</th></tr><tr><td>12</td><td>15%</td><td>85.8%</td></tr><tr><td>30</td><td>15%</td><td>99.2%</td></tr><tr><td></td><td>10%</td><td>95.8%</td></tr><tr><td></td><td>5%</td><td>78.5%</td></tr><tr><td>90</td><td>15%</td><td>>99.9%</td></tr><tr><td></td><td>10%</td><td>>99.9%</td></tr><tr><td></td><td>5%</td><td>99.0%</td></tr></table>
~~The sample size for Part B will be assessed based on the data from Part A and confirmed/adjusted in the planned protocol amendment.~~</td><td>Update to reflect additon of the expansion cohorts and the deletion of Part B.</td></tr>
<tr><td>Section 9.4.1 General considerations

In general, data will be summarized by groups and groups may be combined as appropriate. ~~Part A and Part B will be analyzed separately and may be combined as appropriate.~~
Continuous variables will be summarized by group using the following descriptive statistics: number of subjects (n), mean, standard deviation, median, minimum and maximum.
Categorical variables will be summarized by group presenting absolute and relative frequencies (n and %) of subjects in each category.
~~The planned protocol amendment will include a description of the planned statistical analyses planned for Part B.~~
Baseline is defined as last available value prior to first dose of IMP.</td><td>Update to reflect the deletion of Part B.</td></tr>
</table>

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 8.3.3 Follow-up of AEs and SAEs • Prime immunization up to 7 d after initial immunization. • Prime immunization up to boost immunization or 28 d after initial immunization (whatever comes first). • Boost immunization up to 7 d after boost immunization (only for P/B regimens). • Boost immunization up to 28 d after boost immunization (only for P/B regimens). • Prime immunization up to 28 d after boost immunization or after prime immunization (if no boost was given). ~~P/B regimens:~~ ~~• Day 1-21 (pre-boost)~~ ~~• Day 1 to 7~~ ~~• Day 21 (post-boost) - 28~~ ~~• Day 21 (post-boost) to 50~~ ~~SD regimens:~~ ~~• Day 1-28~~	For clarification.
Section 9.5 Interim analyses ~~No formal interim statistical analysis will be performed. However, the statistical analysis may be performed in the following sequence separately for each type: once all subjects in the respective group have been followed-up for at least 21 d and once all subjects have discontinued the trial, respectively.~~ The final analysis will be performed once all subjects have completed Visit 7 (EoT). An analysis update will be performed once all subjects will have completed Visit 10. No formal interim statistical analysis will be performed. However, preliminary analyses based on all data collected until a pre-defined data cut-off date (snapshot analyses) may be performed for each cohort once subjects within a cohort will have been followed up for at least 7 d following the dose.	Update to reflect additon of expansion cohorts and for clarification.
Section 10.1.1 (Regulatory and ethical considerations) The coordinating investigator or delegate will be responsible for the following: • Providing written summaries of the status of the trial to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC. • Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures. • Providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IEC, European regulation 536/2014 (if applicable), and all other applicable local regulations.	Update for clarification.
Section 10.1.5 Committees - SRC For Part A, the SRC will be comprised by a sponsor medical representative, the Medical Monitor, a sponsor-independent investigator, and a site representative. ~~For the decision to progress to Part B, an independent statistical consultant and a third party expert will also be included.~~ Key roles of the SRC are as follows:	Update to reflect deletion of Part B.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 10.1.7 Data quality assurance Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for ~~30~~ 25 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.	Alignment with other sponsor trials.
Section 10.3.1.1 Events meeting the AE definition • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs, physical examination, measurements), including those that worsen from baseline, and which are considered clinically significant in the medical and scientific judgment of the investigator, may be considered as AEs.	Clarification.
Section 10.3.1.10 Reporting of SAEs For medical questions, the sponsor's Medical Monitor for this trial should be contacted; contact details are given in the trial Safety Management Plan.	Clarification.
Section 10.9 Other standard abbreviations and definitions EoT End of ~~Trial~~ Treatment	Updates in the body text.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 10.10.6 Protocol amendment no. 06 **Amendment rationale** Protocol amendment 6.0 implemented three additional cohorts (Cohorts 11, 12, and 13) comprising up to additional 150 trial subjects aged from 18 to 85 years receiving BNT162b2 only. BNT162b2 has entered a Phase II/III evaluation of efficacy, with the intent to support an application for marketing authorization. The dosing regimen under investigation is two 30 µg BNT162b2 doses given ~21 d apart. The expansion cohorts implemented by this amendment are intended to provide a more in depth characterization of the adaptive immune responses induced by BNT162b2, associated vaccine safety, and the impact of factors such as subject disposition and dosing posology on humoral and cell-mediated immunity. These cohorts will extend the safety data of BNT162b2 to a broader trial population and thus closer to the vaccine target population. Moreover, each of these cohorts will add to a more differentiated understanding of the BNT162b2-induced adaptive immune response composed of antigen-specific antibodies, CD4 and CD8 T-cells, with a view to developing insights into the mechanisms by which immunity to SARS-CoV-2 may be induced and factors driving any variability in response. Alternative treatment approaches for difficult to treat or high risk subjects may be determined. In each of these dose cohorts, a broader characterization of T-cell and antibody responses and their inter-individual variation will be performed. This will include the characterization of the dependency of adaptive immune responses on factors such as age and gender. For further background on the scientific rationale for the expansion cohorts, see Section 4.2. The planned dose of BNT162b2, two 30 µg BNT162b2 doses given ~21 d apart, the same regime that has already been tested in the dose escalation phase of this trial and in almost 17,000 adult subjects, including those with acute and chronic illnesses, in the ongoing global Phase I/II/III trial BNT162-02/C4591001 (ClinicalTrials.gov NCT: 04368728). The three expansion cohorts are as follows: • Cohort 11: Alternative posology cohort with 30 healthy adults who will receive BNT162b2 using one 3 µg prime dose and one 30 µg boost dose of BNT162b2 given approximately 21 d apart (P/B regimen). • Cohort 12: Adaptive immune response cohort (including safety and long term immune response) with 90 healthy adults who will receive of two 30 µg BNT162b2 doses given approximately 21 d apart (P/B regimen). • Cohort 13: Population expansion cohort (including safety and long term immune response) with 30 immunocompromised adults who will receive of two 30 µg BNT162b2 doses given approximately 21 d apart (P/B regimen). This amendment also addresses feedback obtained from the PEI and the IEC on protocol version 8.0. This amendment also introduces logistical simplifications, i.e., except for Cohorts 1 and 8 (which have all been completed) , the minimum interval between dosed trial subjects has been reduced from 30 min to 15 min for the prime and boost doses in the still to be completed Cohorts 2 to 10 (inclusive). Also, the minimum interval has been set to at least 5 min for the prime and boost doses in Cohorts 11 and 12, and to 15 min (prime) and 5 min (boost for Cohort 13. This simplification/design is considered justified: • Because all first-in-human cohorts for the different BNT162 vaccine variants have been completed. • Due to the extensive experience and exposure already achieved with BNT162 vaccine candidates, including that almost 17,000 trial subjects have been dosed at least once with BNT162b2 (see Table 9). Further changes were implemented to align data collection and reporting in this trial with the data collection and reporting in other trials with BNT162 vaccines candidates (to facilitate data merging). This amendment will be issued after some of the planned trial subjects have already been enrolled into the trial.	This amendment.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 11 References ICH E7. Guideline for Industry - Studies in Support of Special Populations: Geriatrics. March 1994. … NCT04537949. A multi-site, Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of a prophylactic SARS-CoV-2 RNA vaccine (BNT162b3) against COVID-19 using different dosing regimens in healthy adults. Ongoing BioNTech clinical trial.	Updates in the body text.

PHARMACY MANUAL

BNT162-01

Version:	02	Date:	10 JUL 2020
Trial title	A Multi-site, Phase I/II, 2-Part, Dose-Escalation Trial Investigating the Safety and Immunogenicity of four Prophylactic SARS-CoV-2 RNA Vaccines Against COVID-2019 Using Different Dosing Regimens in Healthy Adults		
Phase	I/II		
EudraCT	2020-001038-36		
Sponsor:	BioNTech RNA Pharmaceuticals GmbH An der Goldgrube 12, 55131 Mainz, Germany Phone: +49 (0) 6131 9084-0 Fax: +49 (0) 6131 9084-392010		
CRO	CRS Clinical Research Services Mannheim GmbH Grenadierstrasse 1, 68167 Mannheim, Germany Phone: +49 (0) 0621 150450 And CRS Clinical Research Services Berlin GmbH Sellerstr. 31, 13353 Berlin, Germany Phone: + 49 (0) 30 859 949 -300 Principle Office: CRS Clinical Research Services Andernach GmbH Rennweg 72, 56626 Andernach, Germany Phone; +49 (0) 2632 9580406		

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LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Explanation
BNT162	BNT162 is a prophylactic RNA vaccines against SARS-CoV-2, comprising several vaccines BNT162a1, BNT162b1, BNT162b2, and BNT162c2
BNT162-01	Clinical trial code for the FIH trial of BNT162
CMO	Contract manufacturing organization
CRA	Clinical research associate
CRO	Contract research organization
CTP	Clinical trial protocol
DP	Drug product
GCP	Good clinical practice
GMP	Good manufacturing practice
ICH	International conference on harmonisation
IMP	Investigational medicinal product
ISF	Investigator site file
QP	Qualified person
SOP	Standard operating procedure

1 INTRODUCTION

The purpose of this manual is to serve as a guideline for pharmacies and investigational sites regarding the receipt, storage, handling, inspection, preparation, administration and destruction of investigational medicinal products (IMPs) provided by the sponsor.

All handling of IMP must be conducted in compliance with the clinical trial protocol (CTP) in its current version, Good Clinical Practice (GCP), and ICH Guidelines as well as local and regional regulations and guidelines. The CTP can be updated independently of the Pharmacy Manual; in case changes in the CTP also affect the Pharmacy Manual, a new version of the Pharmacy Manual will be provided. Appendices to this Pharmacy Manual can be updated independently of the Pharmacy Manual.

2 TRIAL DESIGN

For information regarding the trial design refer to the CTP.

3 TRAINING AND QUALIFICATION OF STAFF MEMBERS

Before the pharmaceutical staff or other trained staff is allowed to prepare BNT162 solution for injection, all staff members responsible in the preparation and handling must be trained initially by the sponsor representative.

Further training(s) can be performed by already executing staff, even if they were not present at the initial instruction on solution for injection preparation.

Each training must be documented in written form using “Training Logs”. Each delegation of responsibilities must be documented in written form using the “Delegation of Authority Log”. Training and delegation logs have to be filed in the Investigator Site File (ISF) at the corresponding section/pharmacy file.

The Sponsor reserve the right to perform quality checks of the prepared solution for injection.

4 STUDY MEDICATION

For general information and preparation procedure regarding the solution for injection, please refer to the corresponding IMP-specific Appendix 1.

5 REQUEST, SHIPMENT, AND RECEIPT OF DP

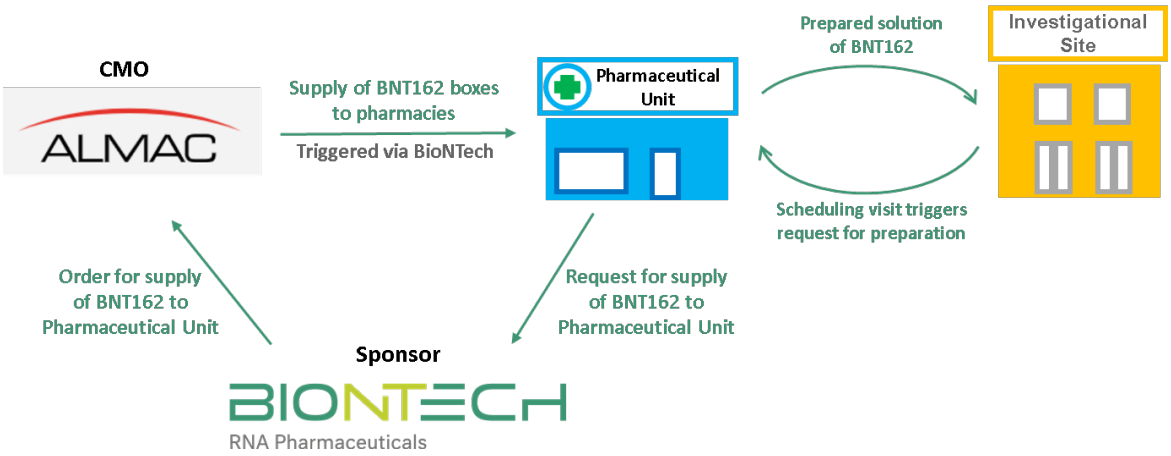

Figure 1: Overview receipt of shipment

5.1 Transport and Receipt of DP Units from Manufacturer to pharmacy

Each shipment of BNT162 DP boxes provided by the sponsor for clinical trial use is flexible in dates and batch size depends on expected recruitment rates, shelf life and storage capacity. The pharmaceutical staff members or trained staff members must be informed about shipping amount and delivery date in advance. Initial shipment of BNT162 for clinical use occurs automatically and is organized by the sponsor´s IMP-Management.

During the clinical trial, resupply must be ordered by the trained staff members of the CRO using the 'Request and Shipment Form' (Annex 1) via email (Drugsupply-BNT162-01@biontech.de) at least 7 working days in advance.

Shipment will be performed by a qualified courier, which is selected by Sponsor´s IMP management or contracted supply vendor. Required certificates (e.g., QP release certificate for labeled DP in EU) and a "Packing List" will be provided by Almac Clinical Services Ltd. with each shipment and must be filed in the ISF. Additionally, CRS specific "Receipt of Investigational Medicinal Products and Receipt Check" (Annex 2) log has to be filled out and filed in the ISF.

Each shipment must be performed temperature controlled (temperature loggers). Upon receipt of a shipment, the receiving clinical or CRO site becomes responsible for product management. The trained personnel must unpack the shipping box, stop the temperature logger, upload the logger data into Almac´s TempEZ system (for uploading instructions see Annex 3) and check the shipment for potential deviations (temperature and integrity

during transition, see Figure 2 and Section 7). The temperature logger date has to be uploaded at each receipt, regardless of an Alarm.

The proper and complete receipt must be documented upon handover of BNT162 DP boxes in the "Packing List" by dated signature and return it to the sponsor via Email (Drugsupply-BNT162-01@biontech.de).

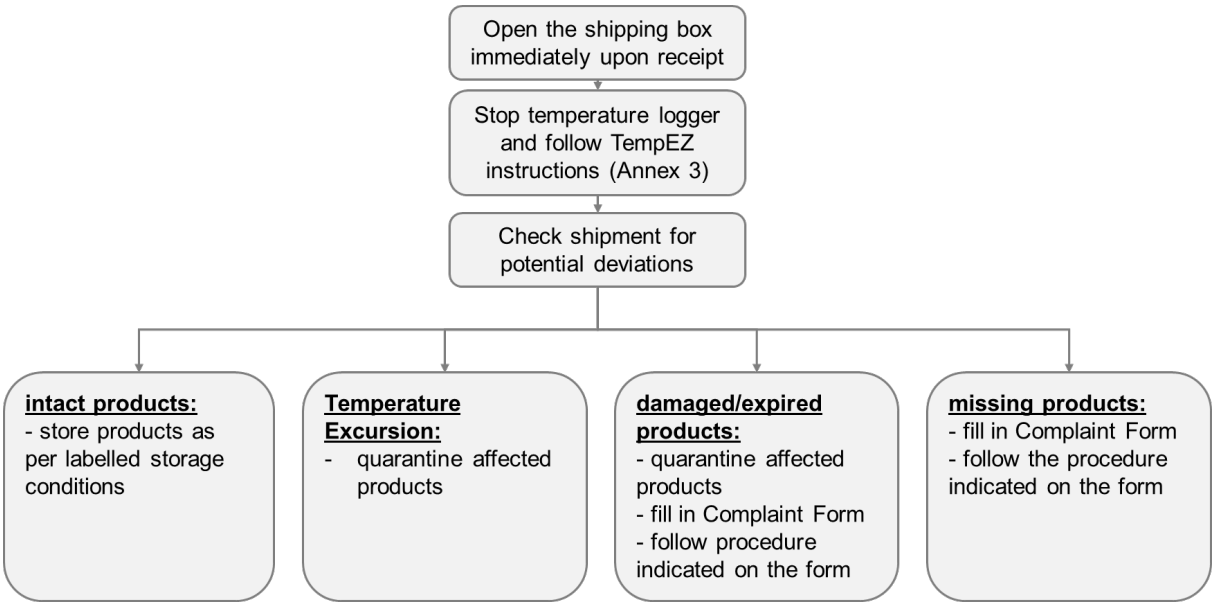

Figure 2: Process Temperature Excursion Management of DP boxes provided by the sponsor

5.2 Transport from Preparation site to Investigational Site

A transfer from the site of preparation of solution for injection to the site of administration might be required. Details are described in IMP-specific Appendix 1.

Preparation of solution for injection must be repeated, if

- the solution for injection was not treated according to the described requirements (please refer to IMP-specific Appendix 1)
- a syringe was damaged/broken during the transfer from the preparation site to the investigational site

In all cases, the preparation and investigational site must be informed directly.

6 STORAGE REQUIREMENTS

BNT162 Drug Product and final solution for injection must be stored as specified in the corresponding Appendix 1. If temperature control is required, every working day temperature must be documented including minimum and maximum values. It must be

ensured that all refrigeration appliances are attached to a controlled safety system (emergency power supply and are monitored). In case of temperature excursion, proceed as described in Section 7. Consumables must be stored according to the manufacturer specifications.

7 DEVIATIONS

7.1 GCP Deviations

All GCP deviations must be documented and communicated to the CRA and the Clinical Study Manager of the Sponsor. Deviations must be evaluated by the responsible CRA and if required by Clinical Study Manager of the Sponsor and documented in the Deviation log, which must be signed by the Principal Investigator.

7.2 Temperature Excursions

Temperature excursions of boxes <5 min that are due to opening and closing of the door of the refrigerator or freezer do not have to be reported. Boxes can be further used. Other temperature excursions that occurred during transport or storage of DP boxes provided by the sponsor must be handled as described in Figure 3.

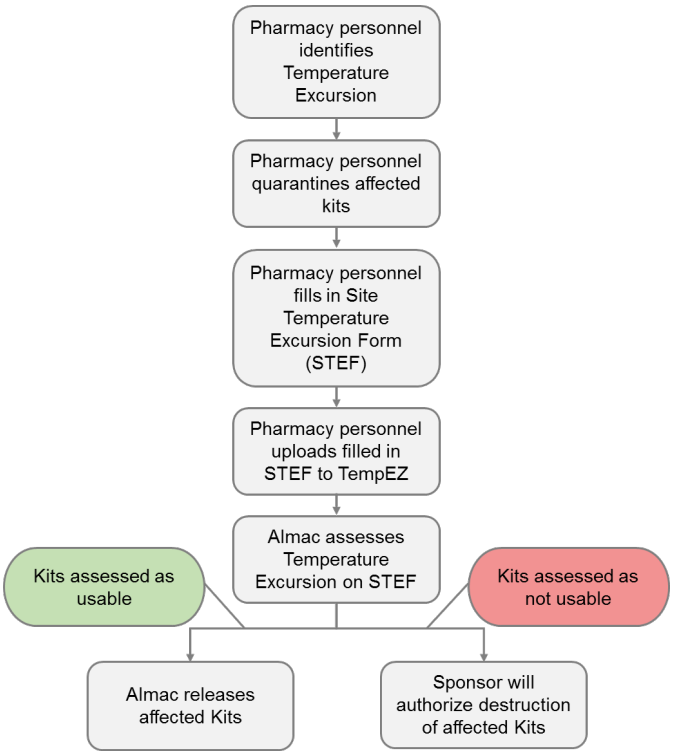

Figure 3: Process Temperature Excursion Management of DP kits provided by the sponsor.

If a temperature excursion occurred storage, please fill out the “Site Temperature Excursion Form” Annex 5 and follow the instructions provided in “TempEZ Connect Site Instructions To Access Template of Excursion Form” in Annex 6.

If a temperature excursion occurred during storage or transport of the prepared solution for injection, the prepared solution for injection must be discarded and a new preparation must be initiated. Destruction must be documented.

Documentation related to the temperature excursion reporting and assessment must be filed in the ISF.

7.3 Quality Issues other than Temperature Excursions with Products supplied by the Sponsor

If the quality issue is related to DP boxes or ancillary supplies provided by the sponsor, e.g.

- Any fault of quality and/or effectiveness, e.g., particles
- Any fault of the containers and outer packages, e.g., surface imperfection, container leakage, broken syringe/plunger, missing contents, device malfunction
- Any fault of the labeling, e.g., missing or illegible label
- Any falsification of the medicinal product or device, e.g., suspected product mix-up, tampering

proceed as described in Figure 4 and Complaint Form (Annex 7).

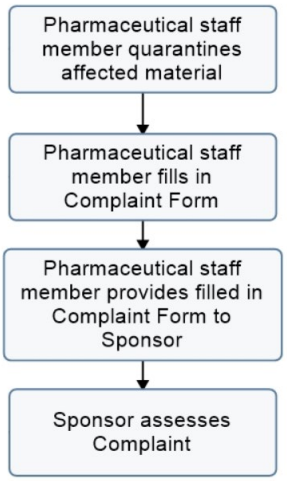

Figure 4: Process Complaint Management

If the quality issue is related to the prepared solution for injection, the prepared solution for injection must be discarded and a new preparation must be initiated. Destruction must be documented.

8 DESTRUCTION AND/OR RETURN OF DP

All BNT162 DP boxes, independent of their use, must be stored at the site until accountability has been finalized and the accountability log has been signed by pharmaceutical or trained staff member. The preferred procedure is that all used vials and incompletely used, damaged or expired DP boxes are destroyed according to sponsor´s requirements after written authorization by the sponsor. In case the pharmacy or CRO site must follow its own policy/SOP regarding used vials and incompletely used or damaged DP boxes, the policy/SOP must be listed in the ISF and a copy must be collected by the CRA for filing in the Trial Master File. Destruction of used vials and incompletely used or damaged DP boxes can be executed according to the process of the pharmacy by a qualified company if such company has been contracted by the pharmacy. A destruction certificate (including DP boxes numbers and quantities to be destroyed, if possible according to internal policies/procedures) must be provided by the contracted company or the pharmacy. Unused vials/boxes will be managed by sponsor requirements.

If required, bags or syringes containing the prepared solution for injection can be destroyed (e.g., short-term cancellation of administration). Destruction must be documented.

9 RECALLS

Possible problems with the quality of ancillary supplies and BNT162 DPs require a recall for the batch concerned. The sponsor is responsible for product recall of all products provided by the sponsor. In such cases, the preparation site and investigational site must be informed by the sponsor.

10 ACCOUNTABILITY

Incoming BNT162 DP boxes must be documented by the pharmacy staff member or trained staff members with signature and date within the “Investigational Medicinal Product Inventory (Bulk)” form (pharmacy level) (Annex 8) containing information like medication number, kit/box number, batch number, expiry date and date of receipt at the site.

Additionally, via the “Investigational Medicinal Product Administration and Accountability” log (Annex 9) consumption per subject is documented (e.g., Drug Products, NaCl vials).

All fully completed logs have to be dated and signed as soon as possible by a pharmacy staff member or trained staff members and the responsible CRA (or comparable). Each change, which has been made, has to be signed with date and signature. If a change was made by a different pharmacy staff member or trained staff members afterwards, the subscribing staff member has to sign the log again.

11 FORMS/TEMPLATES

Forms and templates to this Pharmacy Manual can be updated independently of the Pharmacy Manual.

- Annex 1 to PM-BNT162-01_Request and Order Form_V01
- Annex 2 to PM_BNT162-01_Receipt of Investigational Medicinal Products and Receipt Check _V01
- Annex 3 to PM-BNT162-01_TempEZ Monitor Upload Instructions_V01
- Annex 5 to PM-BNT162-01_Site Temperature Excursion Form_V01
- Annex 6 to PM-BNT162-01_TempEZ Connect Site Instructions To Access Template of Excursion Form_V01
- Annex 7 to PM-BNT162-01_Complaint Form_V01
- Annex 8 to PM-BNT162-01_Investigational Medicinal Product Inventory (Bulk)_V02
- Annex 9 to PM-BNT162-01_Investigational Medicinal Product Administration and Accountability_V04

12 REFERENCES

"Not applicable".

13 DOCUMENT HISTORY

Version	Reason for New Version	Changed Sections/Tables/Figures/Annexes
01	N/A, first document version	N/A, first document version
02	- Change in Temperature Excursion Management and Adjudication Responsibilities - Omitting reference of Versions in Annexes	- 7.2 Temperature Excursions - Figure 3 - Omission of Annex 4 (Annex 4 to PM-BNT162-01_TESS_V02) - Annex 9 to PM and Annex 4,5 and 6 to Appendix 1

14 APPENDICES

IMP-specific Appendix 1

Appendix 1 to the Pharmacy Manual

IMP-specific requirements to the Pharmacy Manual

BNT162-01

Version:	06	Date:	10-JUL-2020
Sponsor:	BioNTech RNA Pharmaceuticals GmbH An der Goldgrube 12, 55131 Mainz, Germany Phone: +49 (0) 6131 9084-0 Fax: +49 (0) 6131 9084-392010		
CRO	CRS Clinical Research Services Mannheim GmbH Grenadierstrasse 1, 68167 Mannheim, Germany Phone: +49 (0) 0621 150450 And CRS Clinical Research Services Berlin GmbH Sellerstr. 31, 13353 Berlin, Germany Phone: + 49 (0) 30 859 949 -300 Principle Office: CRS Clinical Research Services Andernach GmbH Rennweg 72, 56626 Andernach, Germany Phone; +49 (0) 2632 9580406		

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
BNT162	BNT162 is a prophylactic RNA vaccines against SARS-CoV-2, comprising several vaccines BNT162a1, BNT162b1, BNT162b2, and BNT162c2
BNT162-01	Clinical trial code for the FIH trial of BNT162
°C	Degree celsius
CMO	Contract manufacturing organization
CRA	Clinical research associate
CRO	Contract research organization
DEHP	Diethylhexyl phthalate (plasticizer)
DP	Drug product
g	Gram
GMP	Good manufacturing practice
h	Hour(s)
ID	Identifier
IMP	Investigational medicinal product, a synonym for DP
IRT	Interactive response technology
IV	Intravenous
k	Kilo
kg	Kilogram
L	Liter
M	Meter
mL	Milliliter
mm	Millimeter
MSDS	Material safety data sheet
NaCl	Sodium chloride
RT	Room temperature
µL	Microliter
µg	Microgram

1 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

1.1 General Information

The Drug Product (DP) consists of one of four RNA-based vaccines for intramuscular application (BNT162a1, BNT162b1, BNT162b2, or BNT162c2). Each RNA encodes a viral antigen that is translated by the vaccinated organism to protein to induce a protective immune response.

The DP will be provided in a box for preparation of solution for injection. Each box contains one vial of BNT162a1, BNT162b1, BNT162b2 or BNT162c2 (summarized as BNT162 boxes) with an extractable volume of 300 µL and an actual fill volume of 500 µL (for all) or 500 µL and an actual fill volume of 700 µL (for BNT162b1 only) corresponding to a concentration of 0.5 mg/mL DP (concentration refers to the concentration of the active, moisture and solvent free substance in the solution). All BNT162 vaccines used in the clinical trial BNT162-01 and respective content per vial are listed in Table 1.

Table 1: BNT162 vaccines needed for preparation of the solution for injection

Type	Name	Primary packaging	Content
Drug Product	BNT162a1	2R vial	0.15mg/0.3ml
Drug Product	BNT162b1	2R vial	0.25mg/0.5ml **or** 0.15mg/0.3ml
Drug Product	BNT162b2	2R vial	0.15mg/0.3ml
Drug Product	BNT162c2	2R vial	0.15mg/0.3ml

The Drug Product is a concentrate for solution for injection provided as preservative-free, sterile, white to off-white suspension with a pH value of nominal pH 7.4. Each DP vial is for single use only. The concentrate must be diluted with normal saline prior to injection. The one step dilution process will be performed in a syringe – depending on the dose level either directly in the 1mL syringe later used for i.m. injection or in a large-volume mixing syringe followed by a transfer into 1mL injection syringe. At lower dose levels (Table 4 to Table 6) multiple doses will be prepared from the diluted DP in the mixing syringe.

1.2 Shipping and Storage Conditions of Drug Product

BNT162 boxes have to be shipped and stored under temperature control as follows:

Table 2: Shipping and storage temperature of BNT162 boxes.

	Shipping temperature [°C]	Storage temperature [°C]
BNT162 boxes	-60 °C to -80 °C	-60 °C to -80 °C

2 PREPARATION OF SOLUTIONS FOR INJECTION

The preparation of solutions for injection must only be performed by trained pharmaceutical staff other trained staff members (see respective section in the Pharmacy Manual main document) and if the pharmaceutical staff members has received request for IMP preparation by the investigator of CRS Research unit (Annex 6). Request contains information on dose cohort, dose concentration to be administered, the volume to administer as well as date and time for planned injection.

This section describes the preparation of solutions for injection for BNT162a1, BNT162b1, BNT162b2 and BNT162c2.

2.1 Material Needed for Preparation of Solutions for Injection

All disposables that are required for preparation of solution for injection are summarized in Table 3. The overview of the different doses and respective volumes is listed in Table 4 to Table 6.

Pharmacy is responsible to supply the required disposables.

Table 3: Suitable disposables and materials for preparation of the solution for injection

Description/ Company	PZN (Germany)/ Reference No. (Germany)	Usage
0.9 % Saline	N/A (off the shelf saline)	Diluent
Ventilation Spike Mini-spike® Filter V B.Braun	02245272 / 4550579	Sharp
Syringe Filter 0.2 µk, Pharmaassure Membrane, 25mm or comparable (if applicable)	HP1002	Filter
18 G BD™ Needle	N/A	Sharp
30G Needle or comparable and applicable for i.m. injection	N/A	Sharp
Omnifix®-F Solo with Luer-Lock, B.Braun (if available)	12749565	Syringe
1 mL BD Plastipak (polycarbonate)	01319181 / BD309628	Syringe
3 mL BD Plastipak (polypropylene)	08463685 / BD309649	Syringe
5 mL BD Plastipak (polypropylene)	07518220 / BD309649	Syringe
10 mL BD Plastipak (polypropylene)	03086841 / BD305959	Syringe
30 mL BD Plastipak (polypropylene)	N/A	Syringe
Syringe adaptor Baxter (female to female luer lock)	N/A	Adaptor
Combination cap; luer lock; Fresenius Kabi	03460423 / 8501512	Adaptor

2.2 Preparation process for BNT162a1, BNT162b1, BNT162b2 and BNT162c2

The preparation of solution for injection will be performed by aseptic handling procedures by pharmaceutical staff or other trained staff at the sites.

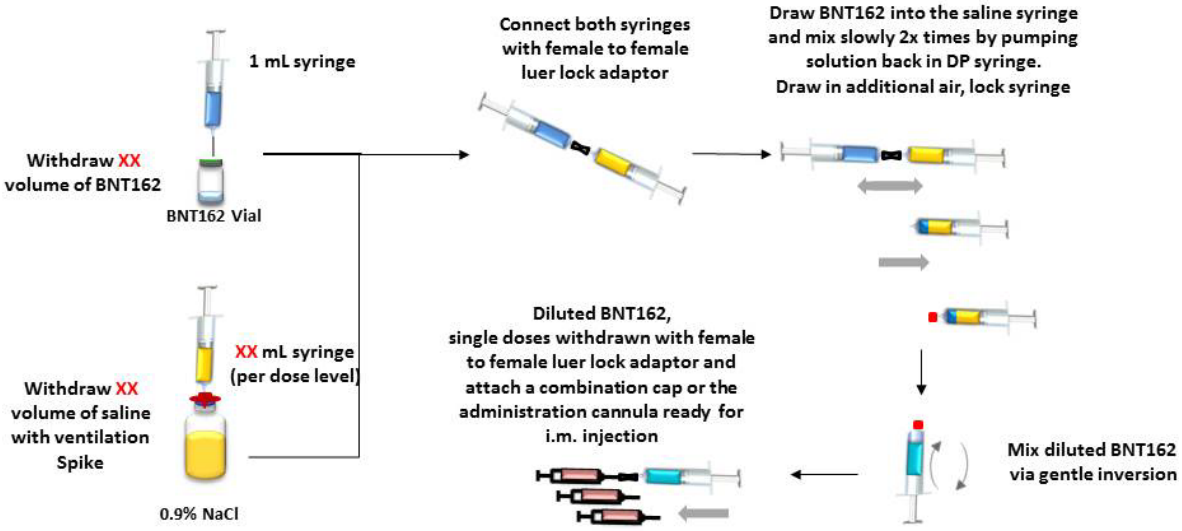

Figure 1: Overview of preparation process of final solution for injection.

Step 1: Thawing of DP BNT162

1. Thaw one vial of DP by removing the vial from -70 °C ± 10°C storage and allowing acclimating to room temperature for approximately 20 minutes.

Step 2: Withdraw of NaCl

1. Perform wiping disinfection of the cap of the NaCl 0.9% bottle using an alcoholic disinfectant.
2. Puncture the stopper of the vial with the Mini-Spike and attach a sterile syringe (see Table 4 to Table 6) via luer lock.
3. Withdraw a bit more than the required volume of NaCl as shown in Table 4 to Table 6.
4. Hold the syringe pointing upwards, remove potential air bubbles by gentle tapping of the syringe, and set the volume inside the syringe to respective volume as shown in Table 4 to Table 6 by pushing out the excess volume of NaCl 0.9% solution into a waste container.
5. Attach a filter and draw in a further 0.2 mL of air and close with cap until dilution process (if necessary, due prolonged time of DP syringe preparation). This is the saline syringe.

Step 3: Withdraw of BNT162 DP

1. Mix the thawed DP by careful agitation. Do not mix vigorously. Do not vortex.
2. Check carefully if any particles are visible.
3. Flip off the flip cap on the thawed DP vial.
4. Perform wiping disinfection on the septum of the DP vial stopper using alcoholic disinfectant.
5. Attach a sterile needle (18G x 1 ½") to a sterile 1 mL syringe.
6. Insert the needle through the stopper into the DP vial, hold vial upright and withdraw a bit more than the respective volume by tilting the vial slightly (Table 4 to Table 6). Alternatively, a second needle with filter can be used for ventilation.

This is the starting point for in-use shelf-life. Please record the time when the DP vial was opened by inserting the needle.

7. Pull the filled syringe out of the vial.

8. Check again carefully if any particles are visible.

9. Hold the syringe with the needle pointing upwards, remove potential air bubbles by tapping of the syringe, and set the volume inside the syringe to respective volume as shown in Table 4 to Table 6 by pushing out the excess volume of DP into a waste container.

10. Discard the needle.

Step 4: Diluting BNT162 DP by mixing with NaCL

1. Connect the DP syringe to the saline syringe using the syringe adaptor and ensure that the luer lock connection is tight.
2. Gently transfer the syringe containing the DP into the saline syringe. Ensure that all fluid is displaced into the saline syringe.
3. For thoroughly mixing pump the solution twice back to DP syringe. Remove the DP syringe, connect a filter and draw air in order to empty the connector from residual solution.
4. Remove the syringe adaptor and the filter from the saline syringe after the final pumping into the saline syringe: this now containing the diluted DP solution.
5. Close the syringe immediately, pointing upwards while screwing on the combination cap. Label the syringe clearly.

6. Mix solution by gently inverting the diluted-DP-containing syringe 5 times.
7. Remove combination cap and carefully displace the air bubble from inside the syringe.

For dose levels 0.1µg to 60 µg: Multiple doses from one preparation (50µ and 60µg only for BNT162b1 with extractable volume of 0.5 mL)

1. Attach 1 mL syringe to the diluted-DP-containing syringe using a sterile syringe connector.
2. Transfer a bit more of the respective injection volume (see Table 4 to Table 6) of the diluted DP to the 1 mL syringe for injection.
3. Disconnect the 1 mL syringe for injection and lock its outlet with a combination cap (alternative: immediately with the administration cannula). This is the preliminary dose for i.m. injection. Label the syringe or alternatively a zip bag containing the syringe clearly including time of expiry. The final dose will be adjusted after connecting and filling the administration cannula.
4. Repeat these 3 steps as appropriate.

For dose level of 50 - 100µg: Single dose from one preparation

1. Lock the outlet with a combination cap. This is the final dose for i.m. injection. Label the syringe or alternatively a zip bag containing the syringe clearly including time of expiry.

Immediately use of the final solution for injection is recommended. If not used immediately, store the closed and labeled syringes for injection at refrigerated temperature.

Instruction of intramuscular injection is provided in the current version of the clinical trial protocol as well as in Section 4.

In case of very low application volume of 50µl please consider the following instructions prior application!

- Make sure the cannula is tightly connected
- The final adjustment of 50 µl at clinical site should be performed very carefully
- Excess administration solution should drain by gravity only
- Remaining solution adhering at the tip of cannula should not be wiped off!

Table 4: Dose Levels for BNT162a1

Dose Levels for BNT162a1							
Dose level	**DP**		**Saline**		**Actual concentration (µg/µL)**	**Injection volume (µL)**	**Theoretical doses per vial**
	Volume (µL)	**Syringe size**	**Volume (µL)**	**Syringe size**			
0.1 µg	100	1 mL	25000	30 mL	0.002	50	>500
0.3 µg	100	1 mL	25000	30 mL	0.002	150	>150
0.6 µg	100	1 mL	25000	30 mL	0.002	300	>75
1 µg	100	1 mL	25000	30 mL	0.002	500	>50
3 µg	300	1 mL	25000	30 mL	0.006	500	50
10 µg	200	1 mL	5000	10 mL	0.0192	500	10
30 µg	300	1 mL	2200	3 mL	0.06	500	5

Table 5: Dose Levels for BNT162b1 and BNT162b2

Dose Levels for BNT162b (BNT162b1 and BNT162b2)								
Dose level	**DP**		**Saline**		**Actual concentration (µg/µL)**	**Injection volume (µL)**	**Theoretical doses per vial**	**Doses used**
	Volume (µL)	**Syringe size**	**Volume (µL)**	**Syringe size**				
1 µg	100	1 mL	25000	30 mL	0.002	500	>50	35
3 µg	300	1 mL	25000	30 mL	0,00593	500	50	30
10 µg	200	1 mL	5000	10 mL	0.0192	500	10	7
20 µg	200	1 mL	2300	3 mL	0.040	500	5	3
30 µg	300	1 mL	2200	3 mL	0.06	500	5	3
50 µg	*400*[1]	*1 ml*	*600*	*3 ml*	*0.2*	*250*	*4*	*2*

50 µg	*200*	*1 ml*	*300*	*1 ml*	*0.2*	*250*	*-*	*1*
60 µg	*400[1]*	*1 mL*	*600*	*3 mL*	*0.2*	*300*	*3*	*2*
60 µg	*200*	*1 mL*	*300*	*1 mL*	*0.2*	*300*	*-*	*1*
100 µg	200	1 mL	300	1 mL	0.2	500	-	1

[1]in case of BNT162b1 with an extractable volume of 0.5ml.

Table 6: Dose Levels for BNT162c2

Dose Levels for BNT162c2								
Dose level	**DP**		**Saline**		**Actual concentration (µg/µL)**	**Injection volume (µL)**	**Theoretical doses per vial**	**Doses used**
	Volume (µL)	**Syringe size**	**Volume (µL)**	**Syringe size**				
0.1 µg	100	1 mL	25000	30 mL	0.002	50	>500	450
0.3 µg	100	1 mL	25000	30 mL	0.002	150	>150	140
0.6 µg	100	1 mL	25000	30 mL	0.002	300	>100	80
1 µg	100	1 mL	25000	30 mL	0.002	500	>50	30

2.3 Transfer and Storage Conditions of the Solutions for Injection of BNT162a1, BNT162b1, BNT162b2 and BNT162c2

The final solution for injection shall be immediately transferred to the investigator for immediately use. During transfer, the final solution for injection shall be kept at room temperature.

If not used immediately, the final solution for injection shall be stored at 2°C to 8°C. Please record time for each injection syringe when storage has been started and stopped.

During transfer and storage: do not expose to direct sunlight and do not shake.

The time of expiry will be indicated on the label of each injection syringe.

2.4 Expiry Date of the prepared Solution for Injection of BNT162a1, BNT162b1, BNT162b2 and BNT162c2

An expiry date will be assigned for each syringe containing the final solution for injection. Date and time of expiry shall be clearly stated on the label of each injection syringe.

Administration has to be performed within 6 hours after begin of preparation. Start of preparation is defined as puncture of DP vial. In this period of 6 hours, two conditions are allowed: room temperature for preparation, handling and transfer as well as 2-8°C for storage.

2.5 Labelling of the prepared Solution for Injection

The pharmaceutical staff member or other trained staff must label the syringe containing the final solution for injection or alternatively a zip bag containing the syringe for the investigational site. Each syringe containing the final solution for injection alternatively a zip bag containing the syringe should at least contain information: subject ID, total dose, storage conditions, date and time of expiration and used DP vial number/batch number.

3 LABELING OF DP VIAL AND BOXES

BNT162 DP vials and boxes are labeled with a label approved by the competent authority. Exemplary content of vial and box label is shown in Figure 2.

Example Content of Primary Label (BNT162 DP vial):

<**DPN**> 0,25mg/0,5ml Protokoll Nr.: BNT162-01
Chargen Nr.: <**BNO**> Vial Nr.: <**MED**> Probanden Nr.: _____
Konzentrat zur Herstellung einer Lösung zur i.m. Injektion gemäß Protokoll.
Sponsor: BioNTech RNA Pharmaceuticals GmbH, An der Goldgrube 12, D-55131 Mainz
Auftragsforschungsinstitut: CRS Clinical Research Services Mannheim GmbH,
Grenadierstrasse 1, D-68167 Mannheim
BNT162VL

Example Content of Secondary Label (BNT162 box):

Protokoll Nr.: BNT162-01 EudraCT-Nr.: **<EUD>** Chargen Nr.: **<BNO>** Verwendbar bis: **<EXPE>** Schachtel Nr.:**<MED>** BNT162-01 Schachtel. Inhalt: 1 Durchstechflasche **<DPN>** | 0,25mg/0,5ml	Konzentrat zur Herstellung einer Lösung zur i.m. Injektion gemäß Protokoll. Lagerung bei -60 °C bis -80 °C Nur zur klinischen Prüfung bestimmt. Durchstechflasche bis zur Verwendung in der Schachtel aufbewahren. Dosierung gemäß Anweisung des Prüfarztes.	Vernichtung oder Rückgabe des Prüfpräparates entsprechend den Anforderungen des Sponsors. Sponsor: BioNTech RNA Pharmaceuticals GmbH, An der Goldgrube 12, D-55131 Mainz, Tel.: +49 (0)6131 9084-0 Auftragsforschungsinstitut: CRS Clinical Research Services Mannheim GmbH, Grenadierstrasse 1, D-68167 Mannheim, Tel.: +49 (0) 0621 150450	Prüfarzt: _____ Probanden Nr.: _____ Nummer des Prüfzentrums: _____ BNT162CT2

Figure 2: Example Label Content of Primary and Secondary Labels.

The pharmaceutical staff member or other trained staff must add specific information (e.g., Subject Number) in handwriting on the labels indicated by corresponding placeholders or add reference where this specific information can be found.

3.1 Relabeling at sites

N/A

4 ADMINISTRATION OF PREPARED SOLUTION FOR INJECTION TO THE SUBJECTS

The solution for injection must be administered with an intramuscular injection in the upper arm (musculus deltoideus). The same arm may be used for both immunizations (if applicable). The non-dominant arm is preferred.

5 POTENTIAL PREPARATION-ASSOCIATED RISKS AND RISK MANAGEMENT

Protective clothing as usually applied during pharmaceutical practice (lab coat and gloves) has to be worn. It has to be operated in accordance to good industrial safety- and hygiene practice.

There are no hints for potential harmful risks which could be traced to the drug product in the applied concentrations (see attached Material Safety Data Sheets).

Information on irritation or toxicity of any form is not known. In case of contact with skin or mucosa, the affected area has to be thoroughly rinsed with water. In each case the company physician has to be consulted and if needed BioNTech RNA Pharmaceuticals GmbH as the Sponsor of the trial has to be informed. The isotonic NaCl solution 0.9 % is unobjectionable, medically-licensed article of trade.

In case of a possible stab wound with a cannula, the wound has to be disinfected, rinsed with water and the company physician has to be consulted.

In case of a potential contamination of the working surface with BNT162, the product has to be taken up with cellulose and has to be disposed according to the usual terms of the pharmacy or preparation site.

6 ANNEXES

Annexes to this Appendix can be updated independently.

- Annex 1 to Appendix 1 to PM-BNT162-01_Material Safety Data Sheet for BNT162a1_V01
- Annex 2 to Appendix 1 to PM-BNT162-01_Material Safety Data Sheet for BNT162b1_V01
- Annex 3 to Appendix 1 to PM-BNT162-01_Material Safety Data Sheet for BNT162c2_V01
- Annex 4 to Appendix 1 to PM-BNT162-01_IMP Preparation_V06
- Annex 5 to Appendix 1 to PM-BNT162-01 Dosierungsetikett_V02
- Annex 6 to Appendix 1 to PM-BNT162-01_IMP Request Form_V06
- Annex 7 to Appendix 1 to PM-BNT162-01_Material Safety Data Sheet for BNT162b2_V01

7 REFERENCES

Not applicable.

8 DOCUMENT HISTORY

Version	Reason for New Version	Changed Sections/Tables/Figures/Annexes
01	N/A, first document version	N/A, first document version
02	- Addition of DL 0.3 µg to BNT162a1 preparation - Adaption of storage temperature after preparation	- 2.2 Preparation process for BNT162a1, BNT162b1 and BNT162b2 - Table 4 - 2.3 Transfer and Storage Conditions of the Solutions for Injection of BNT162a1, BNT162b1 and BNT162b2 - 2.4 Expiry Date of the prepared Solution for Injection of BNT162a1, BNT162b1 and BNT162b2 - Annex 4 and Annex 6
03	- Addition of 5th and 6th DL of 60µg and 50µg for BNT162b1	- Decision of SRC: addition of 0.6µg DL. - Update of Table 5 and preparation procedure for BNT162b1 with fill volume of 0.5ml to reduce vial consumption

		- Annex 4
	- Update of BNT162c2 instruction: Change of dose levels of BNT162c2 to 0.1, 0.3 and 1.0 µg. Extending scope of section 2 for BNT162c2.	- In-use date for BNT162c2 became available supporting preparation, transfer, storage and handling. Sponsor decided to reduce DLs of BNT162c2 as shown in Table 6.
	- Correction of typos	- Theoretical number of doses from one vial for 10µg dose shown in Table 4 and Table 5.
	- Addition of doses used	- Update of Table 4 and 5
	- Addition of DL 0.1µg and 0.6µg for BNT162a1	- Update of Table 4 - Annex 4
V04	- CC-20-0141	- Detailed description for preparation of application volume of 50µl
V05	- Addition of DL 0.6 µg to BNT162c2 preparation - Addition of DL 20 µg to BNT162a1 preparation - Inclusion of Omnifix®-F Solo with Luer-Lock, B.Braun (if available) for DP withdrawn	- 2.2 Preparation process for BNT162b1 and BNT162c2 - Table 5 and 6 - Table 3 - Annex 4
V06	- Addition on guidance to check for visible particles prior DP withdrawn and during preparation of final solution for injection	- 2.2. Preparation process for BNT162a1, BNT162b1, BNT162b2 and BNT162c2 - Annex 4 to Appendix 1

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PROCESS DESCRIPTION

BIOMARKER ANALYTICS

BNT162-01

Title:

A Multi-site, Phase I/II, 2-Part, Dose-Escalation Trial Investigating the Safety and Immunogenicity of four Prophylactic SARS-CoV-2 RNA Vaccines Against COVID-2019 Using Different Dosing Regimens in Healthy Adults

Version 3.0
Version Date: 13AUG2020

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LIST OF ABBREVIATIONS

AB	Antibody
BCR	B cell receptor
BM	Biomarker
BS CF	Biosampling Core Facility
BSU	Biosampling Unit
CD	Cluster of Differentiation
CMI Response	Cell-mediated Immune Response
CO	Clinical Operations Department
CPE	Cytopathogenic Effect
CRA	Clinical Research Associate
CSM	Clinical Study Manager
CSP/CTP	Clinical Study Protocol/Clinical Trial Protocol
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
ELISA	Enzyme-linked Immunosorbent Assay
ELISpot	Enzyme-linked Immunospot Assay
IBM-PM	Immune-Biomarker Project Manager
ICS	Intracellular Cytokine Staining
IFNγ	Interferon gamma
IL-4	Interleukin 4
IM	Intramuscular
IMDC	Immune Monitoring Development & Coordination (a Biolytics unit)
IMP	Investigational Medicinal Product
IRT	Interactive Response Technology
MLM	Medical Labs GmbH (Central Laboratory)
MN	Microneutralization
PBMC	Peripheral blood mononuclear cell
PM	Project Manager
pVN	Pseudo-Virus Neutralization
RNA	Ribonucleic acid
SOP	Standard Operating Procedure
TCR	T cell receptor
TNFα	Tumor Necrosis Factor alpha
VSV	Vesicular Stomatitis Virus

1 SCOPE OF THIS MANUAL

This manual is intended for use within BioNTech to describe the biomarker analytics performed within the clinical trial BNT162-01 at BioNTech group and biomarker specialty labs. It delineates the communication and decision lines between the involved units as well as it provides an overview on sample processing, assays and reporting to be performed within the involved units.

Note: Details on analytical methods performed by external specialty labs will be provided by vendor specific SOPs.

Sample processing and analyses which are performed by the contracted Central lab (i.e. MLM MLM Medical Labs GmbH, Dohrweg 63, 41066 Moenchengladbach, Germany) are not covered within this manual and are described in a separate manual ('Laboratory Instructions Manual for central lab'). However, the responsibilities in coordination of the transport between the involved units are covered by this manual.

2 OVERVIEW OF THE STUDY

This trial will investigate the potential safety and immunogenicity of three anti-viral RNA vaccine classes for active immunization against SARS-CoV-2, namely BNT162a (non-modified uridine containing mRNA), BNT162b (nucleoside modified mRNA), and BNT162c (self-amplifying mRNA). Two variants of the nucleoside modified mRNA, BNT162b1 and BNT162b2, which differ in the encoded antigen, will be tested.

Clinical trial design

Four different vaccine candidates (BNT162a1, BNT162b1, BNT162b2, and BNT162c2) will be tested.

The trial has two parts: a dose-finding part (Part A) with each one FIH starting dose cohort and up to 9 escalation, de-escalation or intermediate dose cohorts (with predefined dose levels or dose ranges) and, a second part (Part B) dedicated to recruit expansion cohorts with dose levels which are selected from data generated in Part A. The vaccines BNT162a1, BNT162b1, BNT162b2, and BNT162c2 will be administered using a prime / boost (P/B) regimen. The vaccine BNT162c2 will also be administered using a single dose (SD) regimen.

Table 2.1: Summary of vaccine dose regimens for younger adults aged 18 to 55 years in Part A.

Vaccine / mRNA type	Vaccine encoded antigen	Vaccine IM dosing regimen	Part A - Dose Groups & Dose (µg) (12 subjects per cohort)						
			1 Starting dose	**2**	**3** De-escalation dose	**4** Maximum dose	**5**	6	7
BNT162a1 / uRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	1A 3 µg	2A 0.6 µg	3A 0.1 µg	4A 6 µg	4A 1 µg		
BNT162b1 / modRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	1B 10 µg	2B 30 µg	3B 1 µg	4B 60 µg	5B 50 µg	6B 3 µg	7B 20 µg
BNT162b2 / modRNA	A modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	1C 10 µg	2C 30 µg	3C 1 µg	4C 60 µg	5C 50 µg	6C 3 µg	7C 20 µg
BNT162c2 / saRNA	A modified version of the full length SARS-CoV-2 S protein	Prime only: Day 1	1D 0.1 µg	2D 0.3 µg	3D 0.1 µg to 3 µg	4D 1 µg	5D 0.6 µg	6D 3 µg	
BNT162c2 / saRNA	A modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	1E 0.1 µg	2E 0.3 µg	3E 0.1 µg to 3 µg	4E 1 µg	5E 0.6 µg	6E 3 µg	

IM = intramuscular; RBD = Receptor Binding Domain; S protein = SARS-CoV-2 Spike protein

Table 2.2: Summary of vaccine dose regimens for older adults aged 56 to 85 years in Part A.

Vaccine / mRNA type	Vaccine encoded antigen	Vaccine IM dosing regimen	Part A - Dose Groups & Dose (µg) (12 subjects per cohort)		
			8 Older adults	**9** Older adults	**10** Older adults
BNT162b1 / modRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	8B 3 µg	9B 10 µg	10B 20 µg
BNT162b2 / modRNA	A modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	8C 3 µg	9C 10 µg	10C 20 µg

IM = intramuscular; RBD = Receptor Binding Domain; S protein = SARS-CoV-2 Spike protein

Part A

The first part of the trial (Part A) will follow a dose-escalation design. The first-in human starting dose and the planned escalation / de-escalation doses are given in Table 2.1 & Table 2.2 and will use a sentinel dosing / subject staggering process as follows:

Starting dose: 1 sentinel subject → 24 h observation → 5 subjects → 48 h observation → 6 subjects → 48h observation → transition to escalation and de-escalation dose after SCR meeting

Escalation dose: 2 sentinel subjects → 24 h observation → 4 subjects → 48 h observation → 6 subjects → 48h observation → transition to next escalation dose after SCR meeting

De-escalation dose: If possible, 12 subjects will be dosed with the planned dose on one day

Part B

Details of Part B will be defined after evaluation of aggregate data from Part A using a protocol amendment.

Progression to Part B will be based on analysis of both immunogenicity and safety data gathered in Part A. Both immunogenicity and safety will be thoroughly assessed to select the vaccine and the dose(s) to be further evaluated in Part B.

Safety data to be evaluated includes the package used by the SRC to assess individual dose levels and in addition any other safety observations that may be reported until the data cut off.

Trial duration
In total, the planned trial duration of Part A is expected to be approximately 12 months. From screening visit (Visit 0) to the last visit (Visit 8 [BNT162c2 SD]; Visit 9 [BNT162a1, BNT162b1, BNT162b2, BNT162c2 P/B]), each trial subject will be in the trial for a maximum of 223 days. For logistical reasons, the different vaccines may not be able to start at the same time.

Population
Healthy adults aged 18 to 55 years (Cohort 1 to 7; younger adults) or aged 56 to 85 years (Cohort 8 to 10; older adults). Subjects aged 56 to 85 years must be enrolled such that at least 6 subjects per cohort are aged 65 to 85 years.

For each vaccine, 12 subjects are required for each of the cohorts planned in Part A (see Table 2.1 & Table 2.2).

The planned number of trial subjects in Part B will be calculated based on the data from Part A and defined in a protocol amendment.

Study sites
Within the trial the following study sites are involved:

Germany:

- CRS Clinical Research Services Mannheim GmbH, Grenadierstrasse 1, 68167 Mannheim, Germany, (PI: Dr. Dr. med. Armin Schultz, Tel.: +49 0621 15045 165)
  Site specific number: 276-01
- CRS Clinical Research Services Berlin GmbH, Sellerstrasse 31, 13353 Berlin, Germany, (PI: Dr. Sybille Baumann, Tel.: +49 30 859 949-101)
  Site specific number: 276-02

Subject number / Sample ID

A subject-specific number will be allocated by the study site, which is created as follows:

- **Specific site number (3-digit numeric country code – 2-digit site number) – 4-digit subject number**

The 4-digit subject number will be counted up for each site individually, e.g. 276-01-0001 for the first subject that was enrolled CRS Mannheim.

For BioNTech-internal biomarker assays, the Biosampling Unit will allocate an additional unique study-specific subject ID for each subject (i.e. B162xxxx) and unique sample IDs for all samples collected from this particular subject (e.g. first serum aliquot: B162xxxx_1WB_1SE_1; WB: whole blood, SE: serum). The internal sample IDs shall be used for all biomarker assays in parallel to the subject number generated by the study site.

3 RESPONSIBILITIES AND CONTACT PERSONS

The main responsibilities are depicted in Table 3.1. The main contact persons for the biomarker program and immune monitoring analytics are listed in Table 3.2 and Table 3.3.

Table 3.1: Main responsibilities of persons and units involved within BNT162-01 biomarker program.

Function/Unit	Main Responsibilities
Project Manager (PM/Deputy PM)	• Initiates the biomarker WP • Maintains tracking list subject overview in coordination with Clinical Operations (CO) Team and Biomarker PM • Releases samples for standard assays • Prepares work orders • Approves sample transport from external peripheral blood mononuclear cell (PBMC) labs to the Biosampling Unit (BSU) for the immune monitoring program in consultation with the respective departments (if applicable) • Orders sample transport to additional partners and CROs (*e.g.* MLM) in coordination with Clinical Operations (CO) Team • Initiates implementation of subject-specific data into Spotfire platform together with Biomarker PM / IBM-PM • Releases Process Description Biomarker Analytics
Biomarker PM	• Maintains overview of biomarker analytics • Coordinates the biomarker program • Communicates with MLM regarding scheduling of frozen sample shipments to BioNTech or external vendors • Determines the necessity that samples are transported from the clinical site to MLM and initialize this transport in coordination with PMs • Orders sample transport to additional partners and CROs (e.g. MLM) in coordination with PM Team • Communicates with the sites regarding scheduling of frozen sample shipments to MLM • Requests HLA typing of individual subjects in coordination with IBM-PM and PM • Owns the biomarker manual • Supports maintenance of subject tracking list • Supports implementation of subject-specific biomarker data into Spotfire platform
Clinical Operations (CO) Team (CSM & CRA)	• Maintains tracking list subject overview in coordination with PMs and Biomarker PM
Immune Biomarker Project Manager (IBM-PM)	• Coordinates all immune-related analyses (CMI response) • Initiates implementation of subject-specific ELISpot data into Spotfire platform together with PM / Biomarker PM • Prepares specific reports for *ex vivo* ELISpots with data from Biolytics-GCP Unit • Prepares and updates respective data for Spotfire dashboard implementation (if applicable)

Function/Unit	Main Responsibilities
Biosampling Unit (BSU)	• Maintains overview / list on available samples according to sample income system/SOPs • Registers and processes incoming samples • Storage and handover of samples according to the valid SOPs • Files 'Visitenbögen'
Biosampling Core Facility (BS CF)	• Performs PBMC isolation from blood samples (if required)
Biolytics-GCP Unit	• Performs interferon-gamma (IFNγ) enzyme-linked immunospot analysis (ELISpot) (*ex vivo*) • Performs human IgG seroconversion ELISA (if required)
Immunogenicity Testing Unit	• Performs intracellular cytokine staining (ICS), epitope mapping (ex vivo IFNγ ELISpot), flow-cytometry-based T cell phenotyping including multimers, post-IVS IFNγ ELISpot analysis and multiplex cytokine analysis • Prepares and updates respective data for Spotfire dashboard implementation (if applicable)
Immunomodulators Unit	• Performs pseudo-virus neutralization (pVNT) assay
TCR Discovery Unit	• Performs TCR repertoire profiling and BCR repertoire profiling • Performs TCR discovery using single cell 10x Genomics 5`V(D)J and gene expression analysis after Multimer staining and single cell sorting
Immunoreceptor Validation Unit	• Performs isolation of CD4+ and CD8+ T cells and CD19+ B cells for TCR and BCR repertoire profiling, respectively • Performs flow cytometry based isolation of SARS-Cov-2-specific CD4+ and CD8+ T cells after antigen-specific re-stimulation for 10x Genomics 5`V(D)J and gene expression analysis • Performs *in vitro* characterization of TCRs discovered from SARS-Cov-2-specific T cells (HLA restriction, epitope specificity)
Data Science and Biomarker Analysis Unit (DS & BM Unit)	• Organizes the timely set-up of data structures required for data transfer / storage / reporting / visualization (e.g. Spotfire dashboard) • Data management (data specifications, data flow and overall reconciliation) of data that will be integrated into the Spotfire platform • Performs descriptive and correlative analysis of data

Table 3.2: Main contact persons for BNT162-01 within the biomarker program.

Role	Contact
PM	Corinna Rosenbaum, PhD Tel: +49 6131 9084-1424 e-mail: Corinna.Rosenbaum@biontech.de
Deputy PM (primary contact)	Ludwig Heesen, PhD Tel: +49 6131 9084-1298 e-mail: Ludwig.Heesen@biontech.de

Biomarker PM responsible for study-specific Biomarker (BM PM)	Carsten Boesler, PhD Tel: +49 6131 9084-7554 e-mail: Carsten.Boesler@biontech.de
Deputy BM PM	Luca Agnetta, PhD Tel: +49 6131 9084-7563 e-mail: Luca.Agnetta@biontech.de
Immune Biomarker Project Manager (IBM-PM)	Evelyna Derhovanessian, PhD Tel.: +49 6131 9084-1677 e-mail: Evelyna.Derhovanessian@biontech.de
CSM	David Langer, PhD Tel: +49 6131 9084-1204 e-mail: David.Langer@biontech.de
Deputy CSM	Stefanie Bolte, PhD Tel: +49 6131 9084-1283 e-mail: Stefanie.Bolte@biontech.de

Email distribution list: CorVac-BM@biontech.de

Table 3.3: Analytical units and contact information of the responsible persons for analytic and analysis.

Analytical Unit	Responsible	Analysis
Biosampling Unit, BioNTech SE	Christine Anft Tel.: +49 6131-9084-1116 e-mail: Christine.Anft@biontech.de Sabrina Jägle Tel.: +49 6131 9084-1050 e-mail: Sabrina.Jaegle@biontech.de	Isolation of PBMCs from Li-heparin blood (Mannheim site, back-up Berlin site)
Biosampling Core Facility, BioNTech RNA Pharmaceuticals	Tanja Kotur, PhD Tel.: +49 6131-9084-1477 e-mail: BiosamplingCF@biontech.de (e-mail: Tanja.Kotur@biontech.de)	Back-up lab for PBMC isolation from Li-heparin blood (Mannheim site, back-up Berlin site)
Precision for Medicine / Epiontis GmbH	Laura Lozza, PhD (Senior Scientist – Cell Biology Laboratory) Precision for Medicine / Epiontis GmbH Barbara-McClintock- Str. 6 12489 Berlin, Germany Tel.: +49 30 6392 3494 e-mail: Laura.Lozza@precisionformedicine.com	Isolation of PBMCs from Li-heparin blood (Berlin site only)
MLM Medical Labs GmbH	Natalie Rothhausen Tel: +49 2161 4642 242 e-mail: nrothhausen@mlm-labs.com	HLA typing
Biolytics-GCP, BioNTech SE	Dirk Becker Tel: +49 6131-9084-1302 e-mail: Dirk.Becker@biontech.de Marie-Cristine Kühnle, PhD Tel.: +49 6131 9084-7609 e-mail: Marie-Cristine.Kuehnle@biontech.de	IFNγ ELISpot (*ex vivo*) analysis of PBMCs
Immunogenicity Testing, BioNTech RNA Pharmaceuticals GmbH	Isabel Vogler, PhD Tel: +49 6131 9084-1410 e-mail: Isabel.Vogler@biontech.de	ICS analysis of PBMCs, epitope mapping (*ex vivo* IFNγ ELISpot), flow cytometry-based T cell phenotyping including multimers, post-IVS ELISpot analysis, multiplex-cytokine analysis
Biolytics-IMDC, BioNTech SE	Alexander Ulges, PhD Tel: +49 6131-9084-1677 e-mail: Alexander.Ulges@biontech.de Evelyna Derhovanessian, PhD Tel.: +49 6131 9084-1677 e-mail: Evelyna.Derhovanessian@biontech.de	Development and support in mulitmer analysis of PBMCs
VisMederi Srl	Giulia Lapini, PhD (Principal Scientist) Strada del Petriccio e Belriguardo, 35 53100 Siena, Italy	Performance of neutralization assays and ELISA using serum samples

Analytical Unit	Responsible	Analysis
	Telefon: +39 0577 381260 E-Mail Adresse: lapini@vismederi.com	
Biolytics-GCP, BioNTech SE	Ulrich Luxemburger Tel.: +49 6131 9084-7052 e-mail: Ulrich.Luxemburger@biontech.de Corinna Schicker Tel.: +49 6131 9084-1309 e-mail: Corinna.Schicker@biontech.de	Back-up lab for ELISA analysis of serum samples
Immunomodulators Unit, BioNTech RNA Pharmaceuticals GmbH	Alexander Muik, PhD Tel: +49 6131 9084-1448 e-mail: Alexander.Muik@biontech.de	Performance of pseudo-virus neutralization assays
TCR Discovery Unit, BioNTech Cell & Gene Therapies GmbH	Tana Omokoko, PhD Tel: +49 6131 9084-1126 e-mail: Tana.Omokoko@biontech.de	TCR / BCR repertoire profiling, 10x Genomics 5' VDJ and gene expression analysis of single T cells, TCR discovery
Immunoreceptor Validation Unit, BioNTech Cell & Gene Therapies GmbH	Petra Oehm, PhD Tel: +49 6131 9084-1100 e-mail: Petra.Oehm@biontech.de	TCR characterization
Data Science & Biomarker Unit, BioNTech SE	Daniel Maurus, PhD Tel: +49 6131 9084-1565 e-mail: Daniel.Maurus@biontech.de	Maintenance of data on Spotfire platform

4 RELEVANT DOCUMENTS AND DATA DOCUMENTATION

A list with relevant documents for the biomarker program is summarized in Table 4.1. Generated biomarker data are saved under P:\BioNTechRNA\RN9391R00_CoV-VAC\06_Biomarker as shown in Table 4.2.

Table 4.1: List with relevant documents for biomarker program of BNT162-01.

Document	Location
Clinical Study Protocol, incl. Schedule of Procedures	P:\BioNTechRNA\RN9391R00_CoV-VAC\07_Core_Documents\04_CSP
Laboratory Instructions Manuals	P:\BioNTechRNA\RN9391R00_CoV-VAC\05_Clinic\08_Central_and_local_Testing\MLM\Lab Manual
Overview on Subject Tracking, incl. planned date of visits, etc.	P:\BioNTechRNA\RN9391R00_CoV-VAC\06_Biomarker\00_Overview
'Visitenbögen'	P:\BioNTechRNA\RN9391R00_CoV-VAC\06_Biomarker\00_Overview\05_Visit_documentation_forms
List of available samples	P:\BioNTechRNA\RN9391R00_CoV-VAC\06_Biomarker\00_Overview\04_List_of_blood_samples
Templates for data presentation (experiment-, subject- and study-specific)	P:\BioNTechRNA\RN9391R00_CoV-VAC\06_Biomarker\01_Templates

Table 4.2: Overview for documentation of biomarker data.

Document/Data	Location
Summary of biomarker analysis	P:\BioNTechRNA\RN9391R00_CoV-VAC\ 06_Biomarker\00_Overview\02_Summary_of_analyses
Date-specific status report presentation	P:\BioNTechRNA\RN9391R00_CoV-VAC\06_Biomarker\00_Overview\01_Presentations
Subject-specific presentations (if required)	P:\BioNTechRNA\RN9391R00_CoV-VAC\ 06_Biomarker*Subject Number*\00_Running_presentation → one *uID* folder for every subject
Experiment-specific presentations (if required)	P:\BioNTechRNA\RN9391R00_CoV-VAC\ 06_Biomarker*Subject Number*\04_Response_monitoring → one *Subject Number* folder for every subject; one sub-folder for every type of experiment; *e.g.* ELISpot
Correlation analysis	P:\BioNTechRNA\RN9391R00_CoV-VAC\ 06_Biomarker\00_Overview\03_Correlation_analysis

5 SCHEDULE OF PROCEDURE AND OVERVIEW ON SAMPLES

Samples from subjects are collected at the study sites according to the clinical trial protocol and the health conditions of the subject.

5.1 Release of samples for biomarker analysis

For the following analyses within the biomarker program, samples can be routinely released by the PM or Biomarker PM without previous consultation of the CSM:

- Assessment of functional antibody titers
  (e.g. Virus Neutralization Assays specific to SARS-CoV-2)
- Antibody binding assays
  (e.g. ELISA specific to SARS-CoV-2 proteins and / or protein domains)
- Assessment of cell-mediated immune responses
  (e.g. *ex vivo* IFNγ ELISpot specific to vaccine-encoded antigens)

The listed analyses are all described in the CTP and are routinely covered by informed consents. However, subjects can exclude particular analyses (even if those are listed as routine analyses here). If this is the case, the CO team has to directly inform the PM about the exclusion of analysis in a written form.

Biomarker samples must not be transferred between labs or external vendors without full documentation of the identity of each single sample in the sample tracking sheet (SOP-020-010). Full documentation of sample identity in the sample tracking sheet requires mandatorily i) the Subject Number (276-xx-xxx), ii) the (Biosampling) Subject ID (B162xxxx) and iii) the (Biosampling) Sample ID (B162xxxx_xxx_xxx_x).

5.2 Blood samples

Processing of blood samples is performed according to the Laboratory Instructions Manual at the study site, at a contracted laboratory (e.g. Precision for Medicine, Berlin) or according to SOP-030-100 for samples that are received at the Biosampling Unit (BioNTech SE) / Biosampling Core Facility (BioNTech RNA Pharmaceuticals). The samples which are further analyzed within the biomarker program in BioNTech group or biomarker specialty laboratories are summarized in Table 5.1.

Table 5.1: Samples to be analyzed within the biomarker program for BNT162-01.

Material	Amount	Visit (V)	Processed Sample	Amount	Analysis
Whole blood (Li-heparin)	100 mL	BNT162a1/b1/b2/c2 (PB)*: V1 (d1), V5 (d29) BNT162c2 (SD): V1 (d1), V5 (d29)* or V6 (d43)	Viable PBMCs	From a healthy adult donor, the expected PBMC yield is 0.8-3.2 x 10^6 cells per mL whole blood.	(1) INF-γ ELIspot (*ex vivo*) (2) ICS analysis
Whole blood (Clotting activator)	10 mL	BNT162a1/b1/b2/c2 (PB)*: V1 (d1), V3 (d8), V4 (d22), V5 (d29)*, V6 (d43), V7 (d50)*, V8 (d85), V9 (d184) BNT162c2 (SD): V1 (d1), V3 (d8), V4 (d22), V5 (d29)*, V6 (d43), V7 (d85), V8 (d184)	Serum	Approx. 5 mL	(1) Assessment of functional antibody titers (2) Antibody binding assays
Whole blood (Li-heparin)	200 mL	BNT162b1/b2/c2 (PB): V6 (d43): 100 mL V8 (d85): 50 mL V9 (d184): 50 mL (please refer to Note to File: BNT162-01_NTF_0010)	Viable PBMCs (plasma)	From a healthy adult donor, the expected PBMC yield is 0.8-3.2 x 10^6 cells per mL whole blood.	Epitope mapping (IFNγ ELISpot), multimer / ICS analysis, TCR/BCR characterization, INFγ ELIspot (post-IVS), multiplex cytokine analysis

*: Time point were added in CTP Version 7 (26JUN2020)

The detailed schedule of procedure is described in the Clinical Trial Protocol located in the following location:

- P:\BioNTechRNA\RN9391R00_CoV-VAC\07_Core_Documents\04_CSP

5.2.1 Preparation of PBMCs for CMI response

Isolation of PBMCs from Li-heparin blood takes place at contracted laboratories (Precision for Medicine, Berlin), at the Biosampling Unit (BioNTech SE) or in the labs of the Biosampling Core Facility (BioNTech RNA Pharmaceuticals), depending on the study site (see Table 5.2). BioNTech is responsible that the contracted laboratories process the blood samples according to BioNTech standards (SOP-030-100).

Table 5.2: Responsible unit / lab for PBMC isolation from heparin blood for the different study sites.

Clinical site	Site of PBMC isolation
CRS Mannheim	BioNTech Biosampling Unit, Mainz, Germany
CRS Mannheim (back-up)	BioNTech Biosampling Core Facility, Mainz, Germany
CRS Berlin	Precision for Medicine, Berlin, Germany
CRS Berlin (back-up)	BioNTech Biosampling Unit / Biosampling Core Facility, Mainz, Germany

The transport of PBMCs from contracted laboratories is either actively requested by the Biosampling Unit / Biomarker PM (in consultation with the CO team) or automatically triggered by the contracted laboratory in consultation with the Biosampling Unit.

6 BIOMARKER PROGRAM

This section describes the biomarker program for all subjects participating in the BNT162-01 trial, including details on communication lines required for its initiation and implementation, the assays to be performed, and finally the reporting of the immune biomarker data.

The biomarker program will be performed at the BioNTech Biolytics-GCP Unit as well as specialty laboratories as outlined in Figure 6-1 and Figure 6-2.

6.1 Objectives of the biomarker program

Within the clinical trial BNT162-01, a continuous immune monitoring program will be performed to analyze subject´s immune responses against vaccine-encoded antigens specific to SARS-CoV-2 S1 protein or S1 RBD domain.

Documentation and Reporting
The status of the (immunological) biomarker analyses of BNT162-01 will be documented in an Excel spreadsheet saved in the following folder:

- **P:\BioNTechRNA\RN9391R00_CoV-VAC\06_Biomarker\00_Overview\02_Summary_of_analyses**

This spreadsheet will be regularly updated by Biomarker PM (with support of the IBM-PM) – the table will be updated upon recruitment of any new subject and / or completion of analyses (however not later than every two weeks). The date of the last update will be documented in each table.

Additionally, the respective data will be transferred to DS & BA Unit und uploaded to Spotfire platform.

Subject-specific information is available on the Spotfire platform for team members that can access the BNT162-01 project.

Optional, if requested: Subject- / date- / experiment-specific presentations based on Spotfire data presentation can be prepared and will be saved in the following folder:

- **P:\BioNTechRNA\RN9391R00_CoV-VAC\06_Biomarker\00_Overview\01_Presentations**

The CO Team will provide subject data, while the Biomarker PM (with support of the IBM-PM) will include (immunological) biomarker data within these presentations.

6.2 Initiation of the biomarker program for each subject

The expected dates of a trial subject visits including general information are summarized in an Excel spreadsheet located in the following folder:

- **P:\BioNTechRNA\RN9391R00_CoV-VAC\06_Biomarker\00_Overview**

The excel sheet is regularly updated by the CO Team.

The IBM-PM will be responsible for internal coordination and initiation of CMI analysis. CMI analysis of individual subject samples should include pre- and post-vaccination samples within the same assay run to allow for direct comparison of results.

The analytical study director at Biolytics GCP will initiate the transfer of the samples from the BSU. Actual sample transfer from the BSU will be performed after the release of the samples by the respective PMs. All samples should be requested using **the sample tracker:**

https://extranet.biontech.de:444/tracker-study-samples/_layouts/15/start.aspx#/SitePages/Home.aspx

By approving the sample request PM simultaneously approves the responsible Analytical Unit to perform the requested analysis.

The request procedure and sample tracking has to be performed according to SOP-020-016.

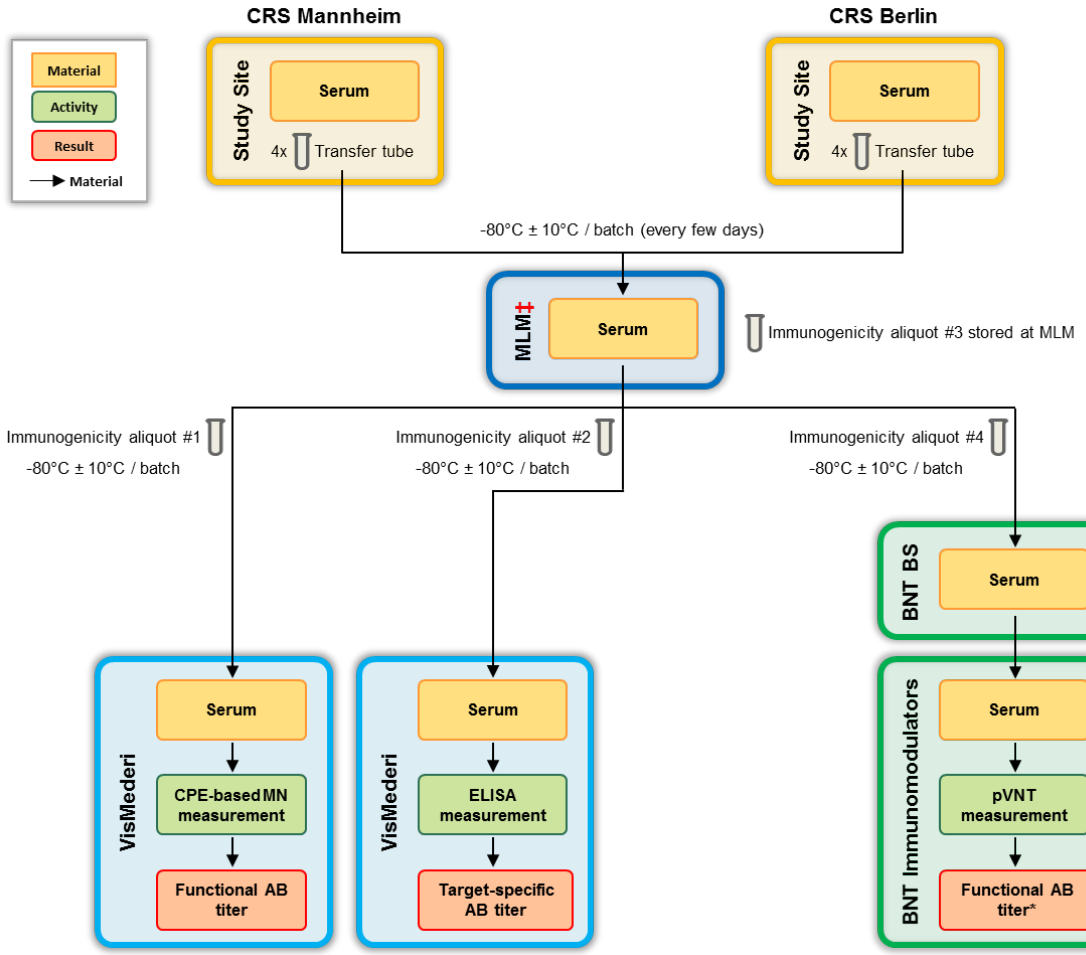
Initiation of biomarker analysis at external specialty labs will occur according to vendor specific Work Orders.

HLA typing (performed MLM Medical Labs GmbH) will be requested by the BM-PM in coordination with the IBM-PM / PM. This analysis of the subject's HLA type will only be initiated upon signature of respective ICF and is based on results in the routinely performed INF-γ ELISpot (*ex vivo*). HLA typing is a pre-requisite for further characterization of T cell-response as described in Table 5.1 and section 6.5. Please refer to Note to File: BNT162-01_NTF_0012.

6.3 Immunogenicity analysis of serum samples

Analysis of immunogenicity will include immunological and molecular techniques, such as virus neutralization assays and ELISA, to characterize the type and specificity of functional (neutralizing) and overall antibody responses in healthy adults after immunization, respectively. The workflow for sample processing, handling and analysis is outlined in Figure 6-1.

Figure 6-1: Summary of immunogenicity analysis performed as part of clinical trial BNT162-01



6.3.1 Virus Neutralization Assay

Serum isolated form peripheral blood of healthy adults will be subjected to virus-specific CPE-based micro neutralization (MN) assay in order to determine the relative abundance of neutralizing antibodies (i.e. inhibition of viral replication) specific to SARS-CoV-2 as a result of immunization.

The virus neutralization assay does not detect all antigen–antibody reactions, but only the fraction of neutralizing (functional) antibodies that actually block virus replication. Briefly, antibodies present in the serum of subjects bind to the SARS-CoV-2 wild-type virus and neutralize the infection of a cell line (e.g. Vero- or Huh7-cell lines). A known concentration of the SARS-CoV-2 virus is supplemented with increasing dilutions of serum and inhibition of virus infection is documented for respective serum dilutions.

This assay format utilizes an end point titration method to determine the serum dilution, which is necessary to reach a distinct threshold level of signal. Comparison of results generated with pre- and post-vaccination samples of each subject are indicative for occurrence of neutralizing antibodies / relative changes of neutralizing antibody titers after vaccination.

6.3.2 ELISA

Serum isolated from peripheral blood of healthy adults will be subjected to ELISA analysis in order to determine the occurrence and relative abundance of antibodies specific to defined proteins / protein domains of SARS-CoV-2 as a result of immunization.

Enzyme-linked immunosorbent assay (ELISA) is a solid phase immunoassay, which allows the detection of specific antigen-antibody interactions. The detection of target specific antibodies in human biological samples is carried out through coating of a plate with a specific antigen. Respective target proteins used in BNT162-01 are SARS-CoV-2 protein S1 and / or protein domains thereof (e.g. RBD domain).

Antibodies present in the serum of subjects bind to the coated target protein and can be detected by use of hu-IgG specific secondary antibody conjugated with peroxidase or phosphatase enzyme. Binding of the secondary antibody allows enzyme-mediated turn-over of a colorimetric substrate, which is measured by spectrometry in an ELISA reader.

This assay format utilizes an end point titration method to determine the serum dilution, which is necessary to reach of distinct threshold level of signal. Comparison of results generated with pre- and post-vaccination samples of each subject are indicative for occurrence of antigen-specific antibodies / relative changes of antigen-specific antibody titers after vaccination.

6.3.3 Pseudo-Virus Neutralization Assay

Serum isolated form peripheral blood of healthy adults will be subjected to SARS-CoV-2 S pseudotyped vesicular stomatitis virus (VSV)-based pseudovirus neutralization (pVN) assay in order to determine the relative abundance of neutralizing antibodies (i.e. inhibition of cell entry) specific to SARS-CoV-2 S as a result of immunization. VSV-based pVN assay is routinely used for determination of neutralization titers in preclinical samples. Thus, ancillary analysis of clinical samples with the VSV-based pVN assay shall allow a relative comparison of neutralization titers determined by CPE-based MN assay to preclinical results.

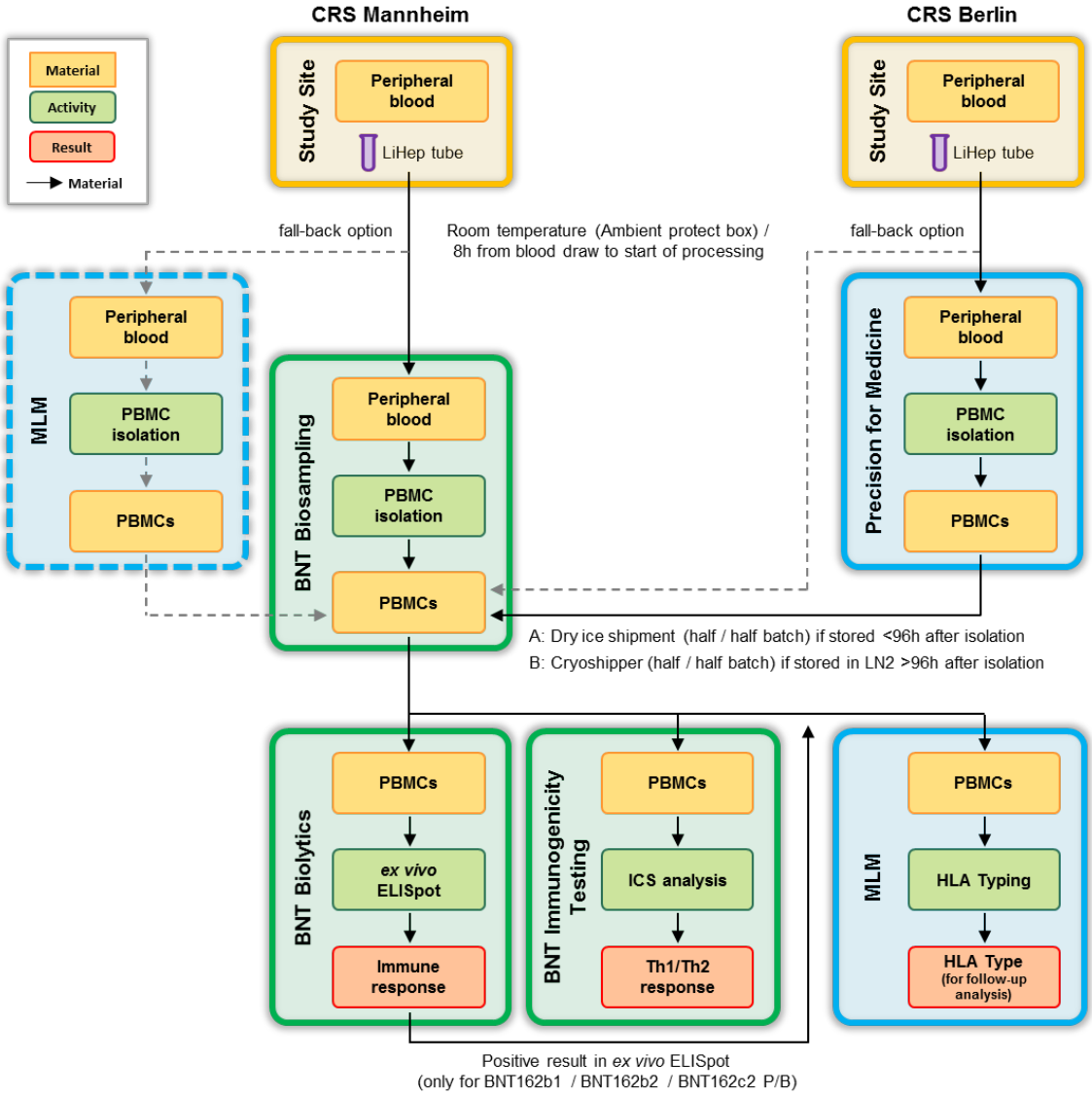
The pseudovirus neutralization assay does not detect all antigen–antibody reactions, but only the fraction of neutralizing (functional) antibodies that actually bind to SARS-CoV-2 S and interfere with host cell binding and cell entry. Briefly, the pVN assay uses a VSV vector that expresses a reporter gene (fluorescent or luminescent) and lacks the VSV G glycoprotein. The pseudotype virus instead bears the SARS-CoV-2 S protein, which mediates cell entry. Antibodies present in the serum of subjects bind to the SARS-CoV-2 S envelope and neutralize the infection of a cell line (e.g. Vero- or Huh7-cell lines), hence reducing the expression of the reporter. A known concentration of the SARS-CoV-2 S pseudotyped VSV is supplemented with increasing dilutions of serum and inhibition of the reporter signal is documented for respective serum dilutions.

This assay format utilizes an end point titration method to determine the serum dilution, which is necessary to reach a distinct threshold level of reporter signal. Comparison of results generated with pre- and post-vaccination samples of each subject are indicative for occurrence of neutralizing antibodies / relative changes of neutralizing antibody titers after vaccination.

6.4 Cell-mediated immune (CMI) response

Analysis of CMI response will include immunological techniques, such as ELISpot, to characterize the type and specificity of vaccine-induced antigen-specific T cells within peripheral blood of healthy adults after immunization. The workflow for sample processing, handling and analysis is outlined in Figure 6-2.

Figure 6-2: Analysis of CMI response performed as part of clinical trial BNT162-01



6.4.1 *ex vivo* IFNγ ELISpot

Peripheral blood mononuclear cell (PBMC) fractions isolated from blood of healthy adults will be directly (*ex vivo*) subjected to ELISpot analysis in order to determine the occurrence and relative abundance of T cells specific to defined proteins / protein domains of SARS-CoV-2 as a result of immunization.

Ex vivo enzyme-linked immunospot (ELISpot) is a method for detection of cytokine-secreting IFNγ T cells upon stimulation with defined target sequences. Stimulation will be performed using peptides covering the encoded antigen for each vaccine antigen (e.g. 15-mer overlapping peptides covering the whole length of the vaccine antigen with 11aa overlap).

In order to discriminate between CD4- and CD8-specific T-cell responses total PBMCs may be separated into $CD4^+$ / $CD8^-$ and $CD4^-$/$CD8^+$ fractions, which will individually be subjected to ELISpot analysis.

After antigen-specific stimulation of T cell fractions, the analyte (IFNγ) secreted by these cells is captured on a membrane and subsequently detected by the enzymatic-catalyzed generation of a visible chromogen. The number of spots is indicative for the frequency of antigen-specific T cells in respective cell fraction. Finally, comparison of results generated with pre- and post-vaccination samples of each subject are used as surrogate for induction / expansion of cellular immune responses upon vaccination.

6.4.2 ICS analysis

Peripheral blood mononuclear cell (PBMC) fractions isolated from blood of healthy adults will be subjected to intracellular cytokine staining (ICS) analysis in order to characterize the Th1 (IFNγ and TNFα) and Th2 (IL-4) cytokine profile of T cells specific to defined proteins / protein domains of SARS-CoV-2 as a result of immunization.

Intracellular cytokine staining is a flow cytometry-based assay to detect the production and accumulation of cytokines intracellularly upon cell stimulation. Stimulation will be performed using synthetic peptides covering the encoded antigen for each vaccine antigen (e.g. 15-mer overlapping peptides covering the whole length of the vaccine antigen with 11aa overlap).

After antigen-specific stimulation of PBMCs, inhibitors of protein transport (e.g. brefeldin A and monensin) are added to retain the produced cytokines within the cells. In order to discriminate between antigen-specific CD4- and CD8-T-cell responses, fluorescently labelled antibodies for CD4, CD8 and CD3 are used for staining of extracellular surface markers. Next, PBMCs are fixed (e.g. with paraformaldehyde) and subsequently permeabilized for intracellular staining of produced cytokines using fluorescently labelled, cytokine-specific antibodies (IFNγ, TNFα and IL-4). After the staining procedure, cells are analyzed on a flow

cytometer to measure the frequency of vaccine antigen-specific Th1 and Th2 as well as cytotoxic CD8 T cells. Finally, comparison of results generated with pre- and post-vaccination samples of each subject are used as surrogate for induction / expansion of cellular immune responses and to characterize the balance of generated Th1 and Th2 responses upon vaccination.

6.4.3 Additional explorative analyses

Up to 3 additional blood draws (with up to 200 mL in total) shall be taken from an individual subject over the complete trial for explorative biomarker / immunogenicity research purposes.

These additional research samples will be collected in order to investigate vaccine-induced immune responses by use of, but not limited to, phenotypic or functional characterization of antigen-specific T cells (e.g., by flow cytometry-based phenotyping including multimer staining) and analysis of TCR repertoire in peripheral blood after vaccination as well as multiplex-cytokine analysis.

Epitope mapping (*ex vivo* IFNγ ELISpot), flow cytometry-based T cell phenotyping including multimer stainings, post-IVS IFNγ ELISpot analysis and multiplex-cytokine analysis will be performed.

For in-depth analysis of vaccine-induced T- and B- cell responses, TCR/ BCR repertoire profiling as well as TCR discovery and characterization for deconvolution of epitope diversity, characterization of HLA restriction will be applied using pre- and post-vaccination PBMCs from selected vaccinated individuals.

Further, research samples may be stored and analysis may be performed on biomarker variants thought to play a role in the mechanism of action of BNT162 to evaluate their association with observed clinical responses to BNT162. Furthermore, samples may be used to develop methods, assays, prognostics and/or companion diagnostics related to BNT162.

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Laboratory Instructions

Manual Version 2

"A Multi-site, Phase I/II, 2-Part, Dose-Escalation Trial Investigating the Safety and Immunogenicity of four Prophylactic SARS-CoV-2 RNA Vaccines Against COVID-2019 Using Different Dosing Regimens in Healthy Adults"

TRIAL ID: BNT162-01
CRS ID: 049/20

Author **Clinical Study Manager (MLM)**	**Dr. T. Goller**	Date 16-Jul-2020 Sign. T. Goller
Reviewed by **Deputy Clinical Study Manager (MLM)**	**Dr. L. Lamertz**	Date 17-Jul.2020 Sign. L. Lamertz
Released by **COO (MLM)**	**Dr. S. Voswinkel**	Date 10-Sep 2020 Sign. S. Voswinkel

Approved by Client CRS Mannheim GmbH		I herewith confirm that the laboratory manual and the corresponding documents comply with the current protocol (Version 7.0, 26-Jun-2020).
Project Manager CRS Mannheim	**Bert Ehrlich**	Date 22/JUL/2020 Sign. Ehrlich

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Content

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Document Log

Lab Manual Version	Date of Implementation	Reference Version of Clinical Protocol	Page / Section	Description of Change
1	21-Apr-2020	Version 3.0 17-Apr-2020	-	-
2	16-Jul-2020	Version 7.0 26-Jun-2020	p. 1 / Title	change of title to “Laboratory Instructions Manual Version 2”
			p. 1 / Approved by Client	update of reference to study protocol version
			p. 2 / Content	complete update
			p. 6 / List of Abbreviations	addition of Abbreviations P/B and SD
			p. 7 / Safety Lab Assessments table	for BNT162c2, addition of Visit 5; for BNT162c2, differentiation between tested P/B or SD
			pp. 10 - 12 / Serum, K3EDTA Blood, NaF Plasma, Urine	for BNT162c2 when tested SD, addition of Visit 5 in all sampling descriptions
			pp. 13 and 14	addition of new chapter Preparation of Blood Smears Using the Manual Wedge-pull Technique
			p. 19 / Immunogenicity Assessments table	for Immunogenicity, addition of Visit 5 and Visit 7; for BNT162c2 when tested SD, for CMI, change from Visit 6 to Visit 5; for CMI addition of purpose HLA Typing addition of note regarding additional samples
			p. 20 / Tubes for Immunogenicity Assessments	for Li-Heparin blood – CMI, addition of purpose HLA Typing addition of sampling tube for optional K_3EDTA blood sampling

			p.21 / Sequence of Blood Sampling for Immunogenicity Assessments	addition of optional K_3EDTA blood sampling for HLA Typing
			p. 22 / Serum: Immunogenicity	addition of Visit 5 and Visit 7; addition of pooling step; amended description of preparing aliquots; amended description of shipment of aliquots
			p. 23 / Li-Heparin Blood: CMI (ELISpot, HLA Typing)	addition of purpose HLA Typing; for BNT162c2 when tested SD, change from Visit 6 to Visit 5
			p. 23 / Optional K3EDTA Blood: HLA Typing)	addition of new chapter
			p. 24 / box	amended description of shipment of Immunogenicity aliquots and K_3EDTA samples
			p. 26 / Example of Requisition Form	exchange of picture from requisition form
			p. 28 / Report of Lab Results	amendment of title and description
			p. 28 / Evaluation of Lab Results	amendment of description
			throughout document	change of “BNT162c1” to “BNT162c2” or “BNT162c2 when tested P/B” or BNT162c2 when tested SD

In case of an amendment of the clinical protocol with substantial changes related to the central lab procedures, this lab manual will be amended accordingly.

Contact Data – MLM

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For complaints you may also contact complaints@mlm-labs.com.

Opening Hours – MLM

Laboratory:	Mon - Fri	08:00 a.m. – 06:00 p.m. CET (UTC+1)
	Sat - Sun	11:00 a.m. – 03:00 p.m. CET (UTC+1)
Office:	Mon - Fri	08:00 a.m. – 06:30 p.m. CET (UTC+1)
Availability by Phone:	Mon - Sun	07:00 a.m. – 11:00 p.m. CET (UTC+1)

List of Abbreviations

ALT	alanine aminotransferase
a.m.	ante meridiem
AST	aspartate aminotransferase
BC	barcode
BUN	blood urea nitrogen
CET	central European time
CMI	cell-mediated immune testing
CRP	c-reactive protein
EoT	end-of-trial (visit)
FSH	follicle-stimulating hormone
g	gravity of Earth
h	hour(s)
GGT	gamma-glutamyltransferase
GOT	glutamate oxaloacetate transaminase
GPT	glutamic-pyruvic transaminase
HIV	human immunodeficiency viruses
ID	identification number
K_3EDTA	tri-potassium ethylenediaminetetraacetic acid
NaF	sodium fluoride
P/B	Prime boost dosing regimen
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
pH	potential of hydrogen
p.m.	post meridiem
PP	polypropylene
r	radius (of centrifuge rotor)
rpm	revolutions per minute
RT	room temperature
SD	single (priming) dose regimen
UTC	coordinated universal time
°C	degree Celsius

Safety Lab Assessments

Assessment	Visit 0	Visit 1 Pre-dose	Visit 2	Visit 3	Visit 5	Visit 6 (EoT)	Visit 7 (EoT)
	Day -30 - 0	Day 1	Day 2	Day 8 ± 1	Day 29 ± 3	Day 43 ± 4	Day 50 ± 4
Clinical Chemistry	✓	✓	✓	✓	✓	only BNT162c2 when tested SD	only BNT162a1, BNT162b1, BNT162b2 and BNT162c2 when tested P/B
Hematology	✓	✓	✓	✓	✓	only BNT162c2 when tested SD	only BNT162a1, BNT162b1, BNT162b2 and BNT162c2 when tested P/B
Plasma Glucose	✓	✓	✓	✓	✓	only BNT162c2 when tested SD	only BNT162a1, BNT162b1, BNT162b2 and BNT162c2 when tested P/B
Urinalysis	✓	✓	✓	✓	✓	only BNT162c2 when tested SD	only BNT162a1, BNT162b1, BNT162b2 and BNT162c2 when tested P/B
Viral Screening	✓						
FSH	✓						

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Laboratory Test Panels

Hematology
Leucocytes
Erythrocytes
Hemoglobin
Hematocrit
Platelets
Neutrophile Granulocytes
Lymphocytes
Eosinophile Granulocytes
Monocytes
Basophile Granulocytes

Viral Screening (only at Visit 0)
Hepatitis Bs antigen
Hepatitis Bc antibodies
Hepatitis C antibodies
HIV-1/2 combi

Clinical Chemistry
Sodium
Potassium
Calcium
Glucose
Albumin
Amylase
Lipase
Bilirubin, total
GOT (AST)
GPT (ALT)
gamma-GT
Alkaline phosphatase
Urea
Urea-N
Creatinine
CRP (high sensitive)
Ferritin

In women only
FSH (only at Visit 0)

Urine Status	
Specific.gravity	<u>in case of pathological findings: Urine Sediment</u>
pH	Erythrocytes
Nitrite	Leucocytes
Erythrocytes/Hemoglobin	Epithelial Cells
Leucocytes	Round Epithelial Cells
Bilirubin	Crystals
Urobilinogen	Bacteria
Protein	Casts
Ketone Bodies	
Glucose	

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Tubes for Safety Assessments

Parameters	Collection tube	Transfer tube	Color coding of labels (Example of label)
Serum - Clinical Chemistry, Viral Screening, FSH	 4.9 ml (13 mm x 90 mm) white Clotting activator **Sarstedt, S-Monovette®, 04.1934**	 4.5 ml (12 mm x 75 mm) transparent, polypropylene **Sarstedt, Order-No.: 60.557.001**	
K_3EDTA Blood - Hematology	 2.6 ml (13 mm x 65 mm) red K_3EDTA **Sarstedt, S-Monovette®, 04.1901**	no transfer tube	
NaF Plasma - Glucose	 2.6 ml (13 mm x 65 mm) yellow Fluoride/EDTA **Sarstedt, S-Monovette®, 04.1903**	 4.5 ml (12 mm x 75 mm) transparent, polypropylene **Sarstedt, Order-No.: 60.557.001**	
Urine - Urinalysis	collection cup	 10 ml (15.3 mm x 92 mm) transparent, polypropylene **Sarstedt, Order-No.: 60.610.100**	

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Mandatory Sequence of Blood Sampling for Safety Assessments

Collection tube	Color code of label
1. Serum tube (Clinical Chemistry, Viral Screening and FSH)	
2. K_3EDTA blood tube (Hematology)	
3. NaF plasma tube (Glucose)	

Serum: Clinical Chemistry, Viral Screening and FSH

Visits: <u>BNT162a1, BNT162b1, BNT162b2 and BNT162c2 when tested P/B:</u>
Visit 0: Clinical Chemistry, Viral Screening, FSH
Visit 1 Pre-dose, Visit 2, Visit 3, Visit 5, Visit 7 (EoT): only Clinical Chemistry

<u>BNT162c2 when tested SD:</u>
Visit 0: Clinical Chemistry, Viral Screening, FSH
Visit 1 Pre-dose, Visit 2, Visit 3, Visit 5, Visit 6 (EoT): only Clinical Chemistry

Collection tube: 4.9 ml serum collection tube white, clotting activator, Sarstedt
Transfer tube: 4.5 ml transfer tube transparent, polypropylene, Sarstedt
Sample: approximately 2.5 ml serum

1. On the requisition form “Safety”, fill in all the required subject, visit and sample specific data.
2. Use the collection tube “Clinical Chemistry” labeled with the same barcode as the requisition form.
3. Draw blood into the collection tube. Please make sure to fill up the tube with the indicated volume of blood.
4. After blood draw gently invert the tube 4 - 6 times.
5. Incubate at room temperature (15 - 26 °C) for 30 - 60 minutes.
6. Centrifuge at room temperature (15 - 26 °C) at 2000 x g for 10 minutes.
7. Immediately transfer approximately 2.5 ml supernatant into the barcode-labeled transfer tube “Clinical Chemistry”.
8. Store **light-protected** (e. g. in the MLM Safeguard Box®) at room temperature (15 - 26 °C) until shipment. (Bilirubin is a light sensitive parameter)

Shipment at ambient condition on the same day as sampling!

K_3EDTA Blood: Hematology

Visits: <u>BNT162a1, BNT162b1, BNT162b2 and BNT162c2 when tested P/B:</u>
Visit 0, Visit 1 Pre-dose, Visit 2, Visit 3, Visit 5, Visit 7 (EoT)

<u>BNT162c2 when tested SD:</u>
Visit 0, Visit 1 Pre-dose, Visit 2, Visit 3, Visit 5, Visit 6 (EoT)

Collection tube: 2.6 ml EDTA blood collection tube red, K3E, Sarstedt

Sample: 2.6 ml EDTA blood

1. Use the collection tube “Hematology” labeled with the same barcode as the requisition form.
2. Draw blood into the collection tube. Please make sure to fill up the tube with the indicated volume of blood.
3. After blood draw gently invert the tube 8 - 10 times.
4. Store the sample at room temperature (15 - 26 °C) until shipment.

Shipment at ambient condition on the same day as sampling!

NaF Plasma: Glucose

Visits: <u>BNT162a1, BNT162b1, BNT162b2 and BNT162c2 when tested P/B:</u>
Visit 0, Visit 1 Pre-dose, Visit 2, Visit 3, Visit 5, Visit 7 (EoT)

<u>BNT162c2 when tested SD:</u>
Visit 0, Visit 1 Pre-dose, Visit 2, Visit 3, Visit 5, Visit 6 (EoT)

Collection tube: 2.6 ml collection tube yellow, FE, Sarstedt

Transfer tube: 4.5 ml transfer tube transparent, polypropylene, Sarstedt

Sample: approximately 1.3 ml NaF plasma

1. Use the collection tube “Glucose” labeled with the same barcode as the requisition form.
2. Draw blood into the collection tube. Please make sure to fill up the tube with the indicated volume of blood.
3. After blood draw gently invert the tube 8 - 10 times.
4. Immediately (not later than 30 minutes after blood draw) centrifuge at room temperature (15 - 26 °C) at 2000 x g for 10 minutes.
5. Immediately transfer approximately 1.3 ml supernatant into the barcode-labeled transfer tube “Glucose”.
6. Store sample at cooling conditions (2 - 8 °C). For less than 1 hour before shipment, the sample can be placed in the MLM Safeguard Box®.

Shipment at ambient condition on the same day as sampling!

Urine: Urinalysis

Visits: <u>BNT162a1, BNT162b1, BNT162b2 and BNT162c2 when tested P/B:</u>
Visit 0, Visit 1 Pre-dose, Visit 2, Visit 3, Visit 5, Visit 7 (EoT)

<u>BNT162c2 when tested SD:</u>
Visit 0, Visit 1 Pre-dose, Visit 2, Visit 3, Visit 5, Visit 6 (EoT)

Collection tube: collection cup

Transfer tubes: 10.0 ml transfer tube yellow, polypropylene, Sarstedt

Sample: approximately 10.0 ml native urine

1. Collect mid-stream urine in a collection cup.
2. Transfer approximately 10.0 ml urine into the barcode-labeled transfer tube “Urinalysis”.
3. Store sample at cooling conditions (2 - 8 °C). For less than 1 hour before shipment, the sample can be placed in the MLM Safeguard Box®.

Shipment at ambient condition on the same day as sampling!

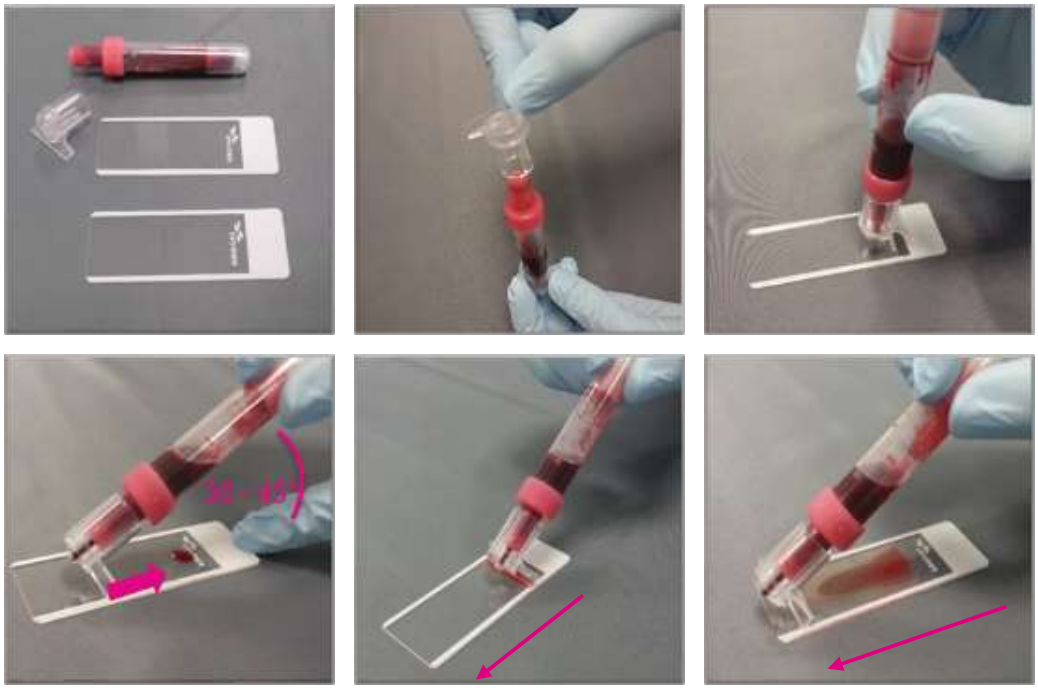
On the day of sampling, ship all safety blood and urine samples at ambient temperature in the MLM Safeguard Box® to MLM Medical Labs.

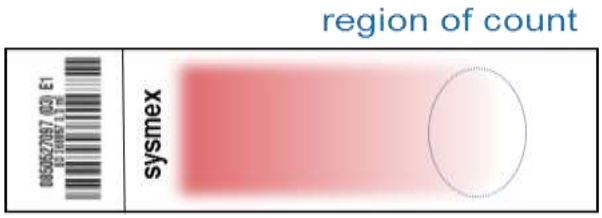
Preparation of Blood Smears Using the Manual Wedge-pull Technique

Purpose: control of results from manual differential blood count
Visit: Unscheduled
Material: 2 x specimen slides (Sysmex)
1 x slide mailer (VWR)
1 x haemo-diff blood dispenser (Sarstedt)
One drop of EDTA blood (ca. 8 µl) for each slide

1. Both blood smears should be prepared as soon as possible but latest within 4 hours after blood collection.
2. Please use the specimen slides with the same barcode number as the requisition form and the collection tube.
3. Place two clean specimen slides on a clean working ground.
   Make sure the white-printed side of the specimen slide is facing upwards!
4. Mix EDTA blood (collected for hematology as described above) by gently inverting the tube at least 5 times.
5. Hold the EDTA tube in an upright position and insert the cannula of the haemo-diff blood dispenser into the membrane of the EDTA tube. Do not insert, when the tube is upside down.
6. Hold the tube upside down. Position the tip of the dispenser ca. 0.5 cm from the white-printed area on the surface of the specimen slide.
7. Gently press tube downwards until a drop forms at the tip of the diff-safe blood dispenser. The instant the blood is deposited on the specimen slide, first slowly relax pressure, then quickly lift the tube off the specimen slide.

⚠ The size of the drop of blood is important! Please make sure to use ca. 8 µl blood.





Schematical example of a well-made periphal blood smear

8. Use the smear edge of the haemo-diff blood dispenser to spread the blood on the specimen slide: The EDTA tube, held securely in the dominant hand at about a 30- to 45-degree angle, is drawn back into the drop of blood. The blood is allowed to spread across the width of the slide.
9. The EDTA tube is then quickly and smoothly pushed forward to the end of the specimen slide to create a wedge film.

⚠ Maintaining an even, gentle pressure on the slide is essential. It is also crucial to keep the same angle all the way to the end of the film.

⚠ Occasionally, the blood film may be cut either too long/too short or the blood film is not spread evenly. These and other poorly made blood smears should be discarded. In this case, please prepare a new blood smear.

10. **Allow blood to air dry** (ca. 15 min).
11. Remove the dispenser from the EDTA tube and discard it according to your institutional regulations.
12. Place the two specimen slides in the slide mailer with the blood facing upwards.
13. Send the <u>two blood smears</u> along with EDTA blood within the leak proof package to MLM on the day of blood sampling.

SARS-CoV2 Assessments

Assessment	Visit 0	Visit 1
	Day -30 to 0	Day -1 or Day 1
SARS-CoV2 Antibodies	✓	
SARS-CoV2 PCR		✓

Tubes for SARS-CoV2 Assessments

Parameters	Collection tube	Transfer tube	Color coding of labels (Example of label)
Serum - SARS-CoV2 Antibodies	 2.6 ml (13 mm x 65 mm) white Clotting activator **Sarstedt, S-Monovette®, 04.1904**	2 x 2.0 ml (10.8 mm x 44 mm) transparent, polypropylene **Sarstedt, Order-No.: 72.694.106**	
Oral Wipe - SARS-CoV2 PCR	 cobas® PCR Media Uni Swab Sample Kit **Roche, 07 958 030 190**	no transfer tube applicable	

Serum: SARS-CoV2 Antibodies

Visits: BNT162a1, BNT162b1, BNT162b2 and BNT162c2:
Visit 0

Collection tubes: 2.6 ml serum collection tube white, clotting activator, Sarstedt

Transfer tubes: 2 x 2.0 ml transfer tubes transparent, polypropylene, Sarstedt

Samples: 2 x approximately 0.6 ml serum

1. On the requisition form “SARS-CoV2 Antibodies”, fill in all the required subject, visit and sample specific data.
2. Use the collection tube “SARS-CoV2 Antibodies” labeled with the same barcode as the requisition form.
3. Draw blood into the collection tubes. Please make sure to fill up the tubes with the indicated volume of blood.
4. After blood draw gently invert the tubes 4 - 6 times.
5. Incubate at room temperature (15 - 26 °C) for 30 - 60 minutes.
6. Centrifuge at room temperature (15 - 26 °C) at 2000 x g for 10 minutes.
7. Immediately transfer approximately 0.6 ml supernatant into both barcode-labeled transfer tubes “IgA / IgG 1” and “IgA / IgG 2”.
8. Immediately cap tubes and store at -80 °C ± 10 °C in an upright position within 90 minutes after blood drawing. Pre storage for a few hours at -20 °C ± 10 °C is possible.

⚠ Primary and back-up samples have to be shipped to MLM on dry ice. Primary and back-up samples should be shipped separately. Shipments are organized by MLM upon request. Please refer to the *Shipment Information Manual*.

Oral Wipe: SARS-CoV2 PCR

Visits: BNT162a1, BNT162b1, BNT162b2 and BNT162c2:
Visit 1 (Day -1 or Day 1)

Collection device: Uni Swab, Roche

Collection tube: transport tube, yellow, cobas® PCR Medium, Roche

Sample: oral wipe in 1.0 ml PCR medium

1. On the requisition form “SARS-CoV2 PCR”, fill in all the required subject, visit and sample specific data.
2. Decide if PCR analysis will be performed at CRS or by MLM in order to use the correct swab and if applicable the collection tube “PCR” with the same barcode as the requisition form.
3. Touch the swab only at the lower end. Take a sample by wiping and twisting the swab with moderate pressure over the mucosa of pharynx, tonsils and palate.
4. Place the swab in the collection tube with the sampling end within the medium. Break the shaft at the predetermined breaking point. Cap the tube.
5. Store sample at room temperature (15 - 26 °C) until analysis or shipment.

6a. Proceed with the PCR analysis at CRS.

6b. Optional: shipment to MLM at ambient condition on the same day as sampling!

Upon request, ship primary and back-up SARS-CoV2 samples separately on dry ice to MLM Medical Labs.

Optional: On the day of sampling, ship the SARS-CoV2 PCR sample at ambient temperature to MLM.

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Immunogenicity Assessments

BNT162a1, BNT162b1, BNT162b2 and BNT162c2 when tested P/B

Assessment	Visit 1 Pre-dose	Visit 3	Visit 4 Pre-dose	Visit 5	Visit 6	Visit 7 (EOT)	Visit 8 (FU)	Visit 9 (FU)
	Day 1	Day 8 ± 1	Day 22 ± 2	Day 29 ± 3	Day 43 ± 4	Day 50 ± 4	Day 85 ± 7	Day 184 ± 9
Immunogenicity	✓	✓	✓	✓	✓	✓	✓	✓
CMI (ELISpot, HLA typing)	✓			✓				

BNT162c2 when tested SD

Assessment	Visit 1 Pre-dose	Visit 3	Visit 4 Pre-dose	Visit 5	Visit 6 (EoT)	Visit 7 (FU)	Visit 8 (FU)
	Day 1	Day 8 ± 1	Day 22 ± 2	Day 29 ± 3	Day 43 ± 4	Day 85 ± 7	Day 184 ± 9
Immunogenicity	✓	✓	✓	✓	✓	✓	✓
CMI (ELISpot, HLA Typing)	✓			✓			

Additional samplings for immunogenicity assessments, HLA typing or biomarker research are recommended.

Tubes for Immunogenicity Assessments

Parameters	Collection tube	Transfer tube	Color coding of labels (Example of label)
Serum - Immuno-genicity	2 x  4.9 ml (13 mm x 90 mm) white Clotting activator **Sarstedt, S-Monovette®, 04.1934**	for pooling:  10 ml (15.3 mm x 92 mm) transparent, polypropylene **Sarstedt, Order-No.: 60.610.100** 4 x  4.5 ml (12 mm x 75 mm) transparent, polypropylene **Sarstedt, Order-No.: 60.557.001**	**not applicable** 
Li-Heparin blood - CMI (ELISpot, HLA Typing)	11 x  9.0 ml (16 mm x 92 mm) orange LH Lithium Heparin **Sarstedt, S-Monovette®, 02.1065**	no transfer tube applicable	
Optional **K_3EDTA Blood - HLA Typing**	 4.0 ml (15 mm x 75 mm) red K_3EDTA **Sarstedt, S-Monovette®, 03.1068**	no transfer tube applicable	

Sequence of Blood Sampling for Immunogenicity Assessments

Collection tube	Color code of label
1. Serum tubes (Immunogenicity)	
2. Li-Heparin tubes (CMI)	
3. Optional K_3EDTA blood tube (HLA Typing)	

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Serum: Immunogenicity

Visits: <u>BNT162a1, BNT162b1, BNT162b2 and BNT162c2 when tested P/B:</u>
Visit 1 Pre-dose, Visit 3, Visit 4 Pre-dose, Visit 5, Visit 6, Visit 7 (EOT), Visit 8 (FU), Visit 9 (FU)

<u>BNT162c2 when tested SD:</u>
Visit 1 Pre-dose, Visit 3, Visit 4 Pre-dose, Visit 5, Visit 6 (EoT), Visit 7 (FU), Visit 8 (FU)

Collection tubes: 2 x 4.9 ml serum collection tube white, clotting activator, Sarstedt

Pooling tube: 10.0 ml transfer tube yellow, polypropylene, Sarstedt

Transfer tubes: 4 x 4.5 ml transfer tubes transparent, polypropylene, Sarstedt

Samples: 4 x approximately 0.9 ml serum

1. On the requisition form “Immunogenicity”, fill in all the required subject, visit and sample specific data.
2. Use the two collection tubes “Immunogenicity A” and “Immunogenicity B” labeled with the same barcode as the requisition form.
3. Draw blood into the collection tubes. Please make sure to fill up the tubes with the indicated volume of blood.
4. After blood draw gently invert the tubes 4 - 6 times.
5. Incubate at room temperature (15 - 26 °C) for 30 - 60 minutes.
6. Centrifuge at room temperature (15 - 26 °C) at 2000 x g for 10 minutes.
7. Immediately pool the serum supernatants from both collection tubes into the 10 ml transfer tube “Immunogenicity C” and gently invert the tube 4 - 6 times.
8. Then transfer 0.9 ml serum into each of the three barcode-labeled transfer tubes “Immunogenicity 1 - 3”.
   Transfer all remaining serum into the barcode-labeled transfer tube “Immunogenicity 4”.
9. Immediately cap tubes and store at -80 °C ± 10 °C in an upright position within 90 minutes after blood drawing. Pre storage for a few hours at -20 °C ± 10 °C is possible.

All samples have to be shipped to MLM on dry ice.
Aliquots “Immunogenicity 1” and “Immunogenicity 4” shall be send together within the same shipment. Aliquots “Immunogenicity 2” and “Immunogenicity 3” shall be send together in another shipment. MLM provides a transport plan which exactly displays which samples shall be sent at defined dates. Shipments are organized by MLM upon request. Please refer to the *Shipment Information Manual*.

Li-Heparin Blood: CMI (ELISpot, HLA Typing)

Visits: BNT162a1, BNT162b1, BNT162b2 and BNT162c2 when tested P/B:
Visit 1 Pre-dose, Visit 5

BNT162c2 when tested SD:
Visit 1 Pre-dose, Visit 5

Collection tubes: 11 x 9.0 ml collection tubes orange, LH, Sarstedt

Samples: 99.0 ml (11 x 9.0 ml) Li-Heparin blood

1. On the requisition form “CMI (ELISpot)”, fill in all the required subject, visit and sample specific data.
2. Use the eleven collection tubes “CMI 1 - 11” labeled with the same barcode as the requisition form.
3. Draw blood into the collection tubes. Please make sure to fill up the tubes with the indicated volume of blood.
4. After blood draw gently invert the tubes 5 times.
5. Store at room temperature (15 - 26 °C) until shipment.

Shipment at ambient condition on the same day as sampling!

The isolation of PBMCs from the samples has to start latest 8 hours after blood draw.

Optional K_3EDTA Blood: HLA Typing

Visit: Unscheduled

Collection tube: 4.0 ml EDTA blood collection tube red, K3E, Sarstedt

Sample: 4.0 ml EDTA blood

1. Use the collection tube “HLA typing” labeled with the same barcode as the requisition form.
2. Draw blood into the collection tube. Please make sure to fill up the tube with the indicated volume of blood.
3. After blood draw gently invert the tube 8 - 10 times.
4. Store at -80 °C ± 10 °C in an upright position within 90 minutes after blood drawing. Pre storage for a few hours at -20 °C ± 10 °C is possible.

All samples have to be shipped to MLM on dry ice.
MLM provides a transport plan which exactly displays which samples shall be sent at defined dates. Shipments are organized by MLM upon request.

Referring to transport plan, ship Immunogenicity aliquots and optional K_3EDTA blood samples for HLA typing on dry ice to MLM Medical Labs.

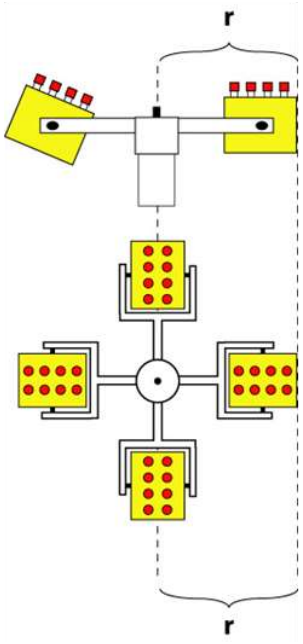
On the day of sampling, ship all CMI (ELISpot) samples at ambient temperature in the MLM Safeguard Box® to the lab mentioned in the Shipment Information Manual. The time between blood draw and start of PBMC preparation must not exceed more than 8 hours.

Centrifugation Table

Use a centrifuge with a swing-out rotor. If it is not possible to enter the speed in “g” on the centrifuge to be used, please use the table below showing the relation between radius of the rotor and speed. Centrifuge the tubes at the appropriate time and “g” (note g ≠ revolutions per minute [rpm]).

Centrifugation radius (cm)	at 2000 x g RPM
5	5981
6	5460
7	5055
8	4729
9	4458
10	4230
11	4033
12	3861
13	3710
14	3575
15	3453
16	3344
17	3244
18	3153
19	3068
20	2991
21	2919
22	2852
23	2789
24	2730
25	2675
26	2623
27	2574
28	2528
29	2484
30	2442

$$rpm = 1000 \times \sqrt{\frac{g}{11.18 \times r}}$$



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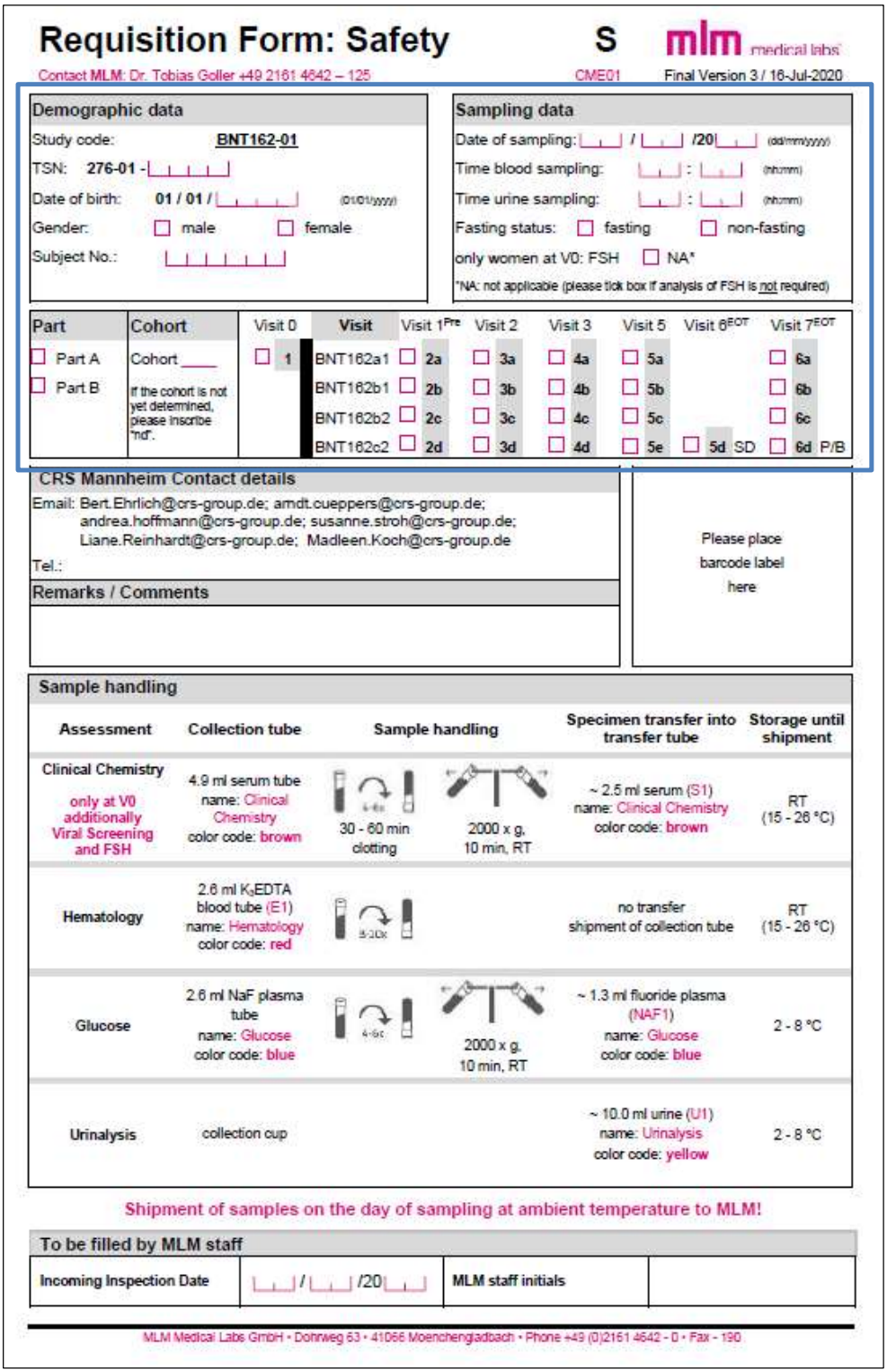
Phone +49 (0)2161 4642 - 0 • Fax - 190

Example of Requisition Form

Fill in all sample and subject specific data (blue framed box) on the requisition form labeled with the barcode corresponding to those of the transfer tubes (required data may vary compared to the example below).



Requisition Form: Safety

S

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Contact MLM: Dr. Tobias Goller +49 2161 4642 – 125 CME01 Final Version 3 / 16-Jul-2020

Demographic data

Study code: BNT162-01

TSN: 276-01 -____

Date of birth: 01 / 01 /____ (01/01/yyyy)

Gender: ☐ male ☐ female

Subject No.: ____

Sampling data

Date of sampling: __ / __ /20__ (dd/mm/yyyy)

Time blood sampling: __ : __ (hh:mm)

Time urine sampling: __ : __ (hh:mm)

Fasting status: ☐ fasting ☐ non-fasting

only women at V0: FSH ☐ NA*

*NA: not applicable (please tick box if analysis of FSH is not required)

Part	Cohort	Visit 0	Visit	Visit 1 Pre	Visit 2	Visit 3	Visit 5	Visit 6 EOT	Visit 7 EOT
☐ Part A	Cohort ____	☐ 1	BNT162a1	☐ 2a	☐ 3a	☐ 4a	☐ 5a		☐ 6a
☐ Part B	If the cohort is not yet determined, please inscribe 'ntd'.		BNT162b1	☐ 2b	☐ 3b	☐ 4b	☐ 5b		☐ 6b
			BNT162b2	☐ 2c	☐ 3c	☐ 4c	☐ 5c		☐ 6c
			BNT162c2	☐ 2d	☐ 3d	☐ 4d	☐ 5e	☐ 5d SD	☐ 6d P/B

CRS Mannheim Contact details

Email: Bert.Ehrlich@crs-group.de; arndt.cueppers@crs-group.de; andrea.hoffmann@crs-group.de; susanne.stroh@crs-group.de; Liane.Reinhardt@crs-group.de; Madleen.Koch@crs-group.de

Tel.:

Please place barcode label here

Remarks / Comments

Sample handling

Assessment	Collection tube	Sample handling		Specimen transfer into transfer tube	Storage until shipment
Clinical Chemistry only at V0 additionally Viral Screening and FSH	4.9 ml serum tube name: Clinical Chemistry color code: brown	30 - 60 min clotting	2000 x g, 10 min, RT	~ 2.5 ml serum (S1) name: Clinical Chemistry color code: brown	RT (15 - 26 °C)
Hematology	2.6 ml K_3EDTA blood tube (E1) name: Hematology color code: red	8-10x		no transfer shipment of collection tube	RT (15 - 26 °C)
Glucose	2.6 ml NaF plasma tube name: Glucose color code: blue	4-6x	2000 x g, 10 min, RT	~ 1.3 ml fluoride plasma (NAF1) name: Glucose color code: blue	2 - 8 °C
Urinalysis	collection cup			~ 10.0 ml urine (U1) name: Urinalysis color code: yellow	2 - 8 °C

Shipment of samples on the day of sampling at ambient temperature to MLM!

To be filled by MLM staff

Incoming Inspection Date	__ / __ /20__	MLM staff initials	

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Important Information

Sampling Material

➔ **PLEASE CHECK THE EXPIRY DATE OF EACH MATERIAL PRIOR USAGE!**
DO NOT USE EXPIRED MATERIAL!
PLEASE CONTACT MLM TO RECEIVE NEW SUPPLIES!

➔ At the end of the study or in case of expired material, discard all components as common waste. For the disposal of a large quantity you may also contact MLM Medical Labs.

Requisition Forms

➔ Fill in all required data in the requisition form. Send the **white copy** together with the ambient samples or in case of frozen batch shipments together with the primary sample to MLM. Keep the **press copy** of each requisition form for your documentation and file it at the study site. For **back-up samples** “IgA / IgG 2” and “Immunogenicity 2”, send the second press copy together with the back-up sample to MLM.

Barcode Labels

➔ Please ensure that all three elements (requisition form, collection tubes, transfer tubes) display the same barcode number.

➔ In the event of lost or damaged barcode labels use indelible ink to write the correct barcode number on tubes and requisition forms.

➔ The use of the MLM supplied barcode labels for the sampling and storage of biological samples for this study is mandatory.

➔ Study code, visit and material are displayed on each barcode label. An example is depicted below:

Withdrawal of Informed Consent

- ➔ If a subject withdraws the informed consent, immediately inform MLM. Please provide instructions whether respective samples should be stored or destroyed.
- ➔ Email: informed-consent@mlm-labs.com

Report of Lab Results

- ➔ Lab results will be provided in an **Analytical Lab Report**.
- ➔ Analytical Lab Reports will be uploaded in mlm online®.
- ➔ Additionally, Analytical Lab Reports can be sent to study site and sponsor specific addressees (investigators) by fax and/or email throughout the study.
- ➔ "Alert values": highly abnormal values will also be reported by phone/email to the principal investigator and further contact persons provided to MLM.
- ➔ **Report Status**

  A final report will be sent to the investigators as soon as all requested laboratory analyses have been conducted and results have been validated.

  A pending report can be sent when
  - almost all results are available but remaining test results will be available days later due to methodological reasons.
  - lab queries (see below) need to be solved by the study site/sponsor
  - alert values occur
  - requested by the study site/sponsor

  If data from a previous final report had been corrected, added or deleted, an amended report with change log will be sent.

Evaluation of Lab Results

- ➔ Clinical results shall be evaluated in mlm online®. For registration on mlm online® please refer to the instructions on page 32.
- ➔ The evaluation of a lab result can be changed by the investigator. All changes to an Analytical Lab Report are recorded in an audit trail.
- ➔ Alternatively, the results can be evaluated on the paper Analytical Report.

Request for Correction of Subject or Visit Data

- ➔ For correction of subject or visit data in the lab reports, please send an email to dbc@mlm-labs.com. Next to the data to be corrected, please provide: Subject ID, year of birth, visit, date/time of sampling and specific barcode. No further confidential information has to be provided. Based on this information you will receive a corrected lab report in due course.

Resolution of Lab Queries

➔ In case of missing or implausible inscriptions on requisition forms, missing or inappropriate samples or incorrect sample shipping, you will receive an automated email from query@mlm-labs.com. Please reply to this email. **Please do not change the subject line of the email!** If you do not answer to this email, you will receive subsequent reminder emails.

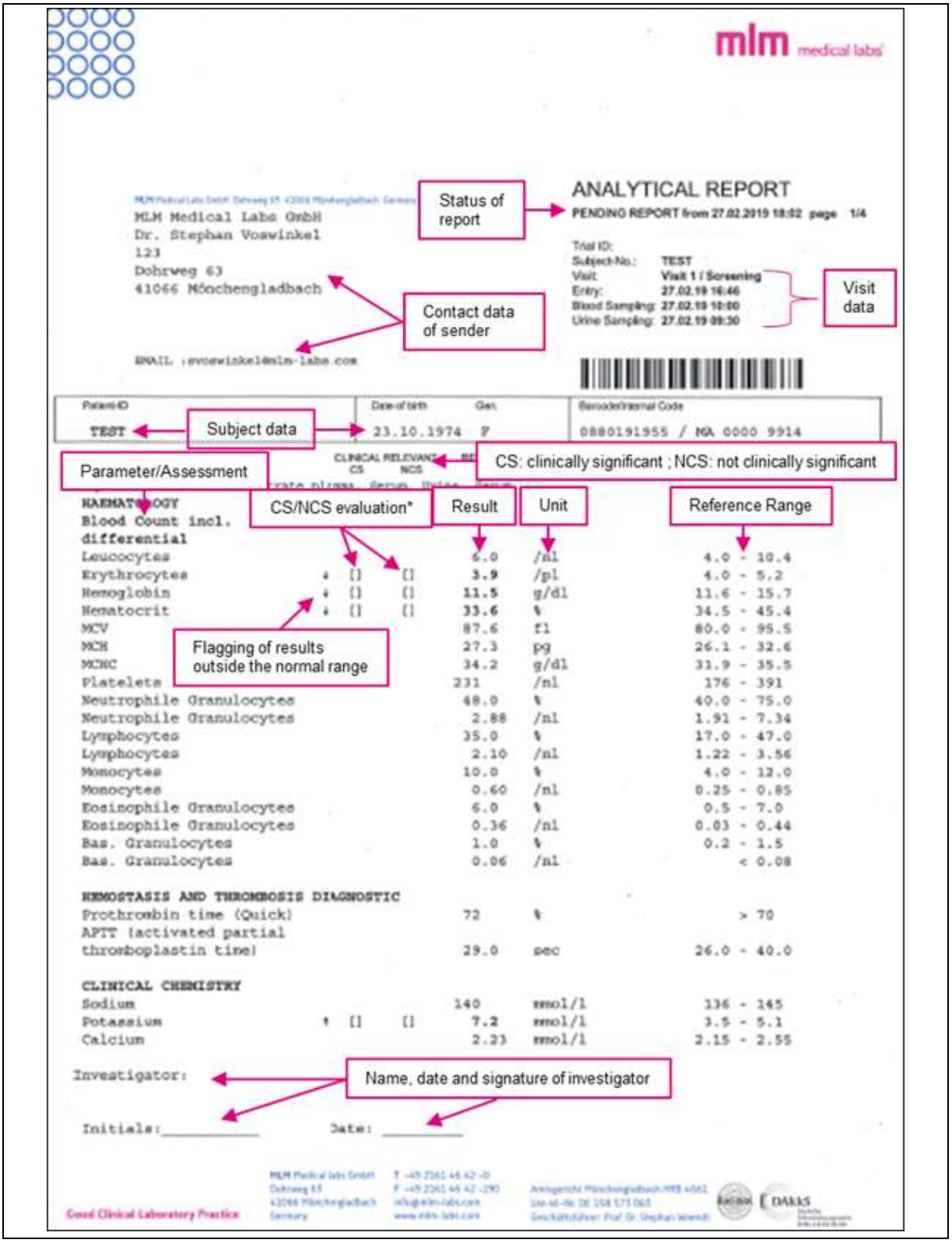
Shipment Information

➔ For detailed information about the order of shipments at DHL and Marken, please refer to the **Shipment Information Manual** and the **Shipment Order Details** provided at the end of the laboratory manual within this study folder.

Any Questions?

➔ In case of any questions please contact us. The contact details are found on page 5.

Example of Laboratory Report



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Status of report

ANALYTICAL REPORT
PENDING REPORT from 27.02.2019 18:02 page 1/4

MLM Medical Labs GmbH
Dr. Stephan Voswinkel
123
Dohrweg 63
41066 Mönchengladbach

Contact data of sender

Trial ID:
Subject-No.: TEST
Visit: Visit 1 / Screening
Entry: 27.02.19 16:46
Blood Sampling: 27.02.19 10:00
Urine Sampling: 27.02.19 09:30

Visit data

EMAIL : svoswinkel@mlm-labs.com

Patient-ID	Date of birth	Gen.	Barcode/Internal Code
TEST	23.10.1974	F	0880191955 / NA 0000 9914

Subject data

CS: clinically significant ; NCS: not clinically significant

Parameter/Assessment	CS/NCS evaluation*	Result	Unit	Reference Range
HAEMATOLOGY				
Blood Count incl. differential				
Leucocytes		6.0	/nl	4.0 - 10.4
Erythrocytes	↓ [] []	3.9	/pl	4.0 - 5.2
Hemoglobin	↓ [] []	11.5	g/dl	11.6 - 15.7
Hematocrit	↓ [] []	33.6	%	34.5 - 45.4
MCV		87.6	fl	80.0 - 95.5
MCH		27.3	pg	26.1 - 32.6
MCHC		34.2	g/dl	31.9 - 35.5
Platelets		231	/nl	176 - 391
Neutrophile Granulocytes		48.0	%	40.0 - 75.0
Neutrophile Granulocytes		2.88	/nl	1.91 - 7.34
Lymphocytes		35.0	%	17.0 - 47.0
Lymphocytes		2.10	/nl	1.22 - 3.56
Monocytes		10.0	%	4.0 - 12.0
Monocytes		0.60	/nl	0.25 - 0.85
Eosinophile Granulocytes		6.0	%	0.5 - 7.0
Eosinophile Granulocytes		0.36	/nl	0.03 - 0.44
Bas. Granulocytes		1.0	%	0.2 - 1.5
Bas. Granulocytes		0.06	/nl	< 0.08
HEMOSTASIS AND THROMBOSIS DIAGNOSTIC				
Prothrombin time (Quick)		72	%	> 70
APTT (activated partial thromboplastin time)		29.0	sec	26.0 - 40.0
CLINICAL CHEMISTRY				
Sodium		140	mmol/l	136 - 145
Potassium	↑ [] []	7.2	mmol/l	3.5 - 5.1
Calcium		2.23	mmol/l	2.15 - 2.55

Parameter/Assessment
CS/NCS evaluation*
Result
Unit
Reference Range
Flagging of results outside the normal range

Investigator:
Initials:_____ Date: _____

Name, date and signature of investigator

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T +49 2161 46 42 -0 · F +49 2161 46 42 -290 · www.mlm-labs.com
Amtsgericht Mönchengladbach HRB 4061 · Geschäftsführer: Prof. Dr. Stephan Voswinkel

Good Clinical Laboratory Practice

Instruction for mlm online® Registration

Follow the step-by-step instruction for your mlm online® registration:

1. **Open the HTML Link www.mlm-labs.com/online in your web browser.**

2. **Select "Register now" (highlighted in magenta) on the login popup.**

3. **Fill out the registration form.**

(If your mlm online® account is only released for downloading proficiency test certificates, please write "Proficiency Tests" in the "Trial-ID" field.)

4. **Your mlm online® registration will be verified by our IT. If your registration is approved, you will receive an email with your login credentials.** (Only authorized email addresses will be unlocked for mlm online® access.)

Instruction for the Evaluation of Analytical Lab Reports in mlm online®

MLM allows the evaluation of analytical lab reports in mlm online®*.

Follow the step-by-step instruction:

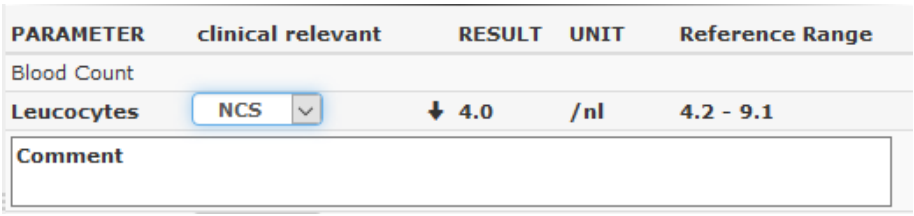
1. Log-in with your mlm online® access.

2. The "Settings" menu bar offers the option "Change signing-pin".

3. Allot or change your signing-pin and confirm it with your mlm online® password.

4. Select the "Evaluation" menu button (highlighted in magenta).

5. Open a report and evaluate the results out of the reference range as clinical significant (CS) or not clinical significant (NCS) and add a comment if applicable.



6. Enter the signing-pin (highlighted in magenta) to evaluate the report.

* Activation for evaluation after approval of Sponsor