

# 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 Schulz, CRS Clinical Research Services Mannheim GmbH, Germany (tel.: PPD [REDACTED])

**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

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First approved version	09 Apr 2020	2.0	Germany
Amendment No. 1	17 Apr 2020	3.0	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 accordance to this protocol, the ethical principles that have their origin in the Declaration of Helsinki, good clinical practice (GCP), and applicable regulatory requirements.

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## 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 <sup>a</sup>
<b>Primary objective</b>	
(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.	<ul style="list-style-type: none"><li>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).</li><li>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).</li><li>The proportion of subjects with at least 1 unsolicited treatment-emergent adverse event (TEAE):<ul style="list-style-type: none"><li>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).</li><li>For BNT162c2 (SD): The proportion of subjects with at least 1 unsolicited TEAE occurring up to 28 d after the immunization (trial day 29).</li></ul></li></ul>
<b>Secondary objectives</b>	
(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.	<p><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 <sup>b</sup>, 21, 28, 63, and 162 d after the boost immunization (trial days 5 to 9):</p> <ul style="list-style-type: none"><li>Functional antibody responses (titers).</li><li>Fold increase in functional antibody titers.</li><li>Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline.</li></ul> <p><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):</p> <ul style="list-style-type: none"><li>Functional antibody responses (titers).</li><li>Fold increase in functional antibody titers.</li><li>Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline.</li></ul>

Objectives	Endpoints <sup>a</sup>
<b>Exploratory objectives</b>	
(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 <sup>b</sup> , 21, 28, 63, and 162 d after the boost immunization (trial days 8 to 184). <ul style="list-style-type: none"><li>• Antibody responses measured (concentrations/titers).</li><li>• Fold increase in antibody (concentrations/titers).</li><li>• Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody concentrations/titers.</li></ul> <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): <ul style="list-style-type: none"><li>• Antibody responses measured (concentrations).</li><li>• Fold increase in antibody (concentrations).</li><li>• Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody concentrations.</li></ul>
(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): <ul style="list-style-type: none"><li>• CMI responses measured, e.g., by enzyme-linked immuno-spot (ELISpot) and intracellular cytokine staining (ICS).</li></ul> As compared to baseline at 7 and 21 d after primary immunization (trial days 8 and 22) and at 7, 14 <sup>b</sup> , 21, 28, 63, and 162, 343, 525, and 708 d after the boost immunization (trial days 8 to 730). <ul style="list-style-type: none"><li>• Functional antibody titers measured (e.g.) using VNT.<ul style="list-style-type: none"><li>○ Measured cross-neutralization of viruses from other coronavirus families.</li></ul></li><li>• Further assays for:<ul style="list-style-type: none"><li>○ Antibody-dependent cellular cytotoxicity (ADCC).</li><li>○ Antibody induced phagocytosis.</li><li>○ Immune cell degranulation.</li><li>○ Activation of immune cells such as lymphocytes and granulocytes.</li><li>○ Antibody mediated uptake and formation of immune complexes.</li></ul></li></ul>
<b>Additional exploratory objective</b> (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.	

Objectives	Endpoints <sup>a</sup>
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): <ul style="list-style-type: none"><li>• Functional antibody titers measured (e.g.) using VNT.<ul style="list-style-type: none"><li>◦ Antibody responses measured (titers).</li><li>◦ Fold increase in antibody titers.</li><li>◦ Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers.</li></ul></li><li>• Functional antibody binding concentrations measured (e.g.) using ELISA.<ul style="list-style-type: none"><li>◦ Antibody responses measured.</li><li>◦ Fold increase in antibody titers.</li><li>◦ Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers.</li></ul></li><li>• CMI responses measured (e.g.) using ELISpot and ICS.</li></ul>
(Only for the Expansion cohorts [Cohorts 11 to 13])  To further characterize the adaptive immune response: Assessment of cell-mediated immunity	<ul style="list-style-type: none"><li>• Further characterization of vaccine and SARS-CoV-2 specific antigen-specific CD4 and CD8 T-cells, e.g., using ELISpot, ICS.</li><li>• Functional characterization of T-cells (e.g. antigen dependent cytokine secretion, activation, proliferation, cytotoxicity, determination of human leukocyte antigen [HLA] restriction).</li><li>• Cellular and molecular phenotyping of immune cells using e.g., immunophenotypic characterization of T-cells to define reactive T-cell subsets.</li><li>• 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.</li></ul>

- 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  $24\pm 2$  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 ( $24\pm 2$  h observation on site and phone interview for assessment  $48\pm 2$  h after immunization; in addition to the available  $48\pm 2$  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 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	<b>1A</b> <b>3 µg<sup>b</sup></b>	2A 0.6 µg <sup>a</sup>	3A 0.1 µg	<b>4A<sup>a</sup></b> <b>2 µg<sup>e</sup></b>	5A 0.3 µg	6A 1 µg	
BNT162b1 / modRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	<b>1B</b> 10 µg	2B 30 µg	3B 1 µg	<b>4B</b> <b>60 µg<sup>d</sup></b>	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	<b>1C</b> 10 µg	<b>2C</b> 30 µg	3C 1 µg	<b>4C<sup>a</sup></b> <b>60 µg<sup>d</sup></b>	5C <sup>a</sup> 20 µg	6C <sup>a</sup> 3 µg	7C <sup>a</sup> 50 µg
BNT162c2 / saRNA	Modified version of the full length SARS-CoV-2 S protein	Prime only: Day 1	<b>1D</b> 0.1 µg	<b>2D</b> 0.3 µg	3D 0.1 µg to <3 µg <sup>c</sup>	4D 1 µg	5D <sup>a</sup> 0.6 µg	<b>6D<sup>a</sup></b> <b>3 µg<sup>d</sup></b>	
BNT162c2 / saRNA	Modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	<b>1E</b> 0.1 µg	<b>2E<sup>a</sup></b> 0.3 µg	3E 1 µg	<b>4E<sup>a</sup></b> <b>3 µg</b>	5E <sup>a</sup> 0.6 µg	6E <sup>a</sup> 5-10 µg <sup>d</sup>	7E 5-10 µg

<sup>a</sup> All dose escalation doses used must be judged acceptable by the Safety Review Committee (SRC) before use.

<sup>b</sup> 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.

<sup>c</sup> Specific doses to be defined, but in the range given. Already given doses will not be repeated.

<sup>d</sup> The planned maximum doses per vaccine candidate.

<sup>e</sup> 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.

**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) <sup>a</sup>		
			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 <sup>a</sup> 20 µg	10B <sup>a</sup> 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 <sup>a</sup> 20 µg	10C <sup>a</sup> 30 µg

<sup>a</sup> 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 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 <a href="#">Table 1</a> , <a href="#">Table 2</a> , and <a href="#">Table 3</a> 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<sup>2</sup> and under 30 kg/m<sup>2</sup>, 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<sup>2</sup> and under 30 kg/m<sup>2</sup>, 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<sup>2</sup> and under 30 kg/m<sup>2</sup>, 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  $\geq$ 6 months after transplantation, or individuals with human immunodeficiency virus (HIV) infection with a CD4<sup>+</sup> T-cell count of  $\geq 200 \times 10^6$  /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<sup>2</sup>)
  - 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<sup>+</sup> count of < 200 x 10<sup>6</sup>/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)

<b>Dosage levels:</b>	Part A cohorts: See <a href="#">Table 1</a> , <a href="#">Table 2</a> , and <a href="#">Table 3</a> . The planned dose per vaccine candidate will not exceed the listed pre-defined maximum doses.
<b>Dosage frequency:</b>	One injection or two injections 21 d apart. Injection volumes will be up to 1.5 mL.
<b>Administration route:</b>	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

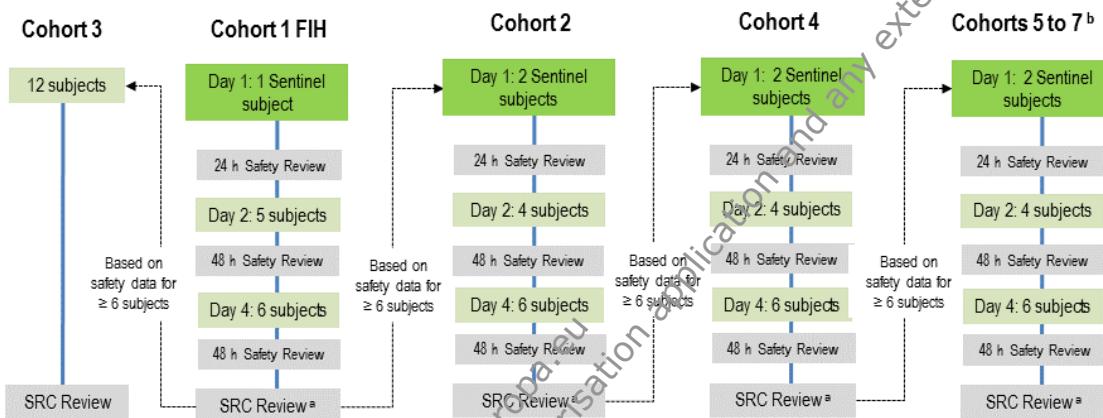
A DMC is not planned. A SRC is planned.

## 1.2 Schema (graphical representation of the trial)

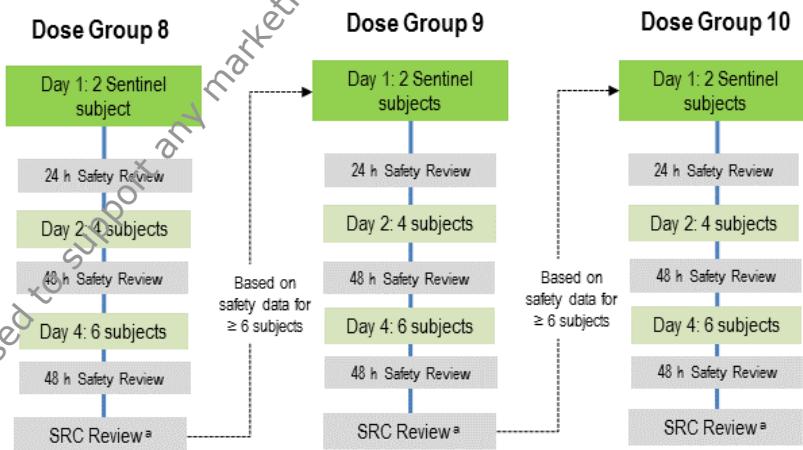
For a graphical depiction of the cohorts in Part A, see [Figure 1](#). For logistical reasons, investigation of the different vaccines may not be able to start at the same time. Should this happen, the expected overall trial duration may be extended.

### Dose ranging cohort schema for BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B)<sup>c</sup>

#### Cohorts 1 to 7 with younger adults

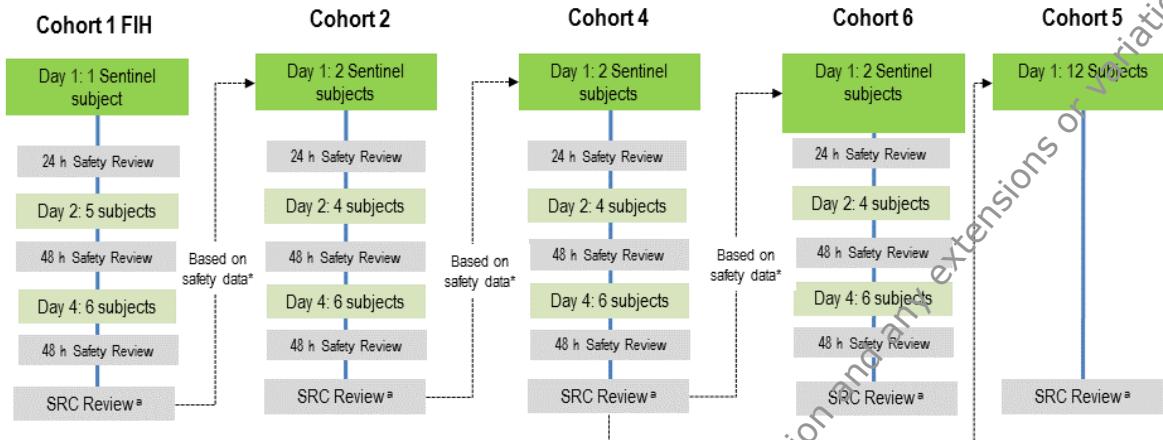


#### Cohorts 8 to 10 with older adults



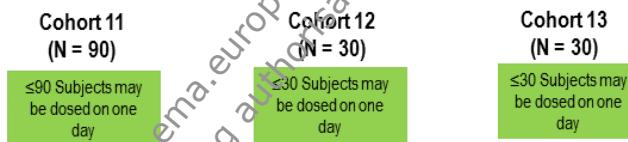
- a) The data assessed by the SRC for progressing comprises 48 h data for 6 subjects.
- b) Subjects will be dosed using a sentinel dosing/subject (2-4-6) staggering process unless the planned dose is the same or lower than previously found to show acceptable tolerability (in which case, all subjects may be dosed on one day).
- c) For the dose regimens, see [Table 1](#) and [Table 2](#).

### Dose ranging cohort schema for BNT162c2 (SD)<sup>b</sup>



- 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<sup>a</sup>



- 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)
<b>Day <sup>h</sup></b>	<b>-30 to 0</b>	<b>1</b>	<b>1</b>	<b>2</b>		<b>8</b>	<b>22</b>	<b>22</b>		<b>29</b>	<b>36 <sup>q</sup></b>	<b>43</b>	<b>50 <sup>r</sup></b>	<b>85</b>	<b>184</b>
<b>Days to last dose <sup>h</sup></b>		<b>0</b>	<b>0</b>			<b>7</b>	<b>21</b>	<b>0</b>		<b>7</b>	<b>14</b>	<b>21</b>	<b>28</b>	<b>63</b>	<b>162</b>
Informed consent	X														
Inclusion/exclusion criteria	X	X (review)													
Medical history	X	X (update)													
Physical examination incl. height	X	X <sup>a</sup>		X <sup>a</sup>		X <sup>a</sup>	X <sup>a</sup>			X <sup>a</sup>		X <sup>a</sup>	X <sup>a</sup>		
Vital signs, body weight <sup>c</sup>	X	X	X <sup>b</sup>	X		X	X	X <sup>b</sup>		X		X	X	X	X
12-lead ECG	X	X													
Urine pregnancy test for WOCBP	X	X						X							
Urine drugs of abuse screen <sup>d</sup>	X	X													
Alcohol breath test	X	X													
Urine collection for clinical laboratory <sup>e</sup>	X	X		X		X				X			X		
Blood draw for clinical laboratory (15 mL) <sup>f</sup>	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 <sup>h</sup>	-30 to 0	1	1	2		8	22	22		29	36 <sup>q</sup>	43	50 <sup>r</sup>	85	184
Days to last dose <sup>h</sup>		0	0			7	21	0		7	14	21	28	63	162
Blood draw for viral screening <sup>g</sup>	X (5 mL)														
Blood draw for SARS-CoV-2 testing <sup>k</sup>	X (2.6 mL)														
Oral swipe for SARS-CoV-2 testing		X <sup>m</sup>													
Allocation to IMP		X													
Immunization			X <sup>l</sup>						X						
Blood draw for immunogenicity (10 mL) <sup>n</sup>		X				X	X			X	X	X	X	X	X
Blood draw for HLA									X (4 mL EDTA-blood) <sup>p</sup>						
Blood draw for CMI (100 mL) <sup>n, o</sup>		X								X					
Blood draw for research												X ( $\leq$ 100 mL)		X ( $\leq$ 50 mL)	X ( $\leq$ 50 mL)
Subject hotline availability	Start	=>	=>	=>		=>	=>	=>		=>	=>	=>	=>	=>	End
Issue subject diaries		X		X		X	X			X		X	X		
Collect subject diaries				X	X <sup>i</sup>	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 <sup>h</sup>	-30 to 0	1	1	2		8	22	22		29	36 <sup>a</sup>	43	50 <sup>r</sup>	85	184
Days to last dose <sup>h</sup>		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 <sup>j</sup>	X <sup>j</sup>
Local reaction assessment/ systemic events			X <sup>b</sup>	X		X	X	X <sup>b</sup>		X		X	X		
Concomitant medication	X	X		X		X	X			X		X	X		
Subject wellbeing questioning					X <sup>i</sup>				X <sup>i</sup>						

<sup>a</sup> Brief (symptom-directed) physical examination; no height measurement.

<sup>b</sup> At 1, 3, and 6 h ( $\pm 15$  min) after immunization.

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

<sup>d</sup> Urine screening for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cocaine, cannabinoids, opiates, methadone, methamphetamine, phencyclidine, tricyclic antidepressants).

<sup>e</sup> 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.

<sup>f</sup> 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.

<sup>g</sup> Viral screening for human immunodeficiency virus (HIV) 1 or 2, hepatitis B, hepatitis C.

<sup>h</sup> 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.

<sup>i</sup> 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.

<sup>j</sup> Only IMP-related AEs and any SAEs.

<sup>k</sup> Blood draw for anti-SARS-CoV-2 antibodies (samples will be stored until a test is commercially available).

<sup>l</sup> 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.

<sup>m</sup> Oral swipe for SARS-CoV-2 testing either on Day -1 or at the Visit 1 on Day 1.

<sup>n</sup> 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).

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Clinical Trial Protocol  
including Amendments Nos. 01 to 06  
BNT162-01

Page 22 of 112  
Version: 9.0  
Date: 05 OCT 2020

- 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)
<b>Day <sup>a</sup></b>	<b>-30 to 0</b>	<b>1</b>	<b>1</b>	<b>2</b>		<b>8</b>	<b>22</b>	<b>29</b>	<b>43 <sup>q</sup></b>	<b>85</b>	<b>184</b>
Informed consent	X										
Inclusion/exclusion criteria	X	X (review)									
Medical history	X	X (update)									
Physical examination incl. height	X	X <sup>b</sup>		X <sup>b</sup>			X <sup>b</sup>	X <sup>b</sup>	X <sup>b</sup>		
Vital signs, body weight <sup>c</sup>	X	X	X <sup>d</sup>	X		X	X	X	X		
12-lead ECG	X	X									
Urine pregnancy test (for WOCBP)	X	X						X			
Urine drugs of abuse screen <sup>e</sup>	X	X									
Alcohol breath test	X	X									
Urine for clinical laboratory <sup>f</sup>	X	X		X		X		X	X		
Blood draw for clinical laboratory <sup>g</sup>	X (15 mL)	X (15 mL)		X (15 mL)		X (15 mL)		X (15 mL)	X (15 mL)		
Blood draw for viral screening <sup>h</sup>	X (5 mL)										
Blood draw for SARS-CoV-2 testing <sup>i</sup>	X (2.6 mL)										
Oral swipe for SARS-CoV-2 testing <sup>j</sup>		X									
Allocation to IMP		X									
Immunization <sup>k</sup>			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 <sup>a</sup>	-30 to 0	1	1	2		8	22	29	43 <sup>b</sup>	85	184			
Blood draw for HLA testing <sup>c</sup>					X (4 mL EDTA-blood)									
Blood draw for CMI testing (100 mL) <sup>d, e</sup>		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 <sup>f</sup>	X	X	X						
Record AEs since last visit		X		X		X	X	X	X	X <sup>g</sup>	X <sup>g</sup>			
Local reaction assessment/ systemic events			X <sup>d</sup>	X		X	X	X						
Concomitant medication	X	X		X		X	X	X	X					
Subject wellbeing questioning					X <sup>g</sup>									

<sup>a</sup> 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.

<sup>b</sup> Brief (symptom-directed) physical examination; no height measurement.

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

<sup>d</sup> At 1, 3, and 6 h (±15 min) after immunization.

<sup>e</sup> Urine screening for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cocaine, cannabinoids, opiates, methadone, methamphetamine, phencyclidine, tricyclic antidepressants).

<sup>f</sup> 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.

<sup>g</sup> 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.

<sup>h</sup> Viral screening for human immunodeficiency virus (HIV) 1 or 2, hepatitis B, hepatitis C.

<sup>i</sup> Blood draw for anti-SARS-CoV-2 antibodies.

<sup>j</sup> Oral swipe for SARS-CoV-2 testing either on Day -1 or at the Visit 1 on Day 1.

<sup>k</sup> 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.

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Clinical Trial Protocol  
including Amendments Nos. 01 to 06  
BNT162-01

Page 25 of 112  
Version: 9.0  
Date: 05 OCT 2020

- <sup>i</sup> 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 \(Biomarkers\)](#).
- <sup>m</sup> 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.
- <sup>n</sup> Only IMP-related AEs and any SAEs.
- <sup>o</sup> 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.
- <sup>p</sup> If HLA typing using the blood sample collected with Lithium Heparin is not conclusive, EDTA-blood will be drawn for HLA testing.
- <sup>q</sup> 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)
<b>Day <sup>h</sup></b>	<b>-30 to 0</b>	1	1	2	8	22	22	29	36	43	50 <sup>i</sup>	85	184	365	547	730
<b>Days to last dose <sup>h</sup></b>		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 <sup>a</sup>		X <sup>a</sup>	X <sup>a</sup>	X <sup>a</sup>		X <sup>a</sup>		X <sup>a</sup>	X <sup>a</sup>					
Vital signs, body weight <sup>c</sup>	X	X	X <sup>b</sup>	X	X	X	X	X		X	X	X	X			
12-lead ECG	X	X														
Urine pregnancy test for WOCBP	X	X				X										
Urine drugs of abuse screen <sup>d</sup>	X	X														
Alcohol breath test	X	X														
Urine collection for clinical lab. <sup>e</sup>	X	X		X	X			X			X					
Blood draw for clin. lab. (15 mL) <sup>f</sup>	X	X		X	X			X			X					
Blood draw for viral screening <sup>g</sup>	(X 5 mL)															
Blood draw for SARS-CoV-2 testing (2.6 mL) <sup>k</sup>	X															
Swipe for SARS-CoV-2 testing			X <sup>m</sup>													

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 <sup>h</sup>	-30 to 0	1	1	2	8	22	22	29	36	43	50 <sup>f</sup>	85	184	365	547	730
Days to last dose <sup>h</sup>		0	0	1	7	21	0	7	14	21	28	63	162	343	525	708
Allocation to IMP		X														
Immunization			X <sup>i</sup>				X									
Blood draw for immunogenicity <sup>n</sup>		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) <sup>n, o</sup>		X											X	X	X	X
Blood draw for research											X ( $\leq$ 100 mL)	X ( $\leq$ 50 mL)	X ( $\leq$ 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				
Record AEs since last visit		X		X	X	X		X		X	X	X <sup>j</sup>	X <sup>j</sup>	X <sup>j</sup>	X <sup>j</sup>	
Local reaction assessment/systemic events			X <sup>b</sup>	X	X	X	X <sup>b</sup>	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								

<sup>a</sup> Brief (symptom-directed) physical examination; no height measurement.

<sup>b</sup> At 1, 3, and 6 h ( $\pm$ 15 min) after immunization.

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

<sup>d</sup> Urine screening for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cocaine, cannabinoids, opiates, methadone, methamphetamine, 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 Flexibility 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 antibodies (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 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.
- 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.

## TABLE OF CONTENTS

1	PROTOCOL SUMMARY	2
1.1	Trial synopsis	2
1.2	Schema (graphical representation of the trial)	17
1.3	Schedule of activities	19
	TABLE OF CONTENTS	29
	LIST OF TABLES	33
	LIST OF FIGURES	33
	TRIAL-SPECIFIC ABBREVIATIONS/TERMS	34
2	INTRODUCTION	36
2.1	Background	36
2.1.1	Overview of the disease	36
2.1.2	Introduction to BioNTech RNA-based vaccines	36
2.2	Trial rationale	37
2.3	Benefit/risk assessment	40
2.3.1	Risk assessment	40
2.3.2	Benefit assessment	44
2.3.3	Overall benefit/risk conclusion	45
3	OBJECTIVES AND ENDPOINTS	46
4	TRIAL DESIGN	48
4.1	Overall design	48
4.1.1	Adaptive trial design elements	52
4.1.2	Planned number of trial subjects	52
4.2	Scientific rationale for the trial design	52
4.3	Justification for dose	53
4.4	End of treatment (EoT) and end of trial definition	55
5	TRIAL POPULATION	56
5.1	Inclusion criteria	56
5.1.1	Inclusion criteria Part A	56
5.2	Exclusion criteria	57
5.2.1	Exclusion criteria Part A	57
5.3	Lifestyle considerations	60
5.4	Screen failures	60
6	TRIAL TREATMENTS	62
6.1	IMP administered	62
6.2	Preparation/handling/storage/accountability	62
6.3	Measures to minimize bias: randomization and blinding	62

6.4	Trial treatment compliance	62
6.5	Concomitant therapy	63
6.5.1	Premedication	63
6.5.2	Rescue medication	63
6.6	Dose modifications	63
6.6.1	Dose limiting toxicity	64
6.6.2	Dose modification guidance/rules	65
6.6.3	Mitigation plans for specific AEs	65
6.6.4	Safety stopping criteria	66
6.7	Treatment after the end of the trial	66
7	<b>DISCONTINUATION OF TRIAL TREATMENT AND TRIAL SUBJECT DISCONTINUATION/WITHDRAWAL</b>	67
7.1	Discontinuation of trial treatment	67
7.1.1	Temporary discontinuation	67
7.1.2	Rechallenge	67
7.2	Trial subject discontinuation/withdrawal from the trial	67
7.3	Lost to follow-up	68
7.4	Replacement of permanently discontinued trial subjects	68
8	<b>TRIAL ASSESSMENTS AND PROCEDURES</b>	69
8.1	Efficacy assessments	69
8.2	Safety assessments	69
8.2.1	Physical examinations	69
8.2.2	Vital signs	69
8.2.3	Electrocardiograms	70
8.2.4	Clinical laboratory tests	70
8.2.5	Drugs of abuse screening	70
8.2.6	Testing for alcohol use	71
8.2.7	Viral screening (for blood-borne viruses)	71
8.2.8	Subject diaries	71
8.2.9	Assessment of local reactions	71
8.2.10	SARS-CoV-2 testing	71
8.2.11	Subject hotline	72
8.2.12	Subject wellbeing questioning	72
8.2.13	Assessment of systemic reactions	72
8.3	Adverse events and serious adverse events	73
8.3.1	Time period and frequency for collecting AE and SAE information	73
8.3.2	Method of detecting AEs and SAEs	73
8.3.3	Follow-up of AEs and SAEs	73

8.3.4	Regulatory reporting requirements for SAEs	74
8.3.5	Pregnancy	74
8.3.6	Death events	75
8.3.7	Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs	75
8.3.8	Adverse events of special interest	75
8.4	Treatment of overdose	75
8.5	Pharmacokinetics	75
8.6	Pharmacodynamics	75
8.7	Genetics	76
8.8	Biomarkers (CMI responses, explorative biomarker, immunogenicity research purposes)	76
8.9	Immunogenicity assessments	77
8.10	Blood collection	78
9	STATISTICAL CONSIDERATIONS	79
9.1	Statistical hypotheses	79
9.2	Sample size determination	79
9.3	Analysis sets	79
9.4	Statistical analyses	79
9.4.1	General considerations	80
9.4.2	Primary endpoints	80
9.4.3	Secondary endpoints	81
9.4.4	Exploratory endpoints	81
9.4.5	Other safety analyses	81
9.4.6	Other analyses	82
9.5	Interim analyses	82
9.6	Data Monitoring Committee	83
10	SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS	84
10.1	Regulatory, ethical, and trial oversight considerations	84
10.1.1	Regulatory and ethical considerations	84
10.1.2	Financial disclosure	85
10.1.3	Informed consent process	85
10.1.4	Data protection	85
10.1.5	Committees - SRC	86
10.1.6	Dissemination of clinical trial data	86
10.1.7	Data quality assurance	86
10.1.8	Source documents	87
10.1.9	Trial and site start and closure	87

10.1.10	Publication policy	88
10.1.11	Protocol preparation and approval	88
10.2	Clinical laboratory tests	88
10.3	Adverse events: Definitions and procedures for recording, evaluating, follow-up, and reporting	89
10.3.1	Definition of AE and TEAE	89
10.4	Contraceptive guidance and collection of pregnancy information	101
10.4.1	Definitions	101
10.4.2	Contraception guidance	101
10.4.3	Collection of pregnancy Information	102
10.4.4	Sperm donation	103
10.5	Genetics	103
10.6	Liver safety: Suggested actions and follow-up assessments	103
10.7	Investigators and trial administrative structure	103
10.7.1	Investigators and trial site personnel	103
10.7.2	Trial site personnel assigned trial-related duties	103
10.7.3	Contract research organizations	104
10.7.4	The sponsor and sponsor's personnel	104
10.8	Country-specific requirements	104
10.9	Other standard abbreviations and definitions	104
10.10	Protocol amendments	105
10.10.1	Protocol amendment no. 01	105
10.10.2	Protocol amendment no. 02	106
10.10.3	Protocol amendment no. 03	107
10.10.4	Protocol amendment no. 04	107
10.10.5	Protocol amendment no. 05	107
10.10.6	Protocol amendment no. 06	108
10.11	Data collection and management	109
10.11.1	Case report forms	109
10.11.2	Trial subject reported outcomes	109
10.11.3	Data management	109
10.11.4	Investigator's Site File and the Trial Master File	110
10.12	Other data	110
10.12.1	Demographic data	110
10.12.2	Medical history	110
11	REFERENCES	111

## LIST OF TABLES

Table 1: Dose ranging: vaccine dose regimens for younger adults aged 18 to 55 years in Part A (Cohorts 1 to 7)	9
Table 2: Dose ranging: vaccine dose regimens for older adults aged 56 to 85 years in Part A (Cohorts 8 to 10)	10
Table 3: Expansion cohorts for BNT162b2 (age 18 to 85 years) in Part A (Cohorts 11 to 13)	11
Table 4: Overview of the total number of subjects for each vaccine in Part A	12
Table 5: Schedule of trial procedures and assessments – BNT162a1, BNT162b1, BNT162b2, and BNT162c2 when tested P/B (excluding Cohorts 11 to 13)	19
Table 6: Schedule of trial procedures and assessments – BNT162c2	23
Table 7: Schedule of trial procedures and assessments – Cohorts 11 to 13 (Expansion cohorts only)	26
Table 8: Status of ongoing and planned clinical trials (as of 24 SEP 2020)	38
Table 9: Number of trial subjects dosed at least once with BNT162 vaccine candidates in the ongoing clinical trials (status 24 SEP 2020)	40
Table 10: Probability to observe a particular TEAE at least once	79
Table 11: Local reaction grading scale	98
Table 12: Systemic reaction grading scale	99
Table 13: Fever grading scale	99
Table 14: Laboratory abnormality grading scale	100

## LIST OF FIGURES

Figure 1: Graphical depiction of the dose-finding process in Part A	18
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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 11<sup>th</sup>, 2020 the World Health Organization (WHO) characterized the COVID-19 outbreak as pandemic.

The WHO Situation Update Report dated April 15<sup>th</sup>, 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	<p>Phase I/II, 2-part, dose escalation trial. Part A is open label and non-randomized. (All subjects receive active vaccine)</p> <p>Part B: Due to changes in the overall clinical development plan, Part B will no longer be conducted.</p>	<p><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)</p> <p><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)</p> <p><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</p> <p><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</p> <p><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</p> <p><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)</p> <p><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</p>

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)	<p><b>Phase I</b></p> <p><u>BNT162b1 (age 18 to 55 years):</u> 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)</p> <p><u>BNT162b1 (age 65 to 85 years):</u> 10 µg 15 subjects prime / 15 boost 20 µg 15 subjects prime / 15 boost 30 µg 15 subjects prime / 15 boost</p> <p><u>BNT162b2 (age 18 to 55 years):</u> 10 µg 15 subjects prime / 15 boost 20 µg 15 subjects prime / 15 boost 30 µg 15 subjects prime / 15 boost</p> <p><u>BNT162b2 (age 65 to 85 years):</u> 10 µg 15 subjects prime / 15 boost 20 µg 15 subjects prime / 15 boost 30 µg 15 subjects prime / 15 boost</p> <p><b>Phase II-III</b></p> <p><u>BNT162b2 (age 18 to 85 years)</u> 30 µg 33,346 subjects (split P/B not available) (Assuming 50% of the subjects are on BNT162b2) 30 µg 16,673 subjects</p>
BNT162-03 (NCT 04523571) China	Phase I, randomized, placebo- controlled, observer-blind trial.	<p><u>BNT162b1 (age 18 to 55 years):</u> 10 µg 24 subjects prime / 24 boost 30 µg 24 subjects prime / 24 boost</p> <p><u>BNT162b1 (age &gt;55 years):</u> 10 µg 24 subjects prime / 0 boost 30 µg 24 subjects prime / 0 boost</p>
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.	<p><u>BNT162b3 (age 18 to 55 years):</u> 10 µg 6 subjects prime / 0 boost</p> <p><u>BNT162b3 (age 56 to 85 years):</u> Recruiting.</p>

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

\* 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.

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- 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  $48\pm 2$  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 <sup>a</sup>
<b>Primary objective</b>	
(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.	<ul style="list-style-type: none"><li>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).</li><li>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).</li><li>The proportion of subjects with at least 1 unsolicited TEAE:<ul style="list-style-type: none"><li>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).</li><li>For BNT162c2 (SD): The proportion of subjects with at least 1 unsolicited TEAE occurring up to 28 d after the immunization (trial day 29).</li></ul></li></ul>
<b>Secondary objectives</b>	
(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.	<p>For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): As compared to baseline at 7 and 21 d after primary immunization (trial days 8 and 22) and at 7, 14<sup>b</sup>, 21, 28, 63, and 162 d after the boost immunization (trial days 5 to 9):</p> <ul style="list-style-type: none"><li>Functional antibody responses (titers).</li><li>Fold increase in functional antibody titers.</li><li>Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline.</li></ul> <p>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):</p> <ul style="list-style-type: none"><li>Functional antibody responses (titers).</li><li>Fold increase in functional antibody titers.</li><li>Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline.</li></ul>
<b>Exploratory objectives</b>	
(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.	<p>For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B) As compared to baseline at 7 and 21 d after primary immunization (trial days 8 and 22) and at 7, 14<sup>b</sup>, 21, 28, 63, and 162 d after the boost immunization (trial days 8 to 184).</p> <ul style="list-style-type: none"><li>Antibody responses measured (concentrations/titers).</li><li>Fold increase in antibody (concentrations/titers).</li><li>Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody concentrations/titers.</li></ul> <p>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):</p> <ul style="list-style-type: none"><li>Antibody responses measured (concentrations).</li><li>Fold increase in antibody (concentrations).</li></ul>

Objectives	Endpoints <sup>a</sup>
(All cohorts) To describe the CMI responses.	<ul style="list-style-type: none"><li>Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody concentrations.</li></ul> <p>For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B) and BNT162c2 (SD)</p> <p>At baseline and at 28 d after the primary immunization (trial day 29):</p> <ul style="list-style-type: none"><li>CMI responses measured, e.g., by enzyme-linked immuno-spot (ELISpot) and ICS.</li></ul>
<b>Additional exploratory objective</b> (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.	<p>As compared to baseline at 7 and 21 d after primary immunization (trial days 8 and 22) and at 7, 14 <sup>b</sup>, 21, 28, 63, and 162, 343, 525, and 708 d after the boost immunization (trial days 8 to 730).</p> <ul style="list-style-type: none"><li>Functional antibody titers measured (e.g.) using VNT.<ul style="list-style-type: none"><li>Measured cross-neutralization of viruses from other coronavirus families.</li></ul></li><li>Further assays for:<ul style="list-style-type: none"><li>Antibody-dependent cellular cytotoxicity (ADCC).</li><li>Antibody induced phagocytosis.</li><li>Immune cell degranulation.</li><li>Activation of immune cells such as lymphocytes and granulocytes.</li><li>Antibody mediated uptake and formation of immune complexes.</li></ul></li></ul>
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.	<p>As compared to baseline at 364, 546, and 729 d after the primary immunization (trial days 365 to 730):</p> <ul style="list-style-type: none"><li>Functional antibody titers measured (e.g.) using VNT.<ul style="list-style-type: none"><li>Antibody responses measured (titers).</li><li>Fold increase in antibody titers.</li><li>Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers.</li></ul></li><li>Functional antibody binding concentrations measured (e.g.) using ELISA.<ul style="list-style-type: none"><li>Antibody responses measured.</li><li>Fold increase in antibody titers.</li><li>Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers.</li></ul></li><li>CMI responses measured (e.g.) using ELISpot and ICS.</li></ul>
(Only for the Expansion cohorts [Cohorts 11 to 13]) To further characterize the adaptive immune response: Assessment of cell-mediated immunity	<ul style="list-style-type: none"><li>Further characterization of vaccine and SARS-CoV-2 specific antigen-specific CD4 and CD8 T-cells, e.g., using ELISpot, ICS.</li><li>Functional characterization of T-cells (e.g. antigen dependent cytokine secretion, activation, proliferation, cytotoxicity, determination of HLA restriction).</li><li>Cellular and molecular phenotyping of immune cells using e.g., immunophenotypic characterization of T-cells to define reactive T-cell subsets.</li><li>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.</li></ul>

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  $24\pm 2$  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 ( $24\pm 2$  h observation on site and phone interview for assessment  $48\pm 2$  h after immunization; in addition to the available  $48\pm 2$  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  $24\pm 2$  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 ( $24\pm 2$  h observation on site and phone interview for assessment  $48\pm 2$  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 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 6<sup>th</sup>, 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<sup>2</sup> and under 30 kg/m<sup>2</sup>, 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<sup>2</sup> and under 30 kg/m<sup>2</sup>, 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.

QR

For the immunocompromised cohort (Cohort 13); volunteers who have previously received solid organ transplant, or peripheral blood stem cell transplantation  $\geq$ 6 months after transplantation, or individuals with HIV infection with a CD4<sup>+</sup> T-cell count of  $\geq 200 \times 10^6 /L$ . 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<sup>2</sup>).
  - 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<sup>+</sup> count of < 200 x 10<sup>6</sup>/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 by a physician.

### 6.1 IMP administered

<b>IMP name:</b>	BNT162 vaccines - Antiviral RNA vaccines for active immunization against COVID-19
<b>Type:</b>	RNA-LNP vaccines utilizing different BioNTech RNA formats, i.e. <i>u</i> RNA (product code BNT162a1), modRNA (2 variants, product codes BNT162b1 and BNT162b2), saRNA (product code BNT162c2)
<b>Dosage levels:</b>	See <a href="#">Table 1</a> , <a href="#">Table 2</a> , and <a href="#">Table 3</a> . The planned dose per vaccine candidate will not exceed the pre-defined maximum dose (see Table 1 and Table 2).
<b>Dosage frequency:</b>	One injection or two injections 21 d apart. Injection volumes will be up to 1.5 mL
<b>Administration route:</b>	Intramuscular (IM); upper arm, <i>musculus deltoideus</i> . 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  $>40.0^{\circ}\text{C}$  ( $>104.0^{\circ}\text{F}$ ) 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.,  $\geq 38^{\circ}\text{C}$ ]).

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 be 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  $\geq$  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%	95.3%
	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 accordance 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 ( $1 \text{ mL} \triangleq 1 \text{ g}$ ), 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 not meeting 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](mailto: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](mailto: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)
<b>Pain at the injection site</b>	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
<b>Tenderness</b>	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
<b>Erythema / redness <sup>a</sup></b>	2.5 cm to 5.0 cm	>5.0 cm to 10.0 cm	>10 cm	Necrosis or exfoliative dermatitis
<b>Induration / swelling <sup>b</sup></b>	2.5 cm to 5.0 cm	>5.0 cm to 10.0 cm	>10 cm	Necrosis

<sup>a</sup> In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

<sup>b</sup> 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**

	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)</b>	<b>Potentially Life-Threatening (Grade 4)</b>
<b>Vomiting</b>	1-2 times in 24 h	>2 times in 24 h	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
<b>Diarrhea</b>	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
<b>Headache</b>	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
<b>Fatigue/ tiredness</b>	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
<b>Chills</b>	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
<b>New or worsened muscle pain</b>	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
<b>New or worsened joint pain</b>	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  $\geq 38.0^{\circ}\text{C}$ . 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**

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

If a fever of  $\geq 39.0^{\circ}\text{C}$  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  $>40.0^{\circ}\text{C}$  for recording in the trial database. If a participant experiences a confirmed fever  $>40.0^{\circ}\text{C}$ , 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 <sup>3</sup>	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	>25,000
WBC decrease - cells/mm <sup>3</sup>	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm <sup>3</sup>	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm <sup>3</sup>	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm <sup>3</sup>	650 – 1500	1501 – 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm <sup>3</sup>	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.<sup>a</sup>
- Intrauterine hormone-releasing system.<sup>a</sup>
- 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<sup>a</sup> hormonal methods of contraception.

<sup>a)</sup> 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

CCI

the

RNA component of BNT162c2 encodes a modified version of the full length S protein.  
**CCI**  
[REDACTED]

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

## 11 REFERENCES

BNT162 Investigator's brochure, current edition.

EMA 2017. Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products. European Medicines Agency (EMA) Science Medicines Health (2017).

FDA Guidance 2007. US FDA Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H1N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well-tolerated in healthy adults in phase 1 randomized clinical trials. *Vaccine*. 2019; 37(25): 3326-34.

Habibzadeh P, Stoneman EK. The Novel Coronavirus: A Bird's Eye View. *Int J Occup Environ Med.* 2020; 11 (2): 65-71.

ICH E7. Guideline for Industry - Studies in Support of Special Populations: Geriatrics. March 1994.

Moyo N, Vogel AB, Buus S, et al. Efficient Induction of T Cells against Conserved HIV-1 Regions by Mosaic Vaccines Delivered as Self-Amplifying mRNA. *Mol Ther Methods Clin Dev.* 2018; 12: 32-46.

Mulligan M, Lyke KE, Kitchinet N, et al. Phase 1/2 Study to Describe the Safety and Immunogenicity of a COVID-19 RNA Vaccine Candidate (BNT162b1) in Adults 18 to 55 Years of Age: Interim Report. 2020. medRxiv preprint doi: <https://doi.org/10.1101/2020.06.30.20142570>. This version posted July 1, 2020.

NCT02410733. Evaluation of the safety and tolerability of IV administration of a cancer vaccine in patients with advanced melanoma (Lipo-MERIT). Ongoing BioNTech clinical trial.

NCT03871348. A first-in-human dose escalation and expansion study to evaluate intratumoral administration of SAR441000 as monotherapy and in combination with cemiplimab in patients with advanced solid tumors. Ongoing BioNTech clinical trial.

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.

Pardi N, Hogan MJ, Pelc RS, et al. Zika virus protection by a single low-dose nucleoside-modified mRNA vaccination. *Nature*. 2017; 543 (7644): 248-51.

Rauch S, Jasny E, Schmidt KE, Petsch B. New Vaccine Technologies to Combat Outbreak Situations. *Front Immunol.* 2018; 9: 1963.

Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics-developing a new class of drugs. *Nature Rev. Drug Disc.* 2014; 13 (10): 759-80.

US Center for Disease control and Prevention (CDC). Coronavirus Disease 2019 (COVID-19) guidance webpage. Accessed July 14<sup>th</sup> 2020: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical->

conditions.html?CDC\_AA\_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html

Vogel AB, Lambert L, Kinnear E, et al. Self-Amplifying RNA Vaccines Give Equivalent Protection against Influenza to mRNA Vaccines but at Much Lower Doses. Mol Ther. 2018; 26 (2): 446-55.

WHO "Protection measures for persons who are in or have recently visited (past 14 days) areas where COVID-19 is spreading". Accessed at:

<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public>

WHO Situation Report Nr. 85, April 15<sup>th</sup>, 2020. Accessed at:

<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/>

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# CLINICAL TRIAL PROTOCOL AMENDMENT HISTORY INCLUDING AMENDMENTS NOS. 01 TO 06

## BNT162-01

<b>Protocol version:</b>	9.0	<b>Date:</b>	05 OCT 2020
<b>Sponsor:</b>	BioNTech RNA Pharmaceuticals GmbH		
<b>Trial title:</b>	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		
<b>Brief title:</b>	A multi-site Phase I/II trial investigating the safety and effects of four BNT162 vaccines against COVID-19 in healthy and immunocompromised adults		
<b>Trial phase:</b>	Phase I/II		
<b>Indication:</b>	Protection against COVID-19		
<b>Product:</b>	BNT162: SARS-CoV-2 - RNA lipid nanoparticle (RNA-LNP) vaccines utilizing different RNA formats, i.e., BNT162a1, BNT162b1, BNT162b, BNT162c2		
<b>Principal investigator:</b>	Dr. Dr. med. Armin Schultz, CRS Clinical Research Services Mannheim GmbH, Germany (tel.: PPD [REDACTED])		
<b>Trial sites:</b>	Multiple sites in Germany. For further details of the study sites and site personnel, see the Trial Master File (TMF).		
<b>Contract research organization:</b>	CRS Clinical Research Services Mannheim GmbH, Germany		
<b>Sponsor's responsible person:</b>	Özlem Türeci, MD, Chief Medical Officer, BioNTech SE		
<b>Sponsor:</b>	BioNTech RNA Pharmaceuticals GmbH, An der Goldgrube 12, 55131 Mainz, Germany		
<b>Regulatory identifiers:</b>	EudraCT no.: 2020-001038-36; ClinicalTrials.gov NCT: 04380701; WHO UTN: U1111-1249-4220		
<b>Medical Monitor:</b>	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 accordance to this protocol, the ethical principles that have their origin in the Declaration of Helsinki, good clinical practice (GCP), and applicable regulatory requirements.

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## TABLE OF CONTENTS

1	Protocol amendments	3
1.1	Protocol amendment no. 01	3
1.2	Protocol amendment no. 02	9
1.3	Protocol amendment no. 03	18
1.4	Protocol amendment no. 04	26
1.5	Protocol amendment no. 05	47
1.6	Protocol amendment no. 06	72

## 1 PROTOCOL AMENDMENTS

### 1.1 Protocol amendment no. 01

#### Amendment rationale

CCI

the RNA component of BNT162c2 encodes a modified version of the full length S protein.

CCI

This amendment describes changes made in response to feedback from the German PEI (April 16<sup>th</sup>, 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
CCI	BioNTech decision based on non-clinical data.
<u>Section 1.1 (Trial design) &amp; Section 4.1.</u> The data assessed by the SRC comprises 48 h data for 6 subjects including observation on site, phone interview ( <del>if available</del> ), vital signs, TEAEs, local reactions...	PEI feedback.
<u>Section 1.1 (Trial design) &amp; Section 4.1.</u> 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. <u>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.</u> <u>This</u> <del>The</del> 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 <del>may</del> <ins>will</ins> 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.
<u>Section 1.1 (Table 1)</u> CCI was replaced with " <u>A modified version of the S protein</u> " for BNT162c2.	BioNTech decision based on non-clinical data.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	Rationale
<u>Section 1.1 (Key inclusion criteria) &amp; Section 5.1.</u> WOCBP must agree to practice <del>one</del> <ins>two</ins> 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.
<u>Section 1 (Objectives and Endpoints) and Section 3 (Objectives and Endpoints/Exploratory Endpoint)</u> <ul style="list-style-type: none"><li>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.</li></ul> <p><u>For BNT162a1, BNT162b1, BNT162b2 (P/B):</u></p> <ul style="list-style-type: none"><li>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.</li></ul> <p><u>For BNT162c2 (SD):</u></p> <ul style="list-style-type: none"><li>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.</li></ul>	Correction of an inconsistency in protocol version 2.0.
<u>Section 1.1 (Key exclusion criteria).</u> Have a positive PCR-based test for <del>anti-</del> SARS-CoV-2 within the 30 d prior to Visit 1.	Correction of an inconsistency in protocol version 2.0.
<u>Section 1.1 (Key exclusion criteria) &amp; Section 5.2. Exclusion criterion 26.</u> Have had contact with persons <ins>diagnosed with COVID-19 or</ins> who tested positive for SARS-CoV-2 <ins>by any diagnostic test</ins> <del>antibodies</del> within the 30 d prior to Visit 0.	PEI feedback.
<u>Section 1.2 (Schema)</u> 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.
<u>Section 2.1.1 (Overview of the disease).</u> <ins>"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)."</ins> <ins>"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)."</ins>	Data was updated.
<u>Section 2.3.1 (Risk assessment).</u> 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
<p><u>Section 2.3.1 (Risk assessment) text was added.</u></p> <p><u>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.</u></p>	PEI feedback.
<p>Section 2.3.1 (Risk assessment) text was updated.</p> <p>“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., <u>enhanced respiratory disease or</u> flu-like symptoms, may trigger diagnostic measures at the discretion of the investigator.”</p>	PEI feedback.
<p><u>Section 4.4 (End of trial definition (EoT))</u></p> <p>A trial subject is considered to have completed the trial if they have completed all planned visits including the <del>Visit 6 (EoT Visit)</del>, and the two follow-up visits (<del>Visits 7 and 8</del>).</p>	PEI feedback triggering scheduling changes.
<p><u>Section 4.4 (End of trial definition (EoT))</u></p> <p>“The end-of-the-trial is defined as the date the last subject completed the <del>Visit 6 (EoT Visit)</del>.”</p>	PEI feedback triggering scheduling changes.
<p><u>Section 5.1 (Inclusion criteria) Inclusion criterion 8.</u></p> <p>“WOCBP must confirm that they practiced <u>at least</u> one highly effective form of contraception for the 14 d prior to Visit 0.”</p>	Correction of an inconsistency in protocol version 2.0.
<p><u>Section 5.2 (Exclusion criteria) Exclusion criterion 11.</u></p> <p>“Have a positive PCR-based test for <del>anti-</del>SARS-CoV-2 within the 30 d prior to Visit 0.”</p>	Correction of an inconsistency in protocol version 2.0.
<p><u>Section 6.6.1 (Dose limiting toxicity).</u></p> <p>“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.”</p>	PEI feedback.
<p><u>Section 6.6.3 (Mitigation plans for specific AEs).</u></p> <p>“If subjects experience <u>enhanced respiratory disease or</u> 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.”</p>	PEI feedback.
<p><u>Section 6.6.4 (Safety stopping criteria).</u></p> <p>“See Section 6.6.1 for the list of events that must prompt discontinuation for the individual subjects.</p> <p>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.</p> <p>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</p>	PEI feedback.

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<p>recommendation to continue or to permanently stop <u>IMP administration of new subjects in the respective dose level cohort for that vaccine.</u></p> <p><u>Guidance for discontinuation of trial treatment is provided in Section 7.1</u> For criteria for discontinuation of individual patients from IMP, see Section 7.1"</p>	
<p><u>Section 7.1 (Discontinuation of trial treatment)</u></p> <p>"Trial subjects permanently discontinued from IMP administration will complete all assessments planned for that visit and for the <u>Visit 6 (EoT Visit)</u>, as listed in the SoA (<u>Section 1.3</u>)."</p>	PEI feedback triggering scheduling changes.
<p><u>Section 8.2.1 (Physical examinations).</u></p> <p>"A brief (symptom directed) physical examination <u>will include, at a minimum, assessments of the skin, lungs, cardiovascular system, abdomen (liver), and lymph nodes.</u>"</p>	Correction of an inconsistency in protocol version 2.0.
<p><u>Section 8.2.10 (SARS-CoV-2 testing).</u></p> <p><u>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).</u></p> <p><u>SARS-CoV-2 testing will be performed at the time points provided in the SoA (Section 1.3).</u></p> <p><u>This include 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.</u></p> <p><u>If required, this reference will allow the discrimination between vaccinated and infected subjects.</u></p> <p><u>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).</u></p> <p><u>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 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.</u></p> <p><u>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.</u></p>	PEI feedback.
<p><u>Section 8.3.1 (Adverse events of special interest) was updated.</u></p> <p><u>"Not applicable.</u></p> <p><u>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 be considered adverse events of special interest (AESI)."</u></p>	PEI feedback.
<p><u>Section 10.3.1 (Definition of AE and TEAE).</u></p> <p>"AEs with an onset date more than <u>24-28</u> d after the last administration of IMP will be considered as treatment emergent only if assessed as related to IMP by the investigator."</p>	Correction of an inconsistency in protocol version 2.0.

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<p><u>Section 8.9 (Immunogenicity assessments).</u></p> <p><del>Immune responses will be assessed at the times listed in the SoA (Section 1.3) using:</del></p> <ul style="list-style-type: none"> <li>• a functional antibody titer, e.g., virus neutralization test (VNT).</li> <li>• an antibody binding assay, e.g., ELISA.</li> <li>• and/or equivalent assays dependent on availability by the time of trial conduct.</li> <li>• (for cell-mediated immune responses) ELISpot (CD4 and CD8 T-cell ELISpot).</li> </ul> <p><u>Immune responses will be assessed at the times listed in the SoA (Section 1.3) using:</u></p> <ul style="list-style-type: none"> <li>• a functional antibody titer, e.g., virus neutralization test (VNT).</li> </ul> <p><u>Seronegative is defined as titers below the starting dilution which corresponds to a titer of &lt;1:10.</u></p> <p><u>Seroconversion after vaccination is defined as a 4-fold increase in titer for seronegative pre-vaccination sera: a titer &gt;1:40.</u></p> <p><u>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 &gt;1:80 after vaccination.</u></p> <ul style="list-style-type: none"> <li>• an antibody binding assay, e.g., ELISA.</li> </ul> <p><u>Seronegative is defined as titers below the starting dilution which corresponds to a titer of &lt;1:100.</u></p> <p><u>Seroconversion after vaccination is defined as a 4-fold increase in titer for seronegative pre-vaccination sera: a titer of &gt;1:400.</u></p> <p><u>for seropositive pre-vaccination sera: a titer which is 4-fold higher than the measured pre-vaccination titer, e.g., titer rise from &lt;200 to &gt;1:800 after vaccination.</u></p> <p><u>and/or</u></p> <ul style="list-style-type: none"> <li>• equivalent assays dependent on availability by the time of trial conduct.</li> </ul> <p><u>Cell-mediated immune (CMI) responses:</u></p> <ul style="list-style-type: none"> <li>• CMI assays, e.g., ELISpot.</li> </ul> <p><u>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.</u></p>	PEI feedback.
<p><u>Section 10.4.2 (Contraception guidance).</u></p> <p>Women of childbearing potential (WOCBP) must practice <del>one two</del> highly effective forms of contraception during the trial, starting after Visit 0 and continuously until 60 d after receiving the last immunization.</p> <p>.....</p> <p>The investigator or delegate should advise the subject how to achieve highly effective contraception. Use of <del>one two</del> of the following birth control methods may be considered as highly effective (trial subjects must use two of the listed methods)</p>	Correction of an inconsistency in protocol version 2.0.
<p><u>Section 10.1.5 (Committees - SRC).</u></p> <ul style="list-style-type: none"> <li>• Before progression to the next cohort, for each vaccine per cohort/dose level, assess the safety and tolerability data of the first <math>\geq 6</math> 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. <u>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..</u></li> </ul>	PEI feedback.

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<ul style="list-style-type: none"><li>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.</li><li><u>Before progression to Part B</u>, 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). <u>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..</u></li></ul>	
<p>Section 10.3.1.9 (Documentation of particular situations).</p> <p><u>,AEs of proven COVID-19 disease of moderate or severe intensity:</u> <u>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."</u></p>	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.

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Throughout the document, the term “COVID- <del>2019</del> ” was harmonized to “COVID- <ins>19</ins> ”.	Harmonization – the protocol used COVID-2019 and COVID-19.
<u>Section 1.1 (Trial Synopsis) “Table 1 - Summary of vaccine dose regimens”</u> The planned dose 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.
<u>Section 1.1 (Trial Synopsis) “Trial design” – Part A</u> 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. <u>Dose de-escalation in the case of possible vaccine-related toxicities will be guided by the Safety Review Committee (SRC), as required.</u>	Additional information added for clarification.
<u>Section 1.1 (Trial Synopsis) “Trial design” – Part A</u> <ul style="list-style-type: none"><li>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).</li></ul> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>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).</u></p>	Additional information added for clarification.
<u>Section 1.1 (Trial Synopsis) Table “Trial treatments (BNT162 vaccines)”</u> Part A dose finding: <ul style="list-style-type: none"><li>For BNT162a1 <del>and BNT162c2</del>: 1 µg, 3 µg, 10 µg, 30 µg (optionally/additionally doses &lt;1 µg [de-escalation] or doses between 1 µg and 30 µg [intermediate doses]).</li></ul>	Non-clinical data suggesting a high potency, thereby allowing the use of a lower dose.

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<ul style="list-style-type: none"><li>For BNT162b1 and BNT162b2: 1 µg, 10 µg, 30 µg, 100 µg (optionally/additionally doses &lt;1 µg [de-escalation] or doses between 1 µg and 100 µg [intermediate doses]).</li><li><u>For BNT162c2: 0.1 µg, 0.3 µg, 1 µg (optionally/additionally doses between 0.1 µg and 1 µg [intermediate doses]).</u></li></ul>	
<b>Section 1.1 (Trial Synopsis) Table “Trial treatments (BNT162 vaccines)”</b> Dosage frequency: <ul style="list-style-type: none"><li>One injection or two injections 21 d apart. Injection volumes will be between <u>0.05 mL</u> <del>0.1 mL</del> and 1 mL.</li></ul>	Non-clinical data suggesting a high potency, thereby allowing the use of a lower dose.
<b>Section 1.2 (Schema (graphical representation of the trial))</b> The figures depicting BNT162a1 and BNT162c2 was split into two figures and due to the changed doses in BNT162c2.	Non-clinical data suggesting a high potency, thereby allowing the use of a lower dose.
<b>Section 1.3 (SoA) Table 2 - Footnote n</b> <u>i Excluding the de-escalation cohorts, only for the first 6 subjects per group.</u> ..... <del>n Only for the first 6 subjects per group.</del>	Clarification of an ambiguity regarding when wellbeing calls are planned.
<b>Section 1.3 (SoA) Table 3 - Footnote o</b> <u>o Excluding the de-escalation cohorts, only <del>Only</del> for the first 6 subjects per group.</u>	Clarification of an ambiguity regarding when wellbeing calls are planned.
<b>Section 2.3.1 Risk Assessment</b> <ul style="list-style-type: none"><li>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.</li></ul>	Addition of preliminary data from the ongoing clinical trial.
<b>Section 2.3.1 Risk Assessment</b> <ul style="list-style-type: none"><li><del>Subject wellbeing questioning by telephone at 48±2 h after each immunization.</del></li><li><u>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.</u></li><li><u>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.</u></li></ul>	Clarification of an ambiguity regarding when wellbeing calls are planned. Addition of the option for wellbeing calls at the discretion of the SRC.
<b>Section 2.3.1 Risk Assessment</b> <u>SRC may make recommendations on increasing observation periods and additional subject wellbeing calls may be included at the discretion of the SRC.</u>	Additional information added for clarification.

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<p><u>Section 4.1 (Trial design) – Part A</u></p> <p>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.</p> <p><u>Dose de-escalation in the case of possible vaccine-related toxicities will be guided by the Safety Review Committee (SRC), as required.</u></p>	Additional information added for clarification.
<p><u>Section 4.1 (Trial design) – Part A</u></p> <ul style="list-style-type: none"> <li>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).</li> </ul> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>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).</u></p>	Additional information added for clarification.
<p><u>Section 4.3 (Justification for dose)</u></p> <p>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 <u>0.1 µg (for BNT162c2)</u>, 3 µg (for BNT162a1 <del>and BNT162c2</del>) 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).</p>	Non-clinical data suggesting a high potency, thereby allowing the use of a lower dose.
<p><u>Section 5.2.1 Exclusion criteria Part A (Criteria 7)</u></p> <p>WOCBP must agree to practice <u>two highly effective forms a highly effective form</u> of contraception during the trial, starting after Visit 0 and continuously until 60 d after receiving the last immunization.</p>	Correction of an inconsistency with the ICF and to expand the eligible population.
<p><u>Section 6.1 (IMP administered) Table “Trial treatments (BNT162 vaccines)”</u></p> <p>Part A dose finding:</p> <ul style="list-style-type: none"> <li>For BNT162a1 <del>and BNT162c2</del>: 1 µg, 3 µg, 10 µg, 30 µg (optionally/additionally doses &lt;1 µg [de-escalation] or doses between 1 µg and 30 µg [intermediate doses]).</li> <li>For BNT162b1 and BNT162b2: 1 µg, 10 µg, 30 µg, 100 µg (optionally/additionally doses &lt;1 µg [de-escalation] or doses between 1 µg and 100 µg [intermediate doses]).</li> <li><u>For BNT162c2: 0.1 µg, 0.3 µg, 1 µg (optionally/additionally doses between 0.1 µg and 1 µg [intermediate doses]).</u></li> </ul>	Non-clinical data suggesting a high potency, thereby allowing the use of a lower dose.
<p><u>Section 6.1 (IMP administered) Table “Trial treatments (BNT162 vaccines)”</u></p> <p>Dosage frequency:</p> <ul style="list-style-type: none"> <li>One injection or two injections 21 d apart. Injection volumes will be between <u>0.05 mL</u> <del>0.1 mL</del> and 1 mL.</li> </ul>	Non-clinical data suggesting a high potency, thereby allowing the use of a lower dose.

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<p><b>Section 6.6 (Dose modifications)</b>  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:</p> <ul style="list-style-type: none"> <li>• <del>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.</del></li> <li>• <u>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.</u></li> <li>• To adapt the planned escalation doses (<u>0.3 µg, 1 µg, 10 µg, 30 µg, and 100 µg doses</u> in Part A), whereby the highest dose will not exceed the highest planned dose for that vaccine.</li> <li>• <u>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.</u></li> </ul>	Non-clinical data suggesting a high potency, thereby allowing the use of a lower dose.
<p><b>Section 6.6.1 (Dose limiting toxicity)</b></p> <ul style="list-style-type: none"> <li>• Anaphylactic reaction considered related</li> <li>• Generalized urticaria considered related</li> <li>• 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, <u>nonsteroidal anti-inflammatory drugs [NSAIDs]</u>)</li> <li>• <u>Any systemic SAE within 7 days of vaccination considered related</u></li> <li>• <u>Any fever &gt;40.0°C (&gt;104.0°F) within 7 days of vaccination considered related</u></li> <li>• <u>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)</u></li> <li>• <del>Any systemic SAE considered related</del></li> <li>• <del>Any severe non-SAE considered related</del></li> </ul>	Harmonization with the relatedness categories given in Section 10.3.1
<p><b>Section 8.2.7 Viral screening</b>  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.</p> <p><u>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.</u></p>	Addition of sentence to enable usage of further local PCR-devices.
<p><b>Section 8.2.9 (Subject wellbeing questioning)</b>  Cross-reference to the section "Assessment of Intensity" inserted.  Table 4 (Grading of local reactions to injectable product) was deleted.</p>	Strategy change for the reporting of AEs (to enable cross-alignment with other planned clinical trials with BNT162 vaccine candidates)
<p><b>Section 8.2.12 (Subject wellbeing questioning)</b>  <u>(Excluding the de-escalation cohorts and after boost immunizations)</u> Structured non-leading subject wellbeing questioning will be performed at the time given in the SoA (Section 1.3) <u>for the first 6 subjects per cohort</u>. Subject responses may trigger more in-</p>	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.	
<b>Section 9.4.5 (Section 10.4.2 Contraception guidance)</b> 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. <u>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).</u>	Strategy change for the reporting of AEs (to enable cross-alignment with other planned clinical trials with BNT162 vaccine candidates)
<b>Section 10.1.5 (Committees – SRC)</b> <ul style="list-style-type: none"><li>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.</li><li>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.</li></ul>	Clarification of the SRC role.
<b>Section 10.3.1.4 (Definition of SAE)</b> <ul style="list-style-type: none"><li>Results in persistent disability/incapacity <b>The term disability means a substantial disruption of a person's ability conduct normal life functions.</b> 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.</li></ul>	Strategy change for the reporting of AEs (to enable cross-alignment with other planned clinical trials with BNT162 vaccine candidates)
<b>Section 10.3.1.7 (Recording and Follow-Up of AE and/or SAE) Assessment of intensity</b> <b><u>The intensity of AEs or SAEs will be graded by the investigator. For further guidance on assessment assessments, see below:</u></b> <ul style="list-style-type: none"><li><b>Grade 1</b> Mild; Signs and symptoms that can be easily tolerated. Symptoms can be ignored and disappear when the subject is distracted.</li><li><b>Grade 2</b> Moderate; Symptoms cause discomfort but are tolerable; they cannot be ignored and affect concentration.</li><li><b>Grade 3</b> Severe; Symptoms which affect usual daily activity.</li></ul> <b>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.</b> <b><u>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</u></b>	Strategy change for the reporting of AEs (to enable cross-alignment with other planned clinical trials with BNT162 vaccine candidates)

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<p><u>not provided, the following general approach should be followed:</u></p> <p><b>FDA_Toxicity_Grading_2007</b></p> <ul style="list-style-type: none"><li>• <u>Grade 1 - Mild: does not interfere with the subject's usual function.</u></li><li>• <u>Grade 2 - Moderate: interferes to some extend with the subject's usual function.</u></li><li>• <u>Grade 3 - Severe: interferes significantly with the subject's usual function.</u></li><li>• <u>Grade 4 - Potentially Life threatening: life-threatening consequences, urgent intervention required.</u></li></ul> <p><u>Please also refer to the intensity tables given in the guideline for intensity of clinical and laboratory abnormalities to be reported as AEs:</u></p> <ul style="list-style-type: none"><li>• <u>Guideline Section III.A for assessment of clinical abnormalities (local and systemic)</u></li></ul> <p><u>Local Reactions</u></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><b>Table 4: Local reaction grading scale</b></p> <table border="1"><thead><tr><th></th><th><u>Mild (Grade 1)</u></th><th><u>Moderate (Grade 2)</u></th><th><u>Severe (Grade 3)</u></th><th><u>Potentially Life Threatening (Grade 4)</u></th></tr></thead><tbody><tr><td><u>Pain at the injection site</u></td><td><u>Does not interfere with activity</u></td><td><u>Interferes with activity</u></td><td><u>Prevents daily activity</u></td><td><u>Emergency room visit or hospitalization for severe pain</u></td></tr><tr><td><u>Redness</u></td><td><u>2.5 cm to 5.0 cm</u></td><td><u>&gt;5.0 cm to 10.0 cm</u></td><td><u>&gt;10 cm</u></td><td><u>Necrosis or exfoliative dermatitis</u></td></tr><tr><td><u>Swelling</u></td><td><u>2.5 cm to 5.0 cm</u></td><td><u>&gt;5.0 cm to 10.0 cm</u></td><td><u>&gt;10 cm</u></td><td><u>Necrosis</u></td></tr></tbody></table> <p><u>Systemic events</u></p> <p><u>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.</u></p> <p><b>Table 5: Systemic event grading scale</b></p> <table border="1"><thead><tr><th></th><th><u>Mild (Grade 1)</u></th><th><u>Moderate (Grade 2)</u></th><th><u>Severe (Grade 3)</u></th><th><u>Potentially Life Threatening (Grade 4)</u></th></tr></thead><tbody><tr><td><u>Vomiting</u></td><td><u>1-2 times in 24 h</u></td><td><u>&gt;2 times in 24 h</u></td><td><u>Requires IV hydration</u></td><td><u>Emergency room visit or hospitalization for hypotensive shock</u></td></tr><tr><td><u>Diarrhea</u></td><td><u>2 to 3 loose stools in 24 h</u></td><td><u>4 to 5 loose stools in 24 h</u></td><td><u>6 or more loose stools in 24 h</u></td><td><u>Emergency room visit or hospitalization for severe diarrhea</u></td></tr></tbody></table>		<u>Mild (Grade 1)</u>	<u>Moderate (Grade 2)</u>	<u>Severe (Grade 3)</u>	<u>Potentially Life Threatening (Grade 4)</u>	<u>Pain at the injection site</u>	<u>Does not interfere with activity</u>	<u>Interferes with activity</u>	<u>Prevents daily activity</u>	<u>Emergency room visit or hospitalization for severe pain</u>	<u>Redness</u>	<u>2.5 cm to 5.0 cm</u>	<u>&gt;5.0 cm to 10.0 cm</u>	<u>&gt;10 cm</u>	<u>Necrosis or exfoliative dermatitis</u>	<u>Swelling</u>	<u>2.5 cm to 5.0 cm</u>	<u>&gt;5.0 cm to 10.0 cm</u>	<u>&gt;10 cm</u>	<u>Necrosis</u>		<u>Mild (Grade 1)</u>	<u>Moderate (Grade 2)</u>	<u>Severe (Grade 3)</u>	<u>Potentially Life Threatening (Grade 4)</u>	<u>Vomiting</u>	<u>1-2 times in 24 h</u>	<u>&gt;2 times in 24 h</u>	<u>Requires IV hydration</u>	<u>Emergency room visit or hospitalization for hypotensive shock</u>	<u>Diarrhea</u>	<u>2 to 3 loose stools in 24 h</u>	<u>4 to 5 loose stools in 24 h</u>	<u>6 or more loose stools in 24 h</u>	<u>Emergency room visit or hospitalization for severe diarrhea</u>
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<u><a href="#">Headache</a></u>	<u><a href="#">Does not interfere with activity</a></u>	<u><a href="#">Some interference with activity</a></u>	<u><a href="#">Prevents daily routine activity</a></u>	<u><a href="#">Emergency room visit or hospitalization for severe headache</a></u>
<u><a href="#">Fatigue/tiredness</a></u>	<u><a href="#">Does not interfere with activity</a></u>	<u><a href="#">Some interference with activity</a></u>	<u><a href="#">Prevents daily routine activity</a></u>	<u><a href="#">Emergency room visit or hospitalization for severe fatigue</a></u>
<u><a href="#">Chills</a></u>	<u><a href="#">Does not interfere with activity</a></u>	<u><a href="#">Some interference with activity</a></u>	<u><a href="#">Prevents daily routine activity</a></u>	<u><a href="#">Emergency room visit or hospitalization for severe chills</a></u>
<u><a href="#">New or worsened muscle pain</a></u>	<u><a href="#">Does not interfere with activity</a></u>	<u><a href="#">Some interference with activity</a></u>	<u><a href="#">Prevents daily routine activity</a></u>	<u><a href="#">Emergency room visit or hospitalization for severe new or worsened muscle pain</a></u>
<u><a href="#">New or worsened joint pain</a></u>	<u><a href="#">Does not interfere with activity</a></u>	<u><a href="#">Some interference with activity</a></u>	<u><a href="#">Prevents daily routine activity</a></u>	<u><a href="#">Emergency room visit or hospitalization for severe new or worsened joint pain</a></u>

#### Fever

Fever is defined as an oral temperature of  $\geq 38.0^{\circ}\text{C}$ . 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

	<u><a href="#">Mild (Grade 1)</a></u>	<u><a href="#">Moderate (Grade 2)</a></u>	<u><a href="#">Severe (Grade 3)</a></u>	<u><a href="#">Potentially Life Threatening (Grade 4)</a></u>
<u><a href="#">Fever</a></u>	<u><a href="#">38.0–38.4°C</a></u>	<u><a href="#">38.5–38.9°C</a></u>	<u><a href="#">39.0–40.0°C</a></u>	<u><a href;"="">&gt;40.0°C</a></u>

#### Laboratory abnormalities

Laboratory abnormalities will be graded according to the grading scheme given in Table 6.

**Table 7:** Laboratory abnormality grading scale

<u><a href="#">Hematology</a></u>	<u><a href="#">Mild (Grade 1)</a></u>	<u><a href="#">Moderate (Grade 2)</a></u>	<u><a href="#">Severe (Grade 3)</a></u>	<u><a href="#">Potentially Life Threatening (Grade 4)</a></u>
<u><a href="#">Hemoglobin (Female) - g/dL</a></u>	<u><a href="#">11.0 – 12.0</a></u>	<u><a href="#">9.5 – 10.9</a></u>	<u><a href="#">8.0 – 9.4</a></u>	<u><a href;"="">&lt;8.0</a></u>
<u><a href="#">Hemoglobin (Female) change from baseline value - g/dL</a></u>	<u><a href="#">Any decrease – 1.5</a></u>	<u><a href="#">1.6 – 2.0</a></u>	<u><a href="#">2.1 – 5.0</a></u>	<u><a href;"="">&gt;5.0</a></u>
<u><a href="#">Hemoglobin (Male) - g/dL</a></u>	<u><a href="#">12.5 – 13.5</a></u>	<u><a href="#">10.5 – 12.4</a></u>	<u><a href="#">8.5 – 10.4</a></u>	<u><a href;"="">&lt;8.5</a></u>
<u><a href="#">Hemoglobin (Male) change from baseline value – g/dL</a></u>	<u><a href="#">Any decrease – 1.5</a></u>	<u><a href="#">1.6 – 2.0</a></u>	<u><a href="#">2.1 – 5.0</a></u>	<u><a href;"="">&gt;5.0</a></u>
<u><a href="#">WBC increase - cells/mm<sup>3</sup></a></u>	<u><a href="#">10,800 – 15,000</a></u>	<u><a href="#">15,001 – 20,000</a></u>	<u><a href="#">20,001 – 25,000</a></u>	<u><a href;"="">&gt;25,000</a></u>

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	Rationale			
<u>WBC decrease - cells/mm<sup>3</sup></u>	<u>2,500 – 3,500</u>	<u>1,500 – 2,499</u>	<u>1,000 – 1,499</u>	<u>&lt;1,000</u>
<u>Lymphocytes decrease - cells/mm<sup>3</sup></u>	<u>750 – 1,000</u>	<u>500 – 749</u>	<u>250 – 499</u>	<u>&lt;250</u>
<u>Neutrophils decrease - cells/mm<sup>3</sup></u>	<u>1,500 – 2,000</u>	<u>1,000 – 1,499</u>	<u>500 – 999</u>	<u>&lt;500</u>
<u>Eosinophils - cells/mm<sup>3</sup></u>	<u>650 – 1500</u>	<u>1501 - 5000</u>	<u>&gt;5000</u>	<u>Hypereosinophilic</u>
<u>Platelets decreased - cells/mm<sup>3</sup></u>	<u>125,000 – 140,000</u>	<u>100,000 – 124,000</u>	<u>25,000 – 99,000</u>	<u>&lt;25,000</u>
<u>Chemistry</u>	<u>Mild (Grade 1)</u>	<u>Moderate (Grade 2)</u>	<u>Severe (Grade 3)</u>	<u>Potentially Life Threatening (Grade 4)</u>
<u>BUN - mg/dL</u>	<u>23 – 26</u>	<u>27 – 31</u>	<u>&gt;31</u>	<u>Requires dialysis</u>
<u>Creatinine – mg/dL</u>	<u>1.5 – 1.7</u>	<u>1.8 – 2.0</u>	<u>2.1 – 2.5</u>	<u>&gt;2.5 or requires dialysis</u>
<u>Alkaline phosphate = increase by factor</u>	<u>1.1 – 2.0 x ULN</u>	<u>2.1 – 3.0 x ULN</u>	<u>3.1 – 10 x ULN</u>	<u>&gt;10 x ULN</u>
<u>Liver function tests – ALT, AST increase by factor</u>	<u>1.1 – 2.5 x ULN</u>	<u>2.6 – 5.0 x ULN</u>	<u>5.1 – 10 x ULN</u>	<u>&gt;10 x ULN</u>
<u>Bilirubin – when accompanied by any increase in liver function test - increase by factor</u>	<u>1.1 – 1.25 x ULN</u>	<u>1.26 – 1.5 x ULN</u>	<u>1.51 – 1.75 x ULN</u>	<u>&gt;1.75 x ULN</u>
<u>Bilirubin – when liver function test is normal - increase by factor</u>	<u>1.1 – 1.5 x ULN</u>	<u>1.6 – 2.0 x ULN</u>	<u>2.0 – 3.0 x ULN</u>	<u>&gt;3.0 x ULN</u>
<u>Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.</u>				
<u>Section 10.4.2 Contraception guidance</u> Women of childbearing potential (WOCBP) must practice <u>two highly effective forms a highly effective form</u> 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. <u>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".</u> The investigator or delegate should advise the subject how to achieve highly effective contraception. <u>Use of the</u> <u>The</u> following birth control methods may be considered as highly effective ( <u>trials subjects must use two of the listed methods</u> ):	Correction of an inconsistency with the ICF and to expand the eligible population.			
<ul style="list-style-type: none"> <li>Intrauterine device. <sup>a</sup></li> <li><u>Intrauterine hormone-releasing system.</u> <sup>a</sup></li> </ul>				

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<ul style="list-style-type: none"><li>Combined estrogen and progestogen-based contraception: established use of oral, intravaginal, or transdermal hormonal methods of contraception.</li><li>Progesterone-based contraception: established use of oral, injected, or implanted a hormonal methods of contraception.</li><li>True abstinence or homosexuality. When the subjects are truly abstinent or homosexual, no second method of contraception is required.</li><li>Vasectomy (for a male subject or male partner of a female subject). <sup>a</sup></li></ul> <p><u>a) Contraception methods that in the context of this guidance are considered to have low user dependency.</u></p>	

## 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.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)									Rationale
<u>Section 1.1 "Trial design" – Table 1 (Summary of vaccine dose regimens)</u>									Due to dose adjustments following IEC feedback and SRC requests.
Vaccine	mRNA type	Vaccine encoded antigen	Vaccine IM dosing regimen	Part A - Dose Groups & Dose (µg) (12 subjects per cohort)					Part B - Optional Expansion Cohorts
			Starting dose	1A 3 µg	2A 10 µg	3A* <del>4 µg</del> <ins>0.1 µg</ins>	4A 30 µg	5A <del>0.3 µg</del>	
BNT162a1	uRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22						Doses to be selected based on Part A data
BNT162b1	modRNA	RBD of the S protein	Prime: Day 1 Boost: Day 22	1B 10 µg	2B 30 µg	3B 1 µg	4B <del>100 µg</del> <ins>60 µg*</ins>	5B <del>50 µg</del>	As above
BNT162b2	modRNA	A modified version of the S protein	Prime: Day 1 Boost: Day 22	1C 10 µg	2C 30 µg	3C 1 µg	4C 100 µg		As above
BNT162c2	saRNA	A modified version of the S protein	Prime only: Day 1	1D 0.1 µg	2D 0.3 µg	Not planned	4D 1 µg		As above
<p>* Dose to be defined/adapted by the Safety Review Committee (SRC). IM = intramuscular; RBD = Receptor Binding Domain; S protein = SARS-CoV-2 Spike protein</p> <p><u>Section 1.1 "Trial design" – Part A and Section 4.1 Overall design and Section 4.1 Overall design</u> <u>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.</u> <u>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).</u> <u>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</u></p>									PEI & IEC feedback to amendment no. 2.

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<p><u>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.</u></p>	
<p><b>Section 1.1 "Trial design" – Part A</b></p> <p>In Cohort 1, the sentinel dosing/subject staggering process will be as follows:</p> <ul style="list-style-type: none"> <li>• One sentinel subject will be dosed on one day.</li> <li>• If the .....</li> <li>• 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): <ul style="list-style-type: none"> <li>◦ The remaining 6 subjects in the group will be dosed.</li> <li>◦ 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.</li> <li>◦ If approved by the SRC, the planned de-escalation dose in Cohort 3 (<del>1 µg</del>) will be initiated.</li> </ul> </li> </ul> <p>In Cohort 2, the subject staggering process will be as follows:</p> <ul style="list-style-type: none"> <li>• Two sentinel subjects will be dosed on one day.</li> <li>• If the .....</li> <li>• 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): <ul style="list-style-type: none"> <li>◦ The remaining 6 subjects .....</li> <li>◦ If approved by the SRC, ...</li> </ul> </li> </ul> <p>In Cohort 3, if possible, 12 subjects will be dosed with the planned <del>1 µg</del> dose on one day.</p>	Due to dose adjustments following IEC feedback and SRC requests.
<p><b>Section 1.1 "Trial treatments" and Section 6.1 "IMP administered"</b></p> <p><b>Dosage levels:</b> <u>See Table 1. The planned dose per vaccine candidate will not exceed the pre-defined maximum dose (see Table 1).</u></p> <p><b>Part A dose finding:</b></p> <ul style="list-style-type: none"> <li>• For BNT162a1: 1 µg, 3 µg, 10 µg, 30 µg (optionally/additionally doses &lt;1 µg [de-escalation] or doses between 1 µg and 30 µg [intermediate doses]).</li> <li>• For BNT162b1 and BNT162b2: 1 µg, 10 µg, 30 µg, 100 µg (optionally/additionally doses &lt;1 µg [de-escalation] or doses between 1 µg and 100 µg [intermediate doses]).</li> <li>• For BNT162c2: 0.1 µg, 0.3 µg, 1 µg (optionally/additionally doses between 0.1 µg and 1 µg [intermediate doses]).</li> </ul>	Due to dose adjustments following IEC feedback and SRC requests.
<p><b>Section 1.2 Schema (graphical representation of the trial)</b></p> <p>The schema were updated to reflect the updated doses.</p>	Due to dose adjustments following IEC feedback and SRC requests.
<p><b>Section 1.3 - Table 2 (Schedule of trial procedures and assessments – BNT162a1, BNT162b1, and BNT162b2)</b></p> <p>A column for subject wellbeing questioning was inserted for 48 h after the boost immunization.</p>	PEI feedback to amendment no. 2.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	Rationale
<p><u>Section 1.3 Schedule of activities Table 2</u></p> <p>i <del>Excluding the de-escalation cohorts, only for the first 6 subjects per group (for P/B regimens only after the prime immunization).</del> <u>Only for the first 6 subjects per group.</u></p>	PEI feedback to amendment no. 2.
<p><u>Section 1.3 Schedule of activities) Table 3</u></p> <p>e <del>Excluding the de-escalation cohorts, only for the first 6 subjects per group.</del> <u>Only for the first 6 subjects per group.</u></p>	PEI feedback to amendment no. 2
<p><u>Section 2.2 Trial rationale</u></p> <p>SARS-CoV-2 infections .....</p> <p>BioNTech has developed a.....</p> <p>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.</p> <p><u>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.</u></p> <p><b><u>This trial (BNT162-01) - Preliminary results (status 22 May 2020)</u></b></p> <p>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-like 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.</p> <p>For the vaccine candidate BNT162a1, 6 subjects were exposure at a 3 µg dose. <b>CCI</b></p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p><b><u>US trial PF-07302048 - Preliminary results (status 22 May 2020)</u></b></p> <p>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.</p> <p>The US trial 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."</p>	Addition of current data from this and related trials at the request of the IEC.

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<p><u>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.</u></p> <p><u>As a 2-dose (separated by 21 or 60 days) or single-dose schedule</u></p> <p><u>At up to 3 different dose levels</u></p> <p><u>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 &gt;55 years of age])</u></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>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 seen, 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.</u></p> <p><u>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.</u></p> <p><b>Chinese trial - BNT162-03</b></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>Subjects who are ≥18 years old and ≤55 years old will be enrolled in adult group, and healthy elderly people who are &gt;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.</u></p> <p><u>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</u></p>	

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<p><u>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.</u></p>	
<p><u>Section 2.3.1 Risk assessment</u></p> <ul style="list-style-type: none"><li>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 <del>S</del>erious AEs have been reported. Fever of severe intensity has been reported. Most AEs <del>were</del>can be managed with simple measures and resolved spontaneously.</li><li>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.</li><li>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.</li></ul> <p><u>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 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).</u></p> <ul style="list-style-type: none"><li><b>CCI</b> </li></ul> <p>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.</p>	Inclusion of current data from this and related trials at the request of the IEC.

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<u>Section 2.3.1 Risk assessment</u> <ul style="list-style-type: none"> <li>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.</li> <li>Subject wellbeing questioning by telephone at 48±2 h after each immunization will be performed for the first 6 subjects per cohort.</li> </ul>	PEI feedback to amendment no. 2
<u>Section 4.3 Justification for dose</u> 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 <u>proposes</u> <u>proposed</u> 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). <u>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).</u> 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 <u>available previous</u> clinical and non-clinical data experience, the sponsor expects the <u>planned maximal</u> doses ( <u>see Table 1</u> ) of up to 100 µg to be safe.	Inclusion of current data from this and related trials at the request of the IEC.
<u>Section 6.6 Dose modifications</u> <ul style="list-style-type: none"> <li>To replace or supplement the planned <u>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.</u></li> <li>To adapt the planned escalation doses (<u>0.3 µg, 1 µg, 10 µg, 30 µg and 100 µg doses in Part A</u>) for Part A, whereby the highest dose will not exceed the highest planned dose for that vaccine (<u>see Table 1</u>).</li> </ul>	Due to dose adjustments following IEC feedback and SRC requests.
<u>Section 6.6.1 Dose limiting toxicity</u> <ul style="list-style-type: none"> <li>Two trial subjects (at any dose level) with the same or similar severe (Grade 3) AE (including <u>clinically significant</u> laboratory abnormalities) within 7 days of vaccination, considered related (for severity grading of adverse events see Section 10.3.1.7)</li> </ul> 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. <u>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</u>	PEI feedback to amendment no. 2.

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<p><u>dosing design, subjects will have been followed for 4 d for the sentinel subjects when this SRC decision is made.</u></p> <p><u>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.</u></p> <p><u>The sum of the above events occurring at any time during the trial conduct (i.e., not just within 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.</u></p>	
<p><u>Section 8.2.7 Viral screening</u></p> <p><b>8.2.7 Viral screening (for blood-borne viruses)</b></p> <p>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).</p> <p>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.</p> <p><del>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.</del></p>	PEI feedback to amendment no. 2.
<p><u>Section 8.2.10 SARS-CoV-2 testing</u></p> <p>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.</p> <p><u>The screen for SARS-CoV-2 can be performed by either a central laboratory or a "point of care" device at the trial site.</u></p> <ul style="list-style-type: none"><li>• <u>If a central laboratory is used: Only the SARS-CoV-2 status will be tested and no further data will be generated.</u></li><li>• <u>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.</u></li></ul>	PEI feedback to amendment no. 2.
<p><u>Section 8.2.10 SARS-CoV-2 testing</u></p> <p>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 <u>at approximately</u> 14 d and 28 d <u>after immunization with the BNT162 candidate vaccine</u>. This data will be used to evaluate the development and progression of an antibody response allowing the diagnosis of a manifest infection.</p>	Clarification of an unclarity.
<p><u>Section 8.2.12 Subject wellbeing questioning</u></p> <ul style="list-style-type: none"><li>• <del>(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.</del> Subject responses may trigger more in-</li></ul>	PEI feedback to amendment no. 2.

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<p>depth questioning on specific topics, and may trigger diagnostic measures (including ad hoc site visits) at the discretion of the investigator.</p> <ul style="list-style-type: none"><li>• <u>Structured non-leading subject wellbeing questioning will be performed at the time given in the SoA (Section 1.3).</u> 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.</li></ul>	
Section 10.3.1.7 (Recording and Follow-Up of AE and/or SAE) Assessment of intensity	PEI feedback to amendment no. 2.

**Table 4: Local reaction grading scale**

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

<sup>a</sup> In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

<sup>b</sup> Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

## 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.

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<u>Section 1.1 (Trial design) and Section 3 (Trial design) - Primary objective</u>  • The proportion of subjects with at least 1 unsolicited treatment emergent adverse event (TEAE): <ul style="list-style-type: none"><li>For BNT162a1, BNT162b1, BNT162b2, <u>and BNT162c2</u> (P/B): occurring up to <math>21\pm 2</math> d after the prime immunization and <math>28\pm 4</math> d after the boost immunization.</li></ul>	Addition of the testing of P/B regimen for BNT162c2.
<u>Section 1.1 (Trial design) and Section 3 (Trial design) - Secondary objectives</u>  For BNT162a1, BNT162b1, BNT162b2, <u>and BNT162c2</u> (P/B): <ul style="list-style-type: none"><li>Functional antibody responses at <math>7\pm 1</math> d and <math>21\pm 2</math> d after primary immunization and at <math>21\pm 2</math> d, <u><math>28\pm 4</math> d</u>, <math>63\pm 5</math> d, and <math>162\pm 7</math> d after the boost immunization.</li><li>Fold increase in functional antibody titers <math>7\pm 1</math> d and <math>21\pm 2</math> d after primary immunization and at <math>21\pm 2</math> d, <u><math>28\pm 4</math> d</u>, <math>63\pm 5</math> d, and <math>162\pm 7</math> d after the boost immunization.</li><li>Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline at <math>7\pm 1</math> d and <math>21\pm 2</math> d after primary immunization and at <math>21\pm 2</math> d, <u><math>28\pm 4</math> d</u>, <math>63\pm 5</math> d, and <math>162\pm 7</math> d after the boost immunization.</li><li>For BNT162c2 (SD):</li></ul>	Addition of sampling for functional antibody responses.

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<ul style="list-style-type: none"><li>Functional antibody responses at <math>7\pm 1</math> d, <math>21\pm 2</math> d, <u><math>29\pm 3</math> d</u>, <math>42\pm 3</math> d, <math>84\pm 5</math> d, and <math>183\pm 7</math> d after the primary immunization.</li><li>Fold increase in functional antibody titers at <math>7\pm 1</math> d, <math>21\pm 2</math> d, <u><math>29\pm 3</math> d</u>, <math>42\pm 3</math> d, <math>84\pm 5</math> d, and <math>183\pm 7</math> d after the primary immunization.</li><li>Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline at <math>7\pm 1</math> d, <math>21\pm 2</math> d, <u><math>29\pm 3</math> d</u>, <math>42\pm 3</math> d, <math>84\pm 5</math> d, and <math>183\pm 7</math> d after the primary immunization.</li></ul>	
<u>Section 1.1 (Trial design) and Section 3 (Trial design) - Exploratory objectives</u> For BNT162a1, BNT162b1, BNT162b2, <u>and BNT162c2</u> (P/B): <ul style="list-style-type: none"><li>Antibody responses at <math>7\pm 1</math> d and <math>21\pm 2</math> d after primary immunization and at <math>21\pm 2</math> d, <u><math>29\pm 3</math> d</u>, <math>63\pm 5</math> d, and <math>162\pm 7</math> d after the boost immunization.</li><li>Fold increase in antibody titers at <math>7\pm 1</math> d and <math>21\pm 2</math> d after primary immunization and at <math>21\pm 2</math> d, <u><math>29\pm 3</math> d</u>, <math>63\pm 5</math> d, and <math>162\pm 7</math> d after the boost immunization.</li><li>Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers as compared to baseline at <math>7\pm 1</math> d and <math>21\pm 2</math> d after primary immunization and at <math>21\pm 2</math> d, <u><math>29\pm 3</math> d</u>, <math>63\pm 5</math> d, and <math>162\pm 7</math> d after the boost immunization.</li></ul> For BNT162c2 (SD): <ul style="list-style-type: none"><li>Antibody responses at <math>7\pm 1</math> d, <math>21\pm 2</math> d, <u><math>29\pm 3</math> d</u>, <math>42\pm 3</math> d, <math>84\pm 5</math> d, and <math>183\pm 7</math> d after the primary immunization.</li><li>Fold increase in antibody titers at <math>7\pm 1</math> d, <math>21\pm 2</math> d, <u><math>29\pm 3</math> d</u>, <math>42\pm 3</math> d, <math>84\pm 5</math> d, and <math>183\pm 7</math> d after the primary immunization.</li><li>Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers as compared to baseline at <math>7\pm 1</math> d, <math>21\pm 2</math> d, <u><math>29\pm 3</math> d</u>, <math>42\pm 3</math> d, <math>84\pm 5</math> d, and <math>183\pm 7</math> d after the primary immunization.</li></ul>	Addition of the testing of P/B regimen for BNT162c2. Addition of sampling for antibody responses.
<u>Section 1.1 (Trial design) and Section 3 (Trial design) - Exploratory objectives</u> For BNT162a1, BNT162b1, BNT162b2, <u>and BNT162c2</u> (P/B): <ul style="list-style-type: none"><li>Cell-mediated immune (CMI) responses measured by Enzyme-Linked Immuno-Spot (ELISpot) at baseline and at <math>29\pm 3</math> d after the primary immunization.</li></ul>	Addition of the testing of P/B regimen for BNT162c2.
<u>Section 1.1 (Trial design) and Section 3 (Trial design)</u> Four different vaccines (BNT162a1, BNT162b1, BNT162b2, and BNT162c2) will be tested. <del>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, <u>and BNT162b2, and BNT162c2</u> will be administered using a P/B regimen. The vaccine BNT162c2 will also be administered using a SD regimen.</del> The chosen trial design reflects discussion and advice from the Paul-Ehrlich Institute (PEI) obtained in <del>two</del> -scientific advice meetings held in February, <u>March, and June</u> 2020.	Addition of the testing of P/B regimen for BNT162c2. Rephrased for clarity.
<u>Section 1.1 (Trial design) and Section 3 (Trial design)</u> The first part of the trial (Part A) will follow a dose-escalation design. <u>For some vaccines, a dose-de-escalation is also planned.</u> ... In Cohort 2, the subject staggering process will be as follows: <ul style="list-style-type: none"><li>Two sentinel subjects will be dosed on one day.</li></ul>	Addition of the testing of P/B regimen for BNT162c2. Addition of additional cohorts for the testing of

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<ul style="list-style-type: none"><li>If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24<u>±2 h</u> observation on site, a 4 further subjects will be dosed.</li></ul> <p>...</p> <p>In Cohort 4, the subject staggering process will be as follows:</p> <ul style="list-style-type: none"><li>Two sentinel subjects will be dosed on one day.</li><li>If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24<u>±2 h</u> observation on site, a 4 further subjects will be dosed.</li></ul> <p>...</p> <p><b><u>Additional dose cohorts</u></b> <u>The optional dose de-escalation cohort</u> (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).</p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>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.</u></p> <p>Note: BNT162b1, and BNT162b2 are <del>both</del> non-modified uridine RNAs, while BNT162a1 and BNT162c2 are both nucleoside-modified pseudomethyl-uridine containing.</p> <p>...</p> <p><del>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).</del></p>	BNT162b1 and later BNT162b2 vaccine candidates in older adults.
<u>Section 1.1 (Trial design) and Section 3 (Trial design) - Table 1</u>  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)
<u>Section 1.1 and Section 3 - Table 1</u>  <del>Details of Part B will be defined after evaluation of aggregate data from Part A using a protocol amendment.</del>  <del>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.</del>  <u>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).</u>  <u>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.</u>	Update to improve clarity.
<u>Section 1.1 (Trial duration)</u>	

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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], <u>and BNT162c2 (P/B))</u> , 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.																			
<p><u>Section 1.1 (Population) and Section 4.1.2 (Planned number of trial subjects)</u></p> <p><u>Healthy adults aged 18 to 55 years.</u></p> <p><u>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.</u></p> <p><u>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).</u></p> <p><u>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.</u></p>	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.																		
<p><b>Table 3: Overview of the total number of subjects for each vaccine in Part A</b></p> <table border="1"><thead><tr><th><u>Vaccine / mRNA type</u></th><th><u>Vaccine dosing regimen</u></th><th><u>Maximum number of subjects (assuming all cohorts planned in Error! Reference source not found. are performed)</u></th></tr></thead><tbody><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></tbody></table>	<u>Vaccine / mRNA type</u>	<u>Vaccine dosing regimen</u>	<u>Maximum number of subjects (assuming all cohorts planned in Error! Reference source not found. are performed)</u>	BNT162a1 / uRNA	Prime/Boost	60 (5 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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<p><u>Section 1.1 (Key inclusion criteria)</u></p> <ul style="list-style-type: none"><li><u>They must be aged 18 to 55 years, have a body mass index over 19 kg/m<sup>2</sup> and under 30 kg/m<sup>2</sup>, and weigh at least 50 kg at Visit 0.</u></li><li>For younger subject cohorts, volunteers must be aged 18 to 55 years, have a body mass index over 19 kg/m<sup>2</sup> and under 30 kg/m<sup>2</sup>, and weigh at least 50 kg at Visit 0 <u>OR</u> <u>For older adult cohorts, volunteers must be aged 56 to 85 years, have a body mass index over 19 kg/m<sup>2</sup> and under 30 kg/m<sup>2</sup>, and weigh at least 50 kg at Visit 0.</u></li><li>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.</li></ul>	Addition of additional subject cohorts for the testing of BNT162b vaccine candidates in older adults.																		
<p><u>Section 1.1 (Key exclusion criteria)</u></p> <ul style="list-style-type: none"><li>Had any chronic use (more than <u>14-21</u> 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</li></ul>	Addition of additional subject cohorts for the testing of BNT162b vaccine																		

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<p><u>significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.</u></p> <ul style="list-style-type: none"><li>• <u>Regular receipt of inhaled/nebulized corticosteroids.</u></li><li>• ....</li><li>• <u>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:</u><ul style="list-style-type: none"><li>– <u>Hypertension</u></li><li>– <u>Diabetes mellitus</u></li><li>– <u>Chronic pulmonary disease</u></li><li>– <u>Asthma</u></li><li>– <u>Chronic liver disease</u></li><li>– <u>Known Stage 3 or worse chronic kidney disease (glomerular filtration rate &lt;60 mL/min/1.73 m<sup>2</sup>)</u></li><li>– <u>BMI ≥30 kg/m<sup>2</sup></u></li><li>– <u>Anticipating the need for immunosuppressive treatment within the next 6 months</u></li><li>– <u>Resident in a long-term facility</u></li><li>– <u>Current vaping or smoking (occasional smoking is acceptable)</u></li><li>– <u>History of chronic smoking within the prior year</u></li></ul></li></ul>	candidates in older adults.
<p><u>Section 1.1 (Trial treatments) and Section 6.1 (IMP administered)</u></p> <p>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.</p>	Addition of volume flexibility due to the added additional cohorts for the BNT162b vaccine candidates.
<p><u>Section 1.2 (Schema)</u></p> <p>The schema was updated to reflect:</p> <p>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.</p>	Addition of additional subject cohorts.
<p><u>Section 1.3 (Schedule of activities)</u></p> <p><b>Table 3 (was 2)</b></p> <p>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.</p> <p>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. <u>Only in women who are not WOCBP: follicle stimulating hormone at Visit 0.</u> .....</p> <p>n The listed blood draw days may be adapted if justified by the collected data.</p> <p>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</p>	Update to reflect the addition of additional of blood draws. Update to reflect the addition of Visit 5 in Table 3 for BNT162c2 (SD).

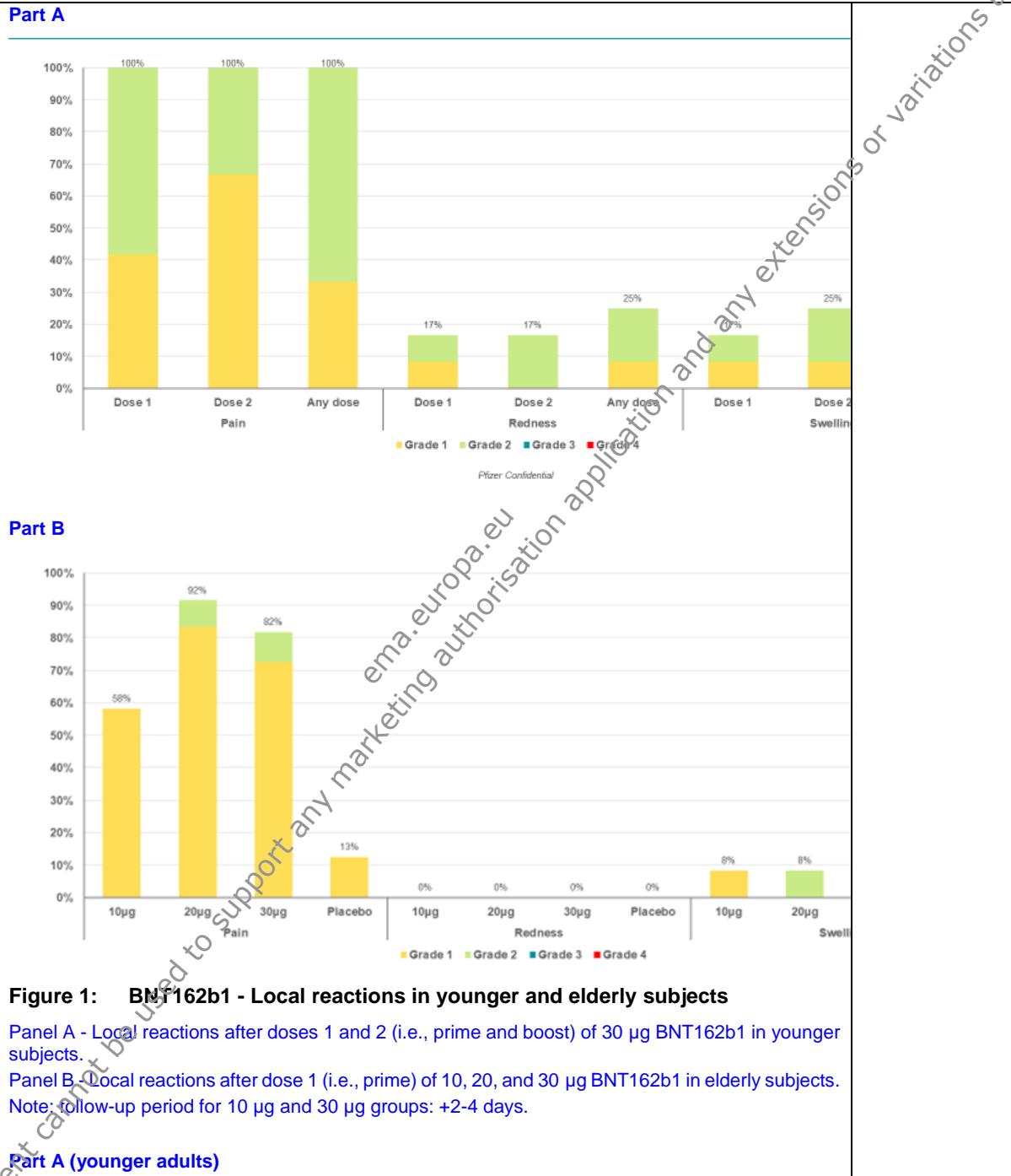
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<p><u>cell receptor repertoire and / or phenotypic characterization of T cells specific to vaccine-encoded antigens.</u></p> <p><u>P If HLA typing using the blood sample collected with Lithium Heparin is not conclusive, EDTA-blood will be drawn for HLA testing.</u></p> <p><b>Table 4 (was 3)</b>  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.</p> <p>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. <u>Only in women who are not WOCBP: follicle stimulating hormone at Visit 0.</u>  .....</p> <p><u>I The listed blood draw days may be adapted if justified by the collected data.</u></p> <p><u>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.</u>  ...</p> <p><u>P If HLA typing using the blood sample collected with Lithium Heparin is not conclusive, EDTA-blood will be drawn for HLA testing.</u></p>	
<p><b>Section 2.2 (Trial rationale)</b>  <u>The four prophylactic BNT162 vaccines against SARS-CoV-2 investigated in this trial BNT162-04 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).</u> 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.</p> <p>For the status of ongoing and planned clinical trials, see <a href="#">Table 5</a>.</p> <p><b>Table 5: Status of ongoing and planned clinical trials (as of June 22nd, 2020)</b>  <a href="#">(Table was updated with June 22nd 2020 data)</a></p>	Status update to provide transparency of ongoing data.
<p><b>2.2.1 This trial (BNT162-01) - Preliminary results (status June 22nd, 2020)</b></p> <p><b>2.2.1 This trial (BNT162-01) - Preliminary results (status 22 May 2020)</b>  <u>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-like 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</u></p>	Status update to provide transparency of ongoing data.

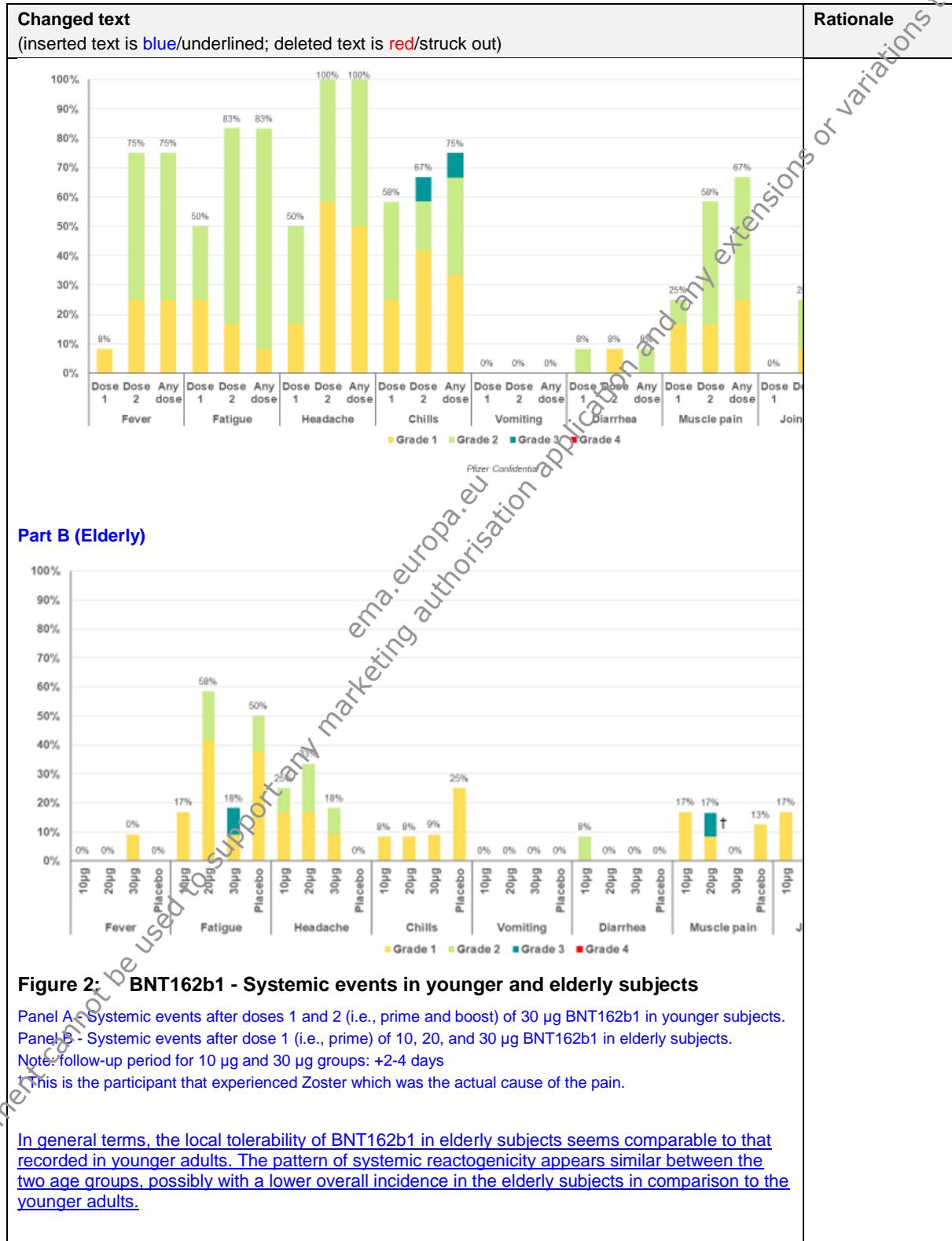
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<p>reported within the post-vaccination observation period. A slight dose dependency for frequency and intensity of symptoms was observed between the 1 µg and 10 µg cohorts, but from 10 µg to 60 µg no clear dose dependency is apparent. On laboratory 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.</p> <p>For the vaccine candidate BNT162a1, 6 subjects were exposed at a 3 µg dose. CCI [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>																																																																																	
<b>Summary of safety in trial BNT162-01 (up to June 22<sup>nd</sup> 2020)</b>																																																																																	
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.																																																																																	
<b>Reactogenicity</b>																																																																																	
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.																																																																																	
<b>Table 6: Number of adults aged 18 to 55 years with local symptoms (diary): BNT162b1</b>																																																																																	
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<p>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.</p>																																																																																			
<p><b>Laboratory findings</b></p> <p>A consistent pattern has been seen in the laboratory assessments with elevation of the C-reactive protein with concomitant reduction in the plasma lymphocyte count 24 h after vaccination. These changes are consistent with the known pharmacology of this technology, with the changes in lymphocytes known to represent a reversible compartmental shift from the vascular space to lymphoid organs. These observations have been self-limiting and without clinical consequence. There have been no other consistent findings on laboratory assessments.</p>																																																																																			
<p><b>Adverse events</b></p> <p>Adverse events are collected throughout the trial and graded by the investigators on a 4-point scale (as per this protocol). Most subjects report adverse events (Table 8), &gt;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.</p>																																																																																			
<p><b>Table 8: Summary BNT162b1 TEAE (prime +/- boost) by number of subjects</b></p> <table border="1"><thead><tr><th rowspan="2">BNT162b1</th><th rowspan="2">Subjects Dosed N =</th><th colspan="6">Number of Subjects with (n=)</th></tr><tr><th>TEAES</th><th>Mild AE</th><th>Moderate AE</th><th>Severe AE</th><th>SAE</th><th>Resolved AE</th></tr></thead><tbody><tr><td>1 µg</td><td>12</td><td>11</td><td>10</td><td>7</td><td>2</td><td>0</td><td>11</td><td></td><td></td></tr><tr><td>10 µg</td><td>12</td><td>12</td><td>12</td><td>8</td><td>1</td><td>0</td><td>12</td><td></td><td></td></tr><tr><td>30 µg</td><td>12</td><td>12</td><td>12</td><td>9</td><td></td><td>0</td><td>12</td><td></td><td></td></tr><tr><td>50 µg</td><td>12</td><td>12</td><td>12</td><td>11</td><td>2</td><td>0</td><td>12</td><td></td><td></td></tr><tr><td>60 µg</td><td>12</td><td>12</td><td>12</td><td>10</td><td>1</td><td>0</td><td>12</td><td></td><td></td></tr><tr><td>Total</td><td>60</td><td>59</td><td>58</td><td>45</td><td>6</td><td>0</td><td>59</td><td></td><td></td></tr></tbody></table>										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		
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60 µg	12	12	12	10	1	0	12																																																																												
Total	60	59	58	45	6	0	59																																																																												
<p><b>Summary</b></p> <p>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</p>																																																																																			

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<p><u>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.</u></p> <p><b>CCI</b> [REDACTED] <u>Most recently dosing has begun with vaccines BNT162b2 and BNT162c2. CCI</u> [REDACTED] <u>Early indications for tolerability of BNT162b2 at a 10 µg dose are very encouraging with only minimal local reactogenicity in initial reports.</u></p>	
<p><b>Section 2.2.2 US trial BNT162-02 - Preliminary results (status, June 22nd, 2020)</b></p> <p><b>Section 2.2.2 (US trial BNT162-02 (PF-07302048) - Preliminary results (status 08 June 2020)</b></p> <p>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.</p> <p>The US trial 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.</p> <p>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:</p> <p>As a 2-dose (separated by 21 or 60 days) or single-dose schedule</p> <p>At up to 3 different dose levels</p> <p>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 &lt;55 or &gt;55 years of age])</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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 seen, 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.</p> <p>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.</p>	Status update to provide transparency of ongoing data.
<p><b>Section 10.10.5 US trial BNT162-02 - Preliminary results (status, June 22nd, 2020)</b></p>	

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<p>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.</p> <p>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.</p> <p><b>Summary of safety in BNT162-02 (status, June 22<sup>nd</sup>, 2020)</b></p> <p>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.</p> <p>Preliminary safety and tolerability data in elderly (aged 65 to 85 years) after dosing with BNT162b1 are presented separately below and are summarized in <b>Figure 2</b> and <b>Figure 3</b>.</p> <p><b>Table 9: Number of adults aged 18 to 55 years dosed in BNT162-02 (status, June 22<sup>nd</sup>, 2020)</b></p> <table border="1"><thead><tr><th rowspan="2"></th><th colspan="2">BNT162b1</th><th colspan="2">Placebo</th></tr><tr><th>Dose 1</th><th>Dose 2</th><th>Dose 1</th><th>Dose 2</th></tr></thead><tbody><tr><td>18-55 years of age</td><td></td><td></td><td></td><td></td></tr><tr><td>10 µg dose level</td><td>N=12</td><td>N=12</td><td>N=3</td><td>N=3</td></tr><tr><td>30 µg dose level</td><td>N=12</td><td>N=12</td><td>N=3</td><td>N=3</td></tr><tr><td>100 µg dose level</td><td>N=12</td><td>Not applicable</td><td>N=3</td><td>Not applicable</td></tr></tbody></table> <p>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.</p> <p><b>Summary of safety in elderly subjects (aged 65 to 85 years) in BNT162-02</b></p> <p>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 <b>Figure 2</b> and <b>Figure 3</b>.</p> <p><b>Table 10 Number of adults aged 65 to 85 years dosed in BNT162-02 (status, June 22<sup>nd</sup>, 2020)</b></p> <table border="1"><thead><tr><th rowspan="2"></th><th colspan="2">BNT162b1</th><th colspan="2">Placebo</th></tr><tr><th>Dose 1</th><th>Dose 2</th><th>Dose 1</th><th>Dose 2</th></tr></thead><tbody><tr><td>65-85 years of age</td><td></td><td></td><td></td><td></td></tr><tr><td>10 µg dose level</td><td>N=12</td><td>N=0</td><td>N=3</td><td>N=0</td></tr><tr><td>20 µg dose level</td><td>N=12</td><td>N=0</td><td>N=3</td><td>N=0</td></tr><tr><td>30 µg dose level</td><td>N=12</td><td>N=0</td><td>N=3</td><td>N=0</td></tr></tbody></table> <p>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 PPD on day 2 after receiving a 20 µg dose, consistent with varicella zoster (shingles). PPD was prescribed Valacyclovir and this AE was reported as fully resolved within 7 days. The investigator reported this AE as not related to vaccine.</p>		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		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
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<p><u>Section 2.2.2 (Chinese trial - BNT162-03)</u></p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Subjects who are ≥18 years old and ≤55 years old will be enrolled in adult group, and healthy elderly people who are &gt;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.</p> <p>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.</p> <p>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).</p> <p>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.</p>	Update reflecting the current preparation status.
<p><u>Section 2.3.1 (Risk assessment)</u></p> <p>The risks linked to the trial-specific procedures and connected mitigations are as follows:</p> <ul style="list-style-type: none"><li>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.)</li><li>...</li><li>...</li></ul> <p>CCI</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <ul style="list-style-type: none"><li>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.</li><li>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</li></ul>	Update reflecting the added blood sampling and the available clinical data from the ongoing trials BNT162-01 and BNT162-02.

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<p><u>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.</u></p> <ul style="list-style-type: none"> <li><u>When assessing the risk for dosing of older subjects with BNT162 vaccine candidates, the follow information is relevant:</u></li> <li><u>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.</u></li> <li><u>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.</u></li> <li><u>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.</u></li> <li><u>In this trial, the doses to be tested in older adults are within the range already shown to show acceptable tolerability in younger adults.</u></li> <li><u>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.</u></li> <li><u>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.</u></li> <li>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.</li> </ul>	
<p><u>Section 5.1.1 (Inclusion criteria Part A)</u></p> <p>4. <u>They must be aged 18 to 55 years, have a body mass index over 19 kg/m<sup>2</sup> and under 30 kg/m<sup>2</sup>, and weigh at least 50 kg at Visit 0.</u></p> <p>4. <u>For younger subject cohorts, volunteers must be aged 18 to 55 years, have a body mass index over 19 kg/m<sup>2</sup> and under 30 kg/m<sup>2</sup>, and weigh at least 50 kg at Visit 0</u>  <u>OR</u>  <u>For older adult cohorts, volunteers must be aged 56 to 85 years, have a body mass index over 19 kg/m<sup>2</sup> and under 30 kg/m<sup>2</sup>, and weigh at least 50 kg at Visit 0.</u></p> <p>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.  <u>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.</u>      ...</p> <p>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.  <u>WOCBP must agree to require their male partners to use condoms during sexual contact (unless male partners are sterilized or infertile).</u></p>	Addition of additional subject cohorts for the testing of BNT162b vaccine candidates in older adults.
<p><u>Section 5.2.1 (Exclusion criteria Part A)</u></p> <p>6. Had any chronic use (more than 44-21 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.  <u>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</u></p>	Addition of additional subject cohorts for the testing of BNT162b vaccine

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<p><u>before enrollment, can be included.</u></p> <p>...</p> <p><u>28. Regular receipt of inhaled/nebulized corticosteroids.</u></p> <p><u>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:</u></p> <ul style="list-style-type: none"><li>- <u>Hypertension</u></li><li>- <u>Diabetes mellitus</u></li><li>- <u>Chronic pulmonary disease</u></li><li>- <u>Asthma</u></li><li>- <u>Chronic liver disease</u></li><li>- <u>Known Stage 3 or worse chronic kidney disease (glomerular filtration rate &lt;60 mL/min/1.73 m<sup>2</sup>)</u></li><li>- <u>BMI ≥30 kg/m<sup>2</sup></u></li><li>- <u>Anticipating the need for immunosuppressive treatment within the next 6 months</u></li><li>- <u>Resident in a long-term facility</u></li><li>- <u>Current vaping or smoking (occasional smoking is acceptable)</u></li><li>- <u>History of chronic smoking within the prior year</u></li></ul>	candidates in older adults.
<p><u>Section 5.3 (Lifestyle considerations)</u></p> <p>For Cohorts 1, 2, <u>4, 7, and 8</u>, 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.</p> <p>For cohorts <u>1, 2, and 4 with P/B dosing</u>, all subjects dosed in each group will be required to remain at the site for approximately 6 h after the boost immunization.</p>	
<p><u>Section 6.3 (Measures to minimize bias: randomization and blinding)</u></p> <p>Not applicable <u>for Part A. Details for Part B will be defined using a protocol amendment.</u></p>	Update for clarification
<p><u>Section 6.5 (Concomitant therapy)</u></p> <p>Paracetamol/acetaminophen at doses of <u>less than up to</u> 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.</p>	Update for clarification
<p><u>Section 6.6 (Dose modifications)</u></p> <p>The trial design allows for a flexible dosing which allows a better evaluation on the optimal dose range. <u>For details see Section 4.1. , i.e., the trial design includes the options:</u></p> <ul style="list-style-type: none"><li>• <u>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.</u></li><li>• <u>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).</u></li><li>• <u>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.</u></li><li>• <u>To add an additional cohort.</u></li></ul>	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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<p><u>Section 6.6.1 (Dose limiting toxicity)</u></p> <p>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:</p> <ul style="list-style-type: none"><li>• ...</li><li>• Any <u>possibly related</u> AEs within 7 days of vaccination assessed <u>by the investigator</u> to be potentially life-threatening (Grade 4) <u>and that is possibly related, or for which there is no alternative, plausible, attributable cause.</u></li><li>• Any systemic SAE within 7 days of vaccination <u>that is assessed by the investigator as possibly considered</u> related, <u>or for which there is no alternative, plausible, attributable cause.</u></li><li>• Any fever &gt;40.0°C (&gt;104.0°F) within 7 days of vaccination considered related</li><li>• Two trial subjects (at any dose level) with the same or similar severe (Grade 3 <u>or higher</u>) AE (including clinically significant laboratory abnormalities) within 7 days of vaccination, considered related, <u>or for which there is no alternative, plausible, attributable cause</u> (for severity grading of adverse events see Section 10.3.1.7)</li></ul> <p><u>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).</u></p> <p>...</p> <p>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.</p> <p><u>The assessment of dose limiting toxicity should be done consistently for all subjects treated with the same treatment and dose.</u></p> <p><b>Part B</b></p> <p>The to be tested doses for each vaccine in Part B will be chosen <u>by the SRC</u> after review of the safety, tolerability, and immunogenicity data from Part A for that vaccine.</p>	Updated to provide additional guidance and clarification when handling dose limiting toxicity.
<p><u>Section 8.2.9 (Assessment of local reactions)</u></p> <p>Local reactions after IM immunization will be assessed <u>by the investigator</u> at the times given in the SoA (Section 1.3).</p> <p>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). <u>This information will be used to validate the solicited assessment of local reactions in the patient diary and potentially support AE reporting.</u></p>	Updated to provide additional guidance and clarification when assessing local reactions.
<p><u>Section 8.2.10 (SARS-CoV-2 testing)</u></p> <p>SARS-CoV-2 testing (<u>PCR-based and antibody-based</u>) will be performed at the time points provided in the SoA (Section 1.3).</p> <p>This includes PCR-based testing for SARS-CoV-2 <u>at Visit 0</u> as an eligibility criterion and blood draws for anti-SARS-CoV-2 antibody testing as baseline reference for immunogenicity analysis.</p>	Clarification of an ambiguity.
<p><u>Section 8.2.13 (Assessment of systemic reactions)</u></p> <p><u>Systemic reactions after IM immunization will be assessed at the times given in the SoA (Section 1.3).</u></p> <p><u>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).</u></p>	Added to provide guidance when assessing systemic reactions.
<p><u>Section 8.3.1 (Time period and frequency for collecting AE and SAE information)</u></p> <p>All AEs and SAEs will be collected from the date of subject consent until discharge from the trial at Visit 8 (BNT162c2) <u>[SD]</u> or Visit 9 (BNT162a1, BNT162b1, BNT162b2), <u>BNT162c2 [P/B]</u>.</p>	Update reflecting the addition of

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	additional cohorts.
<u>Section 8.7 (Genetics)</u> <u>Not applicable.</u> <u>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).</u> <u>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.</u> <u>Blood samples will only be used for genetic analysis if the trial subjects have provided informed consent for this genetic analysis.</u>	Assessments added
<u>Section 8.8 (Biomarkers)</u> <u>Not applicable.</u> <u>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.</u> <u>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.</u> <u>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.</u> <u>Samples for biomarker analysis will be retained for use for up to 5 years after the end of the trial.</u>	Assessments added
<u>Section 8.9 (Immunogenicity assessments)</u> 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 <ul style="list-style-type: none"><li>○ for seronegative pre-vaccination sera: a titer <math>\geq 1:40</math>.</li><li>○ 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 <math>\geq 1:80</math> after vaccination.</li></ul> <u>an antibody binding assay, e.g., ELISA.</u>  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 <ul style="list-style-type: none"><li>○ for seronegative pre-vaccination sera: a titer of <math>\geq 1:400</math>.</li><li>○ 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 <math>\geq 1:800</math> after vaccination.</li></ul> and/or  equivalent assays dependent on availability by the time of trial conduct.  Cell-mediated immune (CMI) responses: CMI assays, e.g., ELISpot, <u>intracellular cytokine staining (ICS)</u> .	Assessments added

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<p>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.</p> <p>Instructions <u>on</u> 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.</p> <p><u>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).</u></p>	
<p>Section 8.10 (Blood collection)</p> <p><u>Up to approximately 568 mL blood will be drawn per subject over the complete trial, i.e., over approximately 7 months.</u></p> <p><u>Additional blood samples may be taken for safety assessments after AEs or SAEs.</u></p> <p><u>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.</u></p>	New section added to describe blood sampling.
<p>Section 9.4.2 (Primary endpoints)</p> <p>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, <u>BNT162c2 SD</u>, and BNT162c2 P/B] and dose level) and for each immunization, i.e., for:</p> <ul style="list-style-type: none"><li>• Prime/boost regimens: Day 1-21 (pre-boost) <del>and (BNT162c2) Day 1-28</del></li><li>• Day 21(post-boost) - 28</li><li>• Single dose regimens: Day 1-28</li><li>• <del>(BNT162a1, BNT162b1, BNT162b2, BNT162c2) Day 1-21 (if applicable, Day 21 pre-boost)</del></li><li>• <del>(BNT162c2) Day 1-28</del></li></ul> <p>Additionally, AEs will be summarized for all dose levels combined for each type.</p> <ul style="list-style-type: none"><li>• Any AE</li><li>• <u>Any AE excluding AEs based on solicited reporting via subject diaries</u></li><li>• Related AE</li><li>• Grade <math>\geq 3</math> AE</li><li>• Related Grade <math>\geq 3</math> AE</li></ul> <p>..</p> <p>For each immunization, the number and percentage of subjects reporting at least one local reaction or systemic reaction (<i>i.e.</i>, <u>solicited data collected using subject diaries</u>) will be summarized for each of the following types using the Safety Set:</p> <ul style="list-style-type: none"><li>• Any local reactions or systemic reactions</li><li>• <del>Related</del><u>Any</u> local reactions or systemic reactions</li><li>• <del>Grade <math>\geq 3</math> local reactions or systemic reactions</del></li><li>• <del>Related-</del>Grade <math>\geq 3</math> local reactions or systemic reactions</li></ul>	Update to correct duplication. Update reflecting the addition of additional cohorts.
<p>Section 9.4.5 (Other safety analyses)</p> <p><b>ECG</b></p> <p>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).</p>	Clarification of an ambiguity

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	Rationale
ECGs will be judged by the investigator as clinically significant (yes/no). <del>The number and percentage of trial subjects with clinically significant ECG findings will be summarized by group for each visit.</del>	
<p><b>Section 10.1.5 (Committees - SRC)</b> Key roles of the SRC are as follows:</p> <ul style="list-style-type: none"> <li>• Before progression to the next cohort, for each vaccine per cohort/dose level,</li> <li>• 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.</li> <li>• 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 <u>or other similar adaptations to protect subject wellbeing.</u></li> </ul>	Updated to reflect additional SRC tasks added by this protocol amendment.
<p><b>Section 10.2 (Clinical laboratory tests)</b> Follicle-stimulating hormone: <del>In women only</del> <u>Only in women who are not of childbearing potential.</u></p>	Clarification of an ambiguity.
<p><b>Section 10.3.1 (Definition of AE and TEAE)</b></p> <ul style="list-style-type: none"> <li>• <del>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.</del></li> <li>• <del>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.</del></li> <li>• <u>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.</u></li> <li>• <u>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.</u></li> <li>• <u>Events after signing ICF and before IMP administration will be handled as AEs.</u></li> <li>• 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.</li> </ul>	Alignment with the trial BNT162-02
<p><b>Section 10.3.1.1 (Events meeting the AE definition)</b></p> <ul style="list-style-type: none"> <li>• 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 <del>which are these</del> considered clinically significant in the medical and scientific judgment of the investigator. <u>may be considered as AEs.</u></li> <li>• <u>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).</u></li> <li>• New conditions or <u>any worsening of a pre-existing condition detected or</u> diagnosed after Visit 0.</li> </ul>	Alignment with the trial BNT162-02
<p><b>Section 10.3.1.7 (Recording and Follow-Up of AE and/or SAE)</b></p> <p><b>Assessment of AE and/or SAE intensity</b></p>	Addition of guidance due to reporting changes

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<p><b>Note:</b> 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.</p> <p>The assessment of AE and/or SAE intensity should be done consistently for all subjects treated with the same treatment and dose.</p> <p>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.</p> <p>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.</p> <p>In case of doubt, the Medical Monitor should be consulted.</p>	implemented to align BNT162-01 with the US trial BNT612-02.
<p><b>Section 10.3.1.7 (Recording and follow-up of AE and/or SAE)</b></p> <p>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).</p>	Adapted to avoid confusion between the assessment of AE/SAEs and the assessments of intensity for solicited local and systemic reactions and laboratory abnormalities.
<p><b>Section 10.3.1.9 (Documentation of particular situations)</b></p> <p><b>Abnormal laboratory results and vital signs values:</b></p> <p>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:</p> <ul style="list-style-type: none"><li>• If a laboratory/vital signs abnormal...</li><li>• If a laboratory/vital signs...</li><li>• If a laboratory/vital ...</li></ul> <p>If a laboratory/vital signs abnormality is not considered clinically significant by the investigator, then an AE does not need to be documented.</p>	Addition of guidance due to reporting changes implemented to align BNT162-01 with the US trial BNT612-02.
<p><b>Section 10.3.1.11 (Assessments of intensity for solicited local and systemic reactions and laboratory abnormalities)</b></p> <p>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.</p>	Adapted to avoid confusion between the assessment of AE/SAEs and the assessments of intensity for solicited local and systemic reactions and

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	Rationale
	laboratory abnormalities.
<p>Section 10.4.2 (Contraception guidance)</p> <p><del>Women of childbearing potential (WOCBP)</del> WOCBP must confirm that they practiced at least one highly effective form of contraception for the 14 d prior to Visit 0.</p> <p>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. <u>WOCBP must agree to require their male partners to use condoms during sexual contact (unless male partners are sterilized or infertile).</u></p> <p>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.</p>	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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<p><u>Section 1 and Section 4 (Objectives and endpoints)</u></p> <p>primary immunization.</p> <p>To describe the cellular immune responses.</p> <p>For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B):</p> <ul style="list-style-type: none"><li>Cell-mediated immune (CMI) responses measured by Enzyme-Linked Immuno-Spot (ELISpot) at baseline and at <math>29\pm3</math> d after the primary immunization.</li></ul> <p>For BNT162c2 (SD)</p> <ul style="list-style-type: none"><li>CMI responses measured by ELISpot at baseline and at <u><math>29\pm3</math> d</u> <del><math>42\pm4</math> d</del> after the primary immunization.</li></ul>	Alignment with other BNT162 trials
<p><u>Section 1 (Trial design) and Section 4 (Overall Trial design)</u></p> <p>Four different vaccines (BNT162a1, BNT162b1, BNT162b2, and BNT162c2) will be tested.</p> <p><u>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.</u></p> <p><u>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.</u></p> <p><del>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.</del></p>	PEI feedback & sponsor prioritization decision
<p><u>Section 1 (Trial design) and Section 4 (Overall Trial design)</u></p> <p><b>Part A</b></p> <p><del>The first part of the trial (Part A) will follow a dose-escalation design. For some vaccines, a dose-de-escalation is also planned.</del></p> <p>Trial subjects with the first-in-human [FIH] immunization will be immunized using a sentinel...</p>	Removal of duplication
<p><u>Section 1 (Trial design) and Section 4 (Overall Trial design)</u></p> <p>In Cohort 1, the sentinel dosing/subject staggering process will be as follows:</p> <ul style="list-style-type: none"><li>One sentinel subject will be dosed on one day.</li><li>If the dosing in this subject was considered to be safe and well tolerated by the investigator after <math>24\pm2</math> h observation on site, a 5 further subjects will be dosed (<u>with intervals of at least 1 h between subjects</u>).</li><li>If the dosing in these 5 subjects was considered to be safe and well tolerated by the investigator based on 48h data (<math>24\pm2</math> h observation on site and phone interview for assessment <math>48\pm2</math> h after immunization; in addition to the available <math>48\pm2</math> h data from the sentinel subject):</li></ul>	PEI feedback

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<ul style="list-style-type: none"><li>○ The remaining 6 subjects in the group will be dosed (with intervals of at least 30 min between subjects).</li><li>○ If approved by the SRC, the next planned escalation dose (see Table 1) <del>in Cohort 2</del> will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects including observation on site, <u>short summary of phone interview (including statement about diary reports)</u>, vital signs, <u>investigator reported local &amp; systemic reactions</u>, TEAEs, <u>solicited local &amp; systemic reactions</u> <del>local reactions</del>, blood/clinical laboratory data, and brief physical examination outcome.</li><li>○ If approved by the SRC, the planned de-escalation dose in Cohort 3 will be initiated.</li></ul>	
<p><u>Section 1 (Trial design) and Section 4 (Overall Trial design)</u></p> <p><u>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:</u></p> <ul style="list-style-type: none"><li>• <u>Two sentinel subjects will be dosed on one day (with intervals of at least 30 min between subjects).</u></li><li>• <u>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).</u></li><li>• <u>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):</u><ul style="list-style-type: none"><li>○ <u>The remaining 6 subjects in the group will be dosed (with intervals of at least 30 min between subjects).</u></li><li>○ <u>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 &amp; systemic reactions, blood/clinical laboratory data, and brief physical examination outcome.</u></li></ul></li></ul> <p><u>The maximum allowed dose for each vaccine candidate is defined in the Table 1.</u></p> <p><u>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.</u></p> <p><u>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 9, 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.</u></p> <p><u>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.</u></p> <p><u>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).</u></p> <p><u>In Cohort 2, the subject staggering process will be as follows:</u></p> <ul style="list-style-type: none"><li>● <del>Two sentinel subjects will be dosed on one day.</del></li><li>● <del>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.</del></li><li>● <del>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):</del></li></ul>	PEI feedback

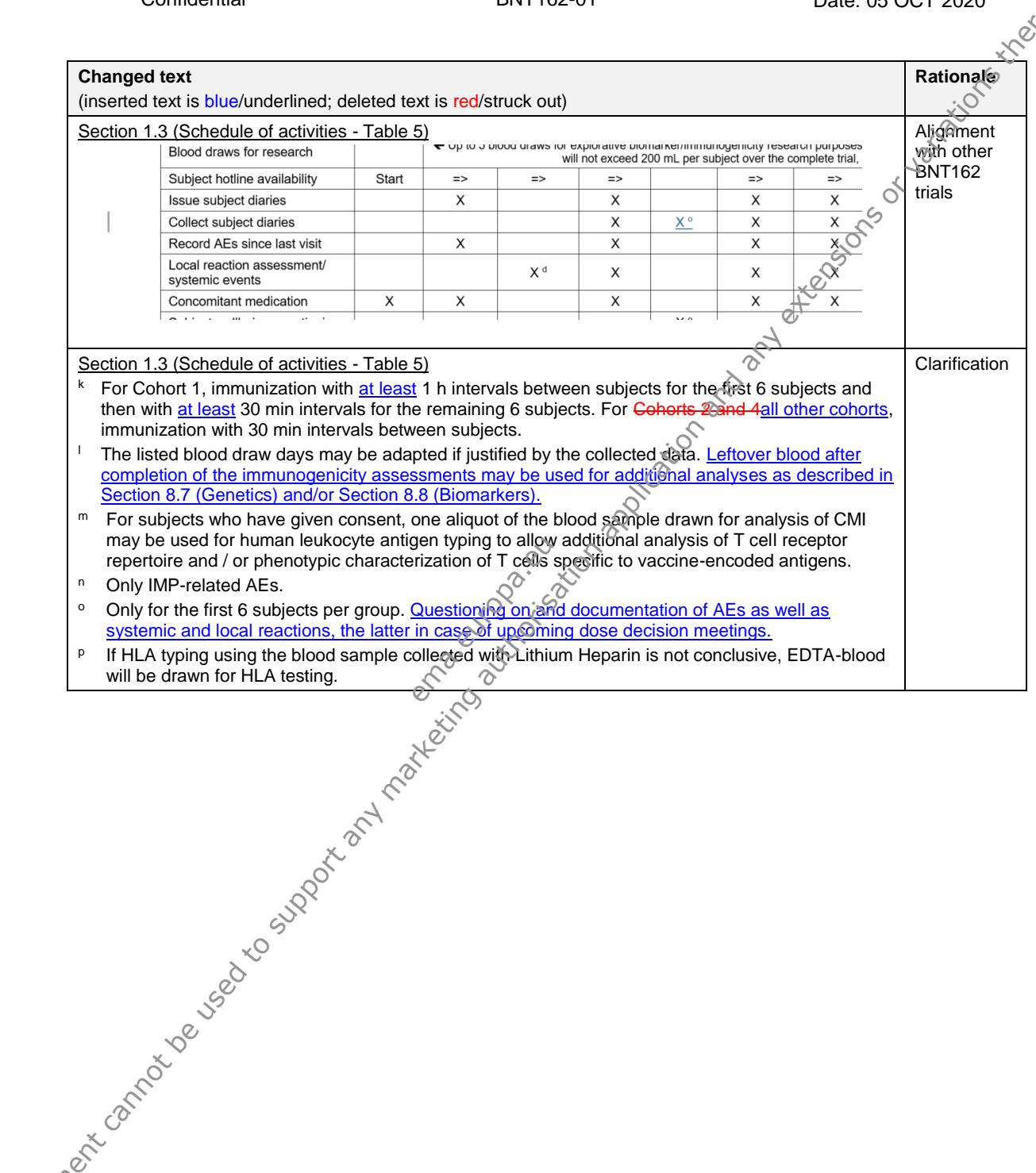
Changed text (inserted text is blue/underlined; deleted text is red/struck out)	Rationale																																																																			
<ul style="list-style-type: none"> <li>• The remaining 6 subjects in the group will be dosed.</li> <li>• If approved by the SRC, the next planned 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).</li> </ul> <p>In Cohort 3, if possible, 12 subjects will be dosed with the planned dose on one day.</p> <p>In Cohort 4, the subject staggering process will be as follows:</p> <ul style="list-style-type: none"> <li>• Two sentinel subjects will be dosed on one day.</li> <li>• 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.</li> <li>• 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): <ul style="list-style-type: none"> <li>◦ The remaining 6 subjects in the group will be dosed.</li> </ul> </li> </ul> <p>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).</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>																																																																				
<p><b>Section 1 (Trial design) Table 1</b></p> <p>Table 1: Summary of vaccine dose regimens for younger adults aged 18 to 55 years in Part A</p> <table border="1"> <thead> <tr> <th rowspan="2">Vaccine / mRNA type</th> <th rowspan="2">Vaccine encoded antigen</th> <th rowspan="2">Vaccine IM dosing regimen</th> <th colspan="7">Part A - Cohort numbers &amp; Dose (ug) (12 subjects per cohort)</th> </tr> <tr> <th>1 Starting dose</th> <th>2</th> <th>3 De-escalation dose</th> <th>4 Maximum dose</th> <th>5 Optional de-escalation dose</th> <th>6</th> <th>7</th> </tr> </thead> <tbody> <tr> <td>BNT162a1 / uRNA</td> <td>RBD of the SARS-CoV-2 S protein</td> <td>Prime: Day 1 Boost: Day 22</td> <td>1A 3 µg<sup>b</sup></td> <td>2A 0.6 µg<sup>a</sup></td> <td>3A 0.1 µg</td> <td>4A * 2 µg<sup>e</sup></td> <td>5A 40.3 µg</td> <td>6A 1 µg</td> <td></td> </tr> <tr> <td>BNT162b1 / modRNA</td> <td>RBD of the SARS-CoV-2 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 * 60 µg<sup>d</sup></td> <td>5B 50 µg</td> <td>6B 3 µg</td> <td>7B 20 µg</td> </tr> <tr> <td>BNT162b2 / modRNA</td> <td>Modified version of the full length SARS-CoV-2 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 * 60 µg<sup>f</sup></td> <td>5C * 620 µg</td> <td>6C * 3 µg</td> <td>7C * 250 µg</td> </tr> <tr> <td>BNT162c1</td> <td>Modified version of the full length SARS-CoV-2 S protein</td> <td>Prime only: Day 1</td> <td>1D 0.1 µg</td> <td>2D 0.3 µg</td> <td>3D 0.1 µg to &lt;3 µg<sup>c</sup></td> <td>4D 1 µg</td> <td>5D * 0.6 µg</td> <td>6D * 3 µg<sup>d</sup></td> <td></td> </tr> <tr> <td>BNT162c2 / sRNA</td> <td>Modified version of the full length SARS-CoV-2 S protein</td> <td>Prime: Day 1 Boost: Day 22</td> <td>1E 0.1 µg</td> <td>2E * 0.3 µg</td> <td>3E 0.1 µg to &lt;3 µg<sup>c</sup></td> <td>4E * 1 µg</td> <td>5E * 0.6 µg</td> <td>6E * 3 µg<sup>d</sup></td> <td></td> </tr> </tbody> </table> <p>All dose escalation doses used must be judged acceptable by the Safety Review Committee (SRC) before use.  <sup>b</sup> 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.  <sup>c</sup> Specific doses to be defined, but in the range given. Already given doses will not be repeated.  <sup>d</sup> The planned maximum doses per vaccine candidate.  <sup>e</sup> 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.</p> <p>IM = intramuscular, RBD = Receptor Binding Domain; S protein = SARS-CoV-2 spike protein: tbd = to be defined.</p>	Vaccine / mRNA type	Vaccine encoded antigen	Vaccine IM dosing regimen	Part A - Cohort numbers & Dose (ug) (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 <sup>b</sup>	2A 0.6 µg <sup>a</sup>	3A 0.1 µg	4A * 2 µg <sup>e</sup>	5A 40.3 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 <sup>d</sup>	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 * 60 µg <sup>f</sup>	5C * 620 µg	6C * 3 µg	7C * 250 µg	BNT162c1	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 <sup>c</sup>	4D 1 µg	5D * 0.6 µg	6D * 3 µg <sup>d</sup>		BNT162c2 / sRNA	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 <sup>c</sup>	4E * 1 µg	5E * 0.6 µg	6E * 3 µg <sup>d</sup>		PEI feedback
Vaccine / mRNA type				Vaccine encoded antigen	Vaccine IM dosing regimen	Part A - Cohort numbers & Dose (ug) (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 <sup>b</sup>	2A 0.6 µg <sup>a</sup>	3A 0.1 µg	4A * 2 µg <sup>e</sup>	5A 40.3 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 <sup>d</sup>	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 * 60 µg <sup>f</sup>	5C * 620 µg	6C * 3 µg	7C * 250 µg																																																											
BNT162c1	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 <sup>c</sup>	4D 1 µg	5D * 0.6 µg	6D * 3 µg <sup>d</sup>																																																												
BNT162c2 / sRNA	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 <sup>c</sup>	4E * 1 µg	5E * 0.6 µg	6E * 3 µg <sup>d</sup>																																																												

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<p><b>Section 1 (Trial design) Table 2</b></p> <p><b>Table 2:</b> Summary of vaccine dose regimens for older adults aged 56 to 85 years in Part A</p> <table border="1"> <thead> <tr> <th rowspan="2">Vaccine / mRNA type</th> <th rowspan="2">Vaccine encoded antigen</th> <th rowspan="2">Vaccine IM dosing regimen</th> <th colspan="3">Part A - Cohort numbers &amp; Dose (µg) (12 subjects per cohort)<sup>a</sup></th> </tr> <tr> <th>8 Older adults</th> <th>9 Older adults</th> <th>10 Older adults</th> </tr> </thead> <tbody> <tr> <td>BNT162b1 / modRNA</td> <td>RBD of the SARS-CoV-2 S protein</td> <td>Prime: Day 1 Boost: Day 22</td> <td>8B <del>103</del> µg</td> <td>9B<sup>b</sup> <del>2040</del> µg</td> <td>10B<sup>b</sup> <del>320</del> µg</td> </tr> <tr> <td>BNT162b2 / modRNA<sup>b</sup></td> <td>Modified version of the full length SARS-CoV-2 S protein</td> <td>Prime: Day 1 Boost: Day 22</td> <td>8C <del>103</del> µg</td> <td>9C<sup>b</sup> <del>2040</del> µg</td> <td>10C<sup>b</sup> <del>320</del> µg</td> </tr> </tbody> </table> <p><sup>a</sup> All dose escalation doses used must be judged acceptable by the Safety Review Committee (SRC) before use.  <sup>b</sup> These cohorts will be activated using a dedicated protocol amendment before any older adults are dosed.</p> <p>IM = intramuscular; RBD = Receptor Binding Domain; S protein = SARS-CoV-2 spike protein.</p> <p><b>Note:</b> 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.</p> <p><b>BNT162b1:</b></p> <ul style="list-style-type: none"> <li>BNT162b1 P/B doses of 1, 10, 30, and 50 µg showed acceptable tolerability in younger adults.</li> <li>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.</li> <li>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.</li> </ul> <p><b>BT162b2:</b></p> <ul style="list-style-type: none"> <li>BNT162b2 P/B doses of 1, 10, and 30 µg showed acceptable tolerability in younger adults.</li> <li>BNT162b2 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.</li> </ul> <p>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.</p> <p>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.</p> <p>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.</p>	Vaccine / mRNA type	Vaccine encoded antigen	Vaccine IM dosing regimen	Part A - Cohort numbers & Dose (µg) (12 subjects per cohort) <sup>a</sup>			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 <del>103</del> µg	9B <sup>b</sup> <del>2040</del> µg	10B <sup>b</sup> <del>320</del> µg	BNT162b2 / modRNA <sup>b</sup>	Modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	8C <del>103</del> µg	9C <sup>b</sup> <del>2040</del> µg	10C <sup>b</sup> <del>320</del> µg	PEI feedback
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<p><b>Section 1 (Trial design) and Section 4 (Overall Trial design)</b></p> <p>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)....</p> <p>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.</p>	PEI feedback																					
<p><b>Section 1 (Population) - Table 3</b></p> <p><b>Table 3:</b> Overview of the total number of subjects for each vaccine in Part A</p> <table border="1"> <thead> <tr> <th>Vaccine / mRNA type</th> <th>Vaccine dosing regimen</th> <th>Maximum number of subjects (assuming all cohorts planned in Table 1 are performed)</th> </tr> </thead> <tbody> <tr> <td>BNT162a1 / uRNA</td> <td>Prime/Boost</td> <td>60-72 (<del>5-6</del> 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> </tbody> </table>	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 ( <del>5-6</del> 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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<p><u>Section 1 (Key exclusion criteria)</u></p> <p>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:</p> <ul style="list-style-type: none"> <li>• Hypertension</li> <li>• Diabetes mellitus</li> <li>• Chronic pulmonary disease</li> <li>• Asthma</li> <li>• Chronic liver disease</li> <li>• Known Stage 3 or worse chronic kidney disease (glomerular filtration rate &lt;60 mL/min/1.73 m<sup>2</sup>)</li> <li>• <del>BMI ≥30 kg/m<sup>2</sup></del></li> <li>• ...</li> </ul>	IEC feedback
<p><u>Section 1 (Trial treatments (BNT162 vaccines) - Dosage levels) and Section 6.1 (IMP administered)</u></p> <p>Part B expansion cohorts:</p> <p>The to be tested doses will be chosen <del>by the SRC</del> after review of the safety, tolerability, and immunogenicity data from Part A. <u>Part B will only be started if approved using a substantial protocol amendment.</u></p>	IEC feedback
<p><u>Section 1.2 (Schema - Dose cohort schema for BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B))</u></p> <p>a) The data assessed by the SRC for progressing comprises 48 h data for 6 subjects.</p> <p>b) <u>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.</u></p> <p>c) For the dose regimens, see Table 1 and Table 2.</p>	PEI feedback
<p><u>Section 1.2 (Schema - Dose cohort schema for BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B) - Cohorts with older adults)</u></p> <pre> graph TD     subgraph Cohort_8 [Cohort 8]         1[Day 1: 2 Sentinel subjects] --&gt; 2[24 h Safety Review]         2 --&gt; 3[Day 2: 4 subjects]         3 --&gt; 4[48 h Safety Review]         4 --&gt; 5[Day 4: 6 subjects]         5 --&gt; 6[48 h Safety Review]         6 --&gt; 7[SRC Review<sup>a</sup>]     end     subgraph Cohort_9 [Cohort 9]         1[Day 1: 2 Sentinel subjects] --&gt; 2[24 h Safety Review]         2 --&gt; 3[Day 2: 4 subjects]         3 --&gt; 4[48 h Safety Review]         4 --&gt; 5[Day 4: 6 subjects]         5 --&gt; 6[48 h Safety Review]         6 --&gt; 7[SRC Review<sup>a</sup>]     end     subgraph Cohort_10 [Cohort 10]         1[Day 1: 2 Sentinel subjects] --&gt; 2[24 h Safety Review]         2 --&gt; 3[Day 2: 4 subjects]         3 --&gt; 4[48 h Safety Review]         4 --&gt; 5[Day 4: 6 subjects]         5 --&gt; 6[48 h Safety Review]         6 --&gt; 7[SRC Review<sup>a</sup>]     end     %% Flow between cohorts     7 -- "Based on safety data for ≥ 6 subjects" --&gt; 1     %% Additional SRC Review for Cohort 10     7 -- "Based on safety data for ≥ 6 subjects" --&gt; 8[SRC Review<sup>a</sup>] </pre>	Clarification
<p>Replaced with (where the column header "Cohort 8" was replaced with "Cohort 8<sup>d</sup>)</p>	

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<p><b>Section 1.2 (Schema - Dose cohort schema for BNT162c2 (SD))</b></p> <p>a) The data assessed by the SRC for progressing comprises 48 h data for 6 subjects.</p> <p>b) <u>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.</u></p> <p>c) For the dose regimens, see Table 1 and Table 2.</p> <p>d) <u>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.</u></p> <p>For the cohorts with BNT162c2 P/B dosing, dosing will only start after SRC assessment of day 28 AE data (solicited and unsolicited).</p>	IEC feedback
<p><b>Section 1.2 (Schema - Dose cohort schema for BNT162c2 (SD))</b></p> <p>*Based on safety data for 6 or more subjects</p> <p>Replaced with (where the column headers "Cohort 5" and "Cohort 6" were switched)</p>	PEI feedback

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<pre> graph TD     FIH[Day 1: 1 Sentinel subject] --&gt; 24 h Safety Review  Day1_2[Day 1: 2 Sentinel subjects]     Day1_2 --&gt; 24 h Safety Review  Day2_4[Day 2: 4 subjects]     Day2_4 --&gt; 24 h Safety Review  Day4_6[Day 4: 6 subjects]     Day4_6 --&gt; 24 h Safety Review  Day1_2_Sentinel[Day 1: 2 Sentinel subjects]     Day1_2_Sentinel --&gt; 24 h Safety Review  Day2_4_Sentinel[Day 2: 4 subjects]     Day2_4_Sentinel --&gt; 24 h Safety Review  Day4_6_Sentinel[Day 4: 6 subjects]     Day4_6_Sentinel --&gt; 24 h Safety Review  Day1_12[Day 1: 12 Subjects]     Day1_12 --&gt; SRC Review<sup>a</sup>  SRC1[SRC Review<sup>a</sup>]     Day1_2_Sentinel -- "Based on safety data*" --&gt; Day2_4_Sentinel     Day2_4_Sentinel -- "Based on safety data*" --&gt; Day4_6_Sentinel     Day4_6_Sentinel -- "Based on safety data*" --&gt; Day1_12   </pre>																																																																																					
<b>Section 1.3 (Schedule of activities - Table 4)</b> <table border="1"> <tr> <td>Oral swipe for SARS-CoV-2 testing</td> <td></td> <td>X<sup>m</sup></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Allocation to IMP</td> <td></td> <td>X</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Immunization<sup>i</sup></td> <td></td> <td></td> <td>X<sup>j</sup></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Blood draw for immunogenicity<sup>n</sup></td> <td>X (10 mL)</td> <td></td> <td></td> <td>X (10 mL)</td> <td>X (10 mL)</td> <td></td> </tr> <tr> <td>Blood draw for HLA</td> <td></td> <td></td> <td></td> <td colspan="3">X (4 mL EDTA<sup>k</sup>)</td> </tr> <tr> <td>Blood draw for CMI (100 mL)<sup>n, o</sup></td> <td>X</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Blood draw for research</td> <td></td> <td colspan="5">Up to 5 blood draws for explorative biomarker/immunogenicity research; 200 mL per subject over the course of the study</td> </tr> <tr> <td>Subject hotline availability</td> <td>Start</td> <td>=&gt;</td> <td>=&gt;</td> <td>=&gt;</td> <td>=&gt;</td> <td>=&gt;</td> </tr> <tr> <td>Issue subject diaries</td> <td>X</td> <td></td> <td>X</td> <td>X</td> <td>X</td> <td></td> </tr> <tr> <td>Collect subject diaries</td> <td></td> <td></td> <td>X</td> <td>X<sup>i</sup></td> <td>X</td> <td>X</td> </tr> <tr> <td>Record AEs since last visit</td> <td>X</td> <td></td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> </tr> <tr> <td>Local reaction</td> <td></td> <td>..</td> <td>..</td> <td>..</td> <td>..</td> <td>..</td> </tr> </table>	Oral swipe for SARS-CoV-2 testing		X <sup>m</sup>					Allocation to IMP		X					Immunization <sup>i</sup>			X <sup>j</sup>				Blood draw for immunogenicity <sup>n</sup>	X (10 mL)			X (10 mL)	X (10 mL)		Blood draw for HLA				X (4 mL EDTA <sup>k</sup> )			Blood draw for CMI (100 mL) <sup>n, o</sup>	X						Blood draw for research		Up to 5 blood draws for explorative biomarker/immunogenicity research; 200 mL per subject over the course of the study					Subject hotline availability	Start	=>	=>	=>	=>	=>	Issue subject diaries	X		X	X	X		Collect subject diaries			X	X <sup>i</sup>	X	X	Record AEs since last visit	X		X	X	X	X	Local reaction		..	..	..	..	..	Alignment with other trials
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<b>Section 1.3 (Schedule of activities - Table 4)</b> <ul style="list-style-type: none"> <li><sup>h</sup> 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.</li> <li><sup>i</sup> Only for the first 6 subjects per group. <a href="#">Questioning on and documentation of AEs as well as systemic and local reactions, the latter in case of upcoming dose decision meetings.</a></li> <li><sup>j</sup> Only IMP-related AEs.</li> <li><sup>k</sup> Blood draw for anti-SARS-CoV-2 antibodies (samples will be stored until a test is commercially available).</li> <li><sup>l</sup> For Cohorts 1 <u>and</u> 8, immunization with <u>at least</u> 1 h intervals between subjects for the first 6 subjects and then with of <u>at least</u> 30 min intervals for the remaining 6 subjects. For <u>all other cohorts</u> <u>Cohorts 2 and 4</u>, immunization with <u>at least</u> 30 min intervals between subjects.</li> <li><sup>m</sup> Oral swipe for SARS-CoV-2 testing either on Day -1 or at the Visit 1 on Day 1.</li> <li><sup>n</sup> The listed blood draw days may be adapted if justified by the collected data. <a href="#">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).</a></li> </ul>	Clarification																																																																																				

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<u>Section 2.2 (Trial rationale - Table 6)</u>		IEC feedback	
<b>Table 6: Status of ongoing and planned clinical trials (as of <u>July 17<sup>th</sup></u> <del>June 22<sup>nd</sup></del>, 2020)</b>			
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.	<p><u>BNT162a1 (age 18-55 years):</u> 0.1 µg <u>12 subjects prime / 12 boost</u> 0.3 µg <u>12 subjects prime / 12 boost</u> 3 µg <u>6 subjects prime</u> <u>(Further dosing with BNT162a1 has been deferred)</u></p> <p><u>BNT162b1 (age 18 to 55 years):</u> 1 µg <u>12 subjects prime / 12 boost</u> 10 µg <u>12 subjects prime / 12 boost</u> 30 µg <u>12 subjects prime / 12 boost</u> 50 µg <u>12 subjects prime / 11 boost</u> 60 µg <u>12 subjects prime</u></p> <p><u>BNT162b2 (age 18 to 55 years):</u> 1 µg <u>9 subjects prime</u> 10 µg <u>12 subjects prime / 12 boost</u> <del>20 µg <u>subjects prime</u></del> 30 µg <u>12 subjects prime / 6 boost</u></p> <p><u>BNT162c2 (age 18 to 55 years):</u> 0.1 µg <u>12 subjects (single dose)</u> 0.3 µg <u>12 subjects (single dose)</u> <del>0.6 µg <u>12 subjects (single dose)</u></del> 1 µg <u>12 subjects (single dose)</u></p>	

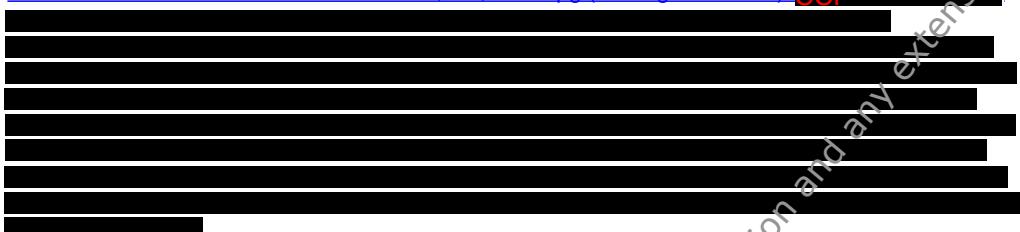
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<u>Section 2.2 (Trial rationale - Table 6)</u>	IEC feedback						
<table border="1"><thead><tr><th>Trial number</th><th>Design</th><th>Current number dosed (subject age)</th></tr></thead><tbody><tr><td><u>BNT162-02 / C4591001</u> <u>(PF-07302048;</u> <u>NCT NCT04368728)</u> US</td><td>Phase I/II, placebo-controlled, randomized, observer-blind, dose-finding trial. (Subjects are randomized: 4 active vaccine to 1 placebo)</td><td><p>BNT162b1 (age 18 to 55 years): 10 µg 15 subjects prime / 15 boost <u>20 µg 15 subjects prime</u> 30 µg 15 subjects prime / 15 boost 100 µg 15 subjects prime</p><p>BNT162b1 (age 65 to 85 years): 10 µg 15 subjects prime / 15 boost 20 µg 15 subjects prime / 15 boost <u>30 µg 15 subjects prime / 15 boost</u></p><p>BNT162b2 (age 18 to 55 years): 10 µg 15 subjects prime / 15 boost 20 µg 15 subjects prime / 15 boost <u>30 µg 15 subjects prime / 15 boost</u></p><p>BNT162b2 (age 65 to 85 years): <u>10 µg 15 subjects prime</u> 20 µg 15 subjects prime / 15 boost 30 µg 15 subjects prime / 15 boost</p></td></tr></tbody></table>	Trial number	Design	Current number dosed (subject age)	<u>BNT162-02 / C4591001</u> <u>(PF-07302048;</u> <u>NCT NCT04368728)</u> US	Phase I/II, placebo-controlled, randomized, observer-blind, dose-finding trial. (Subjects are randomized: 4 active vaccine to 1 placebo)	<p>BNT162b1 (age 18 to 55 years): 10 µg 15 subjects prime / 15 boost <u>20 µg 15 subjects prime</u> 30 µg 15 subjects prime / 15 boost 100 µg 15 subjects prime</p> <p>BNT162b1 (age 65 to 85 years): 10 µg 15 subjects prime / 15 boost 20 µg 15 subjects prime / 15 boost <u>30 µg 15 subjects prime / 15 boost</u></p> <p>BNT162b2 (age 18 to 55 years): 10 µg 15 subjects prime / 15 boost 20 µg 15 subjects prime / 15 boost <u>30 µg 15 subjects prime / 15 boost</u></p> <p>BNT162b2 (age 65 to 85 years): <u>10 µg 15 subjects prime</u> 20 µg 15 subjects prime / 15 boost 30 µg 15 subjects prime / 15 boost</p>	IEC feedback
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<u>BNT162-03 China</u> <u>(NC to be obtained)</u>	<p><u>Phase I, randomized placebo-controlled observer-blind trial..</u></p> <p><u>BNT162b1 (age 18 to 55 years):</u> • Enrollment has not started.</p> <p><u>BNT162b1 (age &gt;55 years):</u> • Enrollment has not started.</p>						
<u>BNT162-04</u> <u>(NCT to be obtained)</u> Germany	<p><u>Phase I/II, 2-part, dose escalation trial.</u> <u>Part A is open label and non-randomized.</u> <u>(All subjects receive active vaccine)</u> <u>Part B will be defined in a protocol amendment.</u></p> <p><u>BNT162a3 (age 18-55 years):</u> Enrollment has not started.</p> <p><u>BNT162b3 (age 18 to 55 years):</u> Enrollment has not started.</p>						
<u>Section 2.2.1 (This trial (BNT162-01)</u> <u>Summary of immunogenicity in trial BNT162-01 (up to July 1<sup>st</sup>, 2020)</u> <u>Two doses of BNT162b1 of 1, 10, 30 and 50 µg of BNT162b1 administered 21 d apart elicited antibody and robust CD4<sup>+</sup> and CD8<sup>+</sup> 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.</u> <u>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.</u> <u>Immunogenicity in for older adults receiving vaccine candidate BNT162b1 were not available at the time of preparation of this summary.</u>	IEC feedback						

**Summary of safety in trial BNT162-01 (up to July 1<sup>st</sup> 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).

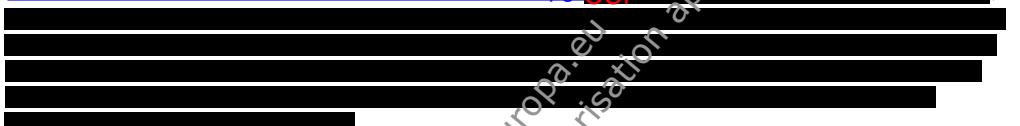
**Summary of safety - BNT162a1**

BNT162a1 has been tested at doses of 0.1, 0.3, and 3 µg (starting dose level). CCI



**Summary of safety BNT162c2**

BNT162c2 has been tested at doses of 0.1, 0.3 and 1 µg. CCI



**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 known pharmacology of this technology, with the changes in lymphocytes known to represent a reversible compartmental shift from the vascular space to lymphoid organs. These observations have been self-limiting and without clinical consequence. There have been no other consistent findings on laboratory assessments.

#### Adverse events - 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 or boost) by number of subjects**

BNT162b1	Subjects dosed <u>N =</u>	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 possibility of a slight increase in reactogenicity following boost dose is noted, as is some inter-individual variability.

#### CCI

Most recently dosing has begun with vaccines BNT162b2 and BNT162c2. CCI

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	-	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. 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

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<b>Table 3: Summary BNT162b1 TEAE (prime +/- boost) by number of subjects</b>								
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	4	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	4	0	12	
Total	60	59	58	45	6	0	59	
<b>Summary</b> 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 possibility of a slight increase in reactogenicity following boost dose is noted, as is some inter-individual variability.								
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<b>Section 2.2.2 (US trial BNT162-02)</b> 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).								
<b>Summary of Immunogenicity in BNT162-02 (status, July 1<sup>st</sup>, 2020)</b> 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.								
<b>Summary of safety in younger adults (aged 18 to 55 years) BNT162-02 (status, July 1<sup>st</sup>, 2020)</b> 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.								

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<p><u>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.</u></p> <p><u>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.</u></p> <p><u><a href="#">BNT162b1 - Summary of safety in elderly adults (aged 65 to 85 years) in BNT162-02 (cut-off 01-JUL-2020)</a></u></p> <p>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).</p> <p><u><a href="#">Local reactions - BNT162b1</a></u></p> <p>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.</p> <p><u><a href="#">Figure 2: BNT162b1 in elderly adults: Local reactions after doses 1 and 2 in trial BNT162-02</a></u></p> <p><u><a href="#">Systemic reactions - BNT162b1</a></u></p> <p>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.</p> <p><u><a href="#">Figure 3: BNT162b1 in elderly adults: Systemic reactions in trial BNT162-02</a></u></p> <p><u><a href="#">Adverse events &amp; laboratory assessments - BNT162b1</a></u></p> <p>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.</p> <p>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.</p> <p><u><a href="#">BNT162b2 - Summary of safety in elderly adults (aged 65 to 85 years) in BNT162-02 (cut-off 01-JUL-2020)</a></u></p> <p>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).</p>	

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<p><u>Local reactions - BNT162b2</u> <u>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.</u></p> <p><u>Figure 4: BNT162b2 in elderly adults: Local reactions after Dose 1 in trial BNT162-02</u></p> <p><u>Systemic reactions - BNT162b2</u> <u>As shown in Figure 5, the most frequent prompted systemic reactions in subjects receiving BNT162b2 were fatigue and headache 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.</u></p> <p><u>Figure 5: BNT162b2 in elderly adults: Systemic events after Dose 1 in trial BNT162-02</u></p> <p><u>Adverse events &amp; laboratory assessments - BNT162b2</u> <u>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.</u></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>Summary of safety in BNT162-02 (status: June 22nd, 2020)</u> <u>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.</u> <u>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.</u></p> <p><b>Table 4: Number of adults aged 18 to 55 years dosed in BNT162-02 (status, June 22<sup>nd</sup>, 2020)</b></p> <table border="1"><thead><tr><th rowspan="2"></th><th colspan="2">BNT162b1</th><th colspan="2">Placebo</th></tr><tr><th>Dose 1</th><th>Dose 2</th><th>Dose 1</th><th>Dose 2</th></tr></thead><tbody><tr><td>18-55 years of age</td><td></td><td></td><td></td><td></td></tr><tr><td>10 µg dose level</td><td>N=12</td><td>N=12</td><td>N=3</td><td>N=3</td></tr><tr><td>30 µg dose level</td><td>N=12</td><td>N=12</td><td>N=3</td><td>N=3</td></tr><tr><td>100 µg dose level</td><td>N=12</td><td>Not applicable</td><td>N=3</td><td>Not applicable</td></tr></tbody></table> <p><u>Overall, all dose levels exhibited a tolerability and safety profile consistent with mRNA-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.</u></p>		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	
		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																										

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<p><b>Summary of safety in elderly subjects (aged 65 to 85 years) in BNT162-02</b> 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.</p> <p><b>Table 11: Number of adults aged 65 to 85 years dosed in BNT162-02 (status, June 22nd, 2020)</b></p> <table border="1"><thead><tr><th rowspan="2"></th><th colspan="2">BNT162b1</th><th colspan="2">Placebo</th></tr><tr><th>Dose 1</th><th>Dose 2</th><th>Dose 1</th><th>Dose 2</th></tr></thead><tbody><tr><td><b>65-85 years of age</b></td><td></td><td></td><td></td><td></td></tr><tr><td>10 µg dose level</td><td>N=12</td><td>N=0</td><td>N=3</td><td>N=0</td></tr><tr><td>20 µg dose level</td><td>N=12</td><td>N=0</td><td>N=3</td><td>N=0</td></tr><tr><td>30 µg dose level</td><td>N=12</td><td>N=0</td><td>N=3</td><td>N=0</td></tr></tbody></table> <p>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 PPD on day 2 after receiving a 20 µg dose, consistent with varicella zoster (shingles). <sup>PPL</sup> was prescribed Valacyclovir and this AE was reported as fully resolved within 7 d. The investigator reported this AE as not related to vaccine.</p> <p><b>Part A</b></p> <p><b>Part B</b></p> <p><b>Figure 2:</b> 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.</p> <p><b>Part A (younger adults)</b></p> <p><b>Part B (Elderly)</b></p> <p><b>Figure 3:</b> 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. <sup>†</sup>This is the participant that experienced Zoster which was the actual cause of the pain.</p> <p>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.</p> <p><b>Section 2.3.1 (Risk assessment)</b></p> <p>The risks linked to the trial-specific procedures and connected mitigations are as follows:</p> <ul style="list-style-type: none"><li>The volume of blood drawn will be kept to a minimum and will remain less than that drawn when donating blood (up to approximately <u>568-582</u> mL blood will be drawn per subject over the complete trial, i.e., over approximately 7 months).</li><li>All trial-specific procedures will be performed by qualified trial site personnel.</li><li>Immunization will be done by a physician.</li><li><u>Human experience with</u> BNT162 vaccines <u>was not available have not been administered to humans</u> prior to this trial. However, clinical data <u>was</u> available for RNAs formulated with related</li></ul>		BNT162b1		Placebo		Dose 1	Dose 2	Dose 1	Dose 2	<b>65-85 years of age</b>					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	Error correction and updating
		BNT162b1		Placebo																										
	Dose 1	Dose 2	Dose 1	Dose 2																										
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10 µg dose level	N=12	N=0	N=3	N=0																										
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30 µg dose level	N=12	N=0	N=3	N=0																										

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but not identical liposomal compositions or non-formulated RNAs and can support risk assessment of the BNT162 vaccines.	
<b>Section 2.2.3 (Chinese trial - BNT162-03)</b>  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).  <u>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 &gt;55 years (older adults). Currently the trial has been approved by the Chinese regulatory authorities and trial set up is ongoing.</u>  <u>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.</u>	Updating
<b>Section 2.2.4 (BNT162-04 for BNT162b3)</b>  <u>The trial BNT162-04 will be conducted and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany).</u>  <u>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.</u>	Updating
<b>Section 2.3.1 (Risk assessment)</b> <ul style="list-style-type: none"><li>• The volume of blood drawn will be kept to a minimum and will remain less than that drawn when donating blood (up to approximately <del>568</del> <ins>582</ins> mL blood will be drawn per subject over the complete trial, i.e., over approximately 7 months).</li><li>• ...</li><li>• <u>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.</u></li><li>• <u>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.</u></li></ul>	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 described 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 (BNT162-03, 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! Reference 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. 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 \(for details, see Section 2.2.2\).](#)

[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 following 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 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.~~

[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 \(e.g., sentinel dosing/staggering of subjects, on-site observation periods after each immunization, wellbeing questioning, frequent on-site visits after immunization\).](#)

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<ul style="list-style-type: none"><li>- <u>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.</u></li><li>• 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.</li><li>• <del>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").</del></li><li>• <u>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").</u></li></ul>	
<u>Section 2.3.1 (Risk assessment)</u> <ul style="list-style-type: none"><li>• After each assessment, the SRC may request a prolongation of the observation periods to up to Day 7 for later cohorts. <u>Experience in this ongoing trial and in the ongoing BNT162-02 trial, has confirmed the adequacy of the implemented observations periods.</u></li><li>• The expanded SRC <u>will</u> review and evaluate at least the Day 21 data per vaccine to <u>decide whether to progress to Part B, and if yes, defineconfirm</u> what doses will be given <u>in Part B</u>.</li><li>• The SRC may make recommendations on increasing observation periods and additional subject wellbeing calls may be included at the discretion of the SRC.</li><li>• 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.</li></ul>	Updating and correction of an error
<u>Section 2.3.1 (Risk assessment)</u>	Updating and correction of an error
<u>Section 4.3 (Justification for dose)</u> <p>Based on the available clinical and non-clinical data experience, the sponsor expects the planned maximal doses (see Table 1) to be safe.</p> <p><u>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.</u></p> <p>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.</p>	IEC feedback
<u>Section 5.2.1 (Exclusion criteria Part A)</u> <p>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:</p> <ul style="list-style-type: none"><li>• ...</li><li>• Known Stage 3 or worse chronic kidney disease (glomerular filtration rate &lt;60 mL/min/1.73 m<sup>2</sup>)</li></ul>	IEC feedback

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<ul style="list-style-type: none"><li>• <del>BMI ≥30 kg/m<sup>2</sup></del></li><li>• ....</li></ul>	
<p><u>Section 5.3 (Lifestyle considerations)</u></p> <p>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.</p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><del>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.</del></p> <p><del>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.</del></p> <p><del>For Cohort 3, subjects will be required to remain at the site for approximately 6 h after immunization.</del></p>	Updated for clarity
<p><u>Section 6.6 (Dose modifications)</u></p> <p>The decision to make dose adaptions <del>or, to initiate add</del> 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).</p>	IEC feedback
<p><u>Section 6.6.1 (Dose limiting toxicity)</u></p> <p>During the time of enrollment into a given dose escalation cohort in Part A, if any of the following events occur, <u>it will be considered an individual dose limiting toxicity and</u> further dosing in that cohort will be stopped:</p> <ul style="list-style-type: none"><li>• Anaphylactic reaction considered related</li><li>• Generalized urticaria considered related</li><li>• ...</li><li>• Any fever &gt;40.0°C (&gt;104.0°F) within 7 days of vaccination considered related <u>and confirmed by an investigator or medically qualified person.</u></li></ul> <p>...</p> <p>The assessment of dose limiting toxicity should be done consistently for all subjects treated with the same treatment and dose.</p> <p><u>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.</u></p>	Clarification and alignment with other BNT162 trials
<p><u>Section 6.6.2 (Dose modification guidance/rules)</u></p> <p>The trial design also allows for:</p> <ul style="list-style-type: none"><li>• The selection of which BNT162 vaccine(s) <u>dose regimens and posologies</u> that will be investigated in Part B <u>following a substantial protocol amendment.</u></li></ul> <p><b>Part A</b></p> <p>See Section 10.1.5 for the data set upon which SRC decisions described below <u>for Part A</u> are made.</p> <p><b>Part A</b></p> <ul style="list-style-type: none"><li>• The decision to test reduced or intermediate doses will be made for each vaccine independently</li></ul>	IEC feedback

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<ul style="list-style-type: none"><li>...</li></ul> <p><b>Part B</b></p> <p>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.</p> <p>Relevant safety and tolerability data collected in Part A will be included in the protocol amendment planned to define details of Part B <u>and / or the BNT162 IB.</u></p>	
<p><u>Section 8.2.8 (Subject diaries)</u></p> <p>Trial subjects will be given subject diaries at Visit 1 and be asked to record any <u>AEs reactions</u> between visits, solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) and solicited systemic <u>AEs reactions</u> (nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever [i.e., <math>\geq 38^{\circ}\text{C}</math>]).</p>	Alignment with other BNT162 trials
<p><u>Section 8.2.9 (Assessment of local reactions)</u></p> <p>Local reactions after IM immunization will be assessed by the investigator at the times given in the SoA (Section 1.3). <u>This information will be used to validate the solicited assessment of local reactions in the patient diary and potentially support AE reporting.</u></p> <p>Local reactions (<u>both investigator assessed and solicited in the subject diaries</u>) will be graded using <u>the criteria based on the guidance</u> 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). <u>This information will be used to validate the solicited assessment of local reactions in the patient diary and potentially support AE reporting.</u></p>	Clarification
<p><u>Section 8.2.13 (Assessment of systemic reactions)</u></p> <p>Systemic reactions after IM immunization will be assessed <u>via daily solicited reports in the subject diaries and</u> at the times given in the SoA (Section 1.3).</p> <p>Systemic reactions will be graded using <u>the criteria based on the guidance</u> 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).</p>	Clarification
<p><u>Section 8.7 (Genetics)</u></p> <p>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). <u>Data generated with these additional analyses may provide information about the HLA dependency of immune response</u> (e.g., if distinct HLA types have stronger / better immune response towards SARS-CoV-2).</p> <p>...</p> <p><u>Leftover blood after completion of the immunogenicity assessments may be used for the genetic analyses as described here.</u></p>	IEC feedback and clarification
<p><u>Section 8.8 (Biomarkers)</u></p> <p>Samples for biomarker analysis will be retained for use for up to 5 years after the end of the trial. <u>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.</u></p>	IEC feedback

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	Rationale
<p><u>Blood samples will only be used for biomarker analysis if the trial subjects have provided informed consent for this biomarker analysis.</u></p>	
<p><u>Section 8.9 (Immunogenicity assessments)</u></p> <ul style="list-style-type: none"><li>an antibody binding assay, e.g., and assays to characterize antibodies (e.g., affinity, IgG subclass), e.g., ELISA.</li></ul> <p>... ... <u>Blood samples will only be used for additional analyses if the trial subjects have provided informed consent for these additional analyses.</u></p>	Clarification
<p><u>Section 8.10 (Blood collection)</u></p> <p>Up to approximately <del>568</del> <ins>582</ins> mL blood will be drawn per subject over the complete trial, i.e., over approximately 7 months.</p>	Error correction
<p><u>Section 9.4.2 (Primary endpoints)</u></p> <p>P/B regimens:</p> <ul style="list-style-type: none"><li>Day 1-21 (pre-boost)</li><li><u>Day 1 to 7</u></li><li>Day 21 (post-boost) - 28</li><li><u>Day 21 (post-boost) to 50</u></li></ul> <p>SD regimens:</p> <ul style="list-style-type: none"><li>Day 1-28</li></ul> <p>... Local reactions and systemic reactions will be graded using <u>the criteria based on the guidance</u> 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). ... <u>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.</u></p>	Corrections of an omission and alignment with other BNT162 trials
<p><u>Section 9.4.5 (Other safety analyses - Clinical laboratory parameters)</u></p> <p>Abnormal laboratory results will be graded using <u>the criteria based on the guidance</u> 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).</p>	Clarification
<p><u>Section 10.1.5 (Committees - SRC)</u></p> <ul style="list-style-type: none"><li><del>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.</del></li></ul>	IEC feedback
<p><u>Section 10.3.1 (Definition of AE and TEAE)</u></p> <ul style="list-style-type: none"><li>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.</li></ul> <p>NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding <u>that is clinically significant</u>), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.</p>	Alignment with other BNT162 trials

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	Rationale
<p><u>Section 10.3.1.1 (Events meeting the AE definition)</u></p> <ul style="list-style-type: none"><li>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.</li><li>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. <b>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).</b></li></ul>	Alignment with other BNT162 trials
<p><u>Section 10.3.1.7 (Recording and Follow-Up of AE and/or SAE - Assessment of AE and/or SAE intensity)</u></p> <p>The intensity of AEs or SAEs will be graded by the investigator. For further guidance <a href="#">on grading of solicited reactions</a>, 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:</p>	Alignment with other BNT162 trials
<p><u>Section 10.3.1.10 (Reporting of SAEs)</u></p> <p>All SAEs <a href="#">or DLTs (even if non-serious)</a> 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.</p>	Alignment with other BNT162 trials
<p><u>Section 10.3.1.11 (Assessments of intensity for solicited local and systemic reactions and laboratory abnormalities - Fever)</u></p> <p><a href="#">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 &gt;40.0°C for recording the trial database. If a participant experiences a confirmed fever &gt;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.</a></p>	Alignment with other BNT162 trials
<p><u>Section 10.10 (Protocol amendments)</u></p> <p><a href="#">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 trial master file.</a></p> <p><a href="#">(The entire Protocol amendments section was made into this standalone Protocol Amendment History)</a></p> <p><b><a href="#">10.10.5 Protocol amendment no. 05</a></b></p> <p><b><a href="#">Amendment rationale</a></b></p> <p><a href="#">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.</a></p>	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 70 (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.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	Rationale				
<p><u>Title page</u></p> <p style="text-align: center;"><b>CLINICAL TRIAL PROTOCOL</b> <b>INCLUDING AMENDMENTS NOS. 01 TO <u>0506</u></b></p> <p style="text-align: center;"><b>BNT162-01</b></p> <table border="1"><tr><td>Version: <u>8.09.0</u></td><td>Date: <u>21-Jul-05 OCT 2020</u></td></tr><tr><td>Sponsor: BioNTech RNA Pharmaceuticals GmbH</td><td></td></tr></table> <p><b>Trial title:</b> 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 <u>and immunocompromised</u> adults</p> <p><b>Brief title:</b> A multi-site Phase I/II trial investigating the safety and effects of four BNT162 vaccines against COVID-19 in healthy <u>and immunocompromised</u> adults</p> <p><b>Trial phase:</b> Phase I/II</p> <p><b>Indication:</b> Protection against COVID-19</p> <p><b>Product:</b> BNT162: SARS-CoV-2 - RNA lipid nanoparticle (RNA LNP) vaccines utilizing different RNA formats, i.e., <u>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, called and BNT162c2)</u></p> <p><b>Coordinating and Principal investigator:</b> Dr. Dr. med. Armin Schultz, CRS Clinical Research Services Mannheim GmbH, Germany (tel.: <u>PPD</u>)</p> <p><b>Trial sites:</b> <u>CRO s</u><u>Multiple sites in Berlin and Mannheim, in Germany. For further details of the study sites and site personnel, see the Trial Master File (TMF).</u></p> <p><b>Contract research organization (CRO):</b> CRS Clinical Research Services Mannheim GmbH, Germany</p> <p><b>Sponsor's responsible person:</b> Özlem Türeci, MD, Chief Medical Officer, BioNTech SE</p> <p><b>Sponsor:</b> BioNTech RNA Pharmaceuticals GmbH, An der Goldgrube 12, 55131 Mainz, Germany</p> <p><b>Regulatory identifiers:</b> EudraCT no.: 2020-001038-36; <u>ClinicalTrials.gov NCT: 04380701</u>; WHO UTN: U1111-1249-4220</p> <p><b>Medical Monitor:</b> The sponsor's Medical Monitor name and contact information will be provided separately</p>	Version: <u>8.09.0</u>	Date: <u>21-Jul-05 OCT 2020</u>	Sponsor: BioNTech RNA Pharmaceuticals GmbH		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.
Version: <u>8.09.0</u>	Date: <u>21-Jul-05 OCT 2020</u>				
Sponsor: BioNTech RNA Pharmaceuticals GmbH					
<p><b>Section 1.1 Trial synopsis</b></p> <p>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 <u>and immunocompromised</u> adults</p>	Update to reflect the added expansion cohorts.				

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<p><u>Section 1.1 Trial synopsis and Section 3 Objectives and endpoints</u></p> <table border="1"><thead><tr><th>Objectives</th><th>Endpoints <sup>a</sup></th></tr></thead><tbody><tr><td><b>Primary objective</b>  <u>(All cohorts)</u> 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.</td><td><ul style="list-style-type: none"><li>Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to <math>7\pm4</math> d after each immunization: <u>(trial days 8 and 29)</u>.</li><li>Solicited systemic reactions (nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever) recorded up to <math>7\pm4</math> d after each immunization: <u>(trial days 8 and 29)</u>.</li><li>The proportion of subjects with at least 1 unsolicited treatment-emergent adverse event (TEAE):<ul style="list-style-type: none"><li>For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): occurring up to <math>21\pm2</math> d after the prime immunization <u>(trial day 22)</u> and <math>28\pm4</math> d after the boost immunization: <u>(trial day 50)</u>.</li><li>For BNT162c2 (SD): The proportion of subjects with at least 1 unsolicited TEAE occurring up to <math>28\pm4</math> d after the immunization: <u>(trial day 29)</u>.</li></ul></li></ul></td></tr></tbody></table>	Objectives	Endpoints <sup>a</sup>	<b>Primary objective</b>  <u>(All cohorts)</u> 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.	<ul style="list-style-type: none"><li>Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to <math>7\pm4</math> d after each immunization: <u>(trial days 8 and 29)</u>.</li><li>Solicited systemic reactions (nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever) recorded up to <math>7\pm4</math> d after each immunization: <u>(trial days 8 and 29)</u>.</li><li>The proportion of subjects with at least 1 unsolicited treatment-emergent adverse event (TEAE):<ul style="list-style-type: none"><li>For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): occurring up to <math>21\pm2</math> d after the prime immunization <u>(trial day 22)</u> and <math>28\pm4</math> d after the boost immunization: <u>(trial day 50)</u>.</li><li>For BNT162c2 (SD): The proportion of subjects with at least 1 unsolicited TEAE occurring up to <math>28\pm4</math> d after the immunization: <u>(trial day 29)</u>.</li></ul></li></ul>	Update to reduce duplication, to make the relationship to trials days clearer (but otherwise without making content changes), and to emphasize that the objective apply to all cohorts including the added expansion cohorts.
Objectives	Endpoints <sup>a</sup>				
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<p><u>Section 1.1 Trial synopsis and Section 3 Objectives and endpoints</u></p> <table border="1"><thead><tr><th>Secondary objectives</th></tr></thead><tbody><tr><td><u>(All cohorts)</u> 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.</td><td><p>For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): <b>Functional antibody responses As compared to baseline at <math>7\pm1</math> d and <math>21\pm2</math> d after primary immunization (trial days 8 and 22) and at <math>14</math> <sup>b</sup>, <math>21\pm2</math> d, <math>28\pm4</math> d, <math>63\pm5</math> d, and <math>162\pm7</math> d after the boost immunization: (trial days 5 to 9):</b></p><ul style="list-style-type: none"><li><b>Functional antibody responses (titers).</b></li><li><b>Fold increase in functional antibody titers <math>7\pm1</math> d and <math>21\pm2</math> d after primary immunization and at <math>21\pm2</math> d, <math>28\pm4</math> d, <math>63\pm5</math> d, and <math>162\pm7</math> d after the boost immunization.</b></li><li><b>Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline at <math>7\pm1</math> d and <math>21\pm2</math> d after primary immunization and at <math>21\pm2</math> d, <math>28\pm4</math> d, <math>63\pm5</math> d, and <math>162\pm7</math> d after the boost immunization.</b></li></ul><p><b>For BNT162c2 (SD):</b></p><ul style="list-style-type: none"><li><b>Functional antibody responses at <math>7\pm1</math> d, <math>21\pm2</math> d, <math>29\pm3</math> d, <math>42\pm3</math> d, <math>84\pm5</math> d, and <math>183\pm7</math> d after the primary immunization.</b></li><li><b>Fold increase in functional antibody titers at <math>7\pm1</math> d, <math>21\pm2</math> d, <math>29\pm3</math> d, <math>42\pm3</math> d, 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<u>(All cohorts)</u> 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.	<p>For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): <b>Functional antibody responses As compared to baseline at <math>7\pm1</math> d and <math>21\pm2</math> d after primary immunization (trial days 8 and 22) and at <math>14</math> <sup>b</sup>, <math>21\pm2</math> d, <math>28\pm4</math> d, <math>63\pm5</math> d, and <math>162\pm7</math> d after the boost immunization: (trial days 5 to 9):</b></p> <ul style="list-style-type: none"><li><b>Functional antibody responses (titers).</b></li><li><b>Fold increase in functional antibody titers <math>7\pm1</math> d and <math>21\pm2</math> d after primary immunization and at <math>21\pm2</math> d, <math>28\pm4</math> d, <math>63\pm5</math> d, and <math>162\pm7</math> d after the boost immunization.</b></li><li><b>Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline at <math>7\pm1</math> d and <math>21\pm2</math> d after primary immunization and at <math>21\pm2</math> d, <math>28\pm4</math> d, <math>63\pm5</math> d, and <math>162\pm7</math> d after the boost immunization.</b></li></ul> <p><b>For BNT162c2 (SD):</b></p> <ul style="list-style-type: none"><li><b>Functional antibody responses at <math>7\pm1</math> d, <math>21\pm2</math> d, <math>29\pm3</math> d, <math>42\pm3</math> d, <math>84\pm5</math> d, and <math>183\pm7</math> d after the primary immunization.</b></li><li><b>Fold increase in functional antibody titers at <math>7\pm1</math> d, <math>21\pm2</math> d, <math>29\pm3</math> d, <math>42\pm3</math> d, <math>84\pm5</math> d, and <math>183\pm7</math> d after the primary immunization.</b></li><li><b>Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline.</b></li></ul> <p><b>For BNT162c2 (SD):</b></p> <p><b>As compared to baseline at <math>7\pm1</math> d, <math>21\pm2</math> d, <math>29\pm3</math> d, <math>28</math>, <math>42\pm3</math> d, <math>84\pm5</math> d, and <math>183\pm7</math> d after the primary immunization (trial days 8 to 184):</b></p> <ul style="list-style-type: none"><li><b>Functional antibody responses (titers).</b></li><li><b>Fold increase in functional antibody titers</b></li><li><b>Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline.</b></li></ul>				

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<u>Section 1.1 Trial synopsis and Section 3 Objectives and endpoints</u>		
<p><b>Exploratory objectives</b></p> <p><b>(All cohorts)</b></p> <p>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.</p>	<p>For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B):</p> <p><b>Antibody responses</b> As compared to baseline at <math>7\pm1</math> d and <math>21\pm2</math> d after primary immunization (<u>trial days 8 and 22</u>) and at <math>7, 14^b, 21\pm2</math> d, <math>29\pm3</math> d, <math>28, 63\pm5</math> d, and <math>162\pm7</math> d after the boost immunization: (<u>trial days 8 to 184</u>).</p> <ul style="list-style-type: none"><li>• Antibody responses measured (concentrations/titers).</li><li>• Fold increase in antibody titers at <math>7\pm1</math> d and <math>21\pm2</math> d after primary immunization and at <math>21\pm2</math> d, <math>29\pm3</math> d, <math>63\pm5</math> d, and <math>162\pm7</math> d after the boost immunization (concentrations/titers).</li><li>• Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers as compared to baseline at <math>7\pm1</math> d and <math>21\pm2</math> d after primary immunization and at <math>21\pm2</math> d, <math>29\pm3</math> d, <math>63\pm5</math> d, and <math>162\pm7</math> d after the boost immunization (concentrations/titers).</li></ul> <p>For BNT162c2 (SD):</p> <p>As compared to baseline at <math>7, 21, 28, 42, 84</math>, and <math>183</math> d after the primary immunization (<u>trial days 8 to 184</u>):</p> <ul style="list-style-type: none"><li>• Antibody responses at <math>7\pm1</math> d, <math>21\pm2</math> d, <math>29\pm3</math> d, <math>42\pm3</math> d, <math>84\pm5</math> d, and <math>183\pm7</math> d after the primary immunization measured (concentrations).</li><li>• Fold increase in antibody titers at <math>7\pm1</math> d, <math>21\pm2</math> d, <math>29\pm3</math> d, <math>42\pm3</math> d, <math>84\pm5</math> d, and <math>183\pm7</math> d after the primary immunization (concentrations).</li><li>• Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers as compared to baseline at <math>7\pm1</math> d, <math>21\pm2</math> d, <math>29\pm3</math> d, <math>42\pm3</math> d, <math>84\pm5</math> d, and <math>183\pm7</math> d after the primary immunization (concentrations).</li></ul>	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 otherwise without making content changes), to emphasize that the objective apply to all cohorts including the added expansion cohorts.

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<p><u>Section 1.1 Trial synopsis and Section 3 Objectives and endpoints</u></p> <p><u><b>Additional exploratory objectives</b></u> <u>(Only for the Expansion cohorts [Cohorts 11 to 13])</u> <u>To further characterize the long term adaptive immune response after P/B immunization with 30 µg BNT162b2.</u></p>	Update to reflect the added expansion cohorts.				
<p><u>Additional exploratory objectives only for the Expansion cohorts [Cohorts 11 to 13])</u> <u>To further characterize the long term adaptive immune response after P/B immunization with 30 µg BNT162b2.</u></p>					
<p><u>Section 1.1 Trial synopsis and Section 3 Objectives and endpoints</u></p> <table border="1"><thead><tr><th>Objectives</th><th>Endpoints <sup>a</sup></th></tr></thead><tbody><tr><td><p><u>(Only for the Expansion cohorts [Cohorts 11 to 13])</u> <u>To further characterize the adaptive immune response: Assessment of cell-mediated immunity</u></p></td><td><ul style="list-style-type: none"><li>Further characterization of vaccine and SARS-CoV-2 specific antigen-specific CD4 and CD8 T-cells, e.g., using ELISpot, ICS.</li><li>Functional characterization of T-cells (e.g. antigen dependent cytokine secretion, activation, proliferation, cytotoxicity, determination of human leukocyte antigen (HLA) restriction).</li><li>Cellular and molecular phenotyping of immune cells using e.g., immunophenotypic characterization of T-cells to define reactive T-cell subsets.</li><li>Bulk or single cell T-cell receptor (TCR) and transcriptome sequencing, quantitative polymerase chain reaction (q-PCR) studies to profile and characterize and track TCRs and quantify the number of antigen-specific T-cells.</li></ul></td></tr></tbody></table>	Objectives	Endpoints <sup>a</sup>	<p><u>(Only for the Expansion cohorts [Cohorts 11 to 13])</u> <u>To further characterize the adaptive immune response: Assessment of cell-mediated immunity</u></p>	<ul style="list-style-type: none"><li>Further characterization of vaccine and SARS-CoV-2 specific antigen-specific CD4 and CD8 T-cells, e.g., using ELISpot, ICS.</li><li>Functional characterization of T-cells (e.g. antigen dependent cytokine secretion, activation, proliferation, cytotoxicity, determination of human leukocyte antigen (HLA) restriction).</li><li>Cellular and molecular phenotyping of immune cells using e.g., immunophenotypic characterization of T-cells to define reactive T-cell subsets.</li><li>Bulk or single cell T-cell receptor (TCR) and transcriptome sequencing, quantitative polymerase chain reaction (q-PCR) studies to profile and characterize and track TCRs and quantify the number of antigen-specific T-cells.</li></ul>	Update to reflect the added expansion cohorts.
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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.

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<p><u>Section 1.1 Trial synopsis and Section 4.1 Overall design</u></p> <p><del>Four different vaccines (BNT162a1, BNT162b1, BNT162b2, and BNT162c2) will be tested.</del> <del>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.</del></p> <p><u>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).</u></p> <p><u>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.</u></p>	Update to reflect the added expansion cohorts.
<p><u>Section 1.1 Trial synopsis and Section 4.1 Overall design</u></p> <p><u>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.</u></p> <p>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 <u>in response to a fast-changing situation</u>.</p>	Update to reflect the added expansion cohorts.
<p><u>Section 1.1 Trial synopsis and Section 4.1 Overall design</u></p> <p><b>Part A</b></p> <p><u>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.</u></p> <p><u>Dose ranging cohorts:</u></p> <p>Trial subjects with the first-in-human [FIH] immunization will be immunized using a sentinel...</p>	Update to introduce the screening, treatment, and follow-up phases.

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<p><u>Section 1.1 Trial synopsis and Section 4.1 Overall design</u></p> <p>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:</p> <ul style="list-style-type: none"><li>• Two sentinel subjects will be dosed on one day (with intervals of at least 30 min between subjects).</li><li>• 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 <del>30</del> <ins>15</ins> min between subjects).</li><li>• 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):<ul style="list-style-type: none"><li>◦ The remaining 6 subjects in the group will be dosed (with intervals of at least <del>30</del> <ins>15</ins> min between subjects).</li><li>◦ ...</li></ul></li></ul> <p>The maximum allowed dose for each vaccine candidate is defined in the Table 1.</p> <p>For the planned dose de-escalation cohorts, 12 subjects may be dosed on one day (with intervals of at least <del>30</del> <ins>15</ins> min between subjects). The doses in these cohorts in younger adults must be lower 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.</p>	Reduction of intervals between subjects for logistical reasons (given the now available clinical experience with BNT162b2 immunization)
<p><u>Section 1.1 Trial synopsis and Section 4.1 Overall design</u></p> <p>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.</p> <p><u>The doses planned for Cohorts 8 to 10 are defined in Table 2.</u></p> <p>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 <del>30</del> <ins>15</ins> min between subjects (as for planned de-escalation cohorts).</p> <p>Note: BNT162b1 and BNT162b2 are <u>nucleoside</u> modified uridine RNAs, while BNT162a1 and BNT162c2 are both <del>nucleoside</del> non-modified <u>pseudomethyl</u>-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.</p>	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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<p><u>Section 1.1 Trial synopsis and Section 4.1 Overall design</u></p> <p><u>Expansion cohorts:</u></p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Moreover, each vaccine candidate individually. Part B 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 initiated 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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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:</p> <ul style="list-style-type: none"><li>• 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).</li><li>• 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).</li><li>• 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).</li></ul> <p>For the scientific rational for the expansion cohorts, see Section 4.2.</p> <p>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.</p>	Update to reflect the added expansion cohorts.

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<p><u>Section 1.1 Trial synopsis and Section 4.1 Overall design</u></p> <p><b>Part B</b></p> <p><del>Part B will only be started if approved using a substantial protocol amendment.</del></p> <p><del>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.</del></p> <p><del>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.</del></p> <p><del>Immunogenicity of all doses will be thoroughly assessed.</del></p> <p><del>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.</del></p> <p><del>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.</del></p> <p><u><a href="#">Due to changes in the overall clinical development plan, Part B will no longer be conducted.</a></u></p>	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).																																																														
<p><u>Section 1.1 Trial synopsis and Section 4.1 Overall design</u></p> <p><b>Table 1:</b> <u>Summary of Dose ranging:</u> vaccine dose regimens for younger adults aged 18 to 55 years in Part A (Cohorts 1 to 7)</p> <table border="1"> <thead> <tr> <th rowspan="2">Vaccine / mRNA type</th> <th rowspan="2">Vaccine-encoded antigen</th> <th rowspan="2">Vaccine IM dosing regimen</th> <th colspan="7">Part A – Cohort numbers &amp; Dose (µg) (12 subjects per cohort)</th> </tr> <tr> <th>Starting dose</th> <th></th> <th>3 De-escalation dose</th> <th>4</th> <th>Optional de-escalation dose</th> <th>6</th> <th>7</th> </tr> </thead> <tbody> <tr> <td>BNT162a1 / uRNA</td> <td>RBD of the SARS-CoV-2 S protein</td> <td>Prime: Day 1 3 µg Boost: Day 22</td> <td><b>1A</b> 0.6 µg <sup>a</sup></td> <td>2A 0.1 µg</td> <td>3A 1 µg</td> <td>4A <sup>a</sup> 2 µg <sup>a</sup></td> <td>5A 0.3 µg</td> <td>6A 1 µg</td> </tr> <tr> <td>BNT162b1 / modRNA</td> <td>RBD of the SARS-CoV-2 S protein</td> <td>Prime: Day 1 10 µg Boost: Day 22</td> <td><b>1B</b> 30 µg</td> <td>2B 1 µg</td> <td>3B 1 µg</td> <td><b>4B</b> <b>60 µg <sup>a</sup></b></td> <td>5B 50 µg</td> <td>6B 3 µg</td> </tr> <tr> <td>BNT162b2 / modRNA</td> <td>Modified version of the full length SARS-CoV-2 S protein</td> <td>Prime: Day 1 10 µg Boost: Day 22</td> <td><b>1C</b> 30 µg</td> <td>2C 1 µg</td> <td>3C 1 µg</td> <td><b>4C <sup>a</sup></b> <b>60 µg <sup>a</sup></b></td> <td>5C <sup>a</sup> 20 µg</td> <td>6C <sup>a</sup> 3 µg</td> </tr> <tr> <td>BNT162c2 / saRNA</td> <td>Modified version of the full length SARS-CoV-2 S protein</td> <td>Prime only: Day 1 1D 0.1 µg</td> <td>2D 0.3 µg</td> <td>3D 0.1 µg to &lt;3 µg <sup>c</sup></td> <td>4D 1 µg</td> <td>5D <sup>a</sup> 0.6 µg</td> <td><b>6D <sup>a</sup></b> <b>3 µg <sup>d</sup></b></td> <td><b>7E</b> <b>35-10 µg <sup>a</sup></b></td> </tr> <tr> <td>BNT162c2 / saRNA</td> <td>Modified version of the full length SARS-CoV-2 S protein</td> <td>Prime: Day 1 0.1 µg Boost: Day 22</td> <td><b>1E</b> 0.3 µg</td> <td><b>2E <sup>a</sup></b> <b>0.1 µg to &lt;3 µg <sup>a</sup></b></td> <td><b>3E</b> <b>1 µg</b></td> <td><b>4E <sup>a</sup></b> <b>3 µg</b></td> <td><b>5E <sup>a</sup></b> 0.6 µg</td> <td><b>6E <sup>a</sup></b> <b>35-10 µg <sup>a</sup></b></td> </tr> </tbody> </table> <p><sup>a</sup> All dose escalation doses used must be judged acceptable by the Safety Review Committee (SRC) before use.  <sup>b</sup> 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.  <sup>c</sup> Specific doses to be defined, but in the range given. Already given doses will not be repeated.  <sup>d</sup> The planned maximum doses per vaccine candidate.  <sup>e</sup> 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.</p> <p>IM = intramuscular; RBD = Receptor Binding Domain; S protein = SARS-CoV-2 spike protein. tbd = to be defined.</p> <p><u>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.</u></p>	Vaccine / mRNA type	Vaccine-encoded antigen	Vaccine IM dosing regimen	Part A – Cohort numbers & Dose (µg) (12 subjects per cohort)							Starting dose		3 De-escalation dose	4	Optional de-escalation dose	6	7	BNT162a1 / uRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 3 µg Boost: Day 22	<b>1A</b> 0.6 µg <sup>a</sup>	2A 0.1 µg	3A 1 µg	4A <sup>a</sup> 2 µg <sup>a</sup>	5A 0.3 µg	6A 1 µg	BNT162b1 / modRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 10 µg Boost: Day 22	<b>1B</b> 30 µg	2B 1 µg	3B 1 µg	<b>4B</b> <b>60 µg <sup>a</sup></b>	5B 50 µg	6B 3 µg	BNT162b2 / modRNA	Modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 10 µg Boost: Day 22	<b>1C</b> 30 µg	2C 1 µg	3C 1 µg	<b>4C <sup>a</sup></b> <b>60 µg <sup>a</sup></b>	5C <sup>a</sup> 20 µg	6C <sup>a</sup> 3 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 <sup>c</sup>	4D 1 µg	5D <sup>a</sup> 0.6 µg	<b>6D <sup>a</sup></b> <b>3 µg <sup>d</sup></b>	<b>7E</b> <b>35-10 µg <sup>a</sup></b>	BNT162c2 / saRNA	Modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 0.1 µg Boost: Day 22	<b>1E</b> 0.3 µg	<b>2E <sup>a</sup></b> <b>0.1 µg to &lt;3 µg <sup>a</sup></b>	<b>3E</b> <b>1 µg</b>	<b>4E <sup>a</sup></b> <b>3 µg</b>	<b>5E <sup>a</sup></b> 0.6 µg	<b>6E <sup>a</sup></b> <b>35-10 µg <sup>a</sup></b>	Updated to reflect implemented doses changes and the terminology „dose ranging“.
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<b>Trial duration</b> <p>In total, the planned trial duration is expected to be approximately 12 months. From screening visit (Visit 0) to the last visit (Visit 8 [BNT162-2 (SD); Visit 9 BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B)]), each trial subject will be in the trial for maximally 223 d.</p> <p>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.</p> <p>For logistical reasons, investigation of the different vaccines may not be able to start at the same time.</p>																														

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<p><u>Section 1.1 Trial synopsis</u></p> <p><b>Population</b></p> <p><del>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).</del></p> <p><del>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.</del></p> <p><del>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.</del></p> <p><u>Dose ranging Cohorts (Cohorts 1 to 10)</u></p> <ul style="list-style-type: none"><li><u>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).</u></li></ul> <p><u>For each vaccine, 12 subjects are required for each of the dose ranging cohorts.</u></p> <p><u>Expansion cohorts (Cohorts 11 to 13)</u></p> <ul style="list-style-type: none"><li><u>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).</u></li><li><u>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).</u></li><li><u>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).</u></li></ul>	Update to reflect the added expansion cohorts. Correction of an error.

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	<del>270</del> <ins>120</ins> (13 <del>10</del> cohorts)
BNT162c2 / saRNA	Prime only	72 (6 cohorts)
BNT162c2 / saRNA	Prime/Boost	<del>84</del> <ins>72</ins> ( <del>7</del> 6 cohorts)

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<p><u>Section 1.1 Trial synopsis and Section 5.1.1</u></p> <p><b>Key inclusion criteria</b></p> <p>Volunteers are only eligible to be enrolled in the trial if they meet the following criteria:</p> <ul style="list-style-type: none"><li>For younger adult cohorts, volunteers must be aged 18 to 55 years, have a BMI over 19 kg/m<sup>2</sup> and under 30 kg/m<sup>2</sup>, and weigh at least 50 kg at Visit 0.</li></ul> <p>OR</p> <p>For older adult cohorts, volunteers must be aged 56 to 85 years, have a BMI over 19 kg/m<sup>2</sup> and under 30 kg/m<sup>2</sup>, and weigh at least 50 kg at Visit 0.</p> <p>OR</p> <p><u>For the immunocompromised adult cohort (Cohort 13), volunteers must be aged 18 to 85 years, have a BMI over 19 kg/m<sup>2</sup> and under 30 kg/m<sup>2</sup>, and weigh at least 50 kg at Visit 0.</u></p> <p>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.</p> <p>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.</p> <p>OR</p> <p><u>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<sup>6</sup> /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.</u></p>	Update to reflect the added expansion cohort with immuno-compromised subjects.

<p><u>Section 1.1 Trial synopsis</u></p> <p><b>Key exclusion criteria</b></p> <p>Volunteers are excluded from the trial if they present any of the following criteria:</p> <ul style="list-style-type: none"><li>• Have had any acute illness...</li><li>• Have a known allergy, hypersensitivity, ...</li><li>• 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. <a href="#">See the inclusion criteria for non-excluded medical conditions for Cohort 13.</a></li><li>• Have any surgery planned during the trial, ...</li><li>• Had any chronic use (more than 21 continuous days) of any systemic medications, including immunosuppressants or other immune-modifying drugs (<a href="#">except for Cohort 13</a>) within the 6 ...</li><li>• Regular receipt of inhaled/nebulized corticosteroids (<a href="#">except for cohort 13</a>).</li><li>• Had any vaccination within the 28 d prior to Visit 0.</li><li>• Had administration of any immunoglobulins and/or any blood products within the ...</li><li>• Had administration of another IMP including vaccines within 60 d or 5 half-lives ...</li><li>• Have a known history or a positive test for any of HIV 1 or 2, Hepatitis B, or Hepatitis C, or (<a href="#">except for Cohort 13</a>) HIV 1 or 2 within the 30 d prior to Visit 0.</li><li>• Have a positive PCR-based test for SARS-CoV-2 within the 30 d prior to Visit 1.</li><li>• Previously participated in an investigational trial involving lipid nanoparticles.</li><li>• Have a history (within the past 5 years) of substance abuse or known medical...</li><li>• Have a history of hypersensitivity or serious reactions to previous vaccinations.</li><li>• Have a history of Guillain-Barré syndrome within 6 wks following a previous vaccination.</li><li>• Have a history of narcolepsy.</li><li>• (<a href="#">Except for Cohort 13</a>) Have a history of or suspected immunosuppressive condition, acquired or congenital, as determined by medical history and/or physical examination at Visit 0.</li><li>• Have symptoms of the coronavirus disease 2019 (COVID-19), e.g., respiratory symptoms, ...</li><li>• Have had contact with persons diagnosed with COVID-19 or who tested positive...</li><li>• Are soldiers, <del>subjects</del> volunteers in detention, CRO or sponsor staff or their family members.</li><li>• For older <del>subjects</del> 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:<ul style="list-style-type: none"><li>○ Hypertension</li><li>○ Diabetes mellitus</li><li>○ Chronic <a href="#">obstructive</a> pulmonary disease</li><li>○ Asthma</li><li>○ Chronic liver disease</li><li>○ Known Stage 3 or worse chronic kidney disease (glomerular filtration rate &lt;60 mL/min/1.73 m<sup>2</sup>)</li><li>○ <a href="#">Anticipating the need for immunosuppressive treatment within the next 6 months</a></li><li>○ <a href="#">Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies.</a></li><li>○ <a href="#">Sickle cell disease</a></li><li>○ <a href="#">Cancer (except for cohort 13)</a></li><li>○ <a href="#">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.</a></li><li>○ <a href="#">Are immune compromised due to HIV infection with a CD4<sup>+</sup> count of &lt; 200 x 10<sup>6</sup> /L at screening or significant medical complications such as opportunistic infections, malignant complications (e.g., lymphoma, Kaposi sarcoma), other organ manifestations consistent</a></li></ul></li></ul>	<p>Update to reflect the added expansion cohort with immuno-compromised subjects.</p>
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<p><u>with advanced acquired immunodeficiency syndrome (AIDS) or other conditions that would be considered a contraindication for vaccination.</u></p> <ul style="list-style-type: none"><li>○ Resident in a long-term facility.</li><li>○ Current vaping or smoking (occasional smoking is acceptable).</li><li>○ History of chronic smoking within the prior year.</li></ul>	

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, subjectsvolunteers in detention, CRO or sponsor staff or their family members.  
28. Regular receipt of inhaled/nebulized corticosteroids.  
29. For older subjectsvolunteers 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<sup>2</sup>)
  - 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
<p><u>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.</u></p> <ul style="list-style-type: none"><li>○ <u>Are immune compromised due to HIV infection with a CD4<sup>+</sup> count of &lt; 200 x 10<sup>6</sup> /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.</u></li><li>○ Resident in a long-term facility.</li><li>○ Current vaping or smoking (occasional smoking is acceptable).</li><li>○ History of chronic smoking within the prior year.</li></ul>	
<p><u>Section 1.1 Trial synopsis and Section 6.1 IMP administered</u></p> <p><b>Trial treatments</b></p> <p><b>Dosage levels:</b> See <b>Error! Reference source not found.</b> The planned dose per vaccine candidate will not exceed the pre-defined maximum doses (see <b>Error! Reference source not found.</b>).</p> <p><b>Part B expansion cohorts:</b> <b>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.</b></p>	Update to reflect the deletion of Part B.
<p><u>Section 1.1 Trial synopsis and Section 5.2.1</u></p> <p><b>Statistics</b></p> <p><b>The statistical analysis will be performed once all subjects have been enrolled and completed all visits according to the SoA (Section 1.3).</b></p> <p><b>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.</b></p> <p><b>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.</b></p> <p><b>The planned protocol amendment will include a description of the planned statistical analyses planned for Part B.</b></p>	Update to reflect the deletion of Part B. Update to reflect the addition of expansion cohorts.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	Rationale
<p><u>Section 1.1 Trial synopsis</u></p> <p><b>Schema</b></p> <p><i>Cohorts 8 to 10 with older adults</i></p> <p>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/sentinel (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 <a href="#">Table 1</a> and <a href="#">Table 2</a>.</p>	Update to reflect the addition of expansion cohorts and the dose ranging terminology.

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<p><u>Section 1.1 Trial synopsis</u></p> <p><b>Schema</b></p> <p><b>Dose ranging cohort schema for BNT162c2 (SD)<sup>b</sup></b></p> <pre> graph LR     FIH[Day 1: Sentinel subject] --&gt; Day1_2[Day 1: 2 Sentinel subjects]     Day1_2 --&gt; Day2_4[Day 2: 4 subjects]     Day2_4 --&gt; Day4_6[Day 4: 6 subjects]     Day4_6 --&gt; Day1_2_6[Day 1: 2 Sentinel subjects]     Day1_2_6 --&gt; Day2_4_6[Day 2: 4 subjects]     Day2_4_6 --&gt; Day4_6_6[Day 4: 6 subjects]     Day4_6_6 --&gt; Day1_12[Day 1: 12 Subjects]     Day1_12 --&gt; SRCReview["SRC Review*"]     subgraph "Based on safety data*"         Day1_2         Day2_4         Day4_6         Day1_2_6         Day2_4_6         Day4_6_6     end     </pre> <p>a) The data assessed by the SRC for progressing comprises 48 h data for 6 subjects. b) For the dose regimens, see <a href="#">Table 1</a>.</p> <p><b>Expansion cohorts - Cohorts 11 to 13<sup>a</sup></b></p> <table border="1"> <tr> <td>Cohort 11 (N = 90)</td> <td>Cohort 12 (N = 30)</td> <td>Cohort 13 (N = 30)</td> </tr> <tr> <td>s≤90 Subjects may be dosed on one day</td> <td>s≤30 Subjects may be dosed on one day</td> <td>s≤30 Subjects may be dosed on one day</td> </tr> </table> <p>a) For the dose regimens, see <a href="#">Table 3</a>.</p> <p><b>Figure 1: Graphical depiction of the dose-finding process in Part A</b></p> <p>FIH = First-in-humans; h = hour(s); SRC = Safety Review Committee.</p> <p><u>Section 1.1 Trial synopsis - Table 5</u></p> <table border="1"> <thead> <tr> <th>Procedure / Assessment</th> <th>Visit 0</th> <th>Visit 1 Pre-dose</th> <th>Visit 1 Post-dose</th> <th>Visit 2 at 24±2h</th> <th>Phone call at 48±2h</th> <th>Visit 3</th> <th>Visit 4 Pre-dose</th> <th>Phone call at 48±2h</th> <th>Visit 5 ~7 d from Visit 4</th> <th>Visit 5a</th> <th>Visit 6 ~21 d from Visit 4</th> <th>Visit 7 ~28 d from Visit 4</th> <th>Visit 8 ~63 d from Visit 4 (FU Visit)</th> <th>Visit 9 ~162 d from Visit 4 (FU Visit)</th> </tr> </thead> <tbody> <tr> <td>Day h</td> <td>-30 to 0</td> <td>1</td> <td>1</td> <td>2</td> <td></td> <td>8</td> <td>22</td> <td>22</td> <td>29</td> <td>36<sup>a</sup></td> <td>43</td> <td>50<sup>a</sup></td> <td>85</td> <td>184</td> </tr> <tr> <td>Days to last dose h</td> <td>0</td> <td>0</td> <td></td> <td></td> <td></td> <td>7</td> <td>21</td> <td>0</td> <td>7</td> <td>14</td> <td>21</td> <td>28</td> <td>63</td> <td>162</td> </tr> <tr> <td>Blood draw for clinical laboratory (15 mL)<sup>c</sup></td> <td>X</td> <td>X (15 mL)</td> <td></td> <td>X (15 mL)</td> <td></td> <td>X (15 mL)</td> <td></td> <td></td> <td>X (15 mL)</td> <td></td> <td></td> <td>X (15 mL)</td> <td></td> <td></td> </tr> <tr> <td>Blood draw for viral screening<sup>c</sup></td> <td>X (5 mL)</td> <td></td> </tr> <tr> <td>Blood draw for SARS-CoV-2 testing<sup>c</sup></td> <td>X (2.6 mL)</td> <td></td> </tr> <tr> <td>Quid-swipe for SARS-CoV-2 testing</td> <td></td> <td>X<sup>m</sup></td> <td></td> </tr> <tr> <td>Allocation to IMP</td> <td>X</td> <td></td> </tr> <tr> <td>Immunization<sup>d</sup></td> <td></td> <td>X<sup>j</sup></td> <td></td> <td></td> <td></td> <td>X</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Blood draw for immunogenicity (10 mL)<sup>n</sup></td> <td>X (10 mL)</td> <td></td> <td></td> <td></td> <td></td> <td>X (10 mL)</td> <td>X (10 mL)</td> <td></td> <td>X (10 mL)</td> </tr> <tr> <td>Blood draw for HLA</td> <td></td> <td></td> <td></td> <td></td> <td>X (4 mL EDTA-blood)<sup>p</sup></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Blood draw for CMI (100 mL)<sup>n,o</sup></td> <td>X</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>X</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Blood draw for research</td> <td></td> <td></td> <td></td> <td></td> <td>← Up to 5 blood draws for explorative biomarker/immunogenicity research purposes. 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<p><b>Section 1.1 Trial synopsis - Table 5</b></p> <p>transpermease, total carbon dioxide, 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 (<a href="#">to confirm postmenopausal status</a>): follicle stimulating hormone at Visit 0.</p> <p>a. Viral screening for human immunodeficiency virus (HIV) 1 or 2, hepatitis B, hepatitis C.</p> <p>b. 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.</p> <p>c. 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> <p>d. Only IMP-related AEs and <a href="#">any SAEs</a>.</p> <p>e. Blood draw for anti-SARS-CoV-2 antibodies (samples will be stored until a test is commercially available).</p> <p>f. For Cohorts 1 and 3, 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 at least <a href="#">30-15</a> min intervals between subjects <a href="#">and for the boost injections</a>.</p> <p>g. Oral swipe for SARS-CoV-2 testing either on Day -1 or at the Visit 1 on Day 1.</p> <p>h. 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 8.8.</p> <p>i. 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> <p>j. If HLA typing using the blood sample collected with Lithium Heparin is not conclusive, EDTA-blood will be drawn for HLA testing.</p> <p>k. Only cohorts starting prime dosing after approval of protocol amendment 06.</p> <p>l. 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.</p> <p>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.</p>	Update to reflect the addition of expansion cohorts.																																																																																																																																																																																																																																																																																																																																																
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Brief (symptom-directed) physical examination, no height measurement.</td></tr> <tr> <td colspan="12">b. Vital signs, systolic/diastolic blood pressure, pulse rate, respiratory rate, and body temperature, body weight only Visit 0.</td></tr> <tr> <td colspan="12">c. All 12 leads ECG.</td></tr> <tr> <td colspan="12">d. Urine screening for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cocaine, cannabinoids, opiates, methadone, methamphetamine, phencyclidine, tricyclic antidepressants). Dipstick urine analysis: glucose, bilirubin, ketone, specific gravity, blood, protein, uric acid, nitrates, 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.</td></tr> <tr> <td colspan="12">e. 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 (<a href="#">to confirm postmenopausal status</a>): follicle stimulating hormone at Visit 0.</td></tr> <tr> <td colspan="12">f. Viral screening for human immunodeficiency virus (HIV) 1 or 2, hepatitis B, hepatitis C.</td></tr> <tr> <td colspan="12">g. Blood draw for anti-SARS-CoV-2 antibodies.</td></tr> <tr> <td colspan="12">h. Oral swipe for SARS-CoV-2 testing either on Day -1 or at the Visit 1 on Day 1.</td></tr> <tr> <td colspan="12">i. 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<p><b>Section 1.1 Trial synopsis - Table 7</b></p> <p>Addition of Table 7.</p>	Update to reflect the addition of expansion cohorts.																																																																																																																																																																																																																																																																																																																																																

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<u>Section - Trial-specific abbreviations/terms</u>  <u>Elderly (adults)</u> As defined in ICH E7, individuals aged 65 years or older <u>Older (adults)</u> Defined in this document to be individuals aged 56 to 85 years <u>VNT</u> Virus neutralization test <u>Younger (adults)</u> Defined in this document to be individuals aged 18 to 55 years	Clarification
<u>Section 2.2 Trial rationale</u>  Some of the prophylactic BNT162 vaccines against SARS-CoV-2 investigated in this trial are under investigation ( <del>BNT162-02</del> or will be investigated) in other <del>clinical</del> ongoing trials (see Table 4 <del>BNT162-03</del> ). 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.
<u>Section 2.2.1 This trial (BNT162-01) - Preliminary results</u>  Given the rapidly changing situation, this section deleted and crossreferences inserted to the current BNT162 IB which contains the current reference safety information.	
<u>Section 2.2.2 US trial BNT162-02 - Preliminary results</u>  Given the rapidly changing situation, this section deleted and crossreferences inserted to the current BNT162 IB which contains the current reference safety information.	
<u>Section 2.2.3 Chinese trial - BNT162-03</u>  Given the rapidly changing situation, this section deleted and crossreferences inserted to the current BNT162 IB which contains the current reference safety information.	
<u>Section 2.2.4 BNT162-04 for BNT162b3</u>  Given the rapidly changing situation, this section deleted and crossreferences inserted to the current BNT162 IB which contains the current reference safety information.	

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<p><u>Section 2.3.1 Risk assessment</u></p> <p>The risks linked to the trial-specific procedures and connected mitigations are as follows:</p> <ul style="list-style-type: none"><li>• The volume of blood drawn will be kept to a minimum and will remain less than that drawn when donating blood (<del>up to approximately 582 mL blood will be drawn per subject over the complete trial, i.e., over approximately 7 months</del>):<ul style="list-style-type: none"><li>◦ <del>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.</del></li><li>◦ <del>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.</del></li></ul></li><li>• All trial-specific procedures will be performed by qualified trial site personnel.</li></ul>	Update to reflect the addition of expansion cohorts. Update to reflect the addition of Visit 5a for still to be started cohorts.
<p><u>Section 2.3.1 Risk assessment</u></p> <p>• Due to the IM route the risk of systemic reactions is considered low.</p> <p>• <del>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).</del></p> <p>• 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.</p> <p>• <b>CCI</b>  [REDACTED]</p> <p>• 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).<ul style="list-style-type: none"><li>◦ <del>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 secretion 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.</del></li><li>◦ <del>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.</del></li><li>◦ <del>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.</del></li></ul></p>	Update to reflect the now available clinical experience with BNT162 vaccine immunization.

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<p><u>Section 2.3.1 Risk assessment</u></p> <p>To date, <del>there is limited based on available</del> clinical experience with BNT162 vaccines in human subjects (<a href="#">see Section 2.2</a>).</p> <ul style="list-style-type: none"><li>• <del>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.</del></li><li>• <del>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.</del></li><li>• <u>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.</u></li><li>• <u>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.</u></li><li>• 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 <a href="#">Section 2.2.2 the BNT162 IB</a>).</li><li>• 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 <a href="#">Section 2.2.2 the BNT162 IB</a>.</li><li>• 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 <a href="#">Section 2.2.2 the BNT162 IB</a>).</li><li>• Preliminary data in elderly adults, show lower <u>but measurable</u> antibody responses in older adults than in younger adults (for details, see <a href="#">Section 2.2.2 the BNT162 IB</a>). The investigation of higher dose range in older adults in this trial <del>is may</del> therefore <u>be</u> required to support the Phase III program planned to support marketing approval.</li></ul>	Update to reflect the now available clinical experience with BNT162 vaccine immunization.
<p><u>Section 2.3.1 Risk assessment</u></p> <p>When assessing the risk for dosing of older subjects with BNT162 vaccine candidates in this trial, the follow information is relevant:</p> <ul style="list-style-type: none"><li>• Preliminary data in subjects treated in the ongoing BNT162 trials backed by non-human ..</li><li>• The risk that older adults may be under dosed with the vaccine doses chosen based on ...</li><li>• Preliminary data in elderly show a comparable to lower reactogenicity based on the ...</li><li>• 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 this trial and/or BNT162-02 trial (for details, see <a href="#">Section 2.2.2 the BNT162 IB</a>). This tolerability in elderly adults appears to be better than seen in younger adults at the same doses.</li></ul>	Update to reflect the deletion of Part B.

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<p><u>Section 2.3.1 Risk assessment</u></p> <p>To further ensure trial subject safety <u>during dose ranging cohorts</u>, the trial protocol foresees that:</p> <ul style="list-style-type: none"><li>On -site observation periods after each immunization (i.e., 24 h for the first 6 subjects...)</li></ul>	Update to reflect the addition of expansion cohorts.
<p><u>Section 2.3.1 Risk assessment</u></p> <p>After each assessment, the SRC may request a prolongation of the observation periods 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.</p> <p><del>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.</del></p> <ul style="list-style-type: none"><li>The SRC may make recommendations on increasing observation periods and ...</li><li>To ensure trial subject safety during the trial, their safety will be monitored from ...</li></ul> <p><u>For the expansion cohorts:</u></p> <ul style="list-style-type: none"><li><u>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).</u></li><li><u>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.</u></li></ul>	Update to reflect the addition of expansion cohorts.
<p><u>Section 4.1.2 Planned number of trial subjects</u></p> <p><u>In Part A</u> <del>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.</del></p> <p><u>In Part B</u> <del>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.</del></p> <p><u>See Table 4.</u></p>	Update to reflect the addition of expansion cohorts.

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<p><u>Section 4.2 Scientific rationale for the trial design</u></p> <p>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”).</p> <p><del>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.</del></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>Part B of the trial will no longer be conducted due to changes in the global clinical development plan in a rapidly evolving situation.</u></p>	Update to reflect the addition of expansion cohorts.

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<p><u>Section 4.3 Justification for dose</u></p> <p>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.</p> <p><del>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.</del></p> <p>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.</p> <p>As summarized in <del>Section 2.2.1 and Section 2.2.2</del> 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.</p> <p>Based on the available clinical and non-clinical data experience, the sponsor expects the planned maximal doses (see Table 1) to be safe.</p> <p>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 <del>Section 2.2.2 the BNT162 IB,</del></p> <p><u>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.</u></p> <p><u>Cohort 12 will explore an alternative posology with low dose prime (3 µg) and standard dose boost (30 µg) as described elsewhere.</u></p> <p>Taken together, the planned starting doses in this trial <del>with healthy subjects</del> are considered to be safe, but still sufficient to induce an antiviral immune response.</p>	Update to reflect the addition of expansion cohorts.
<p><u>Section 4.4 End of treatment (EoT) and end of trial definition</u></p> <p><del>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).</del></p> <p><del>The EoT is defined as the date the last subject completed the EoT visit.</del></p> <p><u>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).</u></p> <p><u>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).</u></p> <p><u>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).</u></p>	Clarification given the addition of expansion cohorts.
<p><u>Section 5.1.2 Inclusion criteria Part B</u></p> <p>This entire section was deleted.</p>	Update to reflect the deletion of Part B.

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<p><u>Section 5.3 Lifestyle considerations</u></p> <p>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.</p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>Dose ranging (Cohorts 1 to 10)</u></p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p><u>Expansion for BNT162b2 (Cohorts 11 to 13)</u></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>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.</u></p>	Update to reflect the addition of expansion cohorts.
<p><u>Section 6.3 Measures to minimize bias: randomization and blinding</u></p> <p>Not applicable for Part A. <u>Details for Part B will be defined using a protocol amendment.</u></p>	Update to reflect the deletion of Part B.

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<p><u>Section 6.5 Concomitant therapy</u></p> <p>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 <del>Visit 8 (BNT162c2) or Visit 9 (BNT162a1, BNT162b1, BNT162b2)</del> the EoT Visit, must be recorded along with the:</p> <ul style="list-style-type: none"><li>• Reason for use</li><li>• Dates of administration including start and end dates</li><li>• Dosage information including dose and frequency</li></ul> <p>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 ... <u>Nonsteroidal anti-inflammatory drugs (NSAIDs), e.g., p</u>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.</p>	Simplification and alignment with Section 6.6.1 (Dose limiting tolerability).
<p><u>Section 6.6.1 Dose limiting toxicity</u></p> <p><u>Applicable to dose ranging cohorts only</u></p> <p>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:</p> <ul style="list-style-type: none"><li>• Anaphylactic reaction considered related</li><li>• Generalized urticaria considered related.</li><li>• Four trial subjects in that cohort with any severe unsolicited local event, if ...</li><li>• AEs within 7 d of vaccination assessed by the investigator to be potentially ...</li><li>• Any systemic SAE within 7 d of vaccination that is assessed by the investigator...</li><li>• Any fever &gt;40.0°C (&gt;104.0°F) within 7 d of vaccination considered related and confirmed by an investigator or medically qualified person.</li><li>• Two trial subjects (at any dose level) with the same or similar severe (Grade 3 or higher) AE <u>or reactogenicity</u> (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).</li></ul>	Update to reflect the addition of expansion cohorts.

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<p><u>Section 6.6.2 Dose modification guidance/rules</u></p> <p><del>The trial design also allows for:</del></p> <ul style="list-style-type: none"><li>• <del>The selection of which BNT162 vaccine(s) dose regimens and posologies that will be investigated in Part B following a substantial protocol amendment.</del></li></ul> <p><b>Part A</b></p> <p>See Section 10.1.5 for the data set upon which SRC decisions described below for Part A are made.</p> <ul style="list-style-type: none"><li>• The decision to test reduced or intermediate doses will be made for each vaccine independently.</li><li>• Any proposal to alter the planned escalation dose, or to test an additional de-escalation dose, must be approved by the SRC.</li></ul> <p><b>Dose escalation:</b></p> <ul style="list-style-type: none"><li>• Dose escalation will only continue if the previous dose was considered safe and well tolerated by the SRC.</li><li>• Any proposal to alter the planned escalation doses must be approved by the SRC.</li></ul> <p><b>Part B</b></p> <p><del>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.</del></p> <p><del>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.</del></p>	Update to reflect deletion of Part B.
<p><u>Section 7.1 Discontinuation of trial treatment</u></p> <p>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. <u>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).</u></p> <p>IMP administration must be stopped if dose limiting toxicities described in Section 6.6.1 are observed.</p> <p>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.</p> <p>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).</p> <p><u>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.</u></p> <p><u>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).</u></p>	Update for clarification.
<p><u>Section 7.1.1 Temporary discontinuation</u></p> <p>Not applicable. <u>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.</u></p>	Update for clarification.

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<p><u>Section 7.2</u> Trial subject discontinuation/withdrawal from the trial</p> <p>If possible, permanently discontinued trial subjects will:</p> <ul style="list-style-type: none"><li>• Complete all assessments planned for that visit and for the <u>EoT Visit Visit 6</u>, if discontinued on a visit day.</li><li>• Complete all assessments planned for the <u>EoT Visit Visit 6</u>, if not discontinued on a visit day.</li></ul>	Update to reflect the addition of expansion cohorts.
<p><u>Section 8.3.1</u> Time period and frequency for collecting AE and SAE information</p> <p><del>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 [PB]). 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.</del></p> <p><u>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.</u></p> <p><u>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.</u></p>	Update to reflect the addition of expansion cohorts.
<p><u>Section 8.3.3</u> Follow-up of AEs and SAEs</p> <p>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 <del>Visit 8 (BNT162c2) or Visit 9 (BNT162a1, BNT162b1, BNT162b2)</del> discharge from the trial, the investigator must confirm the unavailability of a final status.</p>	Update to reflect the addition of expansion cohorts.
<p><u>Section 8.7</u> Genetics</p> <p><u>For Cohorts 1 to 10, a</u> <del>A</del> <u>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).</u></p> <p><u>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.</u></p>	Update to reflect the addition of expansion cohorts.
<p><u>Section 8.8</u> Biomarkers (CMI responses, explorative biomarker, immunogenicity research purposes)</p> <p><del>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.</del></p> <p><u>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.</u></p>	Update to fix the previously flexible blood sampling without altering the total volume of blood drawn.

<p><u>Section 8.9 Immunogenicity assessments</u></p> <p><del>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).</del></p> <p><del>Sero negative is defined as titers below the starting dilution which corresponds to a titer of &lt;1:10.</del></p> <p><del>Seroconversion after vaccination is defined as a 4-fold increase in titer</del></p> <ul style="list-style-type: none"><li><del>o for seronegative pre-vaccination sera: a titer <math>\geq 1:40</math>.</del></li><li><del>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 <math>\geq 1:80</math> after vaccination.</del></li></ul> <p><del>an antibody binding assay, e.g., and assays to characterize antibodies (e.g., affinity IgG subclass), e.g., ELISA.</del></p> <p><del>Sero negative is defined as titers below the starting dilution which corresponds to a titer of &lt;1:100.</del></p> <p><del>Seroconversion after vaccination is defined as a 4-fold increase in titer</del></p> <ul style="list-style-type: none"><li><del>o for seronegative pre-vaccination sera: a titer of <math>\geq 1:100</math>.</del></li><li><del>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 <math>\geq 1:800</math> after vaccination.</del></li></ul> <p><del>and/or</del></p> <p><del>equivalent assays dependent on availability by the time of trial conduct.</del></p> <p><del>Cell mediated immune (CMI) responses:</del></p> <p><del>CMI assays, e.g., ELISpot, intracellular cytokine staining (ICS).</del></p> <p><del>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.</del></p> <p><u>Immune responses as laid down in the trial objectives will be assessed at the times listed in the SoA (Section 1.3) using:</u></p> <ol style="list-style-type: none"><li><u>1) A functional antibody titer determined, e.g., via VNT or an equivalent assay.</u><ul style="list-style-type: none"><li><u>• Sero negative is defined as titers below the starting dilution (i.e., below the LOD [limit of detection] of the assay).</u></li><li><u>• Seroconversion after immunization is defined as a 4-fold increase in titer.</u><ul style="list-style-type: none"><li><u>o for seronegative pre-immunization sera: a titer <math>\geq 4</math>-times the LOD.</u></li><li><u>o for seropositive pre-immunization sera: a titer which is 4-fold higher than the measured pre-immunization titer.</u></li></ul></li></ul></li><li><u>2) An antibody binding assay, e.g., ELISA or an equivalent assay.</u><ul style="list-style-type: none"><li><u>• Seroconversion after immunization is defined as a 4-fold increase in titer/antibody concentration.</u></li></ul></li><li><u>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.</u></li></ol> <p><del>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.</del></p> <p><u>Additional exploratory analyses of IMP-induced antibody responses with selected samples may include:</u></p> <ul style="list-style-type: none"><li><u>• Assessing neutralization activity against variant spike proteins from other SARS-CoV-2 strains or other coronavirus families.</u></li></ul>	<p>Update to reflect the addition of expansion cohorts and for clarification.</p>
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<ul style="list-style-type: none"><li>• <u>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.</u></li><li>• <u>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.</u></li></ul> <p><u>Additional exploratory analyses of vaccine-induced CMI (including non-T-cell based) responses with selected samples may include:</u></p> <ul style="list-style-type: none"><li>• <u>Analysis of immune activation, proliferation, cytotoxicity and cellular, molecular of immune cells subsets.</u></li><li>• <u>Bulk or single cell TCR and transcriptome sequencing, qPCR studies to profile and characterize, and track TCRs and to quantify the number of antigen-specific T-cells.</u></li><li>• <u>Analyses of polymorphism in immune response genes.</u></li></ul> <p><u>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.</u></p> <p><u>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.</u></p>	

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<p><u>Section 8.10 Blood collection</u></p> <p><u>For subjects in Cohorts 1 to 10, up Up</u> to approximately <u>582 592</u> mL blood will be drawn per subject over the complete trial, i.e., over approximately <u>7 months</u> <u>223 d.</u></p> <p><u>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.</u></p>	Update to reflect the addition of expansion cohorts and addition of blood draw at the added Visit (5a).																								
<p><u>Section 9.2 Sample size determination</u></p> <p><u>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).</u></p> <p><u>Table 10: Probability to observe a particular TEAE at least once</u></p> <table border="1"><thead><tr><th><u>Number of subjects</u></th><th><u>TEAE incidence</u></th><th><u>Probability to observe a particular TEAE at least once</u></th></tr></thead><tbody><tr><td><u>12</u></td><td><u>15%</u></td><td><u>85.8%</u></td></tr><tr><td><u>30</u></td><td><u>15%</u></td><td><u>99.2%</u></td></tr><tr><td></td><td><u>10%</u></td><td><u>95.8%</u></td></tr><tr><td></td><td><u>5%</u></td><td><u>78.5%</u></td></tr><tr><td><u>90</u></td><td><u>15%</u></td><td><u>&gt;99.9%</u></td></tr><tr><td></td><td><u>10%</u></td><td><u>&gt;99.9%</u></td></tr><tr><td></td><td><u>5%</u></td><td><u>99.0%</u></td></tr></tbody></table> <p><u>The sample size for Part B will be assessed based on the data from Part A and confirmed/adjusted in the planned protocol amendment.</u></p>	<u>Number of subjects</u>	<u>TEAE incidence</u>	<u>Probability to observe a particular TEAE at least once</u>	<u>12</u>	<u>15%</u>	<u>85.8%</u>	<u>30</u>	<u>15%</u>	<u>99.2%</u>		<u>10%</u>	<u>95.8%</u>		<u>5%</u>	<u>78.5%</u>	<u>90</u>	<u>15%</u>	<u>&gt;99.9%</u>		<u>10%</u>	<u>&gt;99.9%</u>		<u>5%</u>	<u>99.0%</u>	Update to reflect addition of the expansion cohorts and the deletion of Part B.
<u>Number of subjects</u>	<u>TEAE incidence</u>	<u>Probability to observe a particular TEAE at least once</u>																							
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	<u>5%</u>	<u>99.0%</u>																							
<p><u>Section 9.4.1 General considerations</u></p> <p>In general, data will be summarized by groups and groups may be combined as appropriate. <u>Part A and Part B will be analyzed separately and may be combined as appropriate.</u></p> <p>Continuous variables will be summarized by group using the following descriptive statistics: number of subjects (n), mean, standard deviation, median, minimum and maximum.</p> <p>Categorical variables will be summarized by group presenting absolute and relative frequencies (n and %) of subjects in each category.</p> <p><u>The planned protocol amendment will include a description of the planned statistical analyses planned for Part B.</u></p> <p>Baseline is defined as last available value prior to first dose of IMP.</p>	Update to reflect the deletion of Part B.																								

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<p><u>Section 8.3.3 Follow-up of AEs and SAEs</u></p> <ul style="list-style-type: none"><li>• Prime immunization up to 7 d after initial immunization.</li><li>• Prime immunization up to boost immunization or 28 d after initial immunization (whatever comes first).</li><li>• Boost immunization up to 7 d after boost immunization (only for P/B regimens).</li><li>• Boost immunization up to 28 d after boost immunization (only for P/B regimens).</li><li>• Prime immunization up to 28 d after boost immunization or after prime immunization (if no boost was given).</li></ul> <p>P/B regimens:</p> <ul style="list-style-type: none"><li>• Day 1-21 (pre-boost)</li><li>• Day 1 to 7</li><li>• Day 21 (post boost) – 28</li><li>• Day 21 (post boost) to 50</li></ul> <p>SD regimens:</p> <ul style="list-style-type: none"><li>• Day 1-28</li></ul>	For clarification.
<p><u>Section 9.5 Interim analyses</u></p> <p>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.</p> <p>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.</p>	Update to reflect addition of expansion cohorts and for clarification.
<p><u>Section 10.1.1 (Regulatory and ethical considerations)</u></p> <p>The coordinating investigator or delegate will be responsible for the following:</p> <ul style="list-style-type: none"><li>• 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.</li><li>• Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures.</li><li>• 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.</li></ul>	Update for clarification.
<p><u>Section 10.1.5 Committees - SRC</u></p> <p>For Part A, the SRC will be comprised by a sponsor medical representative, the Medical Monitor, a sponsor-independent investigator, and a site representative.</p> <p>For the decision to progress to Part B, an independent statistical consultant and a third party expert will also be included.</p> <p>Key roles of the SRC are as follows:</p>	Update to reflect deletion of Part B.

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<u>Section 10.1.7 Data quality assurance</u>  Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for <del>30</del> <ins>25</ins> 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.
<u>Section 10.3.1.1 Events meeting the AE definition</u>  • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs, <ins>physical examination, measurements</ins> ), 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.
<u>Section 10.3.1.10 Reporting of SAEs</u>  For medical questions, the sponsor's Medical Monitor for this trial should be contacted: <ins>contact details are given in the trial Safety Management Plan.</ins>	Clarification.
<u>Section 10.9 Other standard abbreviations and definitions</u>  EoT      End of <del>Trial</del> <ins>Treatment</ins>	Updates in the body text.

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<p><u>Section 10.10.6 Protocol amendment no. 06</u></p> <p><b><u>Amendment rationale</u></b></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>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.</u></p> <p><u>For further background on the scientific rationale for the expansion cohorts, see Section 4.2.</u></p> <p><u>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).</u></p> <p><u>The three expansion cohorts are as follows.</u></p> <ul style="list-style-type: none"><li>• <u>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).</u></li><li>• <u>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).</u></li><li>• <u>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).</u></li></ul> <p><u>This amendment also addresses feedback obtained from the PEI and the IEC on protocol version 8.0.</u></p> <p><u>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:</u></p> <ul style="list-style-type: none"><li>• <u>Because all first-in-human cohorts for the different BNT162 vaccine variants have been completed.</u></li><li>• <u>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).</u></li></ul> <p><u>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).</u></p> <p><u>This amendment will be issued after some of the planned trial subjects have already been enrolled into the trial.</u></p>	This amendment.

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<p><u>Section 11 References</u></p> <p><u>ICH E7. Guideline for Industry - Studies in Support of Special Populations: Geriatrics. March 1994.</u> ...</p> <p><u>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.</u></p>	Updates in the body text.

Below mentioned section removed as these pages are out scope for publication

Pages removed from 259 to 282 - Out of Scope of phase 1 of Policy 0070 - Pharmacy manual

Pages removed from 283 to 306 - Out of Scope of phase 1 of Policy 0070 - Process description biomarker analytics

Pages removed from 307 to 338 - Out of Scope of phase 1 of Policy 0070 - Laboratory instruction manual

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