CLINICAL TRIAL PROTOCOL INCLUDING AMENDMENTS NOS. 01 TO 04

BNT162-04

Version: 10.0 **Date:** 12 MAY 2021

Sponsor: BioNTech SE

Trial title:	A multi-site, Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of a prophylactic SARS-CoV-2 RNA vaccine (BNT162b3) against COVID-19 using different dosing regimens in healthy adults
Brief title:	A multi-site Phase I/II trial investigating the safety and effects of one BNT162 vaccine against COVID-19 in healthy adults
Trial phase:	Phase I/II
Indication:	Protection against COVID-19
Product:	BNT162b3, SARS-CoV-2 - RNA lipid nanoparticle (RNA-LNP) vaccine utilizing the nucleoside modified messenger RNA (modRNA) format
Coordinating and Principal investigator:	Dr. Dr. med. Armin Schultz, CRS Clinical Research Services Mannheim GmbH, Germany (tel.: +49 621 15045 [redacted])
Contract research organization (CRO):	CRS Clinical Research Services Mannheim GmbH, Germany
Trial sites:	CRO sites in one or more of Berlin, Kiel, and Mannheim (Germany)
Sponsor's medical representative:	Elizabeth Adams, MD, Senior Medical Director, BioNTech US, Inc.
Sponsor:	BioNTech SE, An der Goldgrube 12, 55131 Mainz, Germany
Regulatory identifiers:	EudraCT no.: 2020-003267-26; Universal Trial Number: U1111-1254-4840; Clinicaltrials.gov code: NCT04537949
Medical Monitor:	The name and contact information will be provided separately

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* Denotes BioNTech approved versions.

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

1 PROTOCOL SUMMARY

1.1 Trial synopsis

Trial Summary

BNT162b3 is a liposomally formulated nucleoside modified RNA vaccine candidate that encodes the SARS-CoV-2 spike protein (S protein) including its transmembrane domain. The candidate vaccine was under evaluation for its induction of immune responses in healthy adults for the prevention of COVID-19 disease. BNT162b2 became the lead vaccine candidate to prevent COVID-19 disease and received Conditional Marketing Authorization in the European Union under the name of Comirnaty, [redacted].

Trial number BNT162-04

Trial title

A multi-site, Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of a prophylactic SARS-CoV-2 RNA vaccine (BNT162b3) against COVID-19 using different dosing regimens in healthy adults

Objectives and endpoints

Objectives	Endpoints
Primary objective	
To describe the safety and tolerability profiles of BNT162b3 in healthy adults after prime/boost (P/B) immunization.	• Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7 d after each immunization. • 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. • The proportion of subjects with at least 1 unsolicited treatment emergent adverse event (TEAE) occurring after prime immunization up to boost immunization or 28 d after prime immunization (whichever comes first) and up to 28 d after the boost immunization.
Secondary objectives	
To describe the immune response in healthy adults after 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.	As compared to baseline, at 7 d and 21 d after prime immunization and at 7 d, 14 d, 21 d, 28 d, 63 d, 162 d, and 365 d after the boost immunization: • Functional antibody responses. • Fold increase in functional antibody titers. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers.

Objectives	Endpoints
Exploratory objectives	
[redacted]	[redacted]

Trial design

This trial has two parts, Part A and Part B. [redacted] Part B of the study will no longer be conducted. As of March 12th, 2021, Part A subjects have completed vaccinations and are in follow-up evaluations.

Part A is a dose-finding part, with possible dose escalation cohorts, and discretionary dose de-escalation and refinement cohorts in younger subjects. Cohorts in older subjects are optional and dependent on acceptability of dosing in younger subjects.

The chosen trial design reflects discussion and advice from the PEI obtained in scientific advice meetings for a closely related trial (BNT162-01) held in February, March, and June 2020.

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 treatment phase (screening to Visit 7) and a follow-up phase (Visits 8 to 10).

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

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

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

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

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

For any subsequent dose escalation cohorts, the sentinel/subject staggering process will be as follows:

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

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

For any dose de-escalation or dose-refinement cohorts in younger adults, i.e., cohorts with doses lower than previously tested, 12 subjects will be dosed using a subject staggering

(6-6) process (with intervals of at least 30 min between subjects). The doses in these cohorts 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.

Table 1: Summary of vaccine dose regimens for younger adults aged 18 to 55 years in Part A

Vaccine / mRNA type	Vaccine encoded antigen	Vaccine IM dosing regimen	Part A - Cohort numbers & Dose (µg) (12 subjects per cohort) [a]						
			1 Starting dose	2[c] De-escalation dose	3[c] De-escalation dose	4[c] Maximum dose	5	6	7
BNT162b3 / modRNA	Membrane-anchored RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	1F 10 µg	2F 3 µg	3F 1 µg	4F 60 µg	5F 3 - 50 µg [b]	6F 3 - 50 µg [b]	7F 20 µg

a) All dose escalation decisions and doses used must be judged acceptable by the Safety Review Committee before use.
b) Specific doses to be defined, but in the range given. Already given doses will not be repeated.
c) De-escalation doses are discretionary and need not be administered in numeric order.
IM = Intramuscular; mRNA = messenger RNA; modRNA = nucleoside modified messenger RNA; RBD = receptor binding domain; S protein = SARS-CoV-2 spike protein.

Table 2: Summary of vaccine dose regimens for older adults aged 56 to 85 years in Part A

Vaccine / mRNA type	Vaccine encoded antigen	Vaccine IM dosing regimen	Part A - Cohort numbers & Dose (µg) (12 subjects per cohort) [a]				
			8	9	10	11	12
BNT162b3 / modRNA	Membrane-anchored RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	8F 3 µg [b, d]	9F 10 µg [b, d]	10F 20 µg [b, d]	11F 10 - 60 µg [b, c]	12F 10 - 60 µg [b, c]

a) All dose escalation doses used must be judged acceptable by the Safety Review Committee before use.
b) Specific doses to be defined, but in the range given. Already given doses will not be repeated.
c) A lower prime dose with higher boost dose posology may be used.
d) SRC approved and already initiated cohorts.
IM = intramuscular; mRNA = messenger RNA; modRNA = nucleoside modified messenger RNA; RBD = receptor binding domain; S protein = SARS-CoV-2 spike protein.

Note: The doses planned in this trial reflect emerging clinical data from the ongoing BNT162-01 and BNT162-02 trials with the related vaccine candidates BNT162b1 and BNT162b2 in younger adults (aged between 18 and 55 years) and older adults (adults aged between 56 and 85 years).

For an overview of BNT162b vaccines in ongoing clinical trials, see the current BNT162 IB. See below for a summary and Section 2.1.3 for details.

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 in elderly adults. This tolerability appears to be better than seen in younger adults at the same doses.

Based on the BNT162b1 and BNT162b2 tolerability data summarized above, and the implemented safety measures (sentinel/staggered subject dosing, post-dose observation period, wellbeing questioning, etc.) as described in the section Risk assessment, the planned BNT162b3 doses in older adults in this trial are expected to show acceptable tolerability.

Based on the available immunogenicity and cell-mediated immune response data after dosing with BNT162b1 and BNT162b2 in younger and elderly adults in the BNT162-01 and BNT162-02 trials (see the BNT162 IB), the BNT162b3 doses planned in this trial in older adults are also expected to show measurable responses. These vaccines elicited measurable but lower responses in elderly adults than in younger adults, therefore, this trial includes the option to investigate BNT162b3 doses above the 30 µg BNT162b1/BNT162b2 doses already tested in elderly adults, to support any future Phase III program planned to support marketing approval.

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

Administration of the planned starting dose (3 to 10 µg) 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; including observation on site, short summary of phone interviews [including statement about diary reports], vital signs, investigator reported local and systemic reactions, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome). The dose in Cohort 8 must also be confirmed by the SRC.

For Cohort 8 and any dose escalation cohorts in older adults, 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).

The dose levels for Cohorts 9 to 12 are flexible in Table 2, up to the maximum deemed safe in younger adults, to allow optimal dose selection once BNT162b3 data are available. The same dose level will not be tested twice. Where possible (i.e., given acceptable tolerability), dose levels of up to 30 µg and above will be tested because (based on BNT162b1 and BNT162b2 data) older adults may experience weaker immune responses compared to younger adults. The tolerability at dose levels of up to 30 µg and above is expected to be acceptable because, based on BNT162b1 and BNT162b2 data, the tolerability is expected to be better in older subjects compared to younger adults.

For the unplanned dose de-escalation cohorts, i.e., where the SRC requests the use of a reduced dose for safety reasons, 12 subjects will be dosed using a subject staggering (6-6) process with intervals of at least 30 min between subjects (as for planned de-escalation cohorts).

The on site observation periods for subjects after each BNT162b3 dose are summarized in Section 5.3.

Note: BNT162b3, like BNT162b1 and BNT162b2 as under investigation in the trials BNT162-01, BNT162-02, and BNT162-03, are nucleoside modified RNAs (modRNAs). RNA modification is known to impact the extent of innate immune activation at a given dose level, and thus potentially the extent of reactogenicity (Weissman and Karikó 2015). Therefore, tolerability data obtained with the BNT162b1 and BNT162b2 vaccine variants may be potentially informative for BNT162b3, 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.

Part B

[redacted] Part B will no longer be conducted.

Trial duration

In total, the planned trial duration is expected to be approximately 16 months. From screening visit (Visit 0) to the last visit (Visit 10), each trial subject will be in the trial for maximally 417 days (i.e., from Day -30 to Day 387).

Population

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

Twelve subjects are required for each of the cohorts planned in Part A. Assuming all cohorts planned in Table 1 are performed, 144 subjects will be required.

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 body mass index (BMI) over 19 kg/m^2 and under 30 kg/m^2 (i.e., be neither underweight nor obese), and weigh at least 50 kg at Visit 0.
  OR
  For older adult cohorts, volunteers must be aged 56 to 85 years, have a BMI over 19 kg/m^2 and under 30 kg/m^2 (i.e., be neither underweight nor obese), 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 electrocardiogram (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.
- Women of childbearing potential (WOCBP) must have a negative beta-human chorionic gonadotropin urine test at Visit 0 and Visit 1. Women that are post-menopausal 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 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.
- 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, 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 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.
- 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 of any of human immunodeficiency virus (HIV) 1 or 2, Hepatitis B, or Hepatitis C, 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.
- 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, persons in detention, CRO or sponsor staff or their family members.
- Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors:
  - Cancer
  - COPD (chronic obstructive pulmonary disease)
  - Immunocompromised state (weakened immune system) from solid organ transplant
  - Obesity (BMI of 30 or higher)
  - Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
  - Sickle cell disease
  - Diabetes mellitus
  - Hypertension
  - Asthma
  - Chronic liver disease
  - Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
  - Anticipating the need for immunosuppressive treatment within the next 6 months
  - 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 vaccine)

Name:	BNT162 vaccine - Anti-viral RNA vaccine for active immunization against COVID-19.
Type:	RNA-LNP vaccine utilizing the BioNTech modRNA format: product code BNT162b3.
Dosage levels:	See Table 1. The planned dose per vaccine candidate will not exceed the pre-defined maximum dose (see Table 1).
Dosage frequency:	Two injections 21 d apart. Injection volumes will be up to 1.5 mL.
Administration route:	Intramuscular (IM); upper arm, musculus deltoideus. 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 Visit 10. No formal interim statistical analysis will be performed. However, the preliminary 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.

Committees

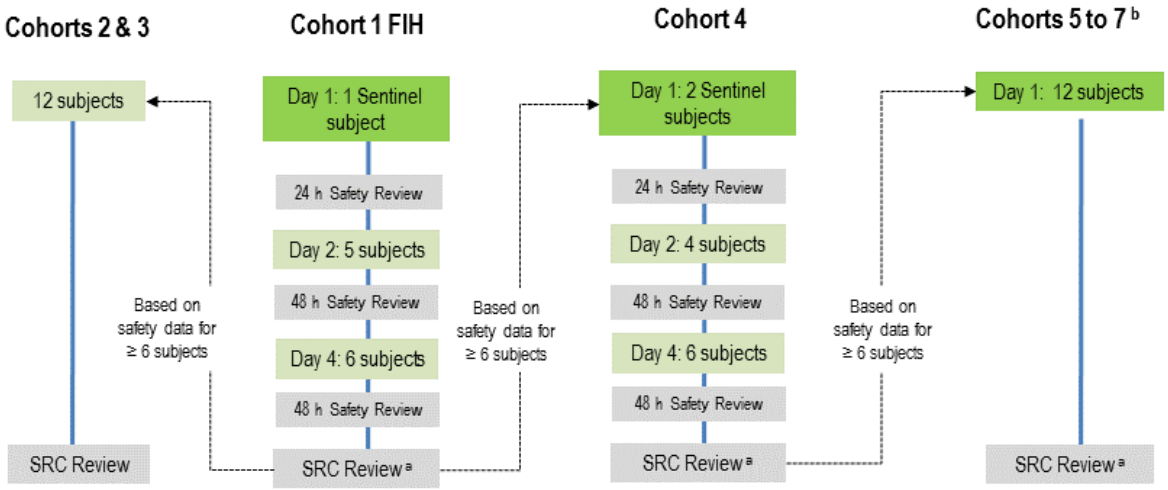
A Safety Review Committee is planned.

1.2 Schema (graphical representation of the trial)

For a graphical depiction of the dose-ranging process in Part A, see Figure 1.

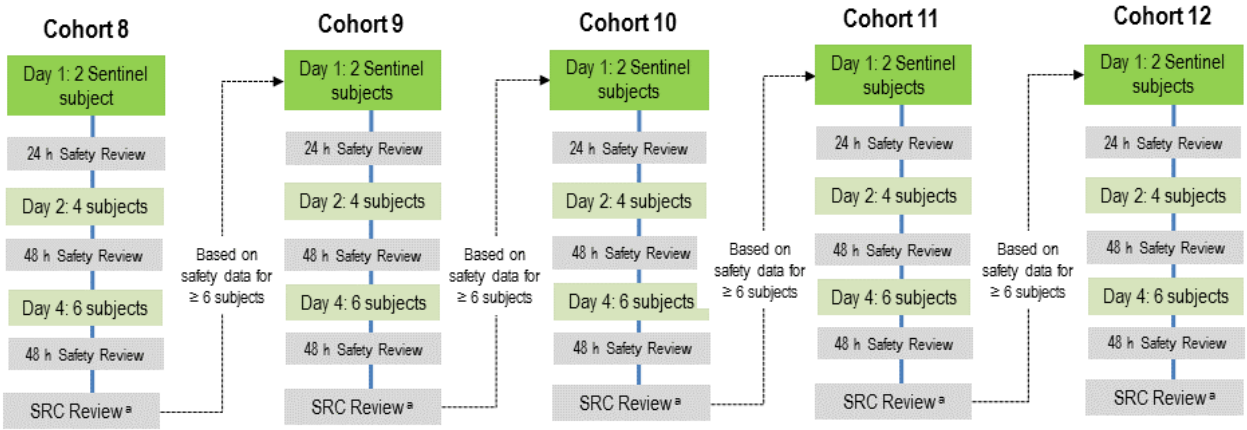
Dose cohort schema for BNT162b3 (P/B) [c]

Cohorts with younger adults



The above schema depicts one sequence of cohorts. Cohorts 5 to 7 include doses lower than Cohort 4 (which uses the maximum planned dose in this trial), and thus the sponsor may decide to perform one or more of Cohorts 5 to 7 before proceeding to Cohort 4.

Cohorts with older adults [d]



a) The data assessed by the SRC for progressing comprises 48 h data for 6 subjects.
b) Cohorts 5 to 7 are planned for dose-refinement. If they use doses lower than already tested, a staggered (6-6) subject dosing process will be used and the cohorts may be conducted in parallel to each other and 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.
c) For the dose regimens, see Table 1 and Table 2.
d) Cohorts 8 to 12 are planned in older adults. For Cohort 8 and any dose escalation cohorts in older adults, 12 subjects will be dosed using a sentinel dosing/subject staggering (2-4-6) process.

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 3: Schedule of trial procedures and assessments – BNT162b3

Procedure / Assessment	Visit 0	Visit 1 Pre-dose	Visit 1 Dosing & Post-dose	Visit 2 at 24±2 h	Phone call at 48±2 h	Visit 3	Visit 4 Pre-dose	Visit 4 Dosing & Post-dose	Phone call at 48±2 h	Visit 5 ~7 d from Visit 4	Visit 5a ~14 d from Visit 4	Visit 6 ~21 d from Visit 4	Visit 7 ~28 d from Visit 4 (EoT Visit)	Visit 8 ~63 d from Visit 4 (FU Visit)	Visit 9 ~162 d from Visit 4 (FU Visit)	Visit 10 ~365 d from Visit 4 (FU Visit)
Day [h]	**-30 to 0**	**1**	**1**	**2**		**8**	**22**	**22**		**29**	**36**	**43**	**50**	**85**	**184**	**387**
Informed consent	X															
Inclusion/ exclusion criteria	X	X (review)														
Medical history	X	X (update)														
Physical examination incl. height	X	X [a]		X [a]		X [a]	X [a]			X [a]		X [a]	X [a]			
Vital signs, body weight [c]	X	X	X [b]	X		X	X	X [b]		X		X	X	X	X	
12-lead ECG	X	X														
Urine pregnancy test for WOCBP	X	X					X									
Urine drugs of abuse screen [d]	X	X														
Alcohol breath test	X	X														
Urine collection for clinical laboratory [e]	X	X		X		X				X			X			

Procedure / Assessment	Visit 0	Visit 1 Pre-dose	Visit 1 Dosing & Post-dose	Visit 2 at 24±2 h	Phone call at 48±2 h	Visit 3	Visit 4 Pre-dose	Visit 4 Dosing & Post-dose	Phone call at 48±2 h	Visit 5 ~7 d from Visit 4	Visit 5a ~14 d from Visit 4	Visit 6 ~21 d from Visit 4	Visit 7 ~28 d from Visit 4 (EoT Visit)	Visit 8 ~63 d from Visit 4 (FU Visit)	Visit 9 ~162 d from Visit 4 (FU Visit)	Visit 10 ~365 d from Visit 4 (FU Visit)
Day [h]	**-30 to 0**	**1**	**1**	**2**		**8**	**22**	**22**		**29**	**36**	**43**	**50**	**85**	**184**	**387**
Blood draw for clinical lab. [f]	X (15 mL)	X (15 mL)		X (15 mL)		X (15 mL)				X (15 mL)			X (15 mL)			
Blood draw for viral screening (5 mL) [g]	X															
Blood draw for SARS-CoV-2 testing (2.6 mL) [k]	X															
Oral swipe for SARS-CoV-2 testing		X [m]														
Allocation to IMP		X														
Immunization [l]			X					X								
Blood draw for immunogenicity (10 mL) [n]		X				X	X			X	X	X	X	X	X	X
Blood draw for HLA [p]				X (4 mL EDTA-blood) [p]												
Blood draw for CMI (100 mL) [n, o]		X								X						
Blood draw for research [n]												X (≤100 mL)		X (≤50 mL)	X (≤50 mL)	
Subject hotline availability	Start	=>	=>	=>		=>	=>	=>		=>		=>	=>	=>	End	
Issue subject diaries		X		X		X	X			X		X	X			

Procedure / Assessment	Visit 0	Visit 1 Pre-dose	Visit 1 Dosing & Post-dose	Visit 2 at 24±2 h	Phone call at 48±2 h	Visit 3	Visit 4 Pre-dose	Visit 4 Dosing & Post-dose	Phone call at 48±2 h	Visit 5 ~7 d from Visit 4	Visit 5a ~14 d from Visit 4	Visit 6 ~21 d from Visit 4	Visit 7 ~28 d from Visit 4 (EoT Visit)	Visit 8 ~63 d from Visit 4 (FU Visit)	Visit 9 ~162 d from Visit 4 (FU Visit)	Visit 10 ~365 d from Visit 4 (FU Visit)
Day [h]	-30 to 0	1	1	2		8	22	22		29	36	43	50	85	184	387
Collect subject diaries				X	X [i]	X	X			X		X	X	X		
Record AEs since last visit		X		X		X	X			X	X	X	X	X [j]	X [j]	X [j]
Local reaction assessment/ systemic events			X [b]	X		X	X	X [b]		X		X	X			
Concomitant medication [g]	X	X		X		X	X			X		X	X	X	X	X
Subject wel being questioning					X [i]				X [i]							

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

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

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

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

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

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

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 5a 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±9 d; Visit 10 Day 387±14 d.

i) Only for the first 6 subjects per group. Questioning on and documentation of adverse events (AEs) as well as systemic and local reactions, the latter in case of upcoming dose decision meetings.
j) Only IMP-related AEs and any SAEs except proven COVID-19 cases which have to be reported regardless on severity and relatedness to the trial drug until the last scheduled FU Visit as described into the Section 10.3.1.9.
k) Blood draw for anti-SARS-CoV-2 antibodies.
l) For Cohorts 1 and 8, prime 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 30 min intervals between subjects. Boost immunization with at least 15 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.
q) Record any medications that trial subjects receive during the trial in the CRF starting after Visit 0 and until the respective EoT Visit; record any vaccination, including SARS-CoV-2 vaccination that subjects receive, after the EoT Visit until the last FU Visit in the CRF.

Note: If the boost dose is not administered, subjects should still complete all assessments planned in the SoA.

Abbreviations: AE = adverse event; CMI = cell-mediated immune testing; CRF = case report form; 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; min = minute(s); Day 0 = one day before Day 1; IMP = investigational medicinal product; min = minute(s); SARS-CoV-2 = the virus leading to COVID-19; WOCBP = women of childbearing potential.

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TRIAL-SPECIFIC ABBREVIATIONS/TERMS

Abbreviation/Term	Explanation
Allocated subject	Enrolled subjects who are allocated to IMP
BNT162a	BNT162 RNA-LNP vaccine utilizing uRNA
BNT162b	BNT162 RNA-LNP vaccine utilizing nucleoside modified mRNA (the variant BNT162b3 will be tested in this trial)
BNT162c	BNT162 RNA-LNP vaccine utilizing self-amplifying mRNA
CMI	Cell-Mediated Immunity
Cohort	In this document, the word cohort refers to groups of subjects receiving the same vaccine dose and belonging to the same age group (younger adults or older adult)
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
Elderly	Adults aged 65 to 85 years
ELISA	Enzyme-Linked Immunosorbent Assay
ELISpot	Enzyme-Linked Immunosorbent Spot
Enrolled subjects	Subjects who signed an informed consent form, i.e., who gave informed consent
HLA	Human leukocyte antigen
IM	Intramuscular(ly)
IV	Intravenous(ly)
modRNA	Nucleoside modified mRNA
mRNA	Messenger RNA
Older adults	Adults aged 56 to 85 years
P/B	Prime/Boost: a dosing regimen, comprising a priming immunization and a boost immunization
PBMC	Peripheral blood mononuclear cell
PEI	(German) Paul-Ehrlich-Institut
RNA-LNP	RNA lipid nanoparticle
RNA-LPX	RNA lipoplex
saRNA	Self-amplifying mRNA
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	The virus leading to COVID-19
uRNA	Non-modified uridine containing mRNA
VNT	Virus neutralization test
Younger adults	Adults aged 18 to 55 years

For standard abbreviations, see Section 10.9.

2 INTRODUCTION

2.1 Background

2.1.1 Overview of the disease

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

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

The WHO Situation Update Report dated June 30th, 2020 noted 9,843,073 confirmed cases with 495,760 deaths globally and 2,656,437 confirmed cases with 196,541 deaths in Europe (WHO Situation Report Nr. 160).There are at least three SARS-CoV-2 vaccines for preventing COVID-19 disease that have received either Conditional Marketing Authorization in Europe or Emergency Use Authorization in the United States.

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 there is pre-existing clinical safety data available (see the BNT162 investigator's brochure [IB] and Section 2.1.3).

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 summary of the available clinical data for the three RNA platforms is given in Section 2.1.3.

2.1.3 Ongoing and planned clinical trials with BNT162 vaccine variants

Multiple SARS-CoV-2 RNA vaccine platforms (BNT162) have undergone evaluation since the advent of the SARS-CoV-2 pandemic. BNT162b3, like BNT162b2, the SARS-CoV-2 vaccine (Comirnaty) that received Conditional Marketing Authorization at the end of 2020, is a modRNA. RNA modifications are known to impact the extent of innate immune activation at a given dose level, and thus potentially the extent of reactogenicity (Weissman and Karikó 2015). Therefore, tolerability data obtained with the BNT162b1 and BNT162b2 vaccine variants was evaluated in the context of the data on BNT162b3 and taken into consideration by the SRC for recommendations of lower or interim doses.

BNT162 vaccine candidates based on the uRNA, modRNA, and saRNA formats are currently under investigation in clinical trials.

For the design, status, number of trial subjects dosed at least once with a BNT162 vaccine candidate, and summary of the available results of the ongoing clinical trials, see the current BNT162 IB.

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 (for more details, see Section 2.1.1).

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 will investigate the potential safety and immunogenicity of a prophylactic BNT162 vaccine against SARS-CoV-2, the candidate BNT162b3.

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 (up to approximately 602 mL blood will be drawn per subject over the complete trial, i.e., over approximately 16 months).
- All trial-specific procedures will be performed by qualified trial site personnel.
- Immunization will be done by a physician.
- BNT162b3 has 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. Also, BNT162b3, like the BNT162b variants BNT162b1 and BNT162b2 that are under investigation in the trials BNT162-01, BNT162-02, and BNT162-03, are modRNAs. RNA modification is known to impact the extent of innate immune activation at a given dose level, and thus potentially the extent of reactogenicity (Weissman and Karikó 2015). Therefore, tolerability data obtained with the BNT162b1 and BNT162b2 vaccine variants may be potentially informative for BNT162b3.

Based on such data, the risks linked to the immunization with the BNT162b 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 reactions or a neurological side effect, 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 severe systemic reactions is considered low.
- An IM vaccine based on modRNA encapsulated into a related but not identical vaccination has reported mostly mild to moderate, mostly local solicited AEs (mostly

injection site pain) of 1-3 d duration that resolved without intervention. Fever was the only systemic solicited AE (Feldman et al. 2019).

- As with other vaccines, and with single stranded RNA being an innate immune sensor-agonist, BNT162 vaccine administration may cause temporary headache, fatigue, or loss of appetite. Rarely, with certain prophylactic vaccines (e.g., as seen for vaccines using attenuated viruses) severe allergic reactions or a neurological side effect, such as seizures, were seen. Although these rare side effects are a concern, the risk of a vaccine causing serious harm or death is considered to be extremely small, in particular for BNT162 vaccines, which are molecularly defined, highly purified, subunit vaccines.

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

- Based on the available clinical and non-clinical data on the individual components (RNA, the specific LNP formulation), that are combined within the BNT162b 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 most of the AEs reported after immunization with BNT162 vaccine candidates, including BNT162b vaccine candidates (BNT162b1, BNT162b2, and BNT162b3), were mild to moderate in intensity.

- Generally, good tolerability was observed. Overall, many of the reported AEs appear to be similar to reactogenicity events anticipated for intramuscularly (IM)-administered vaccines, typically with an onset within first 24 h post-immunization. All AEs / reactogenicity symptoms resolved spontaneously, mostly within 24 h of onset, and were managed with simple measures (e.g., paracetamol). There were no serious adverse events (SAEs) and no unexpected toxicities. Fever of severe intensity has been reported. Most AEs were managed with simple measures and resolved spontaneously. Please refer to the current BNT162 IB.
- 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 BNT162b3 will be defined in this trial and supported by data for other BNT162 vaccine candidates, including BNT162b vaccine candidates, from the ongoing trials (BNT162-01 and BNT162-02).
- When assessing the risk for dosing of older subjects with BNT162b3 in this trial, the follow information is relevant:
  - Preliminary data in younger and elderly adults treated in the ongoing BNT162 trials, backed by non-human primate (rhesus macaque) immunogenicity data, BNT162b1, and non-human primate data for BNT162b3, show immunogenicity in the tested dose ranges.
  - After administration of the prime dose of BNT162b1 and BNT162b2 in (each) 36 healthy elderly adults in the trial BNT162-02, the local tolerability of

BNT162b1 in elderly adults seemed comparable to that recorded in younger adults. 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.

  - Based on the available immunogenicity and cell-mediated immune response data after dosing with BNT162b1 and BNT162b2 in younger and elderly adults in the BNT162-01 and BNT162-02 trials (see the BNT162 IB), the BNT162b3 doses planned in this trial in older adults are also expected to show measurable responses. These vaccines elicited measurable but lower responses in elderly adults than in younger adults, therefore, this trial includes the option to investigate BNT162b3 doses above the 30 µg BNT162b1/BNT162b2 doses already tested in elderly adults, to support any future Phase III program planned to support marketing approval (for details, see the BNT162 IB). This observation may indicate a lower innate immune activation capability of elderly, which in turn may mechanistically be associated with lower immunogenicity at dose levels that are immunogenic in the younger adults.
  - In this trial, the doses to be tested in older adults will only be tested if they have shown acceptable tolerability in younger adults.
  - The planned starting dose with BNT162b3 for older subjects aged 56 to 85 yrs in this trial will be ≤30% of a dose already shown to be acceptable in the subjects aged 18 to 55 years in this trial.
  - This trial includes age-appropriate inclusion/exclusion criteria to exclude potential risk factors relevant for all adults, but additional criteria have been included to further protect the safety of enrolled older adults.

- The listed risks can be managed using routine symptom driven standard of care as described in Section 6.6.3. Treatment of these events is dependent on the discretion of the investigators.
- Since this trial will involve the first immunization of humans with BNT162b3 vaccine, albeit not for the BNT162b vaccines, the trial subjects in Cohort 1 and other cohorts testing dose escalations, 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”).

To further ensure trial subject safety, 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 two 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. Experience in the ongoing trials BNT162-01 and BNT162-02 has confirmed the adequacy of the implemented observations periods.

- 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 two Moderna trials investigating mRNA vaccines against avian H10N8 and H7N9 influenza viruses in healthy adults (Feldman et al. 2019) that used on site visits on Day 8.
- Subject wellbeing questioning by telephone at 48±2 h after each immunization (where applicable, after both the prime and boost immunizations) will be performed for the first 6 subjects per cohort. Additional subject wellbeing calls may be included at the discretion of the SRC.
- In the case that an individual experiences dose limiting toxicities or that the frequency or pattern of AEs within a sub-cohort gives cause for concern, the investigator may request an ad hoc review by the SRC before further doses of a given vaccine construct are administered.
- If the investigator considers necessary, the planned observation periods before proceeding to dose further subjects in the same group may be prolonged by 24 h.
- The SRC must assess the safety and tolerability data of the first 6 subjects before allowing progression to the next cohort, 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.

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.

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 immunocompromised populations.

By participating in this trial, the trial subjects will support the development of a prophylactic vaccine 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
Primary objective	
To describe the safety and tolerability profiles of BNT162b3 in healthy adults after prime/boost (P/B) immunization.	• Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7 d after each immunization. • 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. • The proportion of subjects with at least 1 unsolicited TEAE occurring after prime immunization up to boost immunization or 28 d after prime immunization (whichever comes first) and up to 28 d after the boost immunization.
Secondary objectives	
To describe the immune response in healthy adults after P/B immunization measured by a functional antibody titer, e.g., VNT or an equivalent assay available by the time of trial conduct.	As compared to baseline, at 7 d and 21 d after prime immunization and at 7 d, 14 d, 21 d, 28 d, 63 d, 162 d, and 365 d after the boost immunization: • Functional antibody responses. • Fold increase in functional antibody titers. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers.
Exploratory objectives	
[redacted]	[redacted]

4 TRIAL DESIGN

4.1 Overall design

This trial has two parts, Part A and Part B. [redacted] Part B of the study will no longer be conducted. As of March 12th, 2021, Part A subjects have completed vaccinations and are in follow-up evaluations.

Part A is a dose-finding part, with possible dose escalation cohorts, and discretionary dose de-escalation and refinement cohorts in younger subjects. Cohorts in older subjects are optional and dependent on acceptability of dosing in younger subjects.

The chosen trial design reflects discussion and advice from the PEI obtained in scientific advice meetings for a closely related trial (BNT162-01) held in February, March, and June 2020.

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 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 treatment phase (screening to Visit 7) and a follow-up phase (Visits 8 to 10).

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 SRC, as required.

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

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

- If approved by the SRC, the next planned escalation dose (see Table 1) in Cohort 2 may 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.
- Once dose escalation is approved, the planned dose de-escalations may also be initiated.

For any subsequent dose escalation cohorts, the sentinel/subject staggering process will be as follows:

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

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

For any dose de-escalation or dose-refinement cohorts in younger adults, i.e., cohorts with doses lower than previously tested. 12 subjects will be dosed using a subject staggering (6-6) process (with intervals of at least 30 min between subjects). The doses in these cohorts 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.

Administration of the planned starting dose (3 to 10 µg) 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; including observation on site, short summary of phone interviews [including statement about diary reports], vital signs, investigator reported local and systemic reactions, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome). The dose in Cohort 8 must also be confirmed by the SRC.

For Cohort 8 and any dose escalation cohorts in older adults, 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).

The dose levels for Cohorts 9 to 12 are flexible in Table 2, up to the maximum deemed safe in younger adults, to allow optimal dose selection once BNT162b3 data are available. The same dose level will not be tested twice. Where possible (i.e., given acceptable tolerability), dose levels of up to 30 µg and above will be tested because (based on BNT162b1 and BNT162b2 data) older adults may experience weaker immune responses compared to younger adults. The tolerability at dose levels of up to 30 µg and above is expected to be acceptable because, based on BNT162b1 and BNT162b2 data, the tolerability is expected to be better in older subjects compared to younger adults.

For the unplanned dose de-escalation cohorts, i.e., where the SRC requests the use of a reduced dose for safety reasons, 12 subjects will be dosed using a subject staggering (6-6) process with intervals of at least 30 min between subjects (as for planned de-escalation cohorts).

The on site observation periods for subjects after each BNT162b3 dose are summarized in Section 5.3.

Note: BNT162b3, like BNT162b1 and BNT162b2 as under investigation in the trials BNT162-01, BNT162-02, and BNT162-03, are modRNAs. RNA modification is known to impact the extent of innate immune activation at a given dose level, and thus potentially the extent of reactogenicity (Weissman and Karikó 2015). Therefore, tolerability data obtained with the BNT162b1 and BNT162b2 vaccine variants may be potentially informative for BNT162b3, 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.

Part B

[redacted] Part B will no longer be conducted.

4.1.1 Adaptive trial design elements

Dose de-escalation and escalation rules are defined in Section 6.6.2.

4.1.2 Planned number of trial subjects

In Part A

Twelve subjects are required for each of the cohorts planned in Part A. Assuming all cohorts planned in Table 1 are performed, 144 subjects will be required.

4.2 Scientific rationale for the trial design

The trial design is based on the sponsor's experience with trials of this type, including the ongoing trials BNT162-01 and BNT162-02, and other published trials for vaccine development.

The chosen trial design reflects discussion and advice from the PEI obtained in scientific advice meetings held in February, March, and June 2020 for the related BNT162-01 trial. At these meetings, the PEI supported the high-level design of this trial, specifically the staggered approach, 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, 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").

Part B of the trial will no longer be conducted [redacted]

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 plans a starting dose of 10 µg in this trial based on non-clinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens) and the ongoing trials BNT162-01 and BNT162-02, which test other RNAs with the same chemistry (BNT162b1 and BNT162b2).

The BNT162b3 vaccine 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).

As summarized in Section 2.1.3 (for details, see the BNT162 IB), and discussed in Section 2.3.1, there is currently 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 2.1.3 (for details, see the BNT162 IB), most of the AEs reported after immunization with BNT162 vaccine candidates in the ongoing BNT162-01 and BNT162-02 trials were been mild to moderate in intensity and no SAEs were reported.

Fever of severe intensity was reported. Most AEs were managed with simple measures and resolved spontaneously.

The doses planned in this trial reflect emerging clinical data from the ongoing BNT162-01 and BNT162-02 trials with the related vaccine candidates BNT162b1 and BNT162b2 in younger adults (aged between 18 and 55 years) and elderly (adults aged between 65 and 85 years).

For the status and number of trial subjects dosed at least once with a BNT162b vaccine candidate in ongoing clinical trials, see the current BNT162 IB.

See below for a summary and Section 2.1.3 for details.

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 in elderly adults. This tolerability appears to be better than seen in younger adults at the same doses.

Based on the BNT162b1 and BNT162b2 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 BNT162b3 doses in older adults in this trial are expected to show acceptable tolerability.

Based on the available immunogenicity and CMI response data after dosing with BNT162b1 and BNT162b2 in younger and elderly adults in the BNT162-01 and BNT162-02 trials (see the BNT162 IB), the BNT162b3 doses planned in this trial in older adults are also expected to show measurable responses. The sponsor will continue to evaluate these emerging data from these ongoing studies to inform progression to discretionary dose levels. These vaccines elicited measurable but lower responses in elderly adults than in younger adults, therefore, this trial includes the option to investigate BNT162b3 doses above the 30 µg BNT162b1 / BNT162b2 doses already tested in elderly adults, to support any future Phase III program planned to support marketing approval.

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

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

The planned starting dose with BNT162b3 for older subjects aged 56 to 85 years in this trial will be ≤30% of a dose already shown to be acceptable in the subjects aged 18 to 55 years in this trial. Selection of a lower dose for the first dosing in older adults than found to be acceptable in younger adults reflects is considered good practice when progressing to new populations. The chosen cut-off, ≤30%, is a reflection of the 3-fold safety margin often used by the sponsor, but is otherwise arbitrary.

Taken together, the planned starting dose in this trial with healthy subjects is considered to be safe, but still sufficient to induce an anti-viral 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 End of Treatment is defined as the date the last subject completed the EoT Visit (Visit 7). When entering the follow-up phase, i.e., after completing the EoT Visit, subjects are allowed to participate in other clinical trials.

The end of trial is defined as the date when the last subject completed Visit 10 (Last Subject Last Visit).

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 adult cohorts, volunteers must be aged 18 to 55 years, have a BMI over 19 kg/m^2 and under 30 kg/m^2 (i.e., be neither underweight nor obese), and weigh at least 50 kg at Visit 0.
5. OR
6. For older adult cohorts, volunteers must be aged 56 to 85 years, have a BMI over 19 kg/m^2 and under 30 kg/m^2 (i.e., be neither underweight nor obese), and weigh at least 50 kg at Visit 0.
7. 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.
8. 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.
9. Women of childbearing potential (WOCBP) must have a negative beta-human chorionic gonadotropin urine test at Visit 0 and Visit 1. Women that are post-menopausal or permanently sterilized will be considered as not having reproductive potential.
10. 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).
11. WOCBP must confirm that they practiced at least one highly effective form of contraception for the 14 d prior to Visit 0.
12. 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.

13. 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.
14. Men must be willing to refrain from sperm donation, starting after Visit 0 and continuously until 60 d after receiving the last immunization.
15. They must have confirmation of their health insurance coverage prior to Visit 0.
16. 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.
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, 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 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 IMP 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 of any of HIV 1 or 2, Hepatitis B, or Hepatitis C, 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.
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. 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, persons in detention, CRO or sponsor staff or their family members.
28. Regular receipt of inhaled/nebulized corticosteroids.
29. Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors:
    - Cancer
    - COPD (chronic obstructive pulmonary disease)
    - Immunocompromised state (weakened immune system) from solid organ transplant
    - Obesity (BMI of 30 or higher)
    - Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
    - Sickle cell disease
    - Diabetes mellitus

- Hypertension
- Asthma
- Chronic liver disease
- Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
- Anticipating the need for immunosuppressive treatment within the next 6 months
- 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.

For Cohorts 1 and any subsequent dose escalation cohorts (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 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 (irrespective of whether dose escalation, dose de-escalation, or dose-refinement cohorts), all trial subjects will be required to remain at the site for approximately 6 h after the boost immunization.

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

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.

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 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

Name:	BNT162b3 vaccine - Anti-viral RNA vaccine for active immunization against COVID-19.
Type:	RNA-LNP vaccine utilizing the BioNTech modRNA format: product code BNT162b3.
Dosage levels:	See Table 1. The planned dose per vaccine candidate will not exceed the pre-defined maximum dose (see Table 1).
Dosage frequency:	Two injections 21 d apart. Injection volumes will be up to 1.5 mL.
Administration route:	Intramuscular (IM); upper arm, musculus deltoideus. 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 were 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 Visit 7, must be recorded along with the:

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

Record any vaccination, including SARS-CoV-2 vaccination, received after the EoT Visit until the last FU Visit (Visit 10) in the CRF.

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 16).

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, will be made based on emerging data from this and other ongoing studies with related vaccine constructs. Dose escalation decisions will be validated by the SRC (for details, see Section 10.1.5); any plan to exceed the planned dose escalations will only be implemented after relevant approval of

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

6.6.1 Dose limiting toxicity

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

- Anaphylactic reaction considered related.
- Generalized urticaria considered related.
- 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 days 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 days of vaccination that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.
- Any fever >40.0°C (>104.0°F) within 7 days of vaccination considered related and confirmed by an investigator or medically qualified person.
- Two trial subjects (at any dose level) with the same or similar severe (Grade 3 or higher) AE or reactogenicity (including clinically significant laboratory abnormalities) within 7 days 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).

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 days of vaccination) will be used for the overall assessment of the candidate

vaccine safety profile, i.e., to assess whether any of the observed side effects are possibly linked to vaccination.

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

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 are made for Part A.

- Any proposal to alter a planned escalation dose, or test a lower dose required for safety de-escalation must be approved by the SRC.
- Any plan to exceed the planned maximum dose will only be implemented after relevant approval of a substantial protocol amendment.

Dose escalation:

- Dose escalation will only continue if the previous dose was considered safe and well tolerated by the SRC.
- Any proposed alteration to the planned escalation dose level to a smaller or larger escalation increment than that shown in Table 1 must be approved by the SRC.
- Any proposal to exceed the planned maximum dose for the trial will only be implemented after relevant approval of a substantial amendment.

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 to 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 until the SRC recommendation to continue or to permanently stop IMP administration of new subjects in the respective dose level cohort.

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.

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.

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 should still complete all assessments planned in the SoA (Section 1.3).

7.1.1 Temporary discontinuation

Not applicable.

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 (Visit 7), if discontinued on a visit day.
- Complete all assessments planned for the EoT Visit (Visit 7), 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.

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 AEs between visits, solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling), and solicited systemic reactions (nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever [i.e., ≥38°C]).

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

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

8.2.9 Assessment of local reactions

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

Local reactions (via daily solicited reports in the subject diaries and as assessed on visit days by the investigator) will be graded based on the guidance given in the 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). The reporting of local reactions will be based on the subject's assessments only.

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

All AEs and SAEs will be collected from the date of subject consent until Visit 7; after Visit 7 (at Visits 8 and 9), only IMP-related AEs and 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 between Visit 9 and Visit 10 and 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 Visit 9, 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, IECs, and investigators. The execution of expedited reporting to the different entities may be delegated as detailed in the trial Safety Management Plan.

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

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

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

8.3.5 Pregnancy

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

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

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

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

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

8.3.6 Death events

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

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

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

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

8.3.8 Adverse events of special interest

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

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

[redacted]

8.8 Biomarkers

Blood draws for explorative biomarker/immunogenicity research purposes will be taken at the times listed in the SoA (Section 1.3).

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.

[redacted]

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 will be assessed at the times listed in the SoA (Section 1.3) using:

1. A functional antibody titer, e.g., VNT or an equivalent assay.
   - Seronegative is defined as titers below the starting dilution (i.e., below the LOD [limit of detection] of the assay).
   - Seroconversion after immunization is defined as a 4-fold increase in titer.
     - for seronegative pre-immunization sera: a titer ≥4-times the LOD.
     - for seropositive pre-immunization sera: a titer which is 4-fold higher than the measured pre-immunization titer.
2. An antibody binding assay, e.g., ELISA or an equivalent assay.
   - Seroconversion after immunization is defined as a 4-fold increase in titer/antibody concentration.
3. [redacted]

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

Up to approximately 602 mL blood will be drawn per subject over the complete trial, i.e., over approximately 16 months.

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

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 were performed.

For Part A, the inclusion of 12 subjects per group is considered to be adequate for a safety assessment of 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%.

9.3 Analysis sets

The following analyses sets are defined:

Analysis set	Description
Screened Set	All subjects who signed informed consent.
Safety Set	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.

Solicited local and systemic reactions (from the diary card) will be summarized using the Safety Set. In general, solicited reactions will be analyzed by dose level and for each immunization, i.e.:

- For the prime immunization up to 7 d after prime immunization
- For the boost immunization up to 7 d after boost immunization

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

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

Treatment emergent AEs (TEAEs) are defined in Section 10.3.1 and will be summarized using the Safety Set. In general, AEs will be analyzed by dose level and for each immunization, i.e.:

- For the prime immunization up to 28 d after prime immunization or until boost immunization (whichever comes first)
- For the boost immunization up to 28 d after boost immunization
- For the prime immunization up to 28 d after boost immunization

Additionally, AEs will be summarized for all dose levels combined for each type. Additional AE analyses may be described in the SAP.

For each analysis, the number and percentage of subjects reporting at least one TEAE 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.

The analysis of AEs and local and systemic reactions may be repeated with a reduced set of terms, to enable like-for-like evaluations when these data are informally set alongside the data from other trials in the clinical development program for BNT162 vaccines.

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 time point 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 the EoT Visit (Visit 7). An analysis update will be performed once all subjects will have completed Visit 10. No formal interim statistical analysis will be performed. However, the preliminary 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

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, ethical, and trial oversight considerations

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

10.1.1 Regulatory and ethical considerations

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

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

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

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

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

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

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

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

10.1.2 Financial disclosure

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

10.1.3 Informed consent process

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

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

Trial subjects must be informed that their participation is voluntary.

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

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

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

Informed consent will be obtained for the use of residual biosamples collected for further explorative investigations of the immune response in healthy adults after 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 comprise 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, 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 noncompliance 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 30 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, memorandums, 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 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 Trial Master File (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.

FSH: Only in women who are not of childbearing potential.

Urinalysis

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

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

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

10.3.1 Definition of AE and TEAE

- An AE is any untoward medical occurrence in a 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 measurements), including those that worsen from baseline, and which are considered clinically significant in the medical and scientific judgment of the investigator, may be considered as AEs.

- Reactogenicity need only be reported as an AE if doing so provides clinically significant information not available elsewhere (such as the solicited reactions listings), e.g., severe reactogenicity lasting longer than the period of solicitation of symptoms in the subject diary. Diagnostic AEs for local and/or systemic reactogenicity, e.g., “injection site reaction” or “flu-like illness”, should generally be preferred over AEs reporting of individual signs and symptoms.
- New conditions or (at the discretion of the investigator) any worsening of a pre-existing condition detected or diagnosed after Visit 0.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE.

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

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

10.3.1.3 Suspected adverse reaction

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 reaction (SUSAR)

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 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 as defined in Section 8.3.1. 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 10.3.1.11 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

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

Any case of proven COVID-19 disease occurring until the last planned FU Visit should be reported as an SAE/AE. AEs which are rated as “moderate” or “severe” (according to the criteria provided in Section 10.3.1.7) will need to be reported as an SAE. 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. All mild cases of proven COVID-19 cases which do not correspond to seriousness criteria will need to be reported as an AE in the CRF.

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 [redacted]
- Safety Report Email Address: [redacted]

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: Email: pharmacovigilance@biontech.de.

For medical questions, the sponsor's Medical Monitor for this trial should be contacted.

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 subject 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 4. 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 4.

Table 4: Local reaction grading scale

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

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

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

Systemic reactions (signs and symptoms)

Symptoms of vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain will be assessed by the participant as absent, mild, moderate, severe, or potentially life-threatening, according to the grading scale in Table 5.

Table 5: Systemic reaction grading scale

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

Fever

Fever is defined as an oral temperature of ≥38.0°C. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 6.

Table 6: Fever grading scale

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

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

Laboratory abnormalities

Laboratory abnormalities will be graded according to the grading scheme given in Table 7.

Table 7: Laboratory abnormality grading scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
Hematology				
Hemoglobin (female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (female) change from baseline value - g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
Hemoglobin (male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hemoglobin (male) change from baseline value - g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1,500	1,501 – 5,000	>5,000	Hypereosinophilic

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
Chemistry				
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 phosphatase - increase by factor	1.1 – 2.0x ULN	2.1 – 3.0x ULN	3.1 – 10x ULN	>10x ULN
Liver function tests – ALT, AST - increase by factor	1.1 – 2.5x ULN	2.6 – 5.0x ULN	5.1 – 10x ULN	>10x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25x ULN	1.26 – 1.5x ULN	1.51 – 1.75x ULN	>1.75x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5x ULN	1.6 – 2.0x ULN	2.0 – 3.0x ULN	>3.0x 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 post-menopausal 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.

Post-menopausal female

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

A high FSH level in the post-menopausal range may be used to confirm a post-menopausal 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 post-menopausal status before trial enrollment.

10.4.2 Contraception guidance

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

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

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

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

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

- Intrauterine device. [a]
- Intrauterine hormone-releasing system. [a]
- Combined estrogen and progestogen-based contraception: established use of oral, intravaginal, or transdermal hormonal methods of contraception.

- Progesterone-based contraception: established use of oral, injected, or implanted [a] hormonal methods of contraception.

[a)] Contraception methods that in the context of this guidance are considered to have low user dependency.

10.4.3 Collection of pregnancy information

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

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

The initial and follow-up information must be documented on the paper-based Pregnancy Reporting Form and submitted to the sponsor within 24 h of learning of a trial subject's pregnancy/partner's pregnancy. The completed form needs to be sent to the Safety Report Fax number or Email 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
BMI	Body Mass Index
CRF	Case Report Form
CRO	Contract Research Organization
d	Day(s)
DLT	Dose limiting toxicity(ies)
DMC	Data Monitoring Committee
EDC	Electronic Data Capture (system)
EoT	End of Treatment
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

Abbreviation	Explanation
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SOC	System Organ Class
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
US	United States (of America)
WHO	World Health Organization
wks	Week(s)
WOCBP	Women Of Childbearing Potential

10.10 Protocol amendments and updates

10.10.1 Update to protocol version 2.0

Update rationale

This update describes changes made in response to internal feedback before submission of version 2.0 to the German PEI.

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

10.10.2 Update to protocol version 3.0

Update rationale

This update describes changes made in response to feedback from the German PEI (August 10th, 2020).

This update was issued before any trial subjects were enrolled into the trial. This change had 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) Where appropriate, a simple description of the changes is given.	Rationale
Title page (Document history table) Footnote added. * Denotes BioNTech approved versions.	PEI feedback (Clinical comment 1)

<table>
<tr><th>Changed text
(inserted text is blue/underlined; deleted text is red/struck out)
Where appropriate, a simple description of the changes is given.</th><th>Rationale</th></tr>
<tr><td>Section 1.1 (Trial synopsis)
If consider justified by the sponsor, based on the data collected in younger adults, cohorts with older adults (Cohorts 8 to 10) may be performed at the dose levels listed in Table 2 at any time, provided the initial tested dose is ≤30% of a dose previously found to be acceptable in younger adults.
For dose escalation cohorts in older adults, 12 subjects will be dosed using a sentinel dosing/subject staggering (2-4-6) process. For cohorts at doses lower than already tested, 12 subjects may be dosed on one day.
The dose levels for Cohorts 9 and 10 are flexible in Table 2, up to the maximum deemed safe in younger adults, to allow optimal dose selection once BNT162b3 data are available. The same dose level will not be tested twice. Where possible (i.e., given acceptable tolerability), dose levels of up to 30 µg and above will be tested because (based on BNT162b1 and BNT162b2 data) older adults may experience weaker immune responses compared to younger adults. The tolerability at dose levels of up to 30 µg and above is expected to be acceptable because, based on BNT162b1 and BNT162b2 data, the tolerability is expected to be better in older subjects compared to younger adults.
The dose levels for Cohorts 9 and 10 are flexible in Table 2 to allow optimal dose selection once BNT162b3 data are available, but the same doses will not be tested twice and, where possible, dose levels of up to 30 µg and above will be tested, since (based on BNT162b1 and BNT162b2 data) the immune response is expected to be weaker in older adults compared to younger adults whereby the safety and local/systemic reactivity are expected to be better in older adults compared to younger adults.</td><td>PEI feedback (Clinical comment 6d)</td></tr>
<tr><td>Section 1.1 (Table 1 footnote)
[a] All dose escalation doses used must be judged acceptable by the Safety Review Committee before use.
[b] Specific doses to be defined, but in the range given. Already given doses will not be repeated.</td><td>PEI feedback (Clinical comment 4)</td></tr>
<tr><td>Section 1.1 (Table 2 footnotes)
Table 2: Summary of vaccine dose regimens for older adults aged 56 to 85 years in Part A
<table><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 & Dose (µg) (12 subjects per cohort) [a]</th></tr><tr><th>8</th><th>9</th><th>10</th></tr><tr><td>BNT162b3 / modRNA</td><td>Membrane-anchored RBD of the SARS-CoV-2 S protein</td><td>Prime: Day 1
Boost: Day 22</td><td>8F
3 - 9 µg [b]</td><td>9F
10 - 50 60 µg [b]</td><td>10F
10 - 50 60 µg [b]</td></tr></table>[a] All dose escalation doses used must be judged acceptable by the Safety Review Committee before use.
[b] Specific doses to be defined, but in the range given. Already given doses will not be repeated.
IM = intramuscular; RBD = Receptor Binding Domain; S protein = SARS-CoV-2 spike protein.</td><td>PEI feedback (Clinical comment 4 and comment 6c)</td></tr>
<tr><td>Section 2.3.1 (Risk assessment)
Based on such data, the risks linked to the immunization with the BNT162b 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.</td><td>PEI feedback (Clinical comment 3)</td></tr>
</table>

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
Section 4.3 (Justification for dose) As summarized in Section 2.1.3 (for details, see the BNT162 IB), most of the AEs reported after immunization with BNT162 vaccine candidates in the ongoing BNT162-01 and BNT162-02 trials were been mild to moderate in intensity and no SAEs were reported. Fever of severe intensity was 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 dose (see Table 1) to be safe. The planned starting dose with BNT162b3 for older subjects aged 56 to 85 years in this trial will be ≤30% of a dose already shown to be acceptable in the subjects aged 18 to 55 years in this trial. Selection of a lower dose for the first dosing in older adults than found to be acceptable in younger adults is considered good practice when progressing to new populations. The chosen cut-off, ≤30%, is a reflection of the 3-fold safety margin often used by the sponsor, but is otherwise arbitrary.	PEI feedback (Clinical comment 6b)
Section 8.3.1 (Time period and frequency for collecting AE and SAE information) All AEs and SAEs will be collected from the date of subject consent until Visit ~~9~~ 7; after Visit 7 (at Visits 8 and 9), only IMP-related AEs and 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 between Visit 9 and Visit 10 and 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.	PEI feedback (Clinical comment 5)
Section 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 as defined in Section 8.3.1. ~~(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.	PEI feedback (Clinical comment 5)
Section 10.10.1 (Protocol amendment no. 01) This section was introduced.	This amendment

10.10.3 Update to protocol version 4.0

Update rationale

This update describes changes made in response to feedback from the IEC on version 2.0 (July 10th, 2020). This protocol version reflects the sum of the changes due to the PEI and the IEC feedback on the protocol version 2.0. The updates triggered by the PEI feedback are described in the update to protocol version 3.0 and updates triggered by the IEC feedback are described in this update (i.e., protocol version 4.0).

This update was issued before any trial subjects were enrolled into the trial. This change had 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) Where appropriate, a simple description of the changes is given.	**Rationale**
Section 1.1 (Trial synopsis) and 4.1 (Overall design) In Cohort 1, the sentinel dosing/subject staggering process will be as follows: • One sentinel subject will be dosed on one day. • If the dosing in this subject was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 5 further subjects will be dosed (with intervals of at least 1 h between subjects). • If the dosing in these 5 subjects was considered to be safe and well tolerated by the investigator based on 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48±2 h data from the sentinel subject): o The remaining 6 subjects in the group will be dosed (with intervals of at least 30 min between subjects). o If approved by the SRC, the next planned escalation dose (see Table 1) in Cohort 2 will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects including observation on site, phone interview, vital signs, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome. o If approved by the SRC, the planned de-escalation dose in Cohort 3 will be initiated. For any subsequent dose escalation cohorts, the sentinel/subject staggering process will be as follows: • Two sentinel subjects will be dosed on one day (with intervals of at least 30 min between subjects). • If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 4 further subjects will be dosed (with intervals of at least 30 min between subjects). • If the dosing in these 4 subjects was considered to be safe and well tolerated by the investigator based 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48 h data from the sentinel subjects): o The remaining 6 subjects in the group will be dosed (with intervals of at least 30 min between subjects). o 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, short summary of phone interviews [including statement about diary reports], vital signs, investigator reported local and systemic reactions, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome).	IEC feedback (Comments 2 and 3)
Section 1.1 (Trial synopsis) and 4.1 (Overall design) The maximum allowed dose for each vaccine candidate is defined in the Table 1. For any dose de-escalation or dose-refinement cohorts in younger adults, i.e., cohorts with doses lower than previously found ~~to be acceptable~~ tested, ~~12 subjects may be dosed on one day.~~ 12 subjects will be dosed using a subject staggering (6-6) process (with intervals of at least 30 min between subjects). The doses in these cohorts 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.	IEC feedback (Comments 2, 3, and 4)
Section 1.1 (Trial synopsis) and 4.1 (Overall design)	IEC feedback (Comment 7)

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
~~If consider justified by the sponsor, based on the data collected in younger adults, cohorts with older adults (Cohorts 8 to 10) may be performed at the dose levels listed in Table 2 at any time, provided the initial tested dose is ≤30% of a dose previously found to be acceptable in younger adults.~~ Administration of the planned starting dose (3 to 9 µg) 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; including observation on site, short summary of phone interviews [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 dose in Cohort 8 must also be confirmed by the SRC.	
Section 1.1 (Trial synopsis) and 4.1 (Overall design) ~~For dose escalation cohorts in older adults, 12 subjects will be dosed using a sentinel dosing/subject staggering (2-4-6) process. For cohorts at doses lower than already tested, 12 subjects may be dosed on one day.~~ For Cohort 8 and any dose escalation cohorts in older adults, 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 cohorts at doses lower than already tested in Cohort 8, 12 subjects will be dosed using a subject staggering (6-6) process (with intervals of at least 30 min between subjects). For the unplanned dose de-escalation cohorts, i.e., where the SRC requests the use of a reduced dose for safety reasons, 12 subjects will be dosed using a subject staggering (6-6) process with intervals of at least 30 min between subjects (as for planned de-escalation cohorts). The dose levels for Cohorts 9 and 10 are flexible in Table 2, up to the maximum deemed safe in younger adults, to allow optimal dose selection once BNT162b3 data are available. The same dose level will not be tested twice. Where possible (i.e., given acceptable tolerability), dose levels of up to 30 µg and above will be tested because (based on BNT162b1 and BNT162b2 data) older adults may experience weaker immune responses compared to younger adults. The tolerability at dose levels of up to 30 µg and above is expected to be acceptable because, based on BNT162b1 and BNT162b2 data, the tolerability is expected to be better in older subjects compared to younger adults. Note: BNT162b3, like BNT162b1 and BNT162b2 as under investigation in the trials BNT162-01, BNT162-02, and BNT162-03, are ~~non-modified uridine~~ nucleoside modified RNAs (modRNAs). RNA modification is known to impact the extent of innate immune activation at a given dose level, and thus potentially the extent of reactogenicity (Weissman and Karikó 2015). Therefore, tolerability data obtained with the BNT162b1 and BNT162b2 vaccine variants may be potentially informative for BNT162b3, and should be taken in consideration by the SRC for recommendations of lower or interim doses.	IEC feedback (Comments 2, 3, and 4)
Section 1.1 (Table 2 footnotes) Note: The doses planned in this trial reflect emerging clinical data from the ongoing BNT162-01 and BNT162-02 trials with the related vaccine candidates BNT162b1 and BNT162b2 in younger adults (aged between 18 and 55 years) and elderly (adults aged between 65 and 85 years). As of August 27th, 2020, a total of 10,586 subjects (men and women) were dosed at least once with BNT162 vaccine candidates, and 10,472 with BNT162b vaccine, in ongoing clinical trials (i.e., BNT162-01, BNT162-02, and BNT162-03). Of these subjects, 96 were elderly adults (i.e., aged 65 to 85 years). See below for a summary and Section 2.1.3 for details. BNT162b1: • BNT162b1 P/B doses of 1, 10, 30, and 50 µg showed acceptable tolerability in younger adults. • Based on the tolerability profile after the prime dose at 60 µg (BNT162-01 trial) and 100 µg (BNT162-02 trial), the respective boost doses were not administered. • BNT162b1 P/B doses of 10, 20, and 30 µg showed acceptable tolerability in elderly adults. This tolerability appears to be better than seen in younger adults at the same doses. BT162b2: • BNT162b2 P/B doses of 1, 10, and 30 µg showed acceptable tolerability in younger adults.	IEC feedback (Comment 6)

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
• BNT16b2 P/B doses of 10, 20, and 30 µg in elderly adults. This tolerability appears to be better than seen in younger adults at the same doses. Based on the BNT162b1 and BNT162b2 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 BNT162b3 doses in older adults in this trial are expected to show acceptable tolerability. Based on the available immunogenicity and cell-mediate immune response data after dosing with BNT162b1 and BNT162b2 in younger and elderly adults in the BNT162-01 and BNT162-02 trials (see the BNT162 IB), the BNT162b3 doses planned in this trial in older adults are also expected to show measurable responses. These vaccines elicited measurable but lower responses in elderly adults than in younger adults, therefore, this trial includes the option to investigate BNT162b3 doses above the 30 µg BNT162b1 / BNT162b2 doses already tested in elderly adults, to support any future Phase III program planned to support marketing approval. Altogether, the doses planned in older adults in this trial are considered adequate to support the trial objectives and to pose an acceptable risk to trial subjects.	
Section 1.2 (Schema) a) The data assessed by the SRC for progressing comprises 48 h data for 6 subjects. b) Cohorts 5 to 7 are planned for dose-refinement. If they use doses lower than already tested, a staggered (6-6) subject dosing process will be used ~~12 subjects may be dosed on one day in these cohorts~~ and the cohorts may be conducted in parallel to each other and 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. c) For the dose regimens, see Table 1 and Table 2. d) Cohorts 8 to 10 are planned in older adults. ~~In~~ For Cohort 8, and any dose escalation cohorts, subjects will be dosed using a sentinel dosing/subject (2-4-6) staggering process. ~~If Cohorts 9 and 10 use doses lower than in Cohort 8, 12 subjects may be dosed on one day in these cohorts and the cohorts may be conducted in parallel to each other and to any dose escalation cohorts. If they use doses higher than in Cohort 8, subjects will be dosed using a sentinel dosing/subject (2-4-6) staggering process~~.	IEC feedback (Comment 4)
Section 1.3 (Schedule of Activities) Visit 10 was corrected to (day) 387 from (day) 365.	Error correction
Section 1.3 (Schedule of Activities) [l] For Cohorts 1 and 8, prime immunization with at least 1 h intervals between subjects for the first 6 subjects and then with at least 30 min intervals for the remaining 6 subjects. For ~~Cohorts 2 and 4~~ all other cohorts, immunization with at least 30 min intervals between subjects. Boost immunization with at least 15 min intervals between subjects. [m] Oral swipe for SARS-CoV-2 testing either on Day -1 or at the Visit 1 on Day 1.	IEC feedback (Comments 2 and 3)
Section (Trial-Specific Abbreviations/Terms) Definitions added: Cohort — In this document, the word cohort refers to groups of subjects receiving the same vaccine dose and belonging to the same age group (younger adults or older adult) Older adults — Adults aged 56 to 85 years.	IEC feedback (Comment 1)
Section 2.1.3 (Ongoing and planned clinical trials with BNT162 vaccine variants) This section was completely rewritten and updated. • The table "Status of ongoing and planned clinical trials" was updated.	IEC feedback (Comments 8 and 9)

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
• The table "Number of trial subjects dosed at least once with BNT162 vaccine candidates in the ongoing clinical trials" was added. • The reader is referred to the current IB, which summarizes currently available safety, reactivity, and immunogenicity data.	
Section 2.3.1 (Risk assessment) • As summarized in Section 2.1.3, to date most of the AEs reported after immunization with BNT162 vaccine candidates, including BNT162b vaccine candidates, were mild to moderate in intensity ~~and no SAEs were reported~~. Generally, good tolerability was observed. Overall, many of the reported adverse events (AEs) appear to be similar to reactogenicity events anticipated for intramuscularly (IM)-administered vaccines, typically with an onset within first 24 h post-immunization. All AEs / reactogenicity symptoms resolved spontaneously, mostly within 24 h of onset, and were managed with simple measures (e.g., paracetamol). There were no serious adverse events (SAEs) and no unexpected toxicities. Fever of severe intensity has been reported. Most AEs were managed with simple measures and resolved spontaneously. • To date, there is no clinical experience with the BNT162b3 vaccine in human subjects, but there is some data available for BNT162b1 and BNT162b2 vaccine candidates in the ongoing trials. The most frequent adverse reactions identified for BNT162 vaccines at this time are: injection site pain, fever, fatigue, headache, chills, and muscle pain. ~~from the trial BNT162-01. In the ongoing trial BNT162-01, the pattern of tolerability was as anticipated based on the mode of action of the BNT162 vaccine candidates and the available non-clinical/clinical data, with most subjects reporting flu-like symptoms and injection site reactions (for details, see the BNT162 IB).~~ • 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 BNT162b3 will be defined in this trial and supported by data for other BNT162 vaccine candidates, including BNT162b vaccine candidates, from the ongoing trials (BNT162-01 and BNT162-02).	IEC feedback (Comment 10)
Section 2.3.1 (Risk assessment) • When assessing the risk for dosing of older subjects with BNT162b3 ~~vaccine candidate~~ in this trial, the follow information is relevant: – Preliminary data in younger and elderly adults ~~subjects~~ treated in the ongoing BNT162 trials, backed by non-human primate (rhesus macaque) immunogenicity data, BNT162b1, and non-human primate data for BNT162b3, show immunogenicity in the tested dose ranges. Analog clinical data for BNT162b3 will be collected before dosing older subjects in this trial. – After administration of the prime dose of BNT162b1 and BNT162b2 in (each) 36 healthy elderly adults ~~subjects aged 65 to 85 years~~ in the ~~US~~ trial BNT162-02, the local tolerability of BNT162b1 in elderly adults seemed comparable to that recorded in younger ~~subjects aged 18 to 55 years~~ adults. The pattern of systemic reactogenicity appeared similar between the two age groups, possibly with a lower overall incidence in the elderly adults ~~subjects~~ in comparison to the younger adults ~~subjects~~ at equal doses. – There is the risk that older adults in this trial may be under dosed with the vaccine doses chosen based on data for younger adults (as was observed for other vaccines) must be mitigated. – Based on the available immunogenicity and cell-mediate immune response data after dosing with BNT162b1 and BNT162b2 in younger and elderly adults in the BNT162-01 and BNT162-02 trials (see the BNT162 IB), the BNT162b3 doses planned in this trial in older adults are also expected to show measurable responses. These vaccines elicited measurable may be lower responses in elderly adults than in younger adults, therefore, this trial includes the option to investigate BNT162b3 doses above the 30 µg BNT162b1 / BNT162b2 doses already tested in elderly adults, to support any future Phase III program planned to support marketing approval.	IEC feedback (Comment 6)

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
~~Preliminary data for BNT162b1 in elderly show a comparable to lower reactogenicity based on the observed local reactions and system events in similar doses~~ (for details, see the BNT162 IB). This observation may indicate a lower innate immune activation capability of elderly, which in turn may mechanistically be associated with lower immunogenicity of dose levels that are immunogenic in the younger adults.	
Section 2.3.1 (Risk assessment) To further ensure trial subject safety, 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 two 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. Experience in the ongoing trials BNT162-01 and BNT162-02, has confirmed the adequacy of the implemented observations periods. • More frequent on site visits after…	IEC feedback (Comment 10)
Section 2.3.1 (Risk assessment) To further ensure trial subject safety, the trial protocol foresees that: • … • The expanded SRC review and evaluate at least the Day 21 data per vaccine ~~to decide whether to progress to Part B, and if yes, define~~ confirm what doses will be given in Part B. SRC may make recommendations on increasing observation periods and additional subject wellbeing calls may be included at the discretion of the SRC.	IEC feedback (Comment 12)
Section 4.3 (Justification for dose) As summarized in Section 2.1.3 (for details, see the BNT162 IB), most of the AEs reported after immunization with BNT162 vaccine candidates in the ongoing BNT162-01 and BNT162-02 trials were been mild to moderate in intensity and no SAEs were reported. Fever of severe intensity was reported. Most AEs were managed with simple measures and resolved spontaneously. The doses planned in this trial reflect emerging clinical data from the ongoing BNT162-01 and BNT162-02 trials with the related vaccine candidates BNT162b1 and BNT162b2 in younger adults (aged between 18 and 55 years) and elderly (adults aged between 65 and 85 years). As of August 27th, 2020, a total of 10,586 subjects (men and women) were dosed at least once with BNT162 vaccine candidates, and 10,472 with BNT162b vaccine, in ongoing clinical trials (i.e., BNT162-01, BNT162-02, and BNT162-03). Of these subjects, 96 were elderly adults (i.e., aged 65 to 85 years). See below for a summary and Section 2.1.3 for details. BNT162b1: • BNT162b1 P/B doses of 1, 10, 30, and 50 µg showed acceptable tolerability in younger adults. • Based on the tolerability profile after the prime dose at 60 µg (BNT162-01 trial) and 100 µg (BNT162-02 trial), the respective boost doses were not administered. • BNT162b1 P/B doses of 10, 20, and 30 µg showed acceptable tolerability in elderly adults. This tolerability appears to be better than seen in younger adults at the same doses. BT162b2: • BNT162b2 P/B doses of 1, 10, and 30 µg showed acceptable tolerability in younger adults. • BNT16b2 P/B doses of 10, 20, and 30 µg in elderly adults. This tolerability appears to be better than seen in younger adults at the same doses. Based on the BNT162b1 and BNT162b2 tolerability data summarized above, and the implemented safety measures (sentinel/staggered subject dosing, post-dose observations period, wellbeing	IEC feedback (Comments 6, 7, and 8)

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
questioning, etc.) as described in the section Risk assessment, the planned BNT162b3 doses in older adults in this trial are expected to show acceptable tolerability. Based on the available immunogenicity and cell-mediate immune response data after dosing with BNT162b1 and BNT162b2 in younger and elderly adults in the BNT162-01 and BNT162-02 trials (see the BNT162 IB), the BNT162b3 doses planned in this trial in older adults are also expected to show measurable responses. These vaccines elicited measurable but lower responses in elderly adults than in younger adults, therefore, this trial includes the option to investigate BNT162b3 doses above the 30 µg BNT162b1 / BNT162b2 doses already tested in elderly adults, to support any future Phase III program planned to support marketing approval. Altogether, the doses planned in older adults in this trial are considered adequate to support the trial objectives and to pose an acceptable risk to trial subjects. Based on the available clinical and non-clinical data experience, the sponsor expects the planned maximal dose (see Table 1) to be safe.	
Section 6.6 (Dose modifications) The trial design allows for a flexible dosing which allows a better evaluation on the optimal dose range. For details, see Section 4.1., The decision to make dose adaptions or to initiate ~~add~~ a cohort, ~~or to progress to part B~~ will be made by the SRC (for details, see Section 10.1.5); any plan to alter the planned dose escalations will only be implemented after relevant approval of a substantial protocol amendment. Dose de-escalation and escalation rules have been defined in this protocol (see Section 6.6.2).	IEC feedback (Comment 12)
6.6.2 (Dose modification guidance/rules) The trial design also allows for: • The selection of which BNT162 vaccine dose regimens and posologies that will be investigated in Part B following a substantial protocol amendment. See Section 10.1.5 for the data set upon which SRC decisions described below are made for Part A. **Part A** • Any proposal to alter the planned escalation dose, or to test an additional de-escalation dose, must be approved by the SRC. • Any plan to exceed the planned maximum dose will only be implemented after relevant approval of a substantial protocol amendment. 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, and will be implemented after relevant approval of a substantial amendment.	IEC feedback (Comment 12)
Section 10.10.2 (Protocol amendment no. 2) This section was introduced.	This amendment

10.10.4 Protocol amendment no. 01 (protocol version 5.0)

Amendment rationale

This amendment describes changes made to clarify potential inconsistencies, to align trial reporting with other ongoing BNT162 trials, and to enhance assessments for immunogenicity.

This amendment was issued after the first trial subjects have been enrolled into the trial. This change has no impact on the planned trial objectives or subject safety.

Detailed description of changes

Editorial changes are not listed.

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
Title page **CLINICAL TRIAL PROTOCOL INCLUDING AMENDMENTS NOS. 01 ~~TO 03~~** **BNT162-04**	Sponsor decision to differentiate between sponsor approved versions and versions submitted as amendments
Title page **Regulatory identifiers:** EudraCT no.: 2020-003267-26; Universal Trial Number: U1111-1254-4840; Clinicaltrials.gov code: NCT04537949 **Medical Monitor:** The ~~sponsor's Medical Monitor~~ name and contact information will be provided separately **Document history** First approved version* — 03 JUL 2020 — 1.0 — Germany Second approved version* — 06 JUL 2020 — 2.0 — Germany Third approved version* (implementing Paul-Ehrlich Institute (PEI) feedback on version 2.0) — 16 AUG 2020 — 3.0 — Germany Fourth approved version* (implementing Independent Ethics Committee (IEC) feedback on version 2.0 in version 3.0) — 16 AUG 2020 — 4.0 — Germany Fifth approved version* (implementing amendment 01) — ~~14~~ 15 SEP 2020 — 5.0 — Germany	Sponsor decision to differentiate between sponsor approved versions and versions submitted as amendments
Section 1.1 (Objectives and endpoints) and Section 3 (Objectives and endpoints) (Primary objectives) • Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7~~±1~~ d after each immunization. • Solicited systemic reactions (nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever) recorded up to 7~~±1~~ d after each immunization. • The proportion of subjects with at least 1 unsolicited treatment emergent adverse event (TEAE) occurring up to 21~~±2~~ d after the prime immunization and 28~~±4~~ d after the boost immunization. (Secondary objectives) At 7~~±1~~ d and 21~~±2~~ d after prime~~ary~~ immunization and at 21~~±2~~ d, 28~~±4~~ d, 36 d, 63~~±5~~ d, 162~~±7~~ d, and 365~~±14~~ d after the boost immunization: • Functional antibody responses. • … (Exploratory objectives) [redacted]	Sponsor decision to add an additional blood draw / Visit and to remove visit windows (since considered confusing)

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
[redacted]	
Section 1.1 (Trial design) and Section 4.1 (Overall design) This trial has two parts. Part A, a dose-finding part, with possible dose escalation cohorts, and discretionary dose de-escalation and refinement cohorts in younger subjects. Cohorts in older subjects are optional and dependent on acceptability of dosing in younger subjects. ~~Part A, a dose finding part, with three dose escalation cohorts, one dose de-escalation cohort, three dose refinement cohorts, and up to three optional cohorts in older subjects.~~ Part B, a part with expansion cohorts with dose levels which are selected using data generated in Part A.	Error correction
Section 1.1 (Trial design) and Section 4.1 (Overall design) *Part A* ~~The first part of the trial (Part A) will follow a dose escalation design. A dose de-escalation is also planned.~~ 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 treatment phase (screening to Visit 7) and a follow-up phase (Visits 8 to 10). … … • If the dosing in these 5 subjects was considered to be safe and well tolerated by the investigator based on 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48±2 h data from the sentinel subject): o The remaining 6 subjects in the group will be dosed (with intervals of at least ~~30~~ 15 min between subjects). o If approved by the SRC, the next planned escalation dose (see Table 1) in Cohort 2 ~~will~~ may be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects including observation on site, phone interview, vital signs, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome. o Once dose escalation is approved, the planned dose de-escalations may also be initiated. ~~If approved by the SRC, the planned de-escalation dose in Cohort 3 will be initiated.~~	Clarification and sponsor decision based on site feedback
Section 1.1 (Trial design) and Section 4.1 (Overall design) For any subsequent dose escalation cohorts, the sentinel/subject staggering process will be as follows: • Two sentinel subjects will be dosed on one day (with intervals of at least 30 min between subjects). • If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 4 further subjects will be dosed (with intervals of at least ~~30~~ 15 min between subjects). • If the dosing in these 4 subjects was considered to be safe and well tolerated by the investigator based 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48 h data from the sentinel subjects): o The remaining 6 subjects in the group will be dosed (with intervals of at least ~~30~~ 15 min between subjects). o If approved by the SRC, the next planned escalation dose (see Table 1) in Cohort 2 ~~will~~ may 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.	Clarification and sponsor decision based on site feedback

<table>
<tr><th>Changed text
(inserted text is blue/underlined; deleted text is red/struck out)
Where appropriate, a simple description of the changes is given.</th><th>Rationale</th></tr>
<tr><td>Section 1.1 (Trial design) and Section 4.1 (Overall design)
For any dose de-escalation or dose-refinement cohorts in younger adults, i.e., cohorts with doses lower than previously tested~~.~~, 12 subjects will be dosed using a subject staggering (6-6) process (with intervals of at least ~~30~~ 15 min between subjects). The doses in these cohorts 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.
Administration of the planned starting dose (3 to ~~9~~ 10 µg) 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…</td><td>Sponsor decision based on site feedback</td></tr>
<tr><td>Section 1.1 (Trial design) and Section 4.1 (Overall design)
For Cohort 8 and any dose escalation cohorts in older adults, 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~~ 15 min intervals for the remaining 6 subjects).</td><td>Sponsor decision based on site feedback</td></tr>
<tr><td>Section 1.1 (Trial design) and Section 4.1 (Overall design)
For the unplanned dose de-escalation cohorts, i.e., where the SRC requests the use of a reduced dose for safety reasons, 12 subjects will be dosed using a subject staggering (6-6) process with intervals of at least ~~30~~ 15 min between subjects (as for planned de-escalation cohorts).
Note: BNT162b3, like BNT162b1 and BNT162b2 as under investigation in the trials BNT162-01, BNT162-02, and BNT162-03, are nucleoside modified ~~non-modified uridine~~ RNAs (modRNAs). RNA modification is known to impact the extent of innate immune activation …</td><td>Sponsor decision based on site feedback and correction of an error</td></tr>
<tr><td>Section 1.1 (Trial design) Table 1
<table><tr><td>modRNA</td><td>the SARS-CoV-2 S protein</td><td>Boost: Day 22</td><td>10 µg</td><td>3 µg</td><td>1 µg</td><td>60 µg</td><td>3 - 50 µg</td></tr></table>[a] All dose escalation decisions and doses used must be judged acceptable by the Safety Review Committee before use.
[b] Specific doses to be defined, but in the range given. Already given doses will not be repeated.
[c] De-escalation doses are discretionary and need not be administered in numeric order.
IM = Intramuscular; modRNA = nucleoside modified messenger RNA; RBD = Receptor binding domain.</td><td>Sponsor decision</td></tr>
<tr><td>Section 1.1 (Trial design) Table 1
Table 2: Summary of vaccine dose regimens for older adults aged 56 to 85 years in Part A
<table><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 & Dose (µg) (12 subjects per cohort) [a]</th></tr><tr><th>8</th><th>9</th><th>10</th></tr><tr><td>BNT162b3 / modRNA</td><td>Membrane-anchored RBD of the SARS-CoV-2 S protein</td><td>Prime: Day 1
Boost: Day 22</td><td>8F
3 - 910 µg [b]</td><td>9F
10 - 60 µg [b]</td><td>10F
10 - 60 µg [b]</td></tr></table>[a] All dose escalation doses used must be judged acceptable by the Safety Review Committee before use.
[b] Specific doses to be defined, but in the range given. Already given doses will not be repeated.
IM = intramuscular; RBD = Receptor Binding Domain; S protein = SARS-CoV-2 spike protein.
Note: The doses planned in this trial reflect emerging clinical data from the ongoing BNT162-01 and BNT162-02 trials with the related vaccine candidates BNT162b1 and BNT162b2 in younger adults (aged between 18 and 55 years) and elderly (adults aged between 65 and 85 years).
As of August 276th, 2020, a total of 1,50610,586 subjects (men and women) were dosed at least once with BNT162 vaccine candidates, and 1,40510,472 with BNT162b vaccines, in the ongoing clinical trials (i.e., BNT162-01, BNT162-02, and BNT162-03). Of these subjects, at least 9672 of the dosed subjects were elderly older adults (i.e., aged 6556 to 85 years). See below for a summary and Section 2.1.3 for details.</td><td>Sponsor decision and data update</td></tr>
<tr><td>Section 1.1 (Trial duration)
In total, the planned trial duration is expected to be approximately ~~12~~16 months. From screening visit (Visit 0) to the last visit (Visit 10), each trial subject will be in the trial for maximally 409 days 417 days (i.e., from Day -30 to Day 387).</td><td>Correction</td></tr>
</table>

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
Section 1.1 (Key exclusion criteria) • Are soldiers, ~~subjects~~ persons in detention, CRO or sponsor staff or their family members. • ~~For older subjects: h~~Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors: o Cancer o Chronic kidney disease o COPD (chronic obstructive pulmonary disease) o Immunocompromised state (weakened immune system) from solid organ transplant o Obesity (BMI of 30 or higher) o Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies o Sickle cell disease o Type 2 diabetes mellitus ~~o Hypertension~~ ~~o Diabetes mellitus~~ ~~o Chronic pulmonary disease~~ ~~o Asthma~~ ~~o Chronic liver disease~~ ~~o Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)~~ ~~o Anticipating the need for immunosuppressive treatment within the next 6 months~~ ~~o Resident in a long-term facility~~ ~~o Current vaping or smoking (occasional smoking is acceptable)~~ o ~~History of chronic smoking within the prior year~~	Sponsor decision
Section 1.1 (Statistics) and Section 9.5 (Interim analyses) ~~The statistical analysis will be performed once all subjects have been enrolled and completed all visits according to the SoA (Section 1.3).~~ ~~No formal interim statistical analysis will be performed. However, the statistical analysis may be performed in the following sequence separately for each type: once all subjects in the respective group have been followed up for at least 21 days and once all subjects have discontinued the trial, respectively.~~ The final analysis will be performed once all subjects have completed the End of Treatment (EoT Visit; Visit 7). An analysis update will be performed once all subjects will have completed Visit 10. No formal interim statistical analysis will be performed. However, the preliminary 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.	Clarification
Section 1.3 (Schedule of Activities) Insertion of an additional 10 mL blood draw for immunogenicity assessment and AE recording on Day 36, i.e., Visit 5a (~14 d from Visit 4). To align with BNT162-01, the line "Blood draw for research" and instructions "Up to 5 blood draws for explorative biomarker/immunogenicity research purposes. Blood draw volumes may vary. The total blood volume drawn will not exceed 200 mL per subject between Visit 1 and Visit 9, i.e., over approximately 7 months" was replaced with instructions for blood draws/blood volumes at specific visits (Visits 6 [≤100 mL], 8 [≤50 mL], and 9 [≤50 mL]).	Sponsor decision

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
Section 1.3 (Schedule of Activities) f Clinical laboratory tests: (Chemistry) alkaline phosphatase, creatinine, ferritin, C-reactive protein, albumin, alanine aminotransferase, amylase, aspartate aminotransferase, gamma glutamyl transpeptidase, total bilirubin, blood urea nitrogen, glucose, lipase, sodium, potassium, calcium; (Hematology) hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count. Only in women who are not WOCBP: follicle stimulating hormone (FSH) at Visit 0 to confirm the menopause status. 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 5a 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. i … j … k … l For Cohorts 1 and 8, prime immunization with at least 1 h intervals between subjects for the first 6 subjects and then with at least ~~30~~ 15 min intervals for the remaining 6 subjects. For all other cohorts, immunization with at least ~~30~~ 15 min intervals between subjects. Boost immunization with at least 15 min intervals between subjects. Note: If the boost dose is not administered, subjects should still complete all assessments planned in the SoA.	Clarification and sponsor decision to add an additional blood draw / Visit
Section 2.1.3 (Ongoing and planned clinical trials with BNT162 vaccine variants) - Table 4 Note: BNT162b3, like BNT162b1 and BNT162b2 as under investigation in the trials BNT162-01, BNT162-02, and BNT162-03, are nucleoside modified ~~non-modified uridine~~ RNAs (modRNAs). RNA modification is known to impact the extent of innate immune activation … BNT162 vaccine candidates based on the uRNA, modRNA, and saRNA formats are currently under investigation in three clinical trials with healthy adults (men and women) aged between 18 and 85 years. In these trials, the subjects are either younger adults (aged 18 to 55 years), older adults (aged ~~55~~ 56 to 85 years), or elderly adults (aged 65 to 85 years).	Error correction
Section 2.1.3 (Ongoing and planned clinical trials with BNT162 vaccine variants) - Table 4	Data update to reflect the Aug 27th status

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(inserted text is blue/underlined; deleted text is red/struck out)
Where appropriate, a simple description of the changes is given.

Rationale

Table 4: Status of ongoing and planned clinical trials (as of August 276th, 2020)

Trial number	Design	Current number dosed (subject age)
BNT162-01 (NCT04380701) Germany	Phase I/II, 2-part, dose escalation trial. Part A is open label and non-randomized. (All subjects receive active vaccine) Part B will be defined in a protocol amendment.	BNT162a1 (age 18 to ~~-~~55 yrs): 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) BNT162b1 (age 18 to 55 yrs): 1 µg 12 subjects prime / 12 boost 3 µg 12 subjects prime / ~~0~~ 12 boost 10 µg 12 subjects prime / 11 boost 20 µg 12 subjects prime / ~~0~~ 11 boost 30 µg 12 subjects prime / 12 boost 50 µg 12 subjects prime / 11 boost 60 µg 12 subjects prime / 0 boost (Further dosing with BNT162b1 at 60 µg and the boost dose for already dosed subjects was cancelled) BNT162b1 (age 56 to 85 yrs): 10 µg 12 subjects prime BNT162b2 (age 18 to 55 yrs):

Section 2.1.3 (Ongoing and planned clinical trials with BNT162 vaccine variants) - Table 4

Data update to reflect the Aug 27th status

		BNT162b2 (age 18 to 55 yrs): 1 µg 12 subjects prime / ~~8~~ 11 boost 3 µg ~~10~~ 12 subjects prime / ~~0~~ 12 boost 10 µg 12 subjects prime / 11 boost 20 µg 12 subjects prime / 12 boost 30 µg 12 subjects prime / 12 boost BNT162b2 (age 56 to 85 yrs): 10 µg 12 subjects prime 20 µg 12 subjects prime BNT162c2 P/B (age 18 to 55 yrs): 0.1 µg 12 subjects prime / 1 boost 0.3 µg 11 subjects prime / 0 boost BNT162c2 SD (age 18 to 55 yrs): 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) BNT162c2 P/B (age 18 to 55 yrs): 0.1 µg 12 subjects prime / 12 boost 0.3 µg 12 subjects prime / 12 boost 1 µg 12 subjects prime / 12 boost

<table>
<tr><th>Changed text
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Where appropriate, a simple description of the changes is given.</th><th>Rationale</th></tr>
<tr><td>Section 2.1.3 (Ongoing and planned clinical trials with BNT162 vaccine variants) - Table 4
<table>
<tr><th>Trial number</th><th>Design</th><th>Current number dosed (subject age)</th></tr>
<tr><td>BNT162-02 / C4591001
(NCT NCT04368728)
US, Argentina, Brazil, Turkey, Germany</td><td>Phase I/II/III, placebo-controlled, randomized, observer-blind, dose-finding and efficacy trial.
Phase 1: Subjects are randomized:
4:1 active:placebo.

Phase 2/3: Subjects are randomized:
1:1 active:placebo.</td><td>Phase I
BNT162b1 (age 18 to 55 yrs):
10 µg 15 subjects prime / 15 boost
20 µg 15 subjects prime / 15 boost
30 µg 15 subjects prime / 15 boost
100 µg 15 subjects prime / 0 boost
(Further dosing with BNT162b1 at 100 µg and the boost dose for already dosed subjects was cancelled)

BNT162b1 (age 65 to 85 yrs):
10 µg 15 subjects prime / 15 boost
20 µg 15 subjects prime / 15 boost
30 µg 15 subjects prime / 15 boost

BNT162b2 (age 18 to 55 yrs):
10 µg 15 subjects prime / 15 boost
20 µg 15 subjects prime / 15 boost
30 µg 15 subjects prime / 15 boost

BNT162b2 (age 65 to 85 yrs):
10 µg 15 subjects prime / 15 boost
20 µg 15 subjects prime / 15 boost
30 µg 15 subjects prime / 15 boost

Phase II/III
BNT162b2 (age 18 to 85 yrs):
30 µg 2083 9,961 subjects
(Split P/B not available)prime</td></tr>
</table></td><td>Data update to reflect the Aug 27th status</td></tr>
<tr><td>Section 2.1.3 (Ongoing and planned clinical trials with BNT162 vaccine variants) - Table 4
<table>
<tr><td>BNT162-03 China (NCT04523571NCT to be obtained)
China</td><td>Phase I, randomized, placebo-controlled, observer-blind trial.
Subjects are randomized: 1:1:1 high-, low-dose groups and placebo group.</td><td>BNT162b1 (age 18 to 55 yrs):
10 µg 24 subjects prime / 24 boost
20 µg 24 subjects prime / 24 boost
Placebo 24 subjects prime / 24 boost

BNT162b1 (age >565 to 85 yrs):
10 µg 24 subjects prime
30 µg 24 subjects prime
Placebo 24 subjects primeEnrollment has not started.</td></tr>
</table></td><td>Data update to reflect the Aug 27th status</td></tr>
<tr><td>Section 2.1.3 (Ongoing and planned clinical trials with BNT162 vaccine variants) - Table 4
BNT162-04
<table>
<tr><th>Trial number</th><th>Design</th><th>Current number dosed (subject age)</th></tr>
<tr><td>BNT162-04 (NCT04537949NCT to be obtained)
Germany</td><td>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.</td><td>BNT162b3 (age 18 to -55 yrs):
DosingEnrollment has not started.

BNT162b3 (age 18 to 55 yrs):
Enrollment Dosing has not started.</td></tr>
</table></td><td>Data update to reflect the Aug 27th status</td></tr>
</table>

<table>
<tr><th>Changed text
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Where appropriate, a simple description of the changes is given.</th><th>Rationale</th></tr>
<tr><td>Section 2.1.3 (Ongoing and planned clinical trials with BNT162 vaccine variants)

<table>
<tr><th>BNT162 vaccine candidate
Dosing regimen (age group)</th><th>BNT162a1</th><th>BNT162b1</th><th>BNT162b2</th><th>BNT162c2</th><th></th></tr>
<tr><td>Phase I</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SD (younger adults)</td><td>30</td><td>~~93~~180</td><td>199</td><td>~~7~~184</td><td></td></tr>
<tr><td>P/B (younger adults)</td><td>24</td><td>~~61~~141</td><td>121</td><td>361~~+~~</td><td></td></tr>
<tr><td>SD (~~elderly~~ older adults)</td><td>0</td><td>~~36~~96</td><td>36</td><td>0</td><td></td></tr>
<tr><td>P/B (~~elderly~~ older adults)</td><td>0</td><td>~~36~~72</td><td>36</td><td>0</td><td></td></tr>
<tr><td>Phase II/III</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SD (younger and ~~elderly~~ older adults)</td><td></td><td></td><td>~~1,041~~9,961*</td><td></td><td></td></tr>
<tr><td>Total all adults dosed at least once in Phase I & II/III</td><td>30</td><td>~~129~~276</td><td>~~1,276~~10,196*</td><td>~~7~~184</td><td>Sum = ~~1,506~~10,586</td></tr>
<tr><td></td><td></td><td colspan="2">Sum BNT162b1 + BNT162b2 = ~~1,405~~10,472*</td><td></td><td></td></tr>
</table>
* Estimated / includes estimated number based on 1:1 active: placebo assignment.
Older adults = adults aged 56 to 85 yrs; P/B = prime boost; SD = single dose; Years = yrs; Younger adults = adults aged 18 to 55 yrs; ~~Elderly adults = adults aged 65 to 85 yrs~~.</td><td>Data update to reflect the Aug 27th status</td></tr>
<tr><td>Section 2.3.1 (Risk assessment)
The risks linked to the trial-specific procedures and connected mitigations are as follows:
• The volume of blood drawn will be kept to a minimum and will remain less than that drawn when donating blood (up to approximately ~~592~~ 602 mL blood will be drawn per subject over the complete trial, i.e., over approximately 13~~1~~6 months).
• All trial-specific procedures will be performed by qualified trial site personnel.
• Immunization will be done by a physician.
• BNT162b3 has 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. Also, BNT162b3, like the BNT162b variants BNT162b1 and BNT162b2 that are under investigation in the trials BNT162-01, BNT162-02, and BNT162-03, are modRNAs ~~non-modified uridine RNAs~~. RNA modification …</td><td>Sponsor decision to add an additional blood draw / Visit</td></tr>
<tr><td>Section 2.3.1 (Risk assessment)
Based on such data, the risks linked to the immunization with the BNT162b 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 reactions or a neurological side effect, 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.</td><td>PEI feedback on protocol version 2.0 and data update</td></tr>
<tr><td>Section 2.3.1 (Risk assessment)
Based on such data, the risks linked to the immunization with the BNT162b vaccines are as follows:
• Due to the IM route of administr…</td><td>Data update</td></tr>
</table>

• Due to the IM route the risk of severe systemic reactions is considered low. • An IM vaccine based on … • As with other vaccines, a… • The available non-clinical data of BNT162b suggest a favorable safety profile with events that are short-lived, mild and mostly related to the mode-of-action and the RNA-intrinsic stimulation of innate immune sensors.	
Section 4.3 (Justification for dose) Based on the available immunogenicity and CMI response data after dosing with BNT162b1 and BNT162b2 in younger and elderly adults in the BNT162-01 and BNT162-02 trials (see the BNT162 IB), the BNT162b3 doses planned in this trial in older adults are also expected to show measurable responses. The sponsor will continue to evaluate these emerging data from these ongoing studies to inform progression to discretionary dose levels. These vaccines elicited measurable but lower responses in elderly adults than in younger adults, therefore, this trial includes the option to investigate BNT162b3 doses above the 30 µg BNT162b1 / BNT162b2 doses already tested in elderly adults, to support any future Phase III program planned to support marketing approval. ~~Altogether, the doses planned in older adults in this trial are considered adequate to support the trial objectives and to pose an acceptable risk to trial subjects.~~ Altogether, the doses planned in older adults in this trial are considered adequate to support the trial objectives and to pose an acceptable risk to trial subjects.	Data update and deletion of a duplication
Section 4.4 (End of Treatment (EoT) and end of trial definition) ~~A trial subject is considered to have completed the trial if they have completed all planned visits as listed in the SoA (see Section 1.3). The EoT is defined as the date the last subject completed the EoT Visit.~~ A trial subject is considered to have completed the trial if they have completed all planned visits as listed in the SoA, including all follow-up visits (see Section 1.3). The End of Treatment is defined as the date the last subject completed the EoT Visit (Visit 7). 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. The end of trial is defined as the date when the last subject completed Visit 10 (Last Subject Last Visit).	Data update
Section 5.2.1 (Exclusion criteria Part A) 28. Are soldiers, ~~subjects~~ persons in detention, CRO or sponsor staff or their family members. 29. ~~For older subjects: h~~Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors: o Cancer o Chronic kidney disease o COPD (chronic obstructive pulmonary disease) o Immunocompromised state (weakened immune system) from solid organ transplant o Obesity (BMI of 30 or higher) o Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies o Sickle cell disease o Type 2 diabetes mellitus ~~o Hypertension~~ ~~o Diabetes mellitus~~ ~~o Chronic pulmonary disease~~ ~~o Asthma~~ ~~o Chronic liver disease~~ ~~o Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)~~ ~~o Anticipating the need for immunosuppressive treatment within the next 6 months~~ ~~o Resident in a long-term facility~~	Sponsor decision

~~o Current vaping or smoking (occasional smoking is acceptable)~~ o ~~History of chronic smoking within the prior year~~	
Section 6.6 (Dose modification) The decision to make dose adaptions or to initiate a cohort, will be made ~~by the SRC~~ based on emerging data from this and other ongoing studies with related vaccine constructs. Dose escalation decisions will be validated by the SRC (for details, see Section 10.1.5); any plan to ~~alter~~ exceed the planned dose escalations will only be implemented after relevant approval of a substantial protocol amendment. Dose de-escalation and escalation rules have been defined in this protocol (see Section 6.6.2).	Clarification
Section 6.6.1 (Dose limiting toxicity) • Two trial subjects (at any dose level) with the same or similar severe (Grade 3 or higher) AE or reactogenicity (including clinically significant laboratory abnormalities) within 7 days 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).	Clarification
Section 6.6.2 (Dose modification guidance/rules) **Part A** • Any proposal to alter a planned escalation dose, or test a lower dose required for safety de-escalation must be approved by the SRC. • ~~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 … • ~~Any proposal to alter the planned escalation doses must be approved by the SRC~~ • Any proposed alteration to the planned escalation dose level to a smaller or larger escalation increment than that shown in Table 1 must be approved by the SRC. • Any proposal to exceed the planned maximum dose for the trial will only be implemented after relevant approval of a substantial amendment.	Clarification
Section 8.2.8 (Subject diaries) Trial subjects will be given subject diaries at Visit 1 and be asked to record any AEs between visits, solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling), and solicited systemic reactions ~~AEs~~ (nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever [i.e., ≥38°C]).	Clarification
Section 8.2.9 (Assessment of local reactions) Local reactions after IM immunization will be assessed by the investigator at the times given in the SoA (Section 1.3). This information will be used to validate the solicited assessment of local reactions in the subject diary and potentially support AE reporting. Local reactions (via daily solicited reports in the subject diaries and as assessed on visit days by the investigator) will be graded based on the guidance ~~using the criteria~~ given in the 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). The reporting of local reactions will be based on the subject's assessment only.	Clarification
Section 8.2.13 (Assessment of systemic reactions) Systemic reactions after IM immunization will be assessed via daily solicited reports in the subject diaries and at the times given in the SoA (Section 1.3). Systemic reactions will be graded using criteria based on the guidance ~~the criteria~~ given in US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in	Sponsor decision and clarification of an in-consistency

Preventive Vaccine Clinical Trials" for "systemic reaction grading scale" (see the section "Assessment of intensity" in Section 10.3.1.11).	
Section 8.7 (Genetics) A blood sample (blood and / or isolated peripheral blood mononuclear cells [PBMCs]) …… 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. Any remaining material from the blood sample after completion of the immunogenicity assessments may be used for the analyses as described here.	To enable more genetic analyses
Section 8.8 (Biomarkers) Blood draws for explorative biomarker/immunogenicity research purposes will be taken at the times listed in the SoA (Section 1.3). 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. ~~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.~~	Sponsor decision (alignment with BNT162-01)
Section 8.10 (Blood collection) Up to approximately ~~592~~ 602 mL blood will be drawn per subject over the complete trial, i.e., over approximately ~~13~~ 16 months.	Sponsor decision to add an additional blood draw
Section 9.4.2 (Primary endpoints) 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 ~~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 10.3.1.11). 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 "alignment analysis set"), to enable like-for-like evaluations when these data are informally set alongside the data from other trials in the clinical development program for BNT162 vaccines.	Clarification
Section 9.4.5 (Other safety analyses) - Clinical laboratory parameters Abnormal laboratory results will be graded using criteria based on the guidance ~~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 10.3.1.11).	Clarification of an in-consistency
Section 10.9 (Other standard abbreviations and definitions) EoT End of ~~Trial~~ Treatment	This update
Section 10.10 (Protocol amendments and updates) **10.10 Protocol amendments and updates** 10.10.1 Update to protocol version 2.0 Update rationale This update describes changes made in response to internal feedback before submission of version 2.0 to the German PEI.	Sponsor decision to differentiate between sponsor approved versions and

This update was issued before any trial subjects have been enrolled into the trial.	version submitted as amendments
Section 10.10.2 (Protocol amendments and updates) 10.10.2 Update to protocol version 3.0~~Protocol amendment no. 01~~ Update rationale ~~Amendment rationale~~ This amendment update describes changes made in response to feedback from the German PEI (August 10th, 2020). This ~~amendment~~ update ~~will be~~ was issued before any trial subjects ~~have been~~ were enrolled into the trial. This change ~~has~~ had no impact on the planned trial objectives or trial conduct.	Sponsor decision to differentiate between sponsor approved versions and version submitted as amendments
Section 10.10.3 (Protocol amendments and updates) 10.10.3 Update to protocol version 4.0~~Protocol amendment no. 02~~ Update rationale ~~Amendment rationale~~ This ~~amendment~~ update describes changes made in response to feedback from the IEC on version 2.0 (July 10th, 2020). This protocol version reflects the sum of the changes due to the PEI and the IEC feedback on the protocol version 2.0. The updates triggered by the PEI feedback are described in the update to protocol version 3.0 ~~amendment no. 01~~ and updates triggered by the IEC feedback are described in this ~~amendment~~ update (i.e., ~~no. 02~~ protocol version 4.0). This ~~amendment~~ update ~~will be~~ was issued before any trial subjects have been enrolled into the trial. This change ~~has~~ had no impact on the planned trial objectives or trial conduct.	Sponsor decision to differentiate between sponsor approved versions and version submitted as amendments
Section 10.10.4 (Protocol amendment no. 01 (protocol version 5.0)) This section was introduced.	This amendment

10.10.5 Protocol amendment no. 01 (protocol version 6.0)

Amendment rationale

This amendment describes changes made in response to PEI feedback on protocol version 5.0. This amendment was issued after the first trial subjects have been enrolled into the trial. This change has no impact on the planned trial objectives or subject safety.

Detailed description of changes

Editorial changes are not listed.

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
Title page	This update and clarification that Dr Schultz is both Coordinating Investigator and Principal Investigator

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**

Version:	5.06.0	**Date:**	05 OCT~~15 SEP~~ 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 a prophylactic SARS-CoV-2 RNA vaccine (BNT162b3) against COVID-19 using different dosing regimens in healthy adults
Brief title:	A multi-site Phase I/II trial investigating the safety and effects of one BNT162 vaccine against COVID-19 in healthy adults
Trial phase:	Phase I/II
Indication:	Protection against COVID-19
Product:	BNT162b3, SARS-CoV-2 - RNA lipid nanoparticle (RNA-LNP) vaccine utilizing the nucleoside modified messenger RNA (modRNA) format
Coordinating and **Principal investigator:**	Dr. Dr. med. Armin Schultz, CRS Clinical Research Services Mannheim GmbH, Germany (tel.: +49 621 15045 [redacted]
Contract research organization (CRO):	CRS Clinical Research Services Mannheim GmbH, Germany
Trial sites:	CRO sites in one or more of Berlin, Kiel, and Mannheim (Germany)
Sponsor's responsible person:	Özlem Türeci, M.D., Chief Medical Officer, BioNTech SE
Sponsor:	BioNTech RNA Pharmaceuticals GmbH, An der Goldgrube 12, 55131 Mainz, Germany
Regulatory identifiers:	EudraCT no.: 2020-003267-26; Universal Trial Number: U1111-1254-4840; Clinicaltrials.gov code: NCT04537949
Medical Monitor:	The name and contact information will be provided separately

Document history	Date	Version number	Valid for
First approved version*	03 JUL 2020	1.0	Germany
Second approved version*	06 JUL 2020	2.0	Germany
Third approved version* (implementing Paul-Ehrlich Institute (PEI) feedback on version 2.0)	16 AUG 2020	3.0	Germany
Fourth approved version* (implementing Independent Ethics Committee (IEC) feedback on version 2.0 in version 3.0)	16 AUG 2020	4.0	Germany
Fifth approved version* (implementing amendment 01)	15 SEP 2020	5.0	Germany
Sixth approved version* (implementing PEI feedback on amendment 01)	05 OCT 2020	6.0 draft	Germany

* Denotes BioNTech approved versions.

Section 1.1 (trial synopsis) and 4.1 (Overall design)

For the unplanned dose de-escalation cohorts, i.e., where the SRC requests the use of a reduced dose for safety reasons, 12 subjects will be dosed using a subject staggering (6-6) process with intervals of at least 15 min between subjects (as for planned de-escalation cohorts).

The on site observation periods for subjects after each BNT162b3 dose are summarized in Section 5.3.

Clarification following PEI feedback on protocol version 5.0.

Section 1.2 (Schema [graphical representation of the trial]) - Schema for Cohorts 1 to 7

The above schema depicts one sequence of cohorts. Cohorts 5 to 7 include doses lower than Cohort 4 (which uses the maximum planned dose in this trial), and thus the sponsor may decide to perform one or more of Cohorts 5 to 7 before proceeding to Cohort 4.

Clarification.

Section 1.3 (Schedule of activities)

h Flexibility for visit days: Visit 3 Day 8±1 d; Visit 4 Day 22±2 d; Visit 5 Day 29±3 d; Visit 5a 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~~ 387±14d.

Correction.

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
Section 1.1 (trial synopsis) - Key exclusion criteria • Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors: o Cancer o Chronic kidney disease o COPD (chronic obstructive pulmonary disease) o Immunocompromised state (weakened immune system) from solid organ transplant o Obesity (BMI of 30 or higher) o Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies o Sickle cell disease o ~~Type 2 diabetes mellitus~~ o Diabetes mellitus o Hypertension o Asthma o Chronic liver disease o Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2) o Anticipating the need for immunosuppressive treatment within the next 6 months o Resident in a long-term facility o Current vaping or smoking (occasional smoking is acceptable) o History of chronic smoking within the prior year	PEI feedback on protocol version 5.0.
Section 5.2.1 (Exclusion criteria Part A) 29. Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors: o Cancer o Chronic kidney disease o COPD (chronic obstructive pulmonary disease) o Immunocompromised state (weakened immune system) from solid organ transplant o Obesity (BMI of 30 or higher) o Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies o Sickle cell disease o ~~Type 2 diabetes mellitus~~ o Diabetes mellitus o Hypertension o Asthma o Chronic liver disease o Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2) o Anticipating the need for immunosuppressive treatment within the next 6 months o Resident in a long-term facility o Current vaping or smoking (occasional smoking is acceptable) o History of chronic smoking within the prior year	PEI feedback on protocol version 5.0.

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
Section 10.1.1 (Regulatory and ethical considerations) The coordinating investigator or delegate will be responsible for the following: • Providing written summaries of the status of the trial to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC. • Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures. • Providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IEC, European regulation 536/2014 (if applicable), and all other applicable local regulations.	Clarification.
Section 10.10.5 (Protocol amendment no. 01 (protocol version 6.0)) This section was introduced.	This amendment

10.10.6 Protocol amendment no. 01 (protocol version 7.0)

Update rationale

This update describes changes made in response to IEC feedback on protocol amendment no. 01 (protocol version 5.0). This update reverses the reduction of the minimum time interval between dosed trial subjects from 30 min to 15 min.

This amendment was issued after the first trial subjects have been enrolled into the trial. This change has no impact on the planned trial objectives or subject safety.

Detailed description of changes

Editorial changes are not listed.

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
Section 1.1 (trial synopsis) and 4.1 (Overall design) In Cohort 1, the sentinel dosing/subject staggering process will be as follows: • One sentinel subject will be dosed on one day. • If the dosing in this subject was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 5 further subjects will be dosed (with intervals of at least 1 h between subjects). • If the dosing in these 5 subjects was considered to be safe and well tolerated by the investigator based on 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48±2 h data from the sentinel subject): – The remaining 6 subjects in the group will be dosed (with intervals of at least ~~15~~30 min between subjects). – If approved by the SRC, the next planned escalation dose (see Table 1) in Cohort 2 may be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects including	IEC feedback

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
observation on site, phone interview, vital signs, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome. – Once dose escalation is approved, the planned dose de-escalations may also be initiated. For any subsequent dose escalation cohorts, the sentinel/subject staggering process will be as follows: • Two sentinel subjects will be dosed on one day (with intervals of at least ~~15~~30min 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~~30 min between subjects). • If the dosing in these 4 subjects was considered to be safe and well tolerated by the investigator based 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48 h data from the sentinel subjects): – The remaining 6 subjects in the group will be dosed (with intervals of at least ~~15~~30 min between subjects). – If approved by the SRC, the next planned escalation dose (see Table 1) may be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects (including observation on site, short summary of phone interviews [including statement about diary reports], vital signs, investigator reported local and systemic reactions, TEAEs, solicited local & systemic reactions, blood/clinical laboratory data, and brief physical examination outcome). The maximum allowed dose for each vaccine candidate is defined in the Table 1. For any dose de-escalation or dose-refinement cohorts in younger adults, i.e., cohorts with doses lower than previously tested, 12 subjects will be dosed using a subject staggering (6-6) process (with intervals of at least ~~15~~30 min between subjects). The doses in these cohorts 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.	

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
Section 1.1 (trial synopsis) and 4.1 (Overall design) Administration of the planned starting dose (3 to 10 µg) 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; including observation on site, short summary of phone interviews [including statement about diary reports], vital signs, investigator reported local and systemic reactions, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome). The dose in Cohort 8 must also be confirmed by the SRC. For Cohort 8 and any dose escalation cohorts in older adults, 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 ~~15~~30 min intervals for the remaining 6 subjects). The dose levels for Cohorts 9 and 10 are flexible in Table 2 up to the maximum deemed safe in younger adults, to allow optimal dose selection once BNT162b3 data are available. The same dose level will not be tested twice. Where possible (i.e., given acceptable tolerability), dose levels of up to 30 µg and above will be tested because (based on BNT162b1 and BNT162b2 data) older adults may experience weaker immune responses compared to younger adults. The tolerability at dose levels of up to 30 µg and above is expected to be acceptable because, based on BNT162b1 and BNT162b2 data, the tolerability is expected to be better in older subjects compared to younger adults. For the unplanned dose de-escalation cohorts, i.e., where the SRC requests the use of a reduced dose for safety reasons, 12 subjects will be dosed using a subject staggering (6-6) process with intervals of at least ~~15~~30 min between subjects (as for planned de-escalation cohorts).	IEC feedback.
Section 1.3 (Schedule of activities) k) Blood draw for anti-SARS-CoV-2 antibodies. l) For Cohorts 1 and 8, prime immunization with at least 1 h intervals between subjects for the first 6 subjects and then with at least ~~15~~30 min intervals for the remaining 6 subjects. For all other cohorts, immunization with at least ~~15~~30 min intervals between subjects. Boost immunization with at least 15 min intervals between subjects.	IEC feedback
Section 10.10.6 (Protocol amendment no. 01 (protocol version 7.0)) This section was introduced.	This amendment

10.10.7 Protocol amendment no. 02 (protocol version 8.0)

Update rationale

This update implements: a change in sponsor name; the addition of two additional dosing cohorts in older adults; measures to avoid under reporting of mild COVID-19 related events revealed within the trial; terminology alignment with other ongoing trials; correction so some errors.

The rational for the addition of two older adult cohorts is that based on the available immunogenicity and CMI response data after dosing with BNT162b1 and BNT162b2 in younger and elderly adults in the BNT162-01 and BNT162-02 trials (see the BNT162 IB) elicited measurable but lower responses in elderly adults than in younger adults. Therefore, the additional older adult cohorts will be used to investigate BNT162b3 doses above the already tested 20 µg BNT162b3 dose, to support any future Phase III program planned to support marketing approval.

A detailed description of the changes is given below.

This amendment was issued after the first trial subjects have been enrolled into the trial. This change has no impact on the planned trial objectives or subject safety.

Detailed description of changes

Editorial and formatting changes are not listed.

Changed text (inserted text is blue/underlined; deleted text is red/struck out). Where appropriate, a simple description of the changes is given.	Rationale
Title page **CLINICAL TRIAL PROTOCOL INCLUDING AMENDMENTS NO. 01 & 02** **BNT162-04** **Version:** 8~~7~~.0 draft **Date:** ~~28 OCT~~ 02 DEC 2020 **Sponsor:** BioNTech SE~~RNA Pharmaceuticals GmbH~~ **Trial title:** A multi-site, Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of a prophylactic SARS-CoV-2 RNA vaccine (BNT162b3) against COVID-19 using different dosing regimens in healthy adults **Brief title:** A multi-site Phase I/II trial investigating the safety and effects of one BNT162 vaccine against COVID-19 in healthy adults **Trial phase:** Phase I/II **Indication:** Protection against COVID-19 **Product:** BNT162b3, SARS-CoV-2 - RNA lipid nanoparticle (RNA-LNP) vaccine utilizing the nucleoside modified messenger RNA (modRNA) format **Coordinating and Principal investigator:** Dr. Dr. med. Armin Schultz, CRS Clinical Research Services Mannheim GmbH, Germany (tel.: +49 621 15045[redacted] **Contract research organization (CRO):** CRS Clinical Research Services Mannheim GmbH, Germany **Trial sites:** CRO sites in one or more of Berlin, Kiel, and Mannheim (Germany) **Sponsor's responsible person:** Özlem Türeci, M.D., Chief Medical Officer, BioNTech SE **Sponsor:** BioNTech SE~~RNA Pharmaceuticals~~ GmbH, An der Goldgrube 12, 55131 Mainz, Germany **Regulatory identifiers:** EudraCT no.: 2020-003267-26; Universal Trial Number: U1111-1254-4840; Clinicaltrials.gov code: NCT04537949 **Medical Monitor:** The name and contact information will be provided separately **Document history** / **Date** / **Version No.** / **Valid for** Approved version* / 03 JUL 2020 / 1.0 / Germany Approved version* / 06 JUL 2020 / 2.0 / Germany Approved version* (implementing Paul-Ehrlich Institute (PEI) feedback on version 2.0) / 16 AUG 2020 / 3.0 / Germany Approved version* (implementing Independent Ethics Committee (IEC) feedback on version 2.0 in version 3.0) / 16 AUG 2020 / 4.0 / Germany Approved version* (implementing amendment 01) / 15 SEP 2020 / 5.0 / Germany Approved version* (implementing PEI feedback on amendment 01) / 06 OCT 2020 / 6.0 / Germany Approved version* (implementing IEC feedback on amendment 01) / 28 OCT 2020 / 7.0 / Germany Approved version* (implementing amendment 02) / 02 DEC 2020 / 8.0 / Germany * Denotes BioNTech approved versions. **Statement of Compliance:** This trial will be conducted in according to this protocol, the ethical principles that have their origin in the Declaration of Helsinki, good clinical practice (GCP), and applicable regulatory requirements. **Confidentiality Statement:** The information contained in this document is the property and copyright of BioNTech ~~RNA Pharmaceuticals GmbH~~SE. Therefore, this document is provided in confidence to the recipient. No information contained herein shall be published, disclosed or reproduced without prior written approval of the proprietor(s).	Change of sponsor and this update.

Changed text (inserted text is blue/underlined; deleted text is red/struck out). Where appropriate, a simple description of the changes is given.	Rationale
Section 1.1 Trial synopsis (Table 2) ¶ Table 2: Summary of vaccine dose regimens for older adults aged 56 to 85 years in Part A¶ **Vaccine / mRNA type** | **Vaccine-encoded antigen** | **Vaccine IM dosing regimen** | **Part A – Cohort numbers & Dose (µg) (12 subjects per cohort)**: 8 | 9 | 10 | 11 | 12 BNT162b3 / modRNA | Membrane-anchored RBD of the SARS-CoV-2 S protein | Prime: Day 1¶ Boost: Day 22 | 8F¶ 3 – 40 µg [a,b,c] | 9F¶ 10 – 60 µg [a,b,c] | 10F¶ 10 – 620 µg [a,b,c] | 11F¶ 10 – 60 µg [b,c] | 12F¶ 10 – 60 µg [b,c] a) All dose escalation doses used must be judged acceptable by the Safety Review Committee before use.¶ b) Specific doses to be defined, but in the range given. Already given doses will not be repeated.¶ c) A lower prime dose with higher boost dose posology may be used.¶ d) SRC approved and already initiated cohorts.¶ IM = intramuscular; mRNA = messenger RNA; modRNA = nucleoside modified messenger RNA; RBD = Receptor Binding Domain; S protein = SARS-CoV-2 spike protein.¶ ¶ Note: The doses planned in this trial reflect emerging clinical data from the ongoing BNT162-01 and BNT162-02 trials with the related vaccine candidates BNT162b1 and BNT162b2 in younger adults (aged between 18 and 55 years) and elderly older adults (adults aged between 56 and 85 years). ¶	The addition of two cohorts (for details see above).
Section 1.1 Trial synopsis (Table 2) Note: The doses planned in this trial reflect emerging clinical data from the ongoing BNT162-01 and BNT162-02 trials with the related vaccine candidates BNT162b1 and BNT162b2 in younger adults (aged between 18 and 55 years) and ~~elderly adults aged between 65 and 85 years)~~ older adults (adults aged between 56 and 85 years). As of 30 NOV 2020 ~~August 27th, 2020~~, a total of ~~10,586~~ 22,752 subjects (men and women) were dosed at least once with BNT162b vaccines in ongoing clinical trials (for an overview, see Table 4 and Table 5). ~~(i.e., BNT162-01, BNT162-02, and BNT162-03). Of these subjects, at least 96 were older adults (i.e., aged 56 to 85 years).~~ See below for a summary and Section 2.1.3 for details.	Outdated data.
Section 1.1 Trial synopsis (Trial design) and Section 4.1 Overall design The dose levels for Cohorts 9 to 12~~and 10~~ are flexible in Table 2, up to the maximum deemed safe in younger adults, to allow optimal dose selection once BNT162b3 data are available...	The addition of two cohorts.
Section 1.1 Trial synopsis (Population) and Section 4.1.2 Planned number of trial subjects Twelve subjects are required for each of the cohorts planned in Part A. Assuming all cohorts planned in Table 1 are performed, ~~120~~ 144 subjects will be required.	The addition of two cohorts.
Section 1.1 Trial synopsis (Key exclusion criteria) • Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors: o Cancer o ~~Chronic kidney disease~~ o COPD (chronic obstructive pulmonary disease)	Elimination of duplication (see the later exclusion criteria "Known Stage 3 or worse chronic kidney disease (GFR <60 mL/min/1.73 m^2 ˚).
Section 1.2 Schema (Cohorts with older adults) Graphic updated (depictions of Cohorts 11 and 12 were added).	The addition of two cohorts.

Changed text (inserted text is blue/underlined; deleted text is red/struck out). Where appropriate, a simple description of the changes is given.	Rationale
Section 1.2 Schema (Cohorts with older adults) d) Cohorts 8 to ~~10~~ 12 are planned in older adults. For Cohort 8 and any dose escalation cohorts in older adults, 12 subjects will be dosed using a sentinel dosing/subject staggering (2-4-6) process.	The addition of two cohorts.
Section 1.3 Schedule of activities (Table 3) j) Only IMP-related AEs and any SAEs except proven COVID 19 cases which have to be reported regardless on severity and relatedness to the trial drug till the last scheduled FU visit as described into the Section 10.3.1.9. Abbreviations: AE = adverse event; CMI = cell-mediated immune testing; D or d = day; ECG = electrocardiogram; EDTA = Ethylenediamine Tetraacetic Acid; EoT = End of ~~trial~~ treatment (Visit); …	To enable the relationship between COVID-19 protection and immunology to be investigated.
Section Trial-specific abbreviations/terms (Notes for the reader) ~~NOTES FOR THE READER~~ ~~The BioNTech SE group is a holding comprising several subsidiaries including BioNTech RNA Pharmaceuticals GmbH, the sponsor of this clinical trial.~~	Change of sponsor.
Section 2.1.3 Ongoing and planned clinical trials with BNT162 vaccine variants BNT162 vaccine candidates based on the uRNA, modRNA, and saRNA formats are currently under investigation in ~~three~~ clinical trials. ~~with healthy adults (men and women) aged between 18 and 85 years. In these trials, the subjects are either younger adults (aged 18 to 55 years), older adults (aged 56 to 85 years), or elderly adults (aged 65 to 85 years).~~ For the design and status of the ongoing ~~and planned~~ clinical trials, see Table 4.	Outdated data.
Section 2.1.3 Ongoing and planned clinical trials with BNT162 vaccine variants (Table 4 and Table 5) Tables 4 and 5 were updated to reflect the current dosing status.	Outdated data.
Section 2.3.1 Risk assessment • ~~As summarized in Section 2.1.3, to~~ To date most of the AEs reported after immunization with BNT162 vaccine candidates, including BNT162b vaccine candidates (BNT162b1, BNT162b2, and BNT162b3), were mild to moderate in intensity. Generally, good tolerability was observed. Overall, many of the reported AEs appear to be similar to reactogenicity events anticipated for intramuscularly (IM)-administered vaccines, typically with an onset within first 24 h post-immunization. All AEs / reactogenicity symptoms resolved spontaneously, mostly within 24 h of onset, and were managed with simple measures (e.g., paracetamol). There were no serious adverse events (SAEs) and no unexpected toxicities. Fever of severe intensity has been reported. Most AEs were managed with simple measures and resolved spontaneously. • ~~To date, there is no clinical experience with the BNT162b3 vaccine in human subjects, but there is some data available for BNT162b1 and BNT162b2 vaccine candidates in the ongoing trials. The most frequent adverse reactions identified for~~	Outdated text.

Changed text (inserted text is blue/underlined; deleted text is red/struck out). Where appropriate, a simple description of the changes is given.	Rationale
~~BNT162 vaccines at this time are: injection site pain, fever, fatigue, headache, chills, and muscle pain.~~	
Section 2.3.1 Risk assessment ○ This trial includes age-appropriate 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.	Clarification.
Section 4.3 Justification for dose As of 30 NOV ~~August 27th,~~ 2020, a total of 22,75210,586 subjects (men and women) were dosed at least once with ~~BNT162 vaccine candidates, and 10,472 with~~ BNT162b vaccines, in ongoing clinical trials (~~i.e., BNT162-01, BNT162-02, and BNT162-03~~for details, see Table 4 and Table 5). Of these subjects, 96 of the dosed subjects were elderly adults (i.e., aged 65 to 85 years). See below for a summary and Section 2.1.3 for details.	Outdated data.
Section 5.2.1 Exclusion criteria Part A 29. Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors: ○ Cancer ~~○ Chronic kidney disease~~ ○ COPD (chronic obstructive pulmonary disease)	Elimination of duplication (see the later exclusion criteria "Known Stage 3 or worse chronic kidney disease (GFR <60 mL/min/1.73 m^2*).
Section 7.1 Discontinuation of trial treatment 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. 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 subjects should still complete all assessments planned in the SoA ~~will complete all assessments planned for that visit and for the EoT Visit as listed in the SoA~~ (Section 1.3).	Correction of an inconsistency and alignment with reporting in other trials.
Section 7.2 Trial subject discontinuation/withdrawal from the trial If possible, permanently discontinued trial subjects will: • Complete all assessments planned for that visit and for ~~Visit 6~~ the EoT Visit (Visit 7), if discontinued on a visit day. • Complete all assessments planned for ~~Visit 6~~ the EoT Visit (Visit 7)), if not discontinued on a visit day.	Correction of an error.
Section 8.9 Immunogenicity assessments Immune responses will be assessed at the times listed in the SoA (Section 1.3) using: 1. A functional antibody titer, e.g., VNT or an equivalent assay.	Alignment with the BNT162-01 trial to enable cross-trial comparisons.

Changed text (inserted text is blue/underlined; deleted text is red/struck out). Where appropriate, a simple description of the changes is given.	Rationale

• Sero negative is defined as titers below the starting dilution (i.e., below the LOD [limit of detection] of the assay).
• Seroconversion after immunization is defined as a 4-fold increase in titer.
  ○ for seronegative pre-immunization sera: a titer ≥ 4-times the LOD.
  ○ for seropositive pre-immunization sera: a titer which is 4-fold higher than the measured pre-immunization titer.
~~1. A functional antibody titer, e.g., VNT or an equivalent assay.~~
  • Sero negative is defined as titers below the starting dilution (i.e., below the LOD [limit of detection] of the assay).
  • Seroconversion after immunization is defined as a 4-fold increase in titer.
  ○ for seronegative pre-immunization sera: a titer ≥ 4-times the LOD.
  ○ for seropositive pre-immunization sera: a titer which is 4-fold higher than the measured pre-immunization titer.	

Section 8.9 Immunogenicity assessments 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. ~~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.	Alignment with the BNT162-01 trial to enable cross-trial comparisons.
Section 8.9 Immunogenicity assessments [redacted]	Alignment with the BNT162-01 trial to enable cross-trial comparisons.
Section 10.3.1.1 Events meeting the AE definition Reactogenicity need only be reported as an AE if doing so provides clinically significant information not available elsewhere (such as the solicited reactions listings), e.g., severe reactogenicity lasting longer than the period of solicitation of symptoms in the subject diary. Diagnostic AEs for local and/or systemic reactogenicity, e.g., "injection site reaction" or "flu-like illness", should generally be preferred over AEs reporting of individual signs and symptoms. ~~Only the diagnoses of clinically significant local and/or systemic reactogenicity e.g., injection site reactions need to be reported as AEs (generally, the individual signs and symptoms of local or systemic reactogenicity making up diagnostic AEs are already captured as solicited reactions).~~	Aligned wording with adopting the version with higher precision

Changed text (inserted text is blue/underlined; deleted text is red/struck out). Where appropriate, a simple description of the changes is given.	Rationale
Section 10.3.1.9 Documentation of particular situations **AEs of proven COVID-19 disease ~~of moderate or severe intensity~~:** ~~Any case of proven COVID-19 disease occurring during the observation period should be reported as an SAE, where the intensity of the respective AE is rated as "moderate" or "severe" (according to the criteria provided in Section 10.3.1.7). If none of the other SAE definitions are deemed suitable, then the SAE criterion of being a "medically important event" should be applied (according to the definitions provided in Section 10.3.1.4). An SAE form should be completed, including follow-up information, as detailed in Section 10.3.1.10 such that an SAE report and narrative can be prepared and distributed.~~ Any case of proven COVID-19 disease occurring till the last planned FU visit should be reported as an SAE/AE. AEs which are rated as "moderate" or "severe" (according to the criteria provided in Section 10.3.1.7) will need to be reported as an SAE. 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." All mild cases of proven COVID 19 cases which do not correspond to seriousness criteria will need to be reported as an AE in eCRF.	To enable the relationship between COVID-19 protection and immunology to be investigated.
Section 10.10.7 (Protocol amendment no. 02 (protocol version 8.0) This section was introduced.	This amendment.

10.10.8 Protocol amendment no. 03 (protocol version 9.0)

Update rationale

This update implements the removal of Part B, changes to the primary objective endpoints, and a change to concomitant medication reporting during study follow-up to allow capture of vaccinations, e.g., SARS-CoV-2 vaccinations.

[redacted]

Detailed description of changes

Editorial changes are not listed.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Title page Title page was updated to reflect the changes: • (Date) ~~02 DEC 2020~~ 25 MAR 2021 • (Version) ~~8.0~~9.0 • (Title) CLINICAL TRIAL PROTOCOL INCLUDING AMENDMENTS NOS. 01 ~~&~~TO ~~02~~03 ~~• Sponsor's responsible person: Özlem Türeci, MD, Chief Medical Officer, BioNTech SE~~	This update, addition of new medical person of record on this study, and correction of

<table>
<tr><th>Changed text
(inserted text is blue/underlined; deleted text is red/struck out)</th><th>Rationale</th></tr>
<tr><td>

Sponsor's medical representative: Elizabeth Adams, MD, Senior Medical Director, BioNTech US, Inc.
Sponsor: BioNTech SE~~ GmbH~~, An der Goldgrube 12, 55131 Mainz, Germany
(Document history)

Approved version* (implementing amendment 03) 25 MAR 2021 9.0 Germany
</td><td>company name.</td></tr>
<tr><td>
Section 1.1 (Trial synopsis)

Trial Summary

BNT162b3 is a liposomally formulated nucleoside modified RNA vaccine candidate that encodes the SARS-CoV-2 spike protein (S protein) including its transmembrane domain. The candidate vaccine was under evaluation for its induction of immune responses in healthy adults for the prevention of COVID-19 disease. BNT162b2 became the lead vaccine candidate to prevent COVID-19 disease and received Conditional Marketing Authorization in the European Union under the name of Comirnaty [redacted]
</td><td>Trial summary added for clarity and update on current BNT162 vaccine information.</td></tr>
<tr><td>
Section 1.1 (Trial synopsis) and Section 3 (Objectives and endpoints)

<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>Primary objective</td><td></td></tr>
<tr><td>To describe the safety and tolerability profiles of BNT162b3 in healthy adults after prime/boost (P/B) immunization.</td><td>

Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7 d after each immunization.
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.
The proportion of subjects with at least 1 unsolicited treatment emergent adverse event (TEAE) occurring ~~up to 28 d after the prime immunization and 28 d after the boost immunization~~after prime immunization up to boost immunization or 28 d after prime immunization (whichever comes first) and up to 28 d after the boost immunization.

</td></tr>
<tr><td>Secondary objectives</td><td></td></tr>
<tr><td>To describe the immune response in healthy adults after P/B immunization measured by a functional antibody titer, e.g., virus neutralization test or an equivalent assay available by the time of trial conduct.</td><td>At 7 d and 21 d after prime immunization and at 7 d, 14 d, 21 d, 28 d, ~~36 d,~~ 63 d, 162 d, and 365 d after the boost immunization:

Functional antibody responses.
Fold increase in functional antibody titers.
Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline.

</td></tr>
<tr><td>Exploratory objectives</td><td></td></tr>
<tr><td>[redacted]</td><td></td></tr>
</table>
</td><td>Updates to allow for analysis comparison across studies and corrections.</td></tr>
</table>

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 1.1 (Trial synopsis) and 4.1 (Overall design) This trial has two parts, Part A and Part B. [redacted] Part B of the study will no longer be conducted. As of March 12th, 2021, Part A subjects have completed vaccinations and are in follow-up evaluations. Part A ~~,~~is a dose-finding part, with possible dose escalation cohorts, and discretionary dose de-escalation and refinement cohorts in younger subjects. Cohorts in older subjects are optional and dependent on acceptability of dosing in younger subjects. ~~Part B, a part with expansion cohorts with dose levels which are selected using data generated in Part A.~~	Updates to reflect removal of Part B and current information.
Section 1.1 (Trial synopsis) Table 2: Summary of vaccine dose regimens for older adults aged 56 to 85 years in Part A … Note: The doses planned in this trial reflect emerging clinical data from the ongoing BNT162-01 and BNT162-02 trials with the related vaccine candidates BNT162b1 and BNT162b2 in younger adults (aged between 18 and 55 years) and older adults (adults aged between 56 and 85 years). ~~As of 30 NOV 2020, a total of 22,752 subjects (men and women) were dosed at least once with BNT162b vaccines in ongoing clinical trials (~~For an overview of BNT162b vaccines in ongoing clinical trials, see ~~Table 4 and Table 5 the current BNT162 IB~~).	Updates to reflect current information.
Section 1.1 (Trial synopsis) and 4.1 (Overall design) Part B ~~Part B will only be started if approved using a substantial protocol amendment.~~ ~~Details of Part B will be defined in the protocol amendment after a thorough evaluation of immunogenicity and safety data from Part A. The safety data evaluated will include 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.~~ ~~The protocol amendment will include a summary of relevant safety and tolerability data collected in Part A. This protocol amendment will also include Part B specific inclusion/exclusion criteria, objectives/endpoints, a description of the planned statistical analyses, and descriptions of any added trial assessments and procedures.~~ ~~Part B will use a randomized, placebo-controlled design in the likely target population (e.g., including higher risk populations and/or immunocompromised populations). Part B may employ a surrogate marker as a measure of vaccine efficacy.~~ [redacted] Part B will no longer be conducted.	Updates to reflect removal of Part B.
Section 1.1 (Trial synopsis) Population … ~~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.~~	Deletion to reflect removal of Part B.
Section 1.1 (Trial synopsis) **Trial treatments (BNT162 vaccine)** **Name:** BNT162 vaccine - Anti-viral RNA vaccine for active immunization against COVID-19.	Deletions to reflect removal of Part B.

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Type: RNA-LNP vaccine utilizing the BioNTech modRNA format: product code BNT162b3.

Dosage levels: See Table 1. The planned dose per vaccine candidate will not exceed the pre-defined maximum dose (see Table 1).

~~Part B expansion cohorts: The to be tested doses will be chosen after review of the safety, tolerability, and immunogenicity data from Part A.~~

Dosage frequency: Two injections 21 d apart. Injection volumes will be up to 1.5 mL.

Administration route: Intramuscular (IM); upper arm, musculus deltoideus. 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 Visit 10. No formal interim statistical analysis will be performed. However, the preliminary 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.

~~The planned protocol amendment will include a description of the planned statistical analyses planned for Part B.~~

</td><td></td></tr>
<tr><td>

Section 1.3 (Schedule of activities)

Table 3: Schedule of trial procedures and assessments – BNT162b3

Procedure / Assessment	…	Visit 8 ~63 d from Visit 4 (FU Visit)	Visit 9 ~162 d from Visit 4 (FU Visit)	Visit 10 ~365 d from Visit 4 (FU Visit)
…	…	…	…	…
Record AEs since last visit	…	X [j]	X [j]	X [j]
…	…	…	…	…
Blood draw for HLA [p]	…			
…	…	…	…	…
Concomitant medication [q]	…	X	X	X

…

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.

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

g) Record any medications that trial subjects receive during the trial in the CRF starting after Visit 0 and until the respective EoT Visit; record any vaccination, including SARS-CoV-2 vaccination, that subjects receive after the EoT Visit until the last FU Visit in the CRF.

Note: If the boost dose is not administered, subjects should still complete all assessments planned in the SoA.

Abbreviations: AE = adverse event; CMI = cell-mediated immune testing; CRF = case report form; 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; min = minute(s); Day 0 = one day before Day 1; IMP = investigational medicinal product; min = minute(s); SARS-CoV-2 = the virus leading to COVID-2019; WOCBP = women of childbearing potential.

</td><td>Correction for recording AEs at Visit 10, correction of footnote numbering, and insertion to include updated concomitant medication information.</td></tr>
</table>

<table>
<tr><th>Changed text
(inserted text is blue/underlined; deleted text is red/struck out)</th><th>Rationale</th></tr>
<tr><td>Trial-specific abbreviations/terms

<table><tr><th>Abbreviation/Term</th><th>Explanation</th></tr><tr><td>…</td><td>…</td></tr><tr><td>ELISpot</td><td>Enzyme-Linked Immuno-sorbent Spot</td></tr><tr><td>…</td><td>…</td></tr></table></td><td>Correction.</td></tr>
<tr><td>Section 2.1.1 Overview of the disease

Severe Acute Respiratory Syndrome (SARS) -CoV-2 infections and the caused disease Coronavirus Disease 2019 (COVID-19) are increasing every day and spreading globally, affecting more and more countries.
On March 11th, 2020 the World Health Organization (WHO) characterized the COVID-19 outbreak as a pandemic.
The WHO Situation Update Report dated June 30th, 2020 noted 9,843,073 confirmed cases with 495,760 deaths globally and 2,656,437 confirmed cases with 196,541 deaths in Europe (WHO Situation Report Nr. 160). 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) at least three SARS-CoV-2 vaccines for preventing COVID-19 disease that have received either Conditional Marketing Authorization in Europe or Emergency Use Authorization in the United States.</td><td>Updates to reflect current information.</td></tr>
<tr><td>Section 2.1.3 Ongoing and planned clinical trials with BNT162 vaccine variants

Multiple SARS-CoV-2 RNA vaccine platforms (BNT162) have undergone evaluation since the advent of the SARS-CoV-2 pandemic. BNT162b3, like BNT162b1 and BNT162b2, as under investigation in the trials BNT162-01, BNT162-02, and BNT162-03, arethe SARS-CoV-2 vaccine (Comirnaty) that received Conditional Marketing Authorization at the end of 2020, is a modRNAs. RNA modifications are is known to impact the extent of innate immune activation at a given dose level, and thus potentially the extent of reactogenicity (Weissman and Karikó 2015). Therefore, tolerability data obtained with the BNT162b1 and BNT162b2 vaccine variants may be potentially informative forwas evaluated in the context of the data on BNT162b3, and should be taken into consideration by the SRC for recommendations of lower or interim doses.
BNT162 vaccine candidates based on the uRNA, modRNA, and saRNA formats are currently under investigation in clinical trials.
For the design, and status, number of trial subjects dosed at least once with a BNT162 vaccine candidate, and summary of the available results of the ongoing clinical trials, see Table 4the current BNT162 IB.

Table 4: Status of ongoing and planned clinical trials (as of 30 NOV 2020)
<table><tr><th>Trial number</th><th>Design</th><th>Current number dosed (subject age)</th></tr><tr><td>BNT162-01 (NCT04380701) Germany</td><td>Phase I/II, 2-part, dose escalation trial.
Part A is open-label and non-randomized.
(All subjects receive active vaccine)

Part B: Due to changes in the overall clinical development plan, Part B will no longer be conducted.</td><td>BNT162a1 (age 18 to 55 years):
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)

BNT162b1 (age 18 to 55 years):
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</td></tr></table></td><td>Updated to current BNT162 vaccine information, deletion of Tables 4 and 5, and update of the references to the BNT162 IB instead of Tables 4 and 5.</td></tr>
</table>

Changed text (inserted text is blue/underlined; deleted text is red/struck out)			Rationale
		~~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)~~ ~~BNT162b1 (age 56 to 85 years):~~ ~~10 µg 12 subjects prime / 12 boost~~ ~~20 µg 12 subjects prime / 11 boost~~ ~~30 µg 12 subjects prime / 0 boost~~ ~~BNT162b2 (age 18 to 55 years):~~ ~~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~~ ~~BNT162b2 (age 56 to 85 years):~~ ~~10 µg 12 subjects prime / 12 boost~~ ~~20 µg 12 subjects prime / 12 boost~~ ~~30 µg 12 subjects prime / 12 boost~~ ~~BNT162c2 SD (age 18 to 55 years):~~ ~~0.1 µg 12 subjects (single dose)~~ ~~0.3 µg 12 subjects (single dose)~~ ~~0.6 µg 12 subjects (single dose)~~ ~~1 µg 12 subjects (single dose)~~ ~~BNT162c2 P/B (age 18 to 55 years):~~ ~~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 / 11 boost~~	
~~BNT162-02 / C4591001~~ ~~(NCT 04368728)~~ ~~US, Argentina, Brazil, Turkey, Germany~~	~~Phase I/II/III, placebo-controlled, randomized, observer-blind, dose-finding trial~~ ~~(Subjects are randomized: 4 active vaccine to 1 placebo)~~	~~**Phase I**~~ ~~BNT162b1 (age 18 to 55 years):~~ ~~10 µg 15 subjects prime / 15 boost~~ ~~20 µg 15 subjects prime / 15 boost~~ ~~30 µg 15 subjects prime / 15 boost~~ ~~100 µg 15 subjects prime~~ ~~(Further dosing with BNT162b1 at 100 µg and the boost dose for already dosed subjects was cancelled)~~ ~~BNT162b1 (age 65 to 85 years):~~ ~~10 µg 15 subjects prime / 15 boost~~ ~~20 µg 15 subjects prime / 15 boost~~ ~~30 µg 15 subjects prime / 15 boost~~ ~~BNT162b2 (age 18 to 55 years):~~ ~~10 µg 15 subjects prime / 15 boost~~ ~~20 µg 15 subjects prime / 15 boost~~ ~~30 µg 15 subjects prime / 15 boost~~	

Changed text (inserted text is blue/underlined; deleted text is red/struck out)			Rationale
		~~BNT162b2 (age 65 to 85 years):~~ ~~10 µg 15 subjects prime / 15 boost~~ ~~20 µg 15 subjects prime / 15 boost~~ ~~30 µg 15 subjects prime / 15 boost~~ ~~Phase II III~~ ~~BNT162b2 (age 18 to 85 years)~~ ~~30 µg 43,031 subjects (split P/B not available)~~ ~~(Assuming 50% of the subjects are on BNT162b2~~ ~~30 µg 21,965 subjects)~~	
~~BNT162-03~~ ~~(NCT 04523571)~~ ~~China~~	~~Phase I, randomized, placebo-controlled, observer-blind trial.~~	~~BNT162b1 (age 18 to 55 years):~~ ~~10 µg 24 subjects prime / 24 boost~~ ~~30 µg 24 subjects prime / 24 boost~~ ~~BNT162b1 (age >55 years):~~ ~~10 µg 24 subjects prime / 24 boost~~ ~~30 µg 24 subjects prime / 24 boost~~	
~~BNT162-04~~ ~~(NCT 04537949)~~ ~~Germany~~	~~Phase I/II, 2-part, dose escalation trial.~~ ~~Part A is open-label and non-randomized.~~ ~~(All subjects receive active vaccine)~~ ~~Part B will be defined in a protocol amendment.~~	~~BNT162b3 (age 18 to 55 years):~~ ~~3 µg 12 subjects prime / 12 boost~~ ~~10 µg 12 subjects prime / 12 boost~~ ~~20 µg 12 subjects prime / 12 boost~~ ~~30 µg 12 subjects prime / 10 boost~~ ~~BNT162b3 (age 56 to 85 years):~~ ~~3 µg 12 subjects prime / 11 boost~~ ~~10 µg 12 subjects prime / 0 boost~~	
~~BNT162-05~~ ~~(NCT: Not assigned)~~ ~~Japan~~	~~Phase I/II, placebo-controlled, randomized,~~ ~~observer-blind trial.~~	~~BNT162b3 (age 20 to 64 years):~~ ~~30 µg 130 subjects prime / 120 boost~~ ~~BNT162b3 (age 65 to 85 years):~~ ~~30 µg 30 subjects prime / 25 boost~~	

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

~~See Table 5 for the number of trial subjects dosed at least once with BNT162 vaccines in the ongoing clinical trials~~.

~~Table 5: Number of trial subjects dosed at least once with BNT162 vaccines in the ongoing clinical trials (status 30 NOV 2020)~~

~~BNT162 vaccine~~ ~~*Dosing regimen*~~	~~BNT162a1~~	~~BNT162b1~~	~~BNT162b2~~	~~BNT162b3~~	~~BNT162c2~~
~~Phase I~~					
~~SD (18 to 55 yrs)~~	~~30~~	~~216~~	~~105~~	~~48~~	~~96~~
~~SD (20 to 64 yrs)~~	~~NA~~	~~NA~~	~~130~~	~~NA~~	~~NA~~
~~SD (56 to 85 yrs)~~	~~0~~	~~81~~	~~111~~	~~24~~	~~0~~
~~Phase II/III~~					
~~SD (18 to 88 yrs)~~			~~21,065*~~		

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
~~Total all adults dosed at least once in Phase I & II/III 30 369 22,311* 72 96~~ ~~Sum BNT162b vaccines = 22,752*~~ ~~Sum for all BNT162 vaccines = 22,878*~~ ~~* Estimated - includes estimated number based on 1:1 active:placebo assignment.~~ ~~NA = not tested; SD = single dose.~~ ~~For a summary of the available results from the ongoing trials see the BNT162 IB.~~	
Section 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 anti-viral 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.~~	Deletions to reflect current information.
Section 2.3.1 Risk assessment • Generally, good tolerability was observed. Overall, many of the reported AEs appear to be similar to reactogenicity events anticipated for intramuscularly (IM)-administered vaccines, typically with an onset within first 24 h post-immunization. All AEs / reactogenicity symptoms resolved spontaneously, mostly within 24 h of onset, and were managed with simple measures (e.g., paracetamol). There were no serious adverse events (SAEs) and no unexpected toxicities. Fever of severe intensity has been reported. Most AEs were managed with simple measures and resolved spontaneously. Please refer to the current BNT162 IB.	Addition to reflect current information.
Section 2.3.1 Risk assessment … • ~~The expanded SRC review and evaluate at least the Day 21 data per vaccine to confirm what doses will be given in Part B~~.	Deletion to reflect removal of Part B.
Section 4.1.2 Planned number of trial subjects … ~~In Part B~~ ~~The planned number of trial subjects in Part B will be calculated based on the data from Part A and defined in a protocol amendment.~~	Deletion to reflect removal of Part B.
Section 4.2 Scientific rationale for the trial design ~~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., immunocompromised populations, and other fragile populations, and/or indicated populations).~~ Part B of the trial will no longer be conducted [redacted]	Deletion to reflect removal of Part B.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 4.3 Justification for dose … ~~As of 30 NOV 2020, a total of 22,752 subjects (men and women) were~~For the status and number of trial subjects dosed at least once with a BNT162b vaccine~~s~~ candidate~~,~~ in ongoing clinical trials ~~(for details~~, see ~~Table 4and Table 5~~the current BNT162 IB). ~~Of these subjects, 96 of the dosed subjects were elderly adults (i.e., aged 65 to 85 years).~~ See below for a summary and Section 2.1.3 for details.	Updates to reflect current information.
Section 5.1 Inclusion criteria ~~Section 5.1.2 Inclusion criteria Part B~~ ~~Inclusion criteria for Part B will defined in the planned protocol amendment.~~	Deletion to reflect removal of Part B.
Section 5.2 Exclusion criteria ~~Section 5.2.2 Exclusion criteria Part B~~ ~~Exclusion criteria for Part B will defined in the planned protocol amendment.~~	Deletion to reflect removal of Part B.
Section 6.1 IMP administered **Name:** BNT162b3 vaccine - Anti-viral RNA vaccine for active immunization against COVID-19. **Type:** RNA-LNP vaccine utilizing the BioNTech modRNA format: product code BNT162b3. **Dosage levels:** See Table 1. The planned dose per vaccine candidate will not exceed the pre-defined maximum dose (see Table 1). ~~Part B expansion cohorts: The to be tested doses will be chosen after review of the safety, tolerability, and immunogenicity data from Part A.~~ **Dosage frequency:** Two injections 21 d apart. Injection volumes will be up to 1.5 mL. **Administration route:** Intramuscular (IM); upper arm, musculus deltoideus. The same arm may be used for both immunizations. The non-dominant arm is preferred.	Deletion to reflect removal of Part B.
Section 6.3 Measures to minimize bias: randomization and blinding Not applicable ~~for Part A. Details for Part B will be defined using a protocol amendment~~.	Deletion to reflect removal of Part B.
Section 6.5 Concomitant therapy Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest) that the trial subject receives during the trial, i.e., starting after Visit 0 and until Visit 7, must be recorded along with the: • Reason for use • Dates of administration including start and end dates • Dosage information including dose and frequency Record any vaccination, including SARS-CoV-2 vaccination, received after the EoT Visit until the last FU Visit (Visit 10) in the CRF.	Insertion to include updated concomitant medication information.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 6.6.2 Dose modification guidance/rules ~~The trial design also allows for:~~ ~~• The selection of which BNT162b3 vaccine dose regimens and posologies that will be investigated in Part B following a substantial protocol amendment.~~ ~~See Section 10.1.5 for the data set upon which SRC decisions described below are made for Part A.~~ **Part A** See Section 10.1.5 for the data set upon which SRC decisions described below are made for Part A. • Any proposal to alter a planned escalation dose, or test a lower dose required for safety de-escalation must be approved by the SRC. • Any plan to exceed the planned maximum dose will only be implemented after relevant approval of a substantial protocol amendment. Dose escalation: • Dose escalation will only continue if the previous dose was considered safe and well tolerated by the SRC. • Any proposed alteration to the planned escalation dose level to a smaller or larger escalation increment than that shown in Table 1 must be approved by the SRC. • Any proposal to exceed the planned maximum dose for the trial will only be implemented after relevant approval of a substantial amendment. ~~Part B~~ ~~• The to be tested doses for in Part B will be chosen after review of the safety, tolerability, and immunogenicity data from Part A for that vaccine.~~ ~~• Relevant safety and tolerability data collected in Part A will be included in the protocol amendment planned to define details of Part B and/or in the BNT162 IB.~~	Updates to reflect removal of Part B.
Section 8 Trial Assessments and Procedures … ~~The listed trial assessments and procedures will be updated to reflect the needs of Part B in the planned protocol amendment.~~	Deletion to reflect removal of Part B.
Section 9.2 Sample size determination No formal sample size calculations were performed. For Part A, the inclusion of 12 subjects per group is considered to be adequate for a safety assessment of 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%. ~~The sample size for Part B will be assessed based on the data from Part A and confirmed/adjusted in the planned protocol amendment.~~	Deletion to reflect removal of Part B.
Section 9.4.1 General considerations In general, data will be summarized by groups and groups may be combined as appropriate. ~~Part A and Part B will be analyzed separately and may be combined as appropriate.~~ Continuous variables will be summarized by group using the following descriptive statistics: number of subjects (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by group presenting absolute and relative frequencies (n and %) of subjects in each category. ~~The planned protocol amendment will include a description of the planned statistical analyses planned for Part B.~~	Deletion to reflect removal of Part B.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
Section 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. Solicited local and systemic reactions (from the diary card) will be summarized using the Safety Set. In general, solicited reactions will be analyzed by dose level and for each immunization, i.e.: • For the prime immunization up to 7 d after prime immunization • For the boost immunization up to 7 d after boost immunization 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 Moreover, the number and percentage of subjects reporting at least one local reaction will be summarized by worst grade using the Safety Set. Treatment emergent AEs (TEAEs) are defined in Section 10.3.1~~.1~~ and will be summarized using the Safety Set. In general, AEs will be analyzed by dose level and for each immunization, i.e.~~, for~~: ~~• Day 1 to 7~~ ~~• Day 1 21 (pre boost)~~ ~~• Day 21(post boost) 28~~ ~~• Day 21(post boost) 50~~ • For the prime immunization up to 28 d after prime immunization or until boost immunization (whichever comes first) • For the boost immunization up to 28 d after boost immunization • For the prime immunization up to 28 d after boost immunization Additionally, AEs will be summarized for all dose levels combined for each type. Additional AE analyses may be described in the SAP. For each analysis, the number and percentage of subjects reporting at least one TEAE 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 AEs and local and systemic reactions ~~will~~may be repeated with a reduced set of terms ~~(called the "alignment analysis set")~~, to enable like-for-like evaluations when these data are informally set alongside the data from other trials in the clinical development program for BNT162 vaccines.	Updates for clarity and to allow for analysis comparison across studies.

<table>
<tr><th>Changed text
(inserted text is blue/underlined; deleted text is red/struck out)</th><th>Rationale</th></tr>
<tr><td>~~Moreover, the number and percentage of subjects reporting at least one local reaction will be summarized by worst grade using the Safety Set.~~</td><td></td></tr>
<tr><td><u>Section 10.1.5 Committees - SRC</u>

For Part A, the SRC will ~~be~~ comprise~~d by~~ a sponsor medical representative, the Medical Monitor, a sponsor-independent investigator, and a site representative.
~~For the decision to progress to Part B, an independent statistical consultant and a third party expert will also be included.~~</td><td>Deletions for clarity and to reflect removal of Part B.</td></tr>
<tr><td><u>Section 10.3.1.11 Assessments of intensity for solicited local and systemic reactions and laboratory abnormalities</u>

Table ~~8~~7: Laboratory abnormality grading scale

<table><tr><th>Chemistry</th><th>…</th></tr><tr><td>…</td><td>…</td></tr><tr><td>Alkaline phosphatase – increase by factor</td><td>…</td></tr><tr><td>…</td><td>…</td></tr></table></td><td>Table number updated and correction.</td></tr>
<tr><td><u>Section 10.9 Other standard abbreviations and definitions</u>

For trial-specific abbreviations, see the list of trial-specific abbreviations.
For definitions related to safety, see Section 10.3.

Abbreviation Explanation
… …
~~CIOMS~~BMI ~~Council for International Organizations of Medical Sciences~~Body Mass Index</td><td>Updates.</td></tr>
<tr><td><u>Section 10.10.8 (Protocol amendment no. 03 (protocol version 9.0))</u>
This section was introduced.</td><td>This amendment.</td></tr>
<tr><td><u>Section 11 References</u>

…
~~Habibzadeh P, Stoneman EK. The Novel Coronavirus: A Bird's Eye View. Int J Occup Environ Med. 2020; 11 (2): 65-71.~~
~~Weissman D and Karikó K. mRNA: Fulfilling the Promise of Gene Therapy. 2015; Mol Ther. 2015; 23(9): 1416-17.~~
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.
NCT04523571. BNT162-03. Safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b1) in Chinese healthy subjects: A Phase I, randomized, placebo-controlled, observer-blind study. Ongoing BioNTech clinical trial.
NCT04368728. BNT162-02/C4591001. ~~A Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals.~~Study to describe the safety, tolerability, immunogenicity, and efficacy of RNA vaccine candidates against COVID-19 in healthy individuals. Study Intervention Number: PF-07302048. Ongoing BioNTech clinical trial.</td><td>Deletion of reference no longer used, correction of alphabetical order, and Clinicaltrials.gov entry update.</td></tr>
</table>

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	Rationale
NCT04380701. BNT162-01. A multi-site, Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy adults. 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~~ Nat Rev Drug Discov. 2014; 13 (10): 759-80. US Center for Disease control and Prevention (CDC). Coronavirus Disease 2019 (COVID-19) guidance webpage. Accessed July 14th, 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. Weissman D and Karikó K. mRNA: Fulfilling the Promise of Gene Therapy. 2015; Mol Ther. 2015; 23(9): 1416-17.	

10.10.9 Protocol amendment no. 04 (protocol version 10.0)

Update rationale

This update implements corrections to time points in the exploratory objectives and a deletion within Section 4.4 (End of Treatment and end of trial definition) in order to allow subjects to participate in other clinical trials investigating COVID-19 vaccines and treatments.

Detailed description of changes

Editorial changes are not listed.

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	Rationale
Title page Title page was updated to reflect the changes: • (Date) ~~25 MAR 2021 12~~ MAY 2021 • (Version) ~~9.0~~10.0 • (Title) CLINICAL TRIAL PROTOCOL INCLUDING AMENDMENTS NOS. 01 TO ~~03~~04 • (Document history) Approved version* (implementing amendment 04) 12 MAY 2021 10.0 Germany	This update.

Changed text
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Rationale

Section 1.1 (Trial synopsis)

Corrections and updates for clarity.

Objectives	Endpoints
Primary objective	
To describe the safety and tolerability profiles of BNT162b3 in healthy adults after prime/boost (P/B) immunization.	• Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7 d after each immunization. • 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. • The proportion of subjects with at least 1 unsolicited treatment emergent adverse event (TEAE) occurring after prime immunization up to boost immunization or 28 d after prime immunization (whichever comes first) and up to 28 d after the boost immunization.
Secondary objectives	
To describe the immune response in healthy adults after 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.	As compared to baseline, at~~At~~ 7 d and 21 d after prime immunization and at 7 d, 14 d, 21 d, 28 d, 63 d, 162 d, and 365 d after the boost immunization: • Functional antibody responses. • Fold increase in functional antibody titers. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers~~ as compared to baseline~~.
Exploratory objectives	
[redacted]	

Trial-specific abbreviations/terms

Addition for clarity.

Abbreviation/Term	Explanation
…	…
VNT	Virus neutralization test
…	…

Section 3 (Objectives and endpoints)

Corrections and updates for clarity.

Objectives	Endpoints
Primary objective	

Changed text (inserted text is blue/underlined; deleted text is red/struck out)	**Rationale**
To describe the safety and tolerability profiles of BNT162b3 in healthy adults after prime/boost (P/B) immunization. • Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7 d after each immunization. • 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. • The proportion of subjects with at least 1 unsolicited TEAE occurring after prime immunization up to boost immunization or 28 d after prime immunization (whichever comes first) and up to 28 d after the boost immunization.	
Secondary objectives	
To describe the immune response in healthy adults after P/B immunization measured by a functional antibody titer, e.g., VNT or an equivalent assay available by the time of trial conduct. As compared to baseline, at~~At~~ 7 d and 21 d after prime immunization and at 7 d, 14 d, 21 d, 28 d, 63 d, 162 d, and 365 d after the boost immunization: • Functional antibody responses. • Fold increase in functional antibody titers. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers~~ as compared to baseline~~.	
Exploratory objectives	
[redacted]	
Section 4.4 End of Treatment (EoT) and end of trial definition A trial subject is considered to have completed the trial if they have completed all planned visits as listed in the SoA, including all follow-up visits (see Section 1.3). The End of Treatment is defined as the date the last subject completed the EoT Visit (Visit 7). 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~~. The end of trial is defined as the date when the last subject completed Visit 10 (Last Subject Last Visit).	Deletion to allow subjects to participate in other clinical trials investigating COVID-19 vaccines and treatments.
Section 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.	Deletion to correct error.

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 Guidance 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.

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 H10N8 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.

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.

NCT04523571. BNT162-03. Safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b1) in Chinese healthy subjects: A Phase I, randomized, placebo-controlled, observer-blind study. Ongoing BioNTech clinical trial.

NCT04368728. BNT162-02/C4591001. Study to describe the safety, tolerability, immunogenicity, and efficacy of RNA vaccine candidates against COVID-19 in healthy individuals. Study Intervention Number: PF-07302048. Ongoing BioNTech clinical trial.

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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. Nat Rev Drug Discov. 2014; 13 (10): 759-80.

US Center for Disease control and Prevention (CDC). Coronavirus Disease 2019 (COVID-19) guidance webpage. Accessed July 14th, 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.

Weissman D and Karikó K. mRNA: Fulfilling the Promise of Gene Therapy. 2015; Mol Ther. 2015; 23(9): 1416-17.

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WHO Situation Report Nr. 160, June 30th, 2020. Accessed at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/