CLINICAL TRIAL PROTOCOL
INCLUDING AMENDMENTS NOS. 01 TO 04
BNT162-01

Version: 7.0 **Date:** 26 Jun 2020

Sponsor: BioNTech RNA Pharmaceuticals GmbH

Trial title:	A Multi-site, Phase I/II, 2-Part, Dose-Escalation Trial Investigating the Safety and Immunogenicity of Four Prophylactic SARS-CoV-2 RNA Vaccines Against COVID-19 Using Different Dosing Regimens in Healthy Adults
Brief title:	A Multi-site Phase I/II Trial Investigating the Safety and Effects of Four BNT162 Vaccines Against COVID-19 in Healthy Adults
Trial phase:	Phase I/II
Indication:	Protection against COVID-19
Product:	BNT162: SARS-CoV-2 - RNA lipid nanoparticle (RNA-LNP) vaccines utilizing [redacted] nucleoside modified messenger RNA (modRNA, two variants, called BNT162b1 and BNT162b2), [redacted]
Principal investigator:	[redacted]
Trial sites:	CRO sites in Berlin and Mannheim, Germany
Contract research organization (CRO):	CRS Clinical Research Services Mannheim GmbH, Germany
Sponsor's responsible person:	[redacted]
Sponsor:	BioNTech RNA Pharmaceuticals GmbH, An der Goldgrube 12, 55131 Mainz, Germany
Regulatory identifiers:	EudraCT no.: 2020-001038-36; WHO UTN: U1111-1249-4220
Medical Monitor:	The sponsor's Medical Monitor name and contact information will be provided separately

Document history	Date	Version number	Valid for
First approved version	09 Apr 2020	2.0	Germany
Amendment No. 1	17 Apr 2020	3.0	Germany
Amendment No. 2	13 May 2020	4.0	Germany
Amendment No. 3	26 May 2020	5.0	Germany
Amendment No. 4	09 Jun 2020	6.0	Germany
Amendment No. 4	26 Jun 2020	7.0	Germany

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.

[redacted]

1 PROTOCOL SUMMARY

1.1 Trial synopsis

Trial number: BNT162-01

Trial title

A Multi-site, Phase I/II, 2-Part, Dose-Escalation Trial Investigating the Safety and Immunogenicity of Four Prophylactic SARS-CoV-2 RNA Vaccines Against COVID-19 Using Different Dosing Regimens in Healthy Adults

Objectives and endpoints

Objectives	Endpoints
Primary objective	
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after single dose (SD; prime only) or prime/boost (P/B) immunization.	• Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7±1 d after each immunization. • 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): o For [redacted], BNT162b1, BNT162b2, [redacted](P/B): occurring up to 21±2 d after the prime immunization and 28±4 d after the boost immunization. [redacted]
Secondary objectives	
To describe the immune response in healthy adults after SD or P/B immunization measured by a functional antibody titer, e.g., virus neutralization test or an equivalent assay available by the time of trial conduct.	For [redacted] BNT162b1, BNT162b2, [redacted](P/B): • Functional antibody responses at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 28±4 d, 63±5 d, and 162±7 d after the boost immunization. • Fold increase in functional antibody titers 7±1 d and 21±2 d after primary immunization and at 21±2 d, 28±4 d, 63±5 d, and 162±7 d after the boost immunization. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 28±4 d, 63±5 d, and 162±7 d after the boost immunization. [redacted]

Objectives	Endpoints
	• Fold increase in functional antibody titers at 7±1 d, 21±2 d, 29±3 d, 42±3 d, 84±5 d, and 183±7 d after the primary immunization. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline at 7±1 d, 21±2 d, 29±3 d, 42±3 d, 84±5 d, and 183±7 d after the primary immunization.
Exploratory objectives	
To describe the immune response in healthy adults after SD or P/B immunization measured by an antibody binding assay, e.g., Enzyme-Linked Immunosorbent Assay (ELISA) or an equivalent assay available by the time of trial conduct.	For [redacted] BNT162b1, BNT162b2, [redacted] (P/B): • Antibody responses at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 29±3 d, 63±5 d, and 162±7 d after the boost immunization. • Fold increase in antibody titers at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 29±3 d, 63±5 d, and 162±7 d after the boost immunization. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers as compared to baseline at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 29±3 d, 63±5 d, and 162±7 d after the boost immunization. [redacted]
To describe the cellular immune responses.	For [redacted] BNT162b1, BNT162b2, [redacted] (P/B): • Cell-mediated immune (CMI) responses measured by Enzyme-Linked Immuno-Spot (ELISpot) at baseline and at 29±3 d after the primary immunization. [redacted]

Trial design

Four different vaccines ([redacted] BNT162b1, BNT162b2, [redacted]) will be tested.

The trial has two parts: a dose-finding part (Part A) with three dose escalation cohorts (each with predefined dose levels) and two dose de-escalation cohorts (one pre-defined and one optional dose level) and, a second part (Part B) dedicated to recruit expansion cohorts with dose levels which are selected from data generated in Part A. The vaccines [redacted] BNT162b1, BNT162b2 [redacted] will be administered using a P/B regimen. [redacted]

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

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. For some vaccines, a dose-de-escalation is also planned.

Trial subjects with the first-in-human [FIH] immunization will be immunized using a sentinel 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.
- 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.
    - 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.
    - If approved by the SRC, the planned de-escalation dose in Cohort 3 will be initiated.

In Cohort 2, the subject staggering process will be as follows:

- Two sentinel subjects will be dosed on one day.
- If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 4 further subjects will be dosed.
- If the dosing in these 4 subjects was considered to be safe and well tolerated by the investigator based 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48 h data from the sentinel subjects):

- The remaining 6 subjects in the group will be dosed.
- If approved by the SRC, the next planned escalation dose (see Table 1) in Cohort 4 will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects (including observation on site, phone interview, vital signs, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome).

In Cohort 3, if possible, 12 subjects will be dosed with the planned dose on one day.

In Cohort 4, the subject staggering process will be as follows:

- Two sentinel subjects will be dosed on one day.
- If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 4 further subjects will be dosed.
- If the dosing in these 4 subjects was considered to be safe and well tolerated by the investigator based 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48 h data from the sentinel subjects): The remaining 6 subjects in the group will be dosed.

The dose de-escalation cohort (e.g., Cohort 5) may be investigated at the discretion of the SRC, but the dose used will not exceed the pre-defined maximum dose (see Table 1 and Table 2).

For the BNT162b vaccines, protocol amendment 04 allows additional dose cohorts at the dose levels listed in Table 1. In these cohorts, since at doses lower than already tested, 12 subjects can be dosed with the planned dose on one day.

For the BNT162b1 vaccine, protocol amendment 04 allows three additional cohorts in older adults at the dose levels listed in Table 2. In these cohorts, 12 subjects will be dosed using a sentinel dosing/subject staggering process as done for Cohort 4.

For the BNT162b2 vaccine, additional cohorts in older adults will be added to allow the dosing of 12 subjects using a sentinel dosing/subject staggering process as done for Cohort 4. These additional cohorts will be activated using a dedicated protocol amendment including supportive immunogenicity and safety data in younger adults, before any older adults are dosed with BNT162b2.

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

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

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

Vaccine / mRNA type	Vaccine encoded antigen	Vaccine IM dosing regimen	Part A - Cohort numbers & Dose (µg) (12 subjects per cohort)						
			1 Starting dose	2	3 De-escalation dose	4 Maximum dose	5	6	7
[redacted]									
BNT162b1 / modRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	1B 10 µg	2B 30 µg	3B 1 µg	4B 60 µg	5B 50 µg	6B 3 µg	7B 20 µg
BNT162b2 / modRNA	Modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	1C 10 µg	2C 30 µg	3C 1 µg	4C[a] 60 µg	5C[a] 50 µg	6C[a] 3 µg	7C[a] 20 µg
[redacted]									

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

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

[d] Specific doses to be defined, but in the range given.

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

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

Vaccine / mRNA type	Vaccine encoded antigen	Vaccine IM dosing regimen	Part A - Cohort numbers & Dose (µg) (12 subjects per cohort)[a]		
			8 Older adults	9 Older adults	10 Older adults
BNT162b1 / modRNA	RBD of the SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	8B 3 µg	9B[a] 10 µg	10B[a] 20 µg
BNT162b2 / modRNA[b]	Modified version of the full length SARS-CoV-2 S protein	Prime: Day 1 Boost: Day 22	8C 3 µg	9C[a] 10 µg	10C[a] 20 µg

[a] All dose escalation doses used must be judged acceptable by the Safety Review Committee (SRC) before use.
[b] These cohorts will be activated using a dedicated protocol amendment before any older adults are dosed.

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

Part B

If approved by the SRC, Part B will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects (including observation on site, phone interview, vital signs, TEAEs, local reactions, immunogenicity data, blood/clinical laboratory data, and brief physical examination outcome).

Details of Part B will be defined using a protocol amendment after thorough evaluation of immunogenicity and safety data from Part A for each vaccine candidate individually. Part B may be initiated for one or more vaccines while Part A is still ongoing, depending on the available data.

Safety data to be evaluated includes the package used by the SRC to assess individual dose levels and in addition any other safety observations that may be reported until the data cut off. Immunogenicity of all doses will be thoroughly assessed.

The protocol amendment will include a summary of relevant safety and tolerability data collected in Part A. This protocol amendment will also include Part B specific inclusion/exclusion criteria, objectives/endpoints, a description of the planned statistical analyses, and descriptions of any added trial assessments and procedures.

Part B will use a randomized, placebo-controlled design in the likely target population (e.g., high risk populations such as elderly and/or immunocompromised populations). Part B may employ a surrogate marker as a measure of vaccine efficacy.

Trial duration

In total, the planned trial duration is expected to be approximately 12 months. From screening visit (Visit 0) to the last visit ([redacted] Visit 9 [redacted] BNT162b1, BNT162b2, [redacted] (P/B)]), each trial subject will be in the trial for maximally 223 days. For logistical reasons, investigation of the different vaccines may not be able to start at the same time.

Population

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

For each vaccine, 12 subjects are required for each of the cohorts planned in Part A. See Table 3 for the total number of subjects for each vaccine assuming all cohorts planned in Table 1 and Table 2 are performed.

Table 3: Overview of the total number of subjects for each vaccine in Part A

Vaccine / mRNA type	Vaccine dosing regimen	Maximum number of subjects (assuming all cohorts planned in Table 1 are performed)
[redacted]		
BNT162b1 / modRNA	Prime/Boost	120 (10 cohorts)
BNT162b2 / modRNA	Prime/Boost	120 (10 cohorts)
[redacted]		

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.

Key inclusion criteria

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

- For younger subject cohorts, volunteers must be aged 18 to 55 years, have a body mass index over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0
  OR
  For older adult cohorts, volunteers must be aged 56 to 85 years, have a body mass index over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0.
- They must be healthy, in the clinical judgment of the investigator, based on medical history, physical examination, 12-lead ECG, vital signs (systolic/diastolic blood pressure, pulse rate, body temperature, respiratory rate), and clinical laboratory tests (blood chemistry, hematology, and urine chemistry) at Visit 0.
  Note: Healthy volunteers with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.
- Women of childbearing potential (WOCBP) must have a negative beta-human chorionic gonadotropin urine test at Visit 0 and Visit 1. Women that are postmenopausal or permanently sterilized will be considered as not having reproductive potential.

Key exclusion criteria

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

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

- Have a known allergy, hypersensitivity, or intolerance to the planned investigational medicinal product (IMP) including any excipients of the IMP.
- Had any medical condition or any major surgery (e.g., requiring general anesthesia) within the past 5 years which, in the opinion of the investigator, could compromise their well-being 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 immunosuppressant's or other immune-modifying drugs, within the 6 months prior to Visit 0 unless in the opinion of the investigator the medication would not prevent, limit, or confound the protocol-specified assessments or could compromise subject safety.
- Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks 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 investigational medicinal product 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 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 well-being 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, subjects in detention, CRO or sponsor staff or their family members.
- For older subjects: Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors:
  - Hypertension
  - Diabetes mellitus
  - Chronic pulmonary disease
  - Asthma
  - Chronic liver disease
  - Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
  - BMI ≥30 kg/m^2
  - 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 vaccines)

Name:	BNT162 vaccines - Anti-viral RNA vaccines for active immunization against COVID-19
Type:	RNA-LNP vaccines utilizing different BioNTech RNA formats, i.e., [redacted] modRNA (two variants, product codes BNT162b1 and BNT162b2), [redacted]
Dosage levels:	See Table 1. The planned dose per vaccine candidate will not exceed the pre-defined maximum doses (see Table 1). Part B expansion cohorts: The to be tested doses will be chosen by the SRC after review of the safety, tolerability, and immunogenicity data from Part A.
Dosage frequency:	One injection or two injections 21 d apart. [redacted]
Administration route:	Intramuscular (IM); upper arm, musculus deltoideus. For the P/B regimens the same arm may be used for both immunizations. The non-dominant arm is preferred.

Statistics

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

Data Monitoring Committee (DMC)/SRC

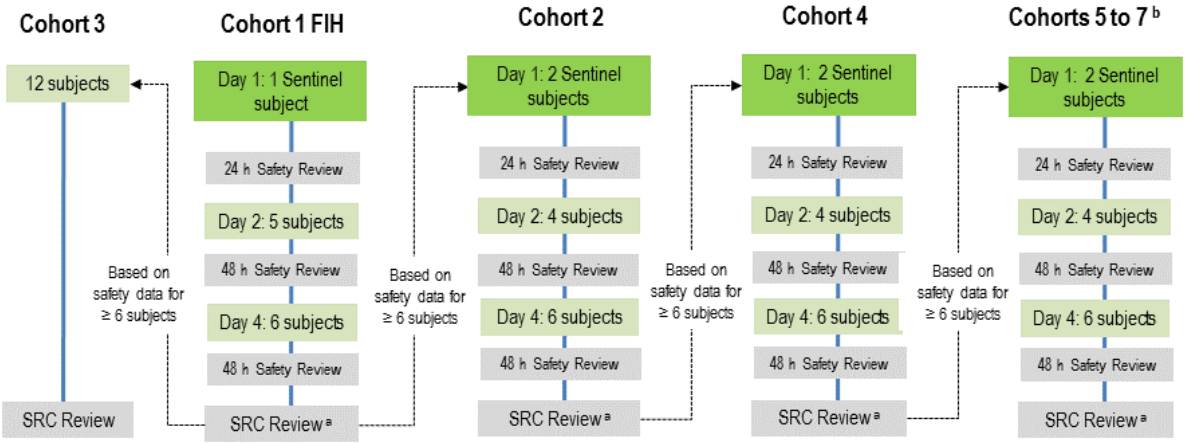
A DMC is not planned. A SRC is planned.

1.2 Schema (graphical representation of the trial)

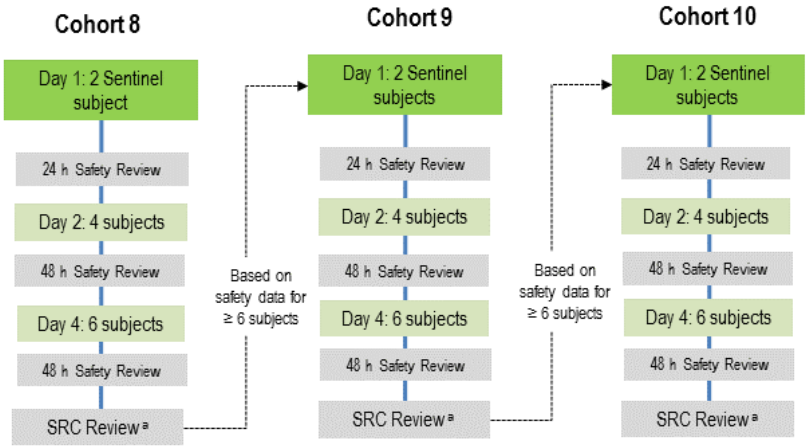
For a graphical depiction of the dose-ranging process in Part A, see Figure 1. For logistical reasons, investigation of the different vaccines may not be able to start at the same time. Should this happen, the expected overall trial duration may be extended.

Dose cohort schema for [redacted] BNT162b1, BNT162b2, [redacted] (P/B) [c]

Cohorts with younger adults



Cohorts with older adults



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

b) For BNT162b1 and BNT162b2 only: Cohorts 5 to 7 are planned for dose finding (12 subjects can be dosed on one day in these cohorts) and Cohorts 8 to 10 for testing in older subjects will use sentinel dosing.

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

[redacted]

[redacted]

1.3 Schedule of activities

Table 4: Schedule of trial procedures and assessments – [redacted] BNT162b1, BNT162b2, [redacted] when tested P/B

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

Procedure / Assessment	Visit 0	Visit 1 Pre-dose	Visit 1 Dosing & Post-dose	Visit 2 at 24±2h	Phone call at 48±2h	Visit 3	Visit 4 Pre-dose	Visit 4 Dosing & Post-dose	Phone call at 48±2h	Visit 5 ~7 d from Visit 4	Visit 6 ~21 d from Visit 4	Visit 7 ~28 d from Visit 4 (EoT Visit)	Visit 8 ~63 d from Visit 4 (FU Visit)	Visit 9 ~162 d from Visit 4 (FU Visit)
Day [h]	-30 to 0	1	1	2		8	22	22		29	43	50	85	184
Blood draw for SARS-CoV-2 testing [k]	X (2.6 mL)													
Oral swipe for SARS-CoV-2 testing		X [m]												
Allocation to IMP		X												
Immunization			X					X						
Blood draw for immunogenicity [n]		X (10 mL)				X (10 mL)	X (10 mL)			X (10 mL)	X (10 mL)	X (10 mL)	X (10 mL)	X (10 mL)
Blood draw for HLA		X (4 mL EDTA blood) [p]												
Blood draw for CMI (100 mL) [n, o]		X								X				
Blood draw for research		← Up to 5 blood draws for explorative biomarker/immunogenicity research purposes. Blood draw volumes may vary. The total blood volume drawn will not exceed 200 mL per subject over the complete trial, i.e., over approximately 7 months. →												
Subject hotline availability	Start	=>	=>	=>		=>	=>	=>		=>	=>	=>	=>	End
Issue subject diaries		X		X		X	X			X	X	X		
Collect subject diaries				X		X	X			X	X	X	X	
Record AEs since last visit		X		X		X	X			X	X	X	X [i]	X [i]
Local reaction assessment/ systemic events			X [b]	X		X	X	X [b]		X	X	X		
Concomitant medication	X	X		X		X	X			X	X	X		
Subject wellbeing questioning					X [i]				X [i]					

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

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

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

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

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

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

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

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

[i] Only for the first 6 subjects per group.

[j] Only IMP-related AEs.

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

[l] For Cohort 1, immunization with 1 h intervals between subjects for the first 6 subjects and then with 30 min intervals for the remaining 6 subjects. For Cohorts 2 and 4, immunization with 30 min intervals between subjects.

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

[n] The listed blood draw days may be adapted if justified by the collected data.

[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.

Abbreviations: AE = adverse events; CMI = cell-mediated immune testing; D or d = day; ECG = electrocardiogram; EDTA = Ethylenediamine Tetraacetic Acid; EoT = End of trial (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.

[redacted]

[redacted]

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

TRIAL-SPECIFIC ABBREVIATIONS/TERMS

Abbreviation/Term	Explanation
Allocated subject	Enrolled subjects who are allocated to IMP
[redacted]	
BNT162b	BNT162 RNA-LNP vaccine utilizing nucleoside modified mRNA (the variants BNT162b1 and BNT162b2 will be tested in this trial)
[redacted]	
CMI	Cell-Mediated Immunity
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
ELISA	Enzyme-Linked Immunosorbent Assay
ELISpot	Enzyme-Linked Immuno-Spot
Enrolled subjects	Subjects who signed an informed consent form, i.e., who gave informed consent
HLA	Human leukocyte antigen
IM	Intramuscular(ly)
IV	Intravenous(ly)
modRNA	Nucleoside modified messenger RNA
mRNA	Messenger RNA
P/B	Prime/Boost: a dosing regimen, comprising a priming immunization and a boost immunization
PEI	(German) Paul-Ehrlich-Institute
RNA-LNP	RNA lipid nanoparticle
RNA-LPX	RNA lipoplex
[redacted]	
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	The virus leading to COVID-19
SD	Single dose (also referred to as “single priming dose” or “single immunization”)
[redacted]	

For standard abbreviations, see Section 10.9.

NOTES FOR THE READER

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

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

2 INTRODUCTION

2.1 Background

2.1.1 Overview of the disease

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

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

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

There are currently no approved vaccines or antiviral drugs to prevent or treat SARS-CoV-2 infections or its associated disease COVID-19 (Habibzadeh and Stoneman 2020). Habibzadeh_et_Stoneman_2020(Habibzadeh and Stoneman 2020).

2.1.2 Introduction to BioNTech RNA-based vaccines

An LNP-formulated RNA based vaccine would provide one of the most flexible, scalable and fastest approaches to provide protection against the emerging viruses like SARS-CoV-2 (Rauch et al. 2018; Sahin et al. 2014). Rauch_et_al_2018Sahin_et_al_2014(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. 2019; Pardi et al. 2017). Vogel_et_al_2018Moyo_et_al_2019Pardi_et_al_2017(Vogel et al. 2018; Moyo et al. 2019; Pardi et al. 2017).

At BioNTech, there are three different RNA platforms under development, namely [redacted] nucleoside modified mRNA (modRNA, BNT162b), [redacted]

All three RNA platforms have been tested in more than a dozen non-clinical GLP safety studies and, for [redacted] modRNA, there is pre-existing clinical safety data (see the BNT162 investigator's brochure [IB]).BNT162 investigator's brochure [IB]). These data have been obtained primarily with RNAs formulated with liposomes which are related, but not identical, to those to be used in this trial. BNT162_IB

The non-clinical toxicity data generated by BioNTech suggest a favorable safety profile for [redacted] modRNA, [redacted] 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 [redacted] modRNA in rodents was predictive for clinical safety. For further details, see the BNT162 IB. BNT162_IBBNT162 IB.

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

A recently published clinical trial using an influenza vaccine based on modRNA encapsulated in LNPs highly related to those used in this trial and also administered IM reported good safety and well tolerability (Feldman et al. 2019). Feldman_et_al_2019(Feldman et al. 2019).

2.2 Trial rationale

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

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

This trial will investigate the potential safety and immunogenicity of four prophylactic BNT162 vaccines against SARS-CoV-2, [redacted] BNT162b1, BNT162b2, and [redacted] The two variants of the BNT162b vaccines, BNT162b1 and BNT162b2, differ in the encoded antigen.

Some of the prophylactic BNT162 vaccines against SARS-CoV-2 investigated in this trial are under investigation (BNT162-02) or will be investigated in other clinical trials (BNT162-

03). The status and preliminary results from all of these are trials are summarized in the following sections.

For the status of ongoing and planned clinical trials, see Table 6.

Table 6: Status of ongoing and planned clinical trials (as of June 22nd, 2020)

Trial number	Design	Current number dosed (subject age)
BNT162-01 (NCT04380701) Germany	Phase I/II, 2-part, dose escalation trial. Part A is open label and non-randomized. (All subjects receive active vaccine) Part B will be defined in a protocol amendment.	[redacted] BNT162b1 (age 18 to 55 years): 1 µg 12 subjects prime / 11 boost; 10 µg 12 subjects prime / 12 boost; 30 µg 12 subjects prime / 12 boost; 50 µg 12 subjects prime / 11 boost; 60 µg 12 subjects prime. BNT162b2 (age 18 to 55 years): 1 µg first dosing planned end of June-2020; 10 µg 12 subjects prime; 30 µg 2 subjects prime. [redacted]
BNT162-02 (PF-07302048; NCT NCT04368728) US	Phase I/II, placebo-controlled, randomized, observer-blind, dose-finding trial. (Subjects are randomized: 4 active vaccine to 1 placebo)	BNT162b1 (age 18 to 55 years): 10 µg 15 subjects prime / 15 boost; 30 µg 15 subjects prime / 15 boost; 100 µg 15 subjects prime. BNT162b1 (age 65 to 85 years): 10 µg 15 subjects prime; 20 µg 15 subjects prime; 30 µg 15 subjects prime. BNT162b2 (age 18 to 55 years): 10 µg 15 subjects prime; 20 µg 15 subjects prime. BNT162b2 (age 65 to 85 years): 20 µg 15 subjects prime

Trial number	Design	Current number dosed (subject age)
BNT162-03 China	[redacted]	

2.2.1 This trial (BNT162-01) - Preliminary results (status June 22nd, 2020)

For the current status of dosing with BNT162 vaccines candidates by dose level in BNT162-01, see Table 6.

Summary of safety in trial BNT162-01 (up to June 22nd 2020)

In the trial BNT162-01, younger adults aged 18 to 55 years were dosed with one of four BNT162 vaccine candidates ([redacted]BNT162b1, BNT162b2, [redacted]). The most complete experience is available for the vaccine BNT162b1, which has been dosed in 5 cohorts of 12 subjects each (all subjects received active vaccine). Except for those in the highest dose cohort (60 µg), all subjects were dosed twice (i.e., prime and boost). The boost dose in the 60 µg dose cohort is pending.

Reactogenicity

Local reactions and systemic events are solicited from the subjects and recorded by them in a diary for 7 days following administration of the vaccine. Most subjects in all cohorts experienced the expected reactogenicity, typically starting within 24 h of dosing and resolving within 24 h. The specific, solicited local and systemic reaction are graded as described in Section 10.3.1.11 and are summarized below in Table 7 and Table 8.

Table 7: Number of adults aged 18 to 55 years with local symptoms (diary): BNT162b1

	Number of Subjects with Local Reactions (n=)								
	7d Post Prime			7d Post Boost			Total (both)	
	Subjects dosed prime	Any event	Any ≥ severe	Subjects dosed boost	Any event	Any ≥ severe	Any event	Any ≥ severe
BNT162b1	60	51	8	46	39	7	54	13
1 µg	12	6	0	11	7	2	7	2
10 µg	12	10	1	12	10	0	11	1
30 µg	12	11	4	12	11	2	12	5
50 µg	12	12	2	11	11	3	12	4
60 µg	12	12	1				12	1

Table 8: Number of adults aged 18 to 55 years with systemic symptoms (diary): BNT162b1

	Number of subjects with Systemic Reactions (n=)									
	7d Post Prime				7d Post Boost				Total (both)	
	Subjects dosed prime	Any event	Any ≥ severe		Subjects dosed boost	Any event	Any ≥ severe		Any event	Any ≥ severe
BNT162b1	60	52	15		46	38	17		57	27
1 µg	12	9			12	7	2		11	2
10 µg	12	8	1		11	9	4		10	5
30 µg	12	11	3		12	11	6		12	6
50 µg	12	12	4		11	11	5		12	7
60 µg	12	12	7						12	7

In local reactions, most subjects reported injection site pain and tenderness, whilst reports of swelling / induration or erythema were scarce. The most common systemic reactions were headache and fatigue, experienced by most subjects. Grade 3 (severe intensity) local reactions were reported for pain, tenderness and swelling. Grade 3 (severe intensity) systemic reactions were fever, headache, myalgia, arthralgia, nausea, vomiting, chills, loss of appetite, malaise and fatigue.

Laboratory findings

A consistent pattern has been seen in the laboratory assessments with elevation of the C-reactive protein with concomitant reduction in the plasma lymphocyte count 24 h after vaccination. These changes are consistent with the know pharmacology of this technology, with the changes in lymphocytes known to represent a reversible compartmental shift from the vascular space to lymphoid organs. These observations have been self-limiting and without clinical consequence. There have been no other consistent findings on laboratory assessments.

Adverse events

Adverse events are collected throughout the trial and graded by the investigators on a 4-point scale (as per this protocol). Most subject report adverse events (Table 9), >90% of which are related to reactogenicity. 6 subjects had AEs rated as severe in intensity (Grade 3) covering 5 preferred terms: muscle tightness, headache, influenza like illness, injection site discomfort, pyrexia.

Table 9: Summary BNT162b1 TEAE (prime +/- boost) by number of subjects

BNT162b1	Subjects Dosed N =	Number of Subjects with (n=)					
		TEAEs	Mild AE	Moderate AE	Severe AE	SAE	Resolved AE
1 µg	12	11	10	7	2	0	11
10 µg	12	12	12	8	1	0	12
30 µg	12	12	12	9		0	12
50 µg	12	12	12	11	2	0	12
60 µg	12	12	12	10	1	0	12
Total	**60**	**59**	**58**	**45**	**6**	**0**	**59**

Summary

For vaccine BNT162b1, generally good tolerability was observed with no SAEs and no unexpected toxicities. To date, there is high acceptance by trial subjects with no withdrawals due to related AEs. Most reported AEs are signs and symptoms of reactogenicity, typical onset within first 24 h post immunization. All AEs / reactogenicity resolve spontaneously, mostly within 24 h. of onset and can be managed with simple measures (e.g., paracetamol). Laboratory assessments suggest a Th1 pattern of immune activation 24 h post dosing. Some dose dependency of tolerability has been observed, with 1 µg dose best tolerated. The possibly of a slight increase in reactogenicity following boost dose is noted, as is some inter-individual variability.

[redacted] Early indications for tolerability of BNT162b2 at a 10 µg dose are very encouraging with only minimal local reactogenicity in initial reports.

2.2.2 US trial BNT162-02 - Preliminary results (status, June 22nd, 2020)

This trial in the US is conducted by Pfizer, Inc. (New York, US) and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany). The trial has been approved by the US regulatory authorities and trial conduct has started.

The US trial BNT162-02 (PF-07302048; NCT NCT04368728) is “a Phase I/II, placebo-controlled, randomized, observer-blind, dose-finding study to describe the safety, tolerability, immunogenicity, and potential efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy adults.

Summary of safety in BNT162-02 (status, June 22nd, 2020)

US Trial C4591001/BNT162-02 is a randomized and placebo-controlled trial, in which the trial subjects are randomized 4:1 to receive active vaccine or placebo. The available safety and tolerability data for younger adults aged 18 to 55 years (see Table 10) who have

received dose 1 and dose 2 of BNT162b1 were broadly comparable to those in trial BNT162-01 and are briefly summarized below.

Preliminary safety and tolerability data in elderly (aged 65 to 85 years) after dosing with BNT162b1 are presented separately below and are summarized in Figure 2 and Figure 3.

Table 10: Number of adults aged 18 to 55 years dosed in BNT162-02 (status, June 22nd, 2020)

	BNT162b1		Placebo	
	Dose 1	Dose 2	Dose 1	Dose 2
18-55 years of age				
10 µg dose level	N=12	N=12	N=3	N=3
30 µg dose level	N=12	N=12	N=3	N=3
100 µg dose level	N=12	Not applicable	N=3	Not applicable

Overall, all dose levels exhibited a tolerability and safety profile consistent with modRNA-based vaccines, and a clear dose level response was observed after dose 1 and dose 2 in younger adults. Reactogenicity was generally higher after the second dose, but the symptoms resolved quickly over the course of a few days. The only reports of Grade ≥3 intensity (severe) were 1 case of fatigue in a subject in the 10 µg cohort and 1 case of chills in a single subject in the 30 µg cohort, both after their boost dose. Based on the tolerability profile observed with the 100 µg dose level after the first dose, an internal decision was made not to give a boost dose at 100 µg.

Summary of safety in elderly subjects (aged 65 to 85 years) in BNT162-02

Preliminary safety and tolerability data after the first dose of 10 µg, 20 µg, and 30 µg in adults aged 65 to 85 years (see Table 11) after one dose of BNT162b1 are shown in Figure 2 and Figure 3**.**

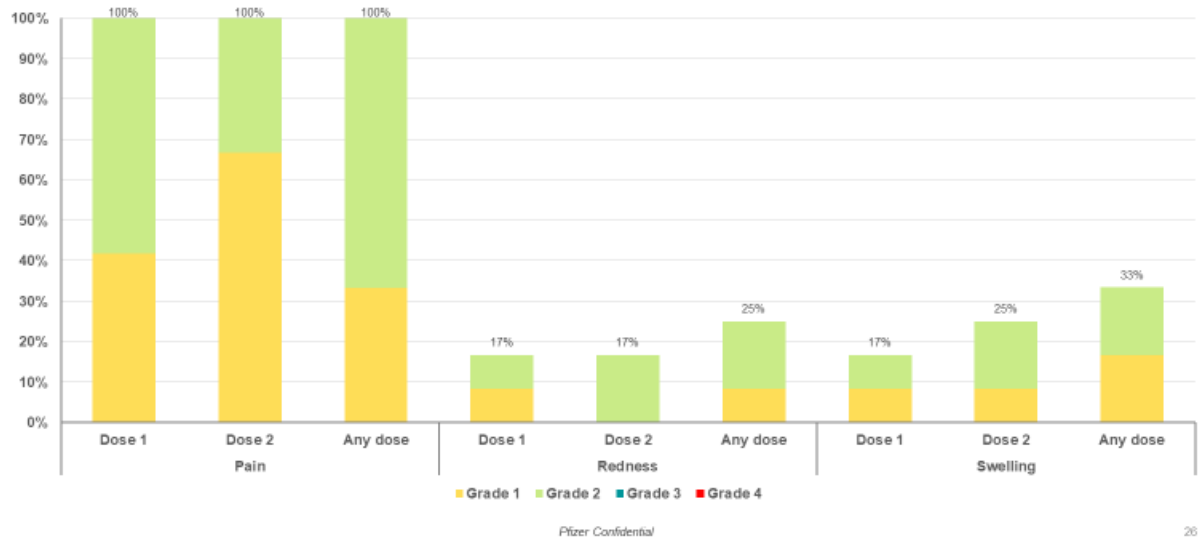
Table 11: Number of adults aged 65 to 85 years dosed in BNT162-02 (status, June 22nd, 2020)

	BNT162b1		Placebo	
	Dose 1	Dose 2	Dose 1	Dose 2
65-85 years of age				
10 µg dose level	N=12	N=0	N=3	N=0
20 µg dose level	N=12	N=0	N=3	N=0
30 µg dose level	N=12	N=0	N=3	N=0

The first dose of BNT162b1 in this age group was generally well tolerated. One episode of severe muscle pain and erythematous rash occurred with mild fever occurred in an 81-year-old man on day 2 after receiving a 20 µg dose, consistent with varicella zoster

(shingles). He was prescribed Valacyclovir and this AE was reported as fully resolved within 7 days. The investigator reported this AE as not related to vaccine.

Part A



Part B

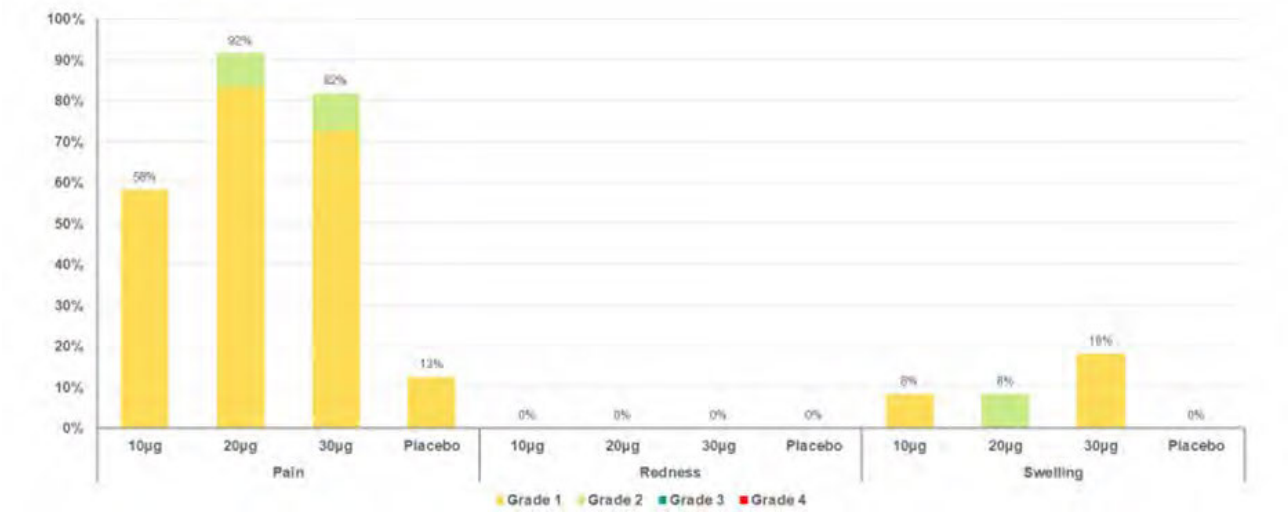
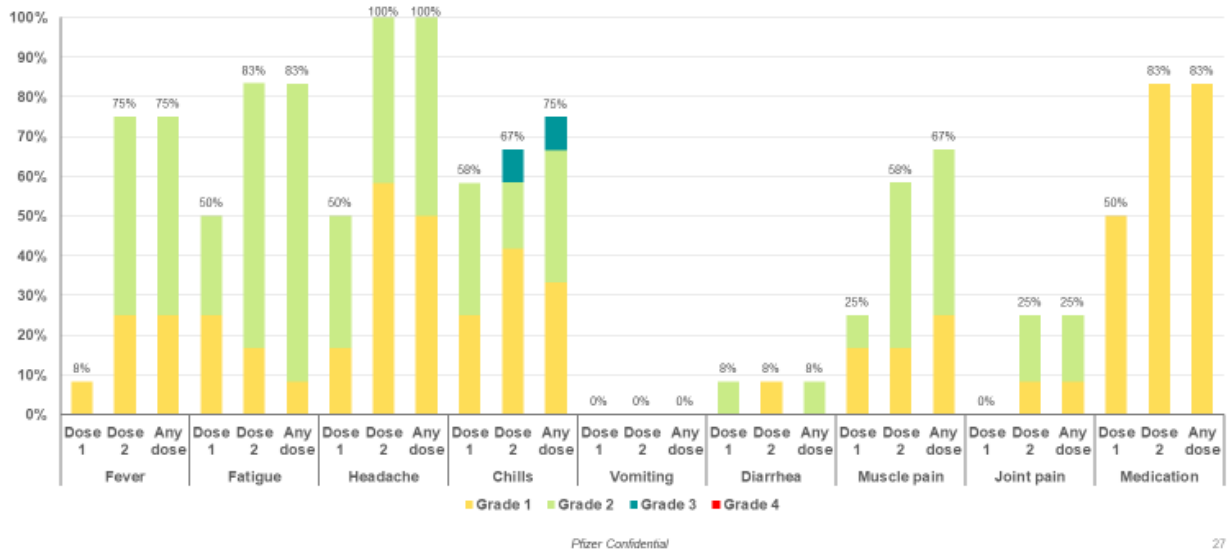


Figure 2: BNT162b1 - Local reactions in younger and elderly subjects

Panel A - Local reactions after doses 1 and 2 (i.e., prime and boost) of 30 µg BNT162b1 in younger subjects.
Panel B - Local reactions after dose 1 (i.e., prime) of 10, 20, and 30 µg BNT162b1 in elderly subjects.
Note: follow-up period for 10 µg and 30 µg groups: +2-4 days.

Part A (younger adults)



Part B (Elderly)

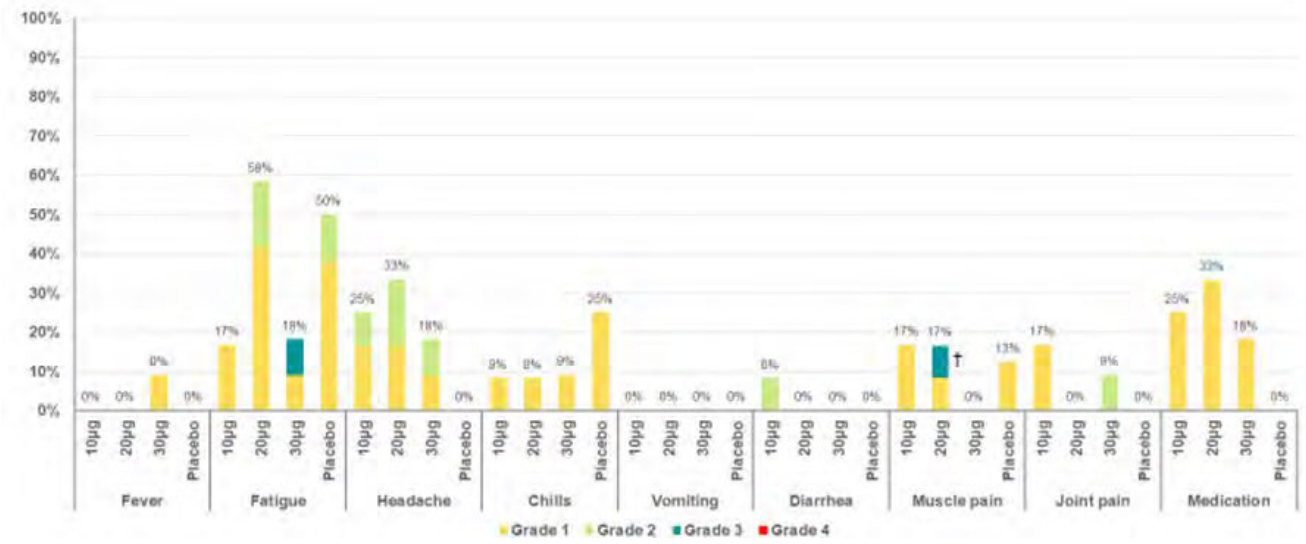


Figure 3: BNT162b1 - Systemic events in younger and elderly subjects

Panel A - Systemic events after doses 1 and 2 (i.e., prime and boost) of 30 µg BNT162b1 in younger subjects.
Panel B - Systemic events after dose 1 (i.e., prime) of 10, 20, and 30 µg BNT162b1 in elderly subjects.
Note: follow-up period for 10 µg and 30 µg groups: +2-4 days
† This is the participant that experienced Zoster which was the actual cause of the pain.

In general terms, the local tolerability of BNT162b1 in elderly subjects seems comparable to that recorded in younger adults. The pattern of systemic reactogenicity appears similar between the two age groups, possibly with a lower overall incidence in the elderly subjects in comparison to the younger adults.

2.2.3 Chinese trial - BNT162-03

The trial BNT162-03 will be conducted in healthy Chinese adults by Shanghai Fosun Pharmaceutical Development, Inc. (Shanghai, China) and sponsored by BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany).

Currently the trial has not been approved and the concrete trial design is under discussion with the Chinese regulatory authorities to ensure alignment with the rapidly progressing overall clinical development and the adequacy of the Chinese trial for regional extension of the potential registrational data package.

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 568 mL blood will be drawn per subject over the complete trial, i.e., over approximately 7 months).
- All trial-specific procedures will be performed by qualified trial site personnel.
- Immunization will be done by a physician.
- BNT162 vaccines have not been administered to humans prior to this trial. However, clinical data is available for RNAs formulated with related but not identical liposomal compositions or non-formulated RNAs and can support risk assessment of the BNT162 vaccines.

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

- Due to the IM route of administration, there is the risk of local reactions at the injection site, e.g., erythema, pruritus, pain, tenderness, swelling, sweating.
- Due to their immune-modulatory effect, vaccines may cause systemic flu-like reactions such as temporary headache, fatigue, loss of appetite, myalgia, arthralgia, fever. Rarely, with certain prophylactic vaccines (e.g., as seen for vaccines using attenuated viruses) severe allergic reaction or a neurological side effects, such as a seizure, were seen. Although these rare side effects are a concern, the risk of a vaccine causing serious harm or death is considered to be extremely small, in particular for BNT162 vaccines, which are molecularly defined, highly purified and based on RNA, which naturally occurs and is metabolized in the human organism.
- Due to the IM route the risk of systemic reactions is considered low.
- 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). (Feldman et al. 2019). Feldman_et_al_2019

- As with other vaccines, and with single stranded RNA being an innate immune sensor-agonist, BNT162 administration may cause temporary headache, fatigue or loss of appetite. Rarely, with certain prophylactic vaccines (e.g., as seen for vaccines using attenuated viruses) severe allergic reactions or neurological side effects, such as seizures, were seen. Although these rare side effects are a concern, the risk of a vaccine causing serious harm or death is considered to be extremely small, in particular for BNT162 vaccines, which are molecularly defined, highly purified, subunit vaccines.
- The available non-clinical data of [redacted] BNT162b, [redacted] suggest a favorable safety profile with events that are mild and mostly related to the mode-of-action and the RNA-intrinsic stimulation of innate immune sensors.
- Based on the available clinical and non-clinical data on the individual components ([redacted] modRNA, [redacted] the specific LNP formulation), that are combined within the BNT162 products, a favorable safety profile of BNT162 products is expected with mild and localized effects (see the BNT162 IBBNT162 IB for details on these trials). BNT162_IB

[redacted]

    - Non-formulated modRNA administered in buffer into tumor lesions of cancer patients was tolerated with occasional mild local reactions. Systemic reactions after local application were not observed.

- To date, there is limited clinical experience with BNT162 vaccines in human subjects (see Section 2.2.1). Reactogenicity is anticipated and considered to contribute to the mode-of-action of inducing vaccine immune responses. Initial dose-ranging studies have suggested AE profiles consistent with previous usage of similar constructs in cancer patients, with AEs generally dividing into 2 groups: local injection site reactions and systemic flu-like illness.
- As summarized in Section 2.2.1 and Section 2.2.2, to date most of the AEs reported after immunization with BNT162 vaccine candidates have been mild to moderate in intensity and no SAEs have been reported. Fever of severe intensity has been

reported. Most AEs were managed with simple measures and resolved spontaneously.

- Whilst the general risk of effects potentially associated with the innate immune activation and transient secretion of associated cytokines are defined above based on the described data, the dose response-relationship, and thus tolerability for this specific set of vaccine candidates will only be defined by the ongoing trials (this trial BNT162-01 and the US trial BNT162-02, see Section 2.2.2) and the planned Chinese trial (BNT162-03, see Section 2.2.3).

  The clinical experience with administration of the prime dose of BNT162b1 in 36 healthy elderly subjects aged 65 to 85 years in the US trial BNT162-02 is described in Section 2.2. The local tolerability of BNT162b1 in elderly subjects aged 56 seemed comparable to that recorded in younger subjects aged 18 to 55 years. The pattern of systemic reactogenicity appeared similar between the two age groups, possibly with a lower overall incidence in the elderly subjects in comparison to the younger subjects at equal doses.

  The local tolerability of BNT162b1 in elderly subjects aged 56 seemed comparable to that recorded in younger subjects aged 18 to 55 years. The pattern of systemic reactogenicity appeared similar between the two age groups, possibly with a lower overall incidence in the elderly subjects in comparison to the younger subjects at equal doses.

- When assessing the risk for dosing of older subjects with BNT162 vaccine candidates, the follow information is relevant:
  - Preliminary data in subjects treated in the ongoing BNT162 trials backed by non-human primate (rhesus macaque) immunogenicity data have shown that BNT162b1 in the tested dose range is immunogenic.
  - There is risk that older adults may be under dosed with the vaccine doses chosen based on data for younger adults (as was observed for other vaccines) must be mitigated.
  - Preliminary data in elderly show a comparable to lower reactogenicity based on the observed local reactions and system events in similar doses (see the figures in Section 2.2.2). This observation may indicate a lower innate immune activatory capability of elderly, which in turn may mechanistically be associated with lower immunogenicity of dose levels that are immunogenic in the younger adults.
  - In this trial, the doses to be tested in older adults are within the range already shown to show acceptable tolerability in younger adults.
  - The planned starting dose with BNT162b1 for older subjects aged 55 to 85 years in this trial (10 µg) is 30% of the dose (30 µg) already shown to be acceptable in the subjects aged 65 to 85 years in the US trial BNT162-02.

  - This trial includes inclusion/exclusion criteria to exclude potential risk factors relevant for all adults, but additional criteria have been included to further protect the safety of enrolled older adults.

- The listed risks can be managed using routine symptom driven standard of care as described in Section 6.6.3. Treatment of these events is dependent on the discretion of the investigators.
- Since this trial will involve the first immunization of humans with the BNT162 vaccines, the trial subjects in Cohorts 1, 2 and 4 will be immunized using a sentinel dosing/staggering of subjects (EMA 2017 guidance "Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products"). EMA_FIH_Guidance_2017"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)(Feldman et al. 2019) that observed trial subjects on-site for only 1 h after each immunization before discharge from the trial site. Feldman_et_al_2019
- 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)(Feldman et al. 2019) that used on-site visits on Day 8. Feldman_et_al_2019
- Subject wellbeing questioning by telephone at 48±2 h after each immunization (where applicable, after both the prime and boost immunizations) will be performed for the first 6 subjects per cohort. Additional subject wellbeing calls may be included at the discretion of the SRC.
- In the case that an individual experiences dose limiting toxicities or that the frequency or pattern of AEs within a sub-cohort gives cause for concern, the investigator may request an ad hoc review by the SRC before further doses of a given vaccine construct are administered.
- If the investigator considers necessary, the planned observation periods before proceeding to dose further subjects in the same group may be prolonged by 24 h.
- The SRC must assess the safety and tolerability data of the first 6 subjects before allowing progression to the next cohort, for each vaccine per cohort/dose level.
- After each assessment, the SRC may request a prolongation of the observation periods to up to Day 7 for later cohorts.

- 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 what doses will be given.

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 trials subjects:

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

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

2.3.2 Benefit assessment

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

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

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

2.3.3 Overall benefit/risk conclusion

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

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary objective	
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after single dose (SD; prime only) or prime/boost (P/B) immunization.	• Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7±1 d after each immunization. • 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): o For [redacted] BNT162b1, BNT162b2, [redacted] occurring up to 21±2 d after the prime immunization and 28±4 d after the boost immunization. o [redacted]
Secondary objectives	
To describe the immune response in healthy adults after SD or P/B immunization measured by a functional antibody titer, e.g., virus neutralization test or an equivalent assay available by the time of trial conduct.	For [redacted] BNT162b1, BNT162b2, [redacted] • Functional antibody responses at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 28±4 d, 63±5 d, and 162±7 d after the boost immunization. • Fold increase in functional antibody titers 7±1 d and 21±2 d after primary immunization and at 21±2 d, 28±4 d, 63±5 d, and 162±7 d after the boost immunization. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 28±4 d, 63±5 d, and 162±7 d after the boost immunization. [redacted]

Objectives	Endpoints
Exploratory objectives	
To describe the immune response in healthy adults after SD or P/B immunization measured by an antibody binding assay, e.g., Enzyme-Linked Immunosorbent Assay (ELISA) or an equivalent assay available by the time of trial conduct.	For [redacted] BNT162b1, BNT162b2, [redacted] (P/B): • Antibody responses at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 29±3 d, 63±5 d, and 162±7 d after the boost immunization. • Fold increase in antibody titers at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 29±3 d, 63±5 d, and 162±7 d after the boost immunization. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody titers as compared to baseline at 7±1 d and 21±2 d after primary immunization and at 21±2 d, 29±3 d, 63±5 d, and 162±7 d after the boost immunization. [redacted]
To describe the cellular immune responses.	For [redacted] BNT162b1, BNT162b2, and [redacted] (P/B): • Cell-mediated immune (CMI) responses measured by Enzyme-Linked Immuno-Spot (ELISpot) at baseline and at 29±3 d after the primary immunization. [redacted]

4 TRIAL DESIGN

4.1 Overall design

Four different vaccines ([redacted] BNT162b1, BNT162b2, [redacted]) will be tested.

The trial has two parts: a dose-finding part (Part A) with three dose escalation cohorts (one each of three predefined dose levels) and two dose de-escalation cohorts (one pre-defined and one optional dose level) and, a second part (Part B) dedicated to recruit expansion cohorts with dose levels which are selected from data generated in Part A. The vaccines [redacted] BNT162b1, BNT162b2, [redacted] will be administered using a P/B regimen. [redacted]

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

For a summary of the trial as a flow diagram, 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. For some vaccines, a dose-de-escalation is also planned.

Trial subjects with the first-in-human [FIH] immunization will be immunized using a sentinel 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.
- 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.
    - 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.
    - If approved by the SRC, the planned de-escalation dose in Cohort 3 will be initiated.

In Cohort 2, the subject staggering process will be as follows:

- Two sentinel subjects will be dosed on one day.
- If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 4 further subjects will be dosed.
- If the dosing in these 4 subjects was considered to be safe and well tolerated by the investigator based 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48 h data from the sentinel subjects):
    - The remaining 6 subjects in the group will be dosed.

- If approved by the SRC, the next planned escalation dose (see Table 1) in Cohort 4 will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects (including observation on site, phone interview, vital signs, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome).

In Cohort 3, if possible, 12 subjects will be dosed with the planned dose on one day.

In Cohort 4, the subject staggering process will be as follows:

- Two sentinel subjects will be dosed on one day.
- If the dosing in these subjects was considered to be safe and well tolerated by the investigator after 24±2 h observation on site, a 4 further subjects will be dosed.
- If the dosing in these 4 subjects was considered to be safe and well tolerated by the investigator based 48 h data (24±2 h observation on site and phone interview for assessment 48±2 h after immunization; in addition to the available 48 h data from the sentinel subjects):
  - The remaining 6 subjects in the group will be dosed.

Additional dose cohorts (e.g., Cohort 5) may be investigated at the discretion of the SRC, but will not exceed the pre-defined maximum dose (see Table 1).

For the BNT162b vaccines, protocol amendment 04 allows additional dose cohorts at the dose levels listed in Table 1. In these cohorts, since at doses lower than already tested, 12 subjects can be dosed with the planned dose on one day.

For the BNT162b1 vaccine, protocol amendment 04 allows three additional cohorts in older adults at the dose levels listed in Table 2. In these cohorts, 12 subjects will be dosed using a sentinel dosing/subject staggering process as done for Cohort 4.

For the BNT162b2 vaccine, additional cohorts in older adults will be added to allow the dosing of 12 subjects using a sentinel dosing/subject staggering process as done for Cohort 4. These additional cohorts will be activated using a dedicated protocol amendment including supportive immunogenicity and safety data in younger adults, before any older adults are dosed with BNT162b2.

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

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

Part B

If approved by the SRC, Part B will be initiated. The data assessed by the SRC comprises 48 h data for 6 subjects (including observation on site, phone interview, vital signs, TEAEs, local reactions, immunogenicity data, blood/clinical laboratory data, and brief physical examination outcome).

Details of Part B will be defined using a protocol amendment after thorough evaluation of immunogenicity and safety data from Part A for each vaccine candidate individually. Part B may be initiated for one or more vaccines while Part A is still ongoing, depending on the available data.

Safety data to be evaluated includes the package used by the SRC to assess individual dose levels and in addition any other safety observations that may be reported until the data cut off. Immunogenicity of all doses will be thoroughly assessed.

The protocol amendment will include a summary of relevant safety and tolerability data collected in Part A. This protocol amendment will also include Part B specific inclusion/exclusion criteria, objectives/endpoints, a description of the planned statistical analyses, and descriptions of any added trial assessments and procedures.

Part B will use a randomized, placebo-controlled design in the likely target population (e.g., high risk populations such as elderly and/or immunocompromised populations). Part B may employ a surrogate marker as a measure of vaccine efficacy.

4.1.1 Adaptive trial design elements

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

4.1.2 Planned number of trial subjects

In Part A

For each vaccine, 12 subjects are required for each of the cohorts planned in Part A. See Table 3 for the total number of subjects for each vaccine assuming all cohorts planned in Table 1 and Table 2 are performed.

In Part B

The planned number of trial subjects in Part B will be calculated based on the data from Part A and defined in a protocol amendment.

4.2 Scientific rationale for the trial design

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

The chosen trial design reflects discussion and advice from the PEI obtained in two scientific advice meetings held in February and March 2020. At these meetings, the PEI supported the high-level design of this trial, specifically the staggered approach, single

dose (single immunization dose) and P/B testing, conditional to performance of lower dose exploration if appropriate and re-consideration of the dose regimens for Part B if appropriate.

Part A of the trial is designed as a classical dose-escalation, investigating the dose range which is most likely to be well-tolerated and induce a virus neutralizing response. To ensure trial subject safety, a staggered approach has been chosen starting with a defined low standard dose. Use of the overlapping escalating doses in Cohorts 1 to 3, i.e., progression to initiation of dosing at the next higher dose when data is available for 6 of 12 trial subjects per group, allows a faster dose escalation whilst 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 follow after evaluation of the Part A. Part B will be used to define the optimal final dose with respect to safety and immunogenicity for further evaluations in Phase III trials. Part B will also investigate vaccine administration in vulnerable populations (e.g., elderly, immunocompromised populations, and other fragile populations, and/or indicated populations.

4.3 Justification for dose

Given that BioNTech proposes a rapid response scenario to a newly emerged pandemic outbreak, sufficient data is currently not available to experimentally validate the dose selection and initial starting dose. Therefore, BioNTech proposed a starting dose of [redacted] 10 µg (for BNT162b1 and BNT162b2) in this trial based on non-clinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). [redacted]

The general safety and effectiveness of [redacted] modRNA platforms have been demonstrated in oncological clinical trials with different administration routes ([redacted], SAR441000 [NCT03871348]).[NCT03871348]). [redacted] NCT03871348

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

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

Based on non-clinical data of the RNA components ([redacted] modRNA, [redacted]), with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this trial, the sponsor expects that doses in the 1 to 5 µg range will be immunogenic and induce neutralizing antibodies. We further expect that 3 to 10-fold higher doses will be required to elicit a stronger antibody response.

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

As summarized in Section 2.2.1 and Section 2.2.2, to date most of the AEs reported after immunization with BNT162 vaccine candidates have been mild to moderate in intensity and no SAEs have been reported. Fever of severe intensity has been reported. Most AEs were managed with simple measures and resolved spontaneously.

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

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

4.4 End of trial (EoT) definition

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

The EoT is defined as the date the last subject completed the EoT Visit.

5 TRIAL POPULATION

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

5.1 Inclusion criteria

5.1.1 Inclusion criteria Part A

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

1. Have given informed consent by signing the informed consent form (ICF) before initiation of any trial-specific procedures.
2. They must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, lifestyle restrictions (e.g., to practice social distancing and to follow

good practices to reduce their chances of being infected or spreading COVID-19), and other requirements of the trial.

3. They must be able to understand and follow trial-related instructions.
4. For younger subject cohorts, volunteers must be aged 18 to 55 years, have a body mass index over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0.

   OR

   For older adult cohorts, volunteers must be aged 56 to 85 years, have a body mass index over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0.
5. They must be healthy, in the clinical judgment of the investigator, based on medical history, physical examination, 12-lead ECG, vital signs (systolic/diastolic blood pressure, pulse rate, body temperature, respiratory rate), and clinical laboratory tests (blood chemistry, hematology, and urine chemistry) at Visit 0.

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

5.1.2 Inclusion criteria Part B

Inclusion criteria for Part B will defined in the planned protocol amendment.

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 well-being 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 well-being 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 immunosuppressant's or other immune-modifying drugs, within the 6 months prior to Visit 0 unless in the opinion of the investigator, the medication would not prevent, limit, or confound the protocol-specified assessments or could compromise subject safety.
   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.
7. Received any vaccination within the 28 d prior to Visit 0.
8. Had administration of any immunoglobulins and/or any blood products within the 3 months prior to Visit 0.
9. Had administration of another investigational medicinal product including vaccines within 60 d or 5 half-lives (whichever is longer), prior to Visit 0.
10. Have a known history or a positive test 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 well-being 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, subjects in detention, CRO or sponsor staff or their family members.
28. Regular receipt of inhaled/nebulized corticosteroids.
29. For older adults only: Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors:
    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma

- Chronic liver disease
- Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2)
- BMI ≥30 kg/m^2
- Anticipating the need for immunosuppressive treatment within the next 6 months
- Resident in a long-term facility
- Current vaping or smoking (occasional smoking is acceptable)
- History of chronic smoking within the prior year

5.2.2 Exclusion criteria Part B

Exclusion criteria for Part B will defined in the planned protocol amendment.

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, 2, 4, 7, and 8, the first 6 subjects dosed in each group will be required to remain at the site for approximately 24 h after the first immunization. The remaining trial subjects in these cohorts will be required to remain at the site for approximately 6 h after the first immunization.

For cohorts with P/B dosing, all subjects dosed in each group will be required to remain at the site for approximately 6 h after the boost immunization.

For Cohort 3, subjects will be required to remain at the site for approximately 6 h after immunization.

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 serious AEs (SAEs), if applicable.

6 TRIAL TREATMENTS

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

6.1 IMP administered

IMP name:	BNT162 vaccines - Anti-viral RNA vaccines for active immunization against COVID-19
Type:	RNA-LNP vaccines utilizing different BioNTech RNA formats, i.e., [redacted] modRNA (two variants, product codes BNT162b1 and BNT162b2), [redacted]
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 by the SRC after review of the safety, tolerability, and immunogenicity data from Part A.
Dosage frequency:	One injection or two injections 21 d apart. [redacted]
Administration route:	Intramuscular (IM); upper arm, musculus deltoideus. For the P/B regimens the same arm may be used for both immunizations. The non-dominant arm is preferred.

6.2 Preparation/handling/storage/accountability

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

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

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

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

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

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

6.3 Measures to minimize bias: randomization and blinding

Not applicable for Part A. Details for Part B will be defined using a protocol amendment.

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 [redacted] Visit 9 ([redacted] BNT162b1, BNT162b2)**,** must be recorded along with the:

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

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

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

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

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, to add a cohort, or to progress to Part B for each vaccine will be made by the SRC (for details, see Section 10.1.5). Dose de-escalation and escalation rules have been defined in this protocol (see Section 6.6.2).

6.6.1 Dose limiting toxicity

During the time of enrollment into a given dose escalation cohort in Part A, if any of the following events occur, further dosing in that cohort will be stopped:

- 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
- Two trial subjects (at any dose level) with the same or similar severe (Grade 3 or higher) AE (including clinically significant laboratory abnormalities) within 7 days of vaccination, considered related, or for which there is no alternative, plausible, attributable cause (for severity grading of adverse events see Section 10.3.1.7)

[redacted]

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.

6.6.2 Dose modification guidance/rules

The trial design also allows for:

- The selection of which BNT162 vaccine(s) will be investigated in Part B.

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

Part A

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

Dose-escalation:

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

Part B

The to be tested doses for each vaccine in Part B will be chosen after review of the safety, tolerability, and immunogenicity data from Part A for that vaccine.

Relevant safety and tolerability data collected in Part A will be included in the protocol amendment planned to define details of Part B.

6.6.3 Mitigation plans for specific AEs

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

- Treat fever with acetaminophen or NSAIDs with a dose per trial site recommendation.
- After the first occurrence of flu-like symptomatology, subjects can be treated with standard therapeutic dose of acetaminophen, or NSAIDs, starting at least 2 h after the immunization.
- Corticosteroids should be avoided as either prophylaxis or treatment as it counteracts the effects of immunization.
- Ensure adequate hydration of trial subjects on the day of immunization. Consider administering fluids (e.g., water for drinking, 0.5 - 1.0 L) within approximately 2 h following the immunization per trial site standard.

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

6.6.4 Safety stopping criteria

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

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

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

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

6.7 Treatment after the end of the trial

Not applicable.

7 DISCONTINUATION OF TRIAL TREATMENT AND TRIAL SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of trial treatment

In rare instances, it may be necessary for a trial subject to permanently discontinue IMP administration (i.e., to not receive the boost dose for groups with P/B regimens). If IMP administration is definitively discontinued, the trial subject will remain in the trial to be evaluated for safety.

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. Trials subjects who tolerated initial vaccinations will be allowed to receive a second vaccination during this time.

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

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 Visit 6, if discontinued on a visit day.
- Complete all assessments planned for Visit 6, if not discontinued on a visit day.

7.3 Lost to follow up

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

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

- The trial site must attempt to contact the trial subject and reschedule the missed visit as soon as possible and counsel the trial subject on the importance of

maintaining the assigned visit schedule and ascertain whether or not the trial subject wishes to and/or should continue in the trial.

- Before a trial subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the trial subject (where possible, three telephone calls and, if necessary, a certified letter to the trial subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the trial subject's medical record.
- If the trial subject continues to be unreachable, they will be considered to have withdrawn from the trial.

7.4 Replacement of permanently discontinued trial subjects

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

8 TRIAL ASSESSMENTS AND PROCEDURES

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

Protocol waivers or exemptions are not allowed.

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

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

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

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

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

8.1 Efficacy assessments

Not applicable.

8.2 Safety assessments

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

8.2.1 Physical examinations

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

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height (in cm) will also be measured and recorded during complete physical examinations.
- A brief (symptom directed) physical examination. The brief physical examination includes an overall health judgement. 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 AEs (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).

Local reactions will be graded using the criteria given in US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" for "Local Reaction to Injectable Products" (see the

section “Assessment of intensity” in Section 10.3.1.11). This information will be used to validate the solicited assessment of local reactions in the patient diary and potentially support AE reporting.

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 at the times given in the SoA (Section 1.3).

Systemic reactions will be graded using the criteria given in US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" for "Systemic reaction grading scale" (see the section "Assessment of intensity" in Section 10.3.1.11).

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 discharge from the trial at [redacted] Visit 9 ([redacted] BNT162b1, BNT162b2, [redacted] [P/B]).

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

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

8.3.2 Method of detecting AEs and SAEs

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

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

8.3.3 Follow-up of AEs and SAEs

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

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

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

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

All ongoing AEs/SAEs will be followed until resolution, considered by the investigator to be stable or chronic (resolved with sequelae), the trial subject is lost to follow-up or the trial subject withdraws consent. If no final status is reached by the time of [redacted] Visit 9 ([redacted] BNT162b1, BNT162b2), the investigator must confirm the unavailability of a final status.

8.3.4 Regulatory reporting requirements for SAEs

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

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

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

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

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor should

review it and then file it together with the IB. If required by local requirements, the investigator will notify the relevant IEC.

8.3.5 Pregnancy

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

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

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

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

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

8.3.6 Death events

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

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

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

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

8.3.8 Adverse events of special interest

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

8.4 Treatment of overdose

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

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

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

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

8.5 Pharmacokinetics

Not applicable.

8.6 Pharmacodynamics

Not applicable.

8.7 Genetics

A blood sample (blood and / or isolated PBMCs) may be used for HLA typing of a subject to allow additional analysis, e.g., characterization of T cell receptor (TCR) repertoire and/or phenotypic characterization of antigen-specific T cells as further specified in Section 8.8 (Biomarkers).

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

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

8.8 Biomarkers

Up to 5 additional blood draws (with up to 200 mL in total) will be taken over the complete trial for explorative biomarker/immunogenicity research purposes.

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

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

Samples for biomarker analysis will be retained for use for up to 5 years after the end of the trial.

8.9 Immunogenicity assessments

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

- a functional antibody titer, e.g., virus neutralization test (VNT).
- Seronegative is defined as titers below the starting dilution which corresponds to a titer of <1:10.
- Seroconversion after vaccination is defined as a 4-fold increase in titer
    - for seronegative pre-vaccination sera: a titer ≥1:40.
    - for seropositive pre-vaccination sera: a titer which is 4-fold higher than the measured pre-vaccination titer, e.g., titer rise from 1:20 to ≥1:80 after vaccination.
- an antibody binding assay, e.g., ELISA.
- Seronegative is defined as titers below the starting dilution which corresponds to a titer of <1:100.
- Seroconversion after vaccination is defined as a 4-fold increase in titer
    - for seronegative pre-vaccination sera: a titer of ≥1:400.
    - for seropositive pre-vaccination sera: a titer which is 4-fold higher than the measured pre-vaccination titer, e.g., titer rise from 1:200 to ≥1:800 after vaccination.
- and/or
- equivalent assays dependent on availability by the time of trial conduct.

Cell-mediated immune (CMI) responses:

- CMI assays, e.g., ELISpot, intracellular cytokine staining (ICS).

  CMI analysis will include Th1-specific cytokines (e.g., IFN-gamma, TNF-alpha, IL-2, or IL12) and Th2-specific cytokines (e.g., IL4, IL-5, IL-10, IL-13) to analyze the induction of either balanced Th1/Th2 responses, or of unbalanced Th1-dominant or Th2-dominant immune responses, respectively.

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).

8.10 Blood collection

Up to approximately 568 mL blood will be drawn per subject over the complete trial, i.e., over approximately 7 months.

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

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

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

There is no formal statistical hypothesis under test.

9.2 Sample size determination

No formal sample size calculations have been performed.

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

The sample size for Part B will be assessed based on the data from Part A and confirmed/adjusted in the planned protocol amendment.

9.3 Analysis sets

The following analyses sets are defined:

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

9.4 Statistical analyses

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

The statistical analysis plan (SAP) will be finalized prior to database snapshot for the primary analysis and it will include a more technical and detailed description of the statistical analyses described in this section. Any deviations from the planned analyses described in the final SAP will be described and justified in the clinical trial report.

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

9.4.1 General considerations

In general, data will be summarized by groups and groups may be combined as appropriate. Part A and Part B will be analyzed separately and may be combined as appropriate.

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

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

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

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

9.4.2 Primary endpoints

The primary endpoints are defined in Section 3.

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

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

- P/B regimens: Day 1-21 (pre-boost)
- Day 21(post-boost) - 28
- SD regimens: Day 1-28

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

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

- Any AE
- Any AE excluding AEs based on solicited reporting via subject diaries.
- Related AE
- Grade ≥3 AE
- Related Grade ≥3 AE
- Any SAE
- Related SAE

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

Local reactions and systemic reactions will be graded using 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

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

9.4.3 Secondary endpoints

The secondary endpoints are defined in Section 3.

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

9.4.4 Exploratory endpoints

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

9.4.5 Other safety analyses

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

Clinical laboratory parameters

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

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

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

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

Abnormal laboratory results will be graded using 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).

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

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.

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, 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 Good Clinical Practice (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 investigator will be responsible for the following:

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

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

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

10.1.2 Financial disclosure

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

10.1.3 Informed consent process

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

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

Trial subjects must be informed that their participation is voluntary.

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

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

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

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

10.1.4 Data protection

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

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

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

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

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

10.1.5 Committees - SRC

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

For the decision to progress to Part B, an independent statistical consultant and a third party expert will also be included.

Key roles of the SRC are as follows:

- Before progression to the next cohort, for each vaccine per cohort/dose level, assess the data, decide whether to approve initiation of the next cohort/dose level and to confirm the planned dose or define another dose for use. The data assessed by the SRC is defined in Section 1.1.
- After completing its evaluation of the 48 h data for the first 6 subjects per group in cohort, the SRC may request a prolongation of the observation period to up to Day 7 data for later cohorts or other similar adaptations to protect subject wellbeing.
- Before progression to Part B, review and evaluate both safety and immunogenicity data per vaccine to decide whether to progress to Part B, and if yes, define what doses will be given. The data assessed by the SRC is defined in Section 1.1.
- 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., 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, memoranda, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

10.1.9 Trial and site start and closure

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

The sponsor designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

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

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

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

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

10.1.10 Publication policy

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

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

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

10.1.11 Protocol preparation and approval

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

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

Urinalysis

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

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

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

10.3.1 Definition of AE and TEAE

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
  NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), 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.
- Only the diagnoses of clinically significant local and/or systemic reactogenicity e.g., injection site reactions need to be reported as AEs (generally, the individual signs and symptoms of local or systemic reactogenicity making up diagnostic AEs are already captured as solicited reactions).
- New conditions or (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 "suspected unexpected serious adverse reactions" or SUSAR. SUSARs are subject to expedited reporting.

10.3.1.6 Use of the terms “severe” and “serious”

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

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

10.3.1.7 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

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

- Data pertaining to AEs will be collected during each trial visit either based on the trial subject’s spontaneous description or investigator’s inquiry or discovered in the course of examinations done during the visit, clinical significance of any sign or symptom needs to be evaluated by the investigator.
- Clinically significant findings need to be documented as AEs in the source data and CRF. Findings that are evaluated and documented in the source data as not clinically significant (e.g., an abnormal laboratory value without any clinical manifestation), should not be documented as AE.

- The investigator will then record all relevant AE information in the CRF and perform an assessment on:
  - Intensity, see the section “Assessment of intensity” in Section 10.3.1.7 for guidance on the assessment of intensity
  - Seriousness
  - Outcome
  - Causal relationship of the AE to the trial treatment
  - Any trial treatment action and/or any other action taken
- All assessments as well as AE term (diagnosis/description), start date and time of onset, end date and time need to be documented in the CRF.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all trial subject identifiers, with the exception of the trial subject number, will be redacted on the copies of the medical records before submission to the sponsor.
- To avoid colloquial expressions, the AE should be reported in standard medical terminology. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded.

Assessment of AE and/or SAE intensity

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

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

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

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

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

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

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

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

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

Actions taken by the investigator

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

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

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

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

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

Outcome

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

- Recovered/resolved* (= complete resolution of the AE)
- Recovering/resolving (= AEs which are improving but not yet resolved completely, e.g., decrease in an intensity grade)
- Not recovered/not resolved (= AEs which are ongoing without improving or still present when the trial subject deceases due to another cause)
- Recovered/resolved with sequelae* (= trial subject recuperated but retained pathological conditions resulting from the AE; the sequelae should be indicated)

- Fatal** (= death due to the AE)
- Unknown (e.g., in case the trial subject is lost to follow-up)

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

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

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

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

Assessment of causality

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

The investigator will use clinical judgment to determine the relationship.

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

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

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

Relationship to trial treatment

- The relationship or association of an AE or SAE to a trial treatment will be made by the investigator after having evaluated all accessible data and, if necessary, he/she will re-evaluate the case as new information becomes available.
- Events caused by the procedure of trial treatment administration should be differentiated from events caused by the trial treatment itself. Only events suspected to be caused by the IMPs itself should be documented as suspected Relationship to trial procedures
- In this trial, it cannot be excluded that during the course of the trial some procedures give rise to AEs which are related to the trial procedure and not to the

trial treatment. Procedure-related AEs can occur on the site of injection of the trial treatment e.g., redness, swelling, hematoma or itching or during or after trial-specific procedure, e.g., discomfort after blood drawing.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.1.8 SAE Exemptions

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

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

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

10.3.1.9 Documentation of particular situations

AEs that are secondary to other events:

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

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

Abnormal laboratory results and vital signs values:

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

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

AEs associated with an overdose or error in drug administration:

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

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

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

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

10.3.1.10 Reporting of SAEs

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

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

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

For the period of observation, see Section 8.3.1.

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

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

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

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

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

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

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

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

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

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

Local reactions

Redness and swelling / induration will be measured and recorded in centimeters and then categorized during analysis as absent, mild, moderate, severe or potentially life-threatening, based on the grading scale in Table 12. 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 12.

Table 12: 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 13.

Table 13: 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 14.

Table 14: Fever grading scale

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

Laboratory abnormalities

Laboratory abnormalities will be graded according to the grading scheme given in Table 15.

Table 15: Laboratory abnormality grading scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Female) change from baseline value - g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hemoglobin (Male) change from baseline value – g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Chemistry	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

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

10.4 Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

WOCBP

A woman is considered fertile following menarche and until becoming 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.

Postmenopausal female

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

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

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

10.4.2 Contraception guidance

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

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

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

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

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

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

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

10.4.3 Collection of pregnancy Information

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

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

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

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

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

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

10.4.4 Sperm donation

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

10.5 Genetics

Not applicable.

10.6 Liver safety: Suggested actions and follow-up assessments

Not applicable.

10.7 Investigators and trial administrative structure

10.7.1 Investigators and trial site personnel

There must be an investigator at each trial site.

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

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

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

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

10.7.2 Trial site personnel assigned trial-related duties

The principal investigator or deputy may define appropriately qualified personnel at a trial site to perform significant trial-related procedures and/or to make trial-related decisions under his/her supervision. In this case, the principal investigator must maintain a signed list of the persons to whom they delegate significant trial-related duties/responsibilities; the delegated trial-related duties/responsibilities must be specified in the list.

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

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

10.7.3 Contract research organizations

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

10.7.4 The sponsor and sponsor’s personnel

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

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

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

10.8 Country-specific requirements

Not applicable.

10.9 Other standard abbreviations and definitions

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

For definitions related to safety, see Section 10.3.

Abbreviation	Explanation
AE	Adverse Event
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CRO	Contract Research Organization
d	Day(s)
DLT	Dose limit toxicity(ies)
DMC	Data Monitoring Committee
EDC	Electronic Data Capture (system)
EoT	End of Trial
FDA	(US) Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
h	Hour(s)
HIV	Human Immunodeficiency Virus
HRT	Hormonal Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation (of technical requirements for registration of pharmaceuticals for human use)
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product; in this trial, BNT162 vaccines
ISF	Investigator's Site File
min	Minute(s)
NSAID	Nonsteroidal Anti-Inflammatory Drug
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities

Abbreviation	Explanation
SOC	System Organ Class
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
US	United States (of America)
WHO	World Health Organization
wks	Week(s)
WOCBP	Women Of Child Bearing Potential

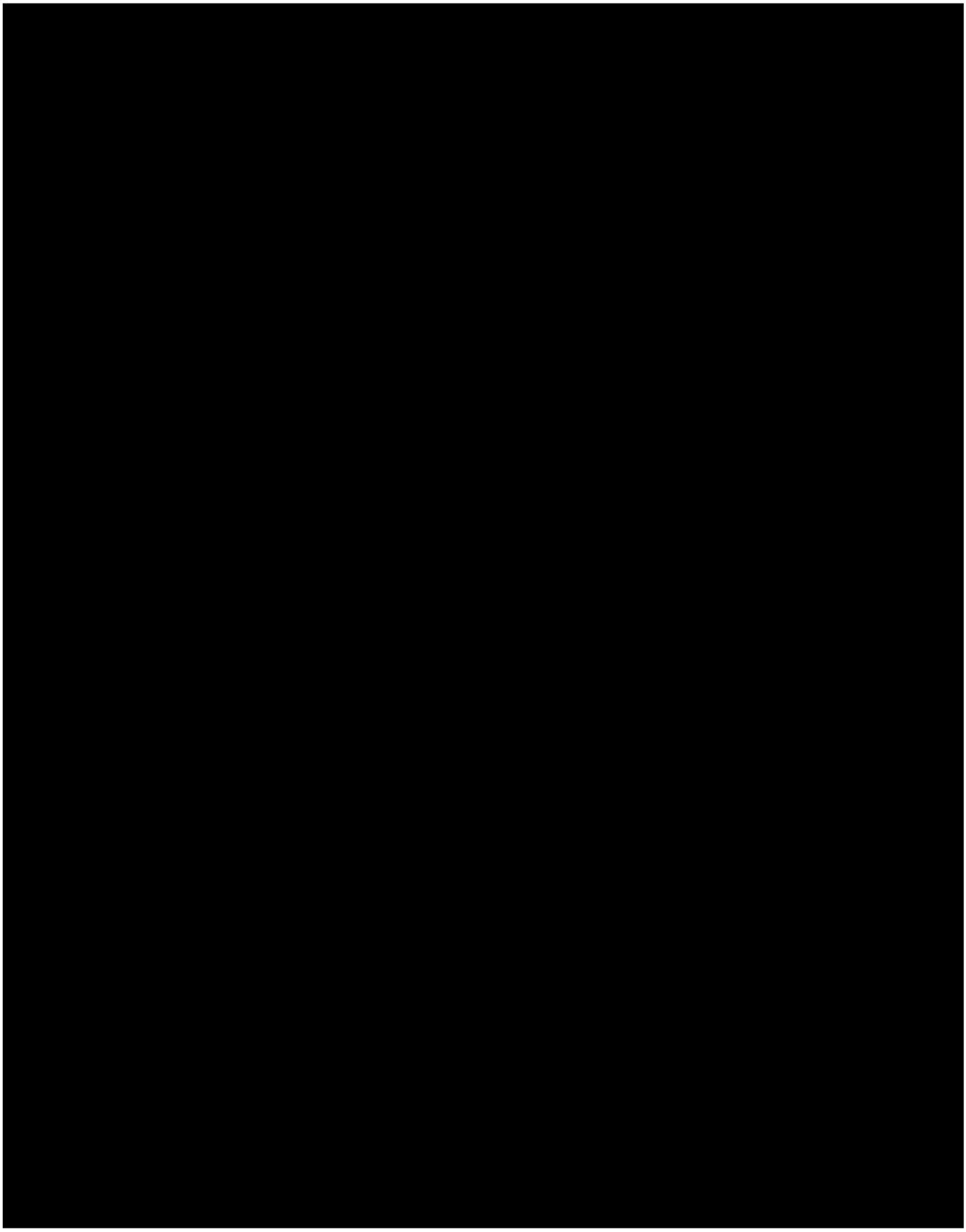
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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. Acknowledgement of receipt of the trial subject data will be required.

10.11.2 Trial subject reported outcomes

Not applicable.

10.11.3 Data management

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

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

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

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

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

10.11.4 Investigator's Site File and the Trial Master File

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

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

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

10.12 Other data

10.12.1 Demographic data

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

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

10.12.2 Medical history

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

11 REFERENCES

BNT162 Investigator's brochure, current edition.

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

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

Feldman RA, Fuhr R, Smolenov I, Mick Ribeiro A, Panther L, Watson M, 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.

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

Moyo N, Vogel AB, Buus S, Erbar S, Wee EG, Sahin U, 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.

NCT02410733. Evaluation of the Safety and Tolerability of IV Administration of a Cancer Vaccine in Patients with Advanced Melanoma (Lipo-MERIT). Ongoing BioNTech clinical trial.

NCT03871348. A First-in-Human Dose Escalation and Expansion Study to Evaluate Intratumoral Administration of SAR441000 as Monotherapy and in Combination with Cemiplimab in Patients with Advanced Solid Tumors. Ongoing BioNTech clinical trial.

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

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

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

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

WHO “Protection measures for persons who are in or have recently visited (past 14 days) areas where COVID-19 is spreading”. Accessed at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public

WHO Situation Report Nr. 85, April 15h, 2020. Accessed at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/