CLINICAL TRIAL PROTOCOL

Trial number: BNT165-01

Document version:	4.0	**Date:**	13 FEB 2023
Sponsor name:	BioNTech SE 55131 Mainz, Germany		

Trial title:	An exploratory Phase I, randomized, observer-blind, placebo-controlled dose escalation trial evaluating the safety, tolerability and immunogenicity of an investigational RNA-based vaccine for active immunization against malaria
Brief lay title:	Safety and immune responses after vaccination with an investigational RNA-based vaccine against malaria
Trial phase:	Phase I
Indication:	Active immunization against malaria
Investigational medicinal product (IMP):	BNT165b1
Regulatory identifiers:	US IND number 28991
Trial sites:	Sites are planned in the United States (US)
Trial Medical Monitor:	For the name and contact details, see the Study Contact List filed in the Investigator's Site File (ISF)

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, will be maintained. These personnel include the sponsor's medical expert for the trial and the person authorized to sign (approve) the protocol and any protocol amendment(s) for the sponsor.

Some sponsor tasks in the conduct of this trial may be delegated, e.g., to contract research organization (CRO) personnel. Documentation of any delegation of responsibilities will be maintained.

Document history	Date	Version number
First sponsor approved version	09 SEP 2022	1.0
Second sponsor approved version	13 OCT 2022	2.0
Third sponsor approved version	08 DEC 2022	3.0
Fourth sponsor approved version	13 FEB 2023	4.0

See Section 10.8 for summaries/rationales for all protocol updates.

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

1 PROTOCOL SYNOPSIS

1.1 Summary

Trial rationale

The World Health Organization (WHO) estimated that there were ~241 million cases of malaria and 627,000 malaria-associated deaths in 2020, of which 98% were caused by the parasite *Plasmodium falciparum (P. falciparum)* (WHO Malaria Report 2021). The WHO has stated the goal to reduce the incidence and mortality due to malaria by 90% until 2030. Despite programmatic efforts, recent gains to decrease malaria morbidity and mortality have been partially reversed, underscoring the need for effective malaria vaccines and other new tools to prevent malaria and achieve the WHO goals.

The world's first approved malaria vaccine (RTS,S/AS01; Mosquirix™) received favorable opinion from the European Medicines Agency (EMA) in 2015. It has a relatively low vaccine efficacy in preventing clinical malaria cases (it prevented ~36% of cases of clinical malaria over a median follow-up of 48 months in children aged 5 to 17 months) and its efficacy also wanes over time (RTS,S Clinical Trials Partnership 2015). The WHO has therefore encouraged the development of new and improved next-generation malaria vaccines with higher efficacy and improved durability.

BioNTech seeks to develop a highly efficacious vaccine that prevents blood stage infection, thereby directly preventing clinical disease and on a population level, reducing the malaria incidence and secondary transmission. The planned malaria vaccine is intended to induce poly-specific humoral and cellular immune responses against multiple *P. falciparum* antigens expressed in different stages of its life cycle rather than relying on targeting sporozoites alone, as done by Mosquirix™.

For the development of this malaria vaccine, BioNTech will use the same RNA technology platform used for the BNT162b2 severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) vaccine licensed as "COMIRNATY®" (BLA 125742) and given emergency use authorization as "Pfizer-BioNTech COVID-19 vaccine" (Emergency use authorization [EUA] 27034). The lipid nanoparticle (LNP) carrier system, the chemistry (nucleoside-modified) and the sequence design of the RNA molecule's untranslated backbone elements (cap, untranslated regions, polyA tail) will remain unchanged. Only the encoded open reading frames (ORFs) will change and will represent *P. falciparum* derived antigens. Also, the same well characterized manufacturing process, controls and possibly also manufacturing facilities, used for BNT162b2 will be utilized, as well as the same route of administration.

For this development, BioNTech plans to make reference to the platform data aggregated with development and marketing experience of BNT162b2, including toxicology data (e.g., RNA-LNP platform data from repeat-dose toxicity studies and pharmacokinetic studies) and the platform-intrinsic safety profile, to support first-in-human (FIH) clinical trials of *P. falciparum* vaccine components.

The final multi-antigen malaria vaccine (designated BNT165) will consist of a single co-formulation of distinct RNAs encoding different *P. falciparum* antigens each

encapsulated in LNP. Initially, the different RNAs planned for inclusion in the final vaccine formulation will be investigated separately or in combination as investigational vaccine candidates referred to as "components" throughout this document.

The BNT165 clinical development will begin with this FIH clinical trial, a dose escalation trial designed to assess the safety, tolerability, and exploratory immunogenicity of the vaccine component BNT165b1, that focuses on generating an immune response against a region of *P. falciparum* circumsporozoite protein (*Pf*CSP) not included in RTS,S. Later other vaccine components that encode distinct regions of *Pf*CSP or the full length *Pf*CSP, or antigens associated with other *P. falciparum* life cycle stages and/or combinations thereof, will also be assessed. The final composition of the BNT165 multi-antigen vaccine will be defined based on aggregate data from pre-clinical studies and clinical testing of the components (used alone or in combination) before progressing to Phase II/III clinical development.

Objectives, estimands and endpoints

OBJECTIVES	ESTIMANDS	ENDPOINTS
Primary objectives		
To describe the safety and tolerability of BNT165b1 vaccination in healthy adults.	For each DL cohort: • Frequency of solicited local reactions at the injection site recorded up to 7 d after each dose. • Frequency of solicited systemic reactions recorded up to 7 d after each dose. • Proportion of subjects with at least one AE occurring up to 28 d after each dose. • Proportion of subjects with at least one MAAE occurring up to 28 d after each dose. • Proportion of subjects in each cohort with at least one SAE occurring up to 24 weeks after Dose 3.	• Solicited local reactions (pain, erythema/redness, induration/swelling) • Solicited systemic reactions (vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, and fever) • AEs • SAEs • MAAEs
Exploratory objectives		
To describe the humoral immune responses induced by BNT165b1 vaccination at different DLs in healthy adults.	Not applicable	• Levels of antigen-specific serum and/or plasma antibodies (total IgG) measured using ELISA and/or similar assays CCI [redacted]

OBJECTIVES	ESTIMANDS	ENDPOINTS
CCI		

Abbreviations: AE = adverse event; CCI d(s) = day; DL(s) = dose level(s); ELISA = enzyme-linked immunosorbent assay; IgG = immunoglobulin G; MAAE = medically attended adverse event; CCI SAE = serious adverse event.

Overall design

The BNT165 multi-antigen vaccine clinical development will begin with this FIH clinical trial, a dose escalation multi-center trial designed to assess the safety, tolerability, and exploratory immunogenicity of the vaccine component. The vaccine component assessed in this trial will be BNT165b1, an RNA-LNP encoding for part of *Pf*CSP. Subsequently, multiple other vaccine components will be assessed (either individually or combinations) as well.

BNT165b1 will be evaluated at three dose levels (DLs) to select a safe and tolerable dose in a 3-dose schedule. A sponsor Internal Review Committee (IRC) will be used for the BNT165-01 clinical trial.

In total 60 healthy subjects divided into three cohorts by DL will be randomized 4:1 BNT165b1:placebo. Cohort 1 will receive 3 µg doses, Cohort 2 will receive 10 µg or lower doses, and Cohort 3 will receive 30 µg or lower doses.

For a flow diagram summary of the trial, see the schema in Section 1.2. For the planned assessments and visits, see the schedule of activities (SoA) in Section 1.3. This trial will use a staggered dose escalation schema with sentinel subjects in all cohorts (see Figure 1).

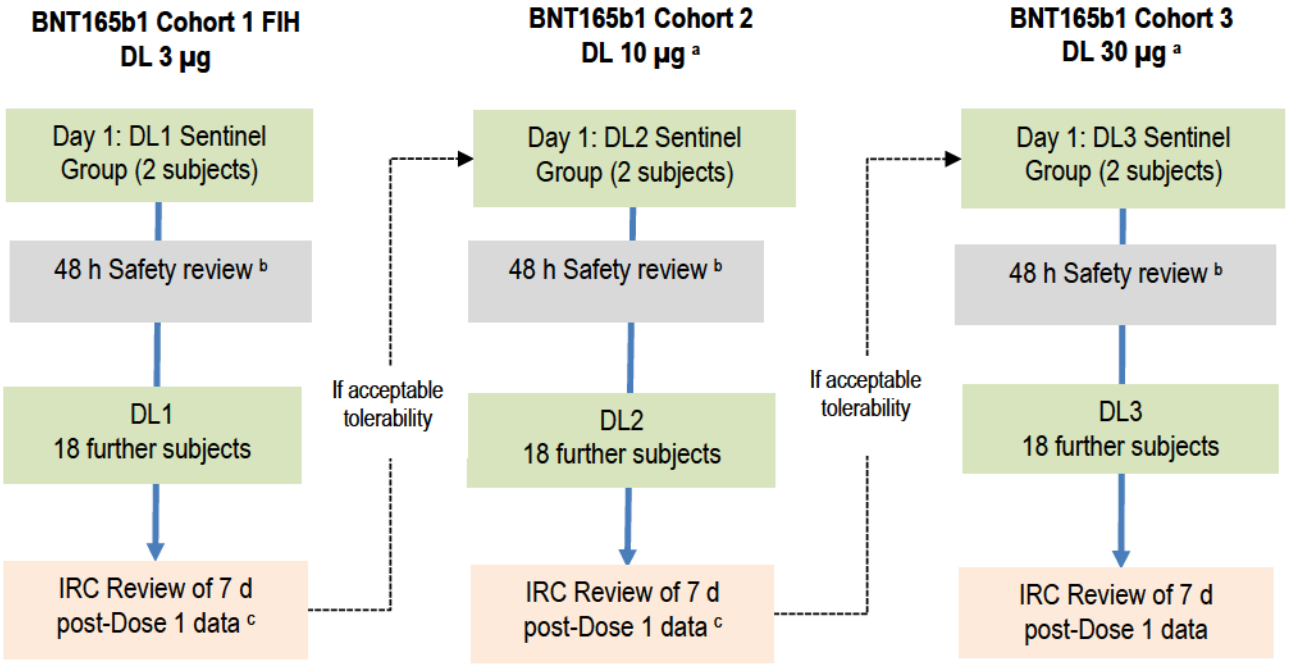

Figure 1: The staggered dosing process for the cohorts

a In case of safety concerns the IRC can decide to reduce to an intermediate dose.

b Further dosing of subjects will proceed if the investigator considers the vaccine reactogenicity is acceptable and no stopping/pausing rules are met.

c Further opening of new cohorts will proceed if the IRC considers the vaccine reactogenicity is acceptable and no stopping/pausing rules are met.

Abbreviations: d = days; DL = dose level; h = hour(s); FIH = first-in-human; IRC = Internal Review Committee.

This trial will be initiated with Cohort 1 (3 µg), where two subjects (sentinel group) will be dosed. The randomization will be done at the same clinical site at least 1 hour (h) apart and the two subjects will complete 48 h of follow-up post-Dose 1 (sentinel dosing approach), making sure that at least one subject will receive the vaccine. If the investigator considers the vaccine reactogenicity is acceptable and no stopping/pausing rules are met, 18 more subjects will be dosed. Once these additional 18 subjects complete the 7 days (d) follow-up post-Dose 1, all available clinical, laboratory and other relevant data of these 20 subjects will be reviewed by the IRC. If the IRC considers vaccine reactogenicity is acceptable and no stopping/pausing rules are met, dosing will be opened for the next DL cohort.

Subsequent DL cohorts will dose under the same trial rules and will follow the same dose escalation/assessment process.

Provided no cohort trial treatment pausing rules are met throughout the dosing period and the IRC does not determine safety findings judged to be of clinical concern, subjects who received Dose 1 (Day 1) in each DL will proceed to receive Dose 2 (Week 8) and Dose 3 (Week 26). If a pausing rule is met, administration of Dose 2 and/or 3 for the affected and higher DL(s) will be halted, pending IRC review.

The trial Medical Monitor and Safety Physician will review the safety data on an ongoing basis, interact with trial sites as needed, and assess whether any pausing rules are met.

Trial duration

The planned trial duration for each trial subject is ~19 months (up to 4 weeks screening, ~26 weeks treatment phase, and ~52 weeks follow-up phase).

Trial population

This trial will enroll healthy volunteers aged 18 to 55 years with no history of previous or current malaria infection. Trial subjects must not have received any approved or investigational malaria vaccine or have participated in a previous malaria challenge trial. All subjects must meet the trial eligibility criteria listed in Section 5.

Number of trial subjects

A total of 60 subjects are expected to enroll in the cohorts evaluating BNT165b1, such that there are 20 trial subjects for each of the cohorts as planned. Per cohort, trial subjects will be randomized 4:1, using an online randomization tool to receive either vaccine or placebo (i.e., of 20 subjects, 16 subjects and 4 subjects will receive the vaccine or placebo, respectively).

Trial treatments

IMP name	BNT165b1
Type	Investigational
Route of administration	IM injection in the deltoid muscle of the non-dominant arm. Other injection sites may be used if necessary.
Dose levels	• 3 µg BNT165b1 or isotonic NaCl solution (0.9%) • 10 µg or lower BNT165b1 or isotonic NaCl solution (0.9%) • 30 µg or lower BNT165b1 or isotonic NaCl solution (0.9%)
Vaccination schedules	Three (one each on Days 1, 57, and 183) injections given at each dose level.
Packaging and labeling	IMP will be provided in glass vials. Each vial will be labeled as per country requirements. For details, see the Pharmacy Manual.

Abbreviations: IM = intramuscular; IMP = investigational medicinal product.

The trial design follows a staggered dose escalation schema (see Figure 2).

Dose escalation decisions to the next DL and DL modifications (i.e., dropping the DL to the previous acceptable DL or to an 'in-between' DL) will be confirmed by the IRC.

Cohort DL reductions: The IRC may require that the planned escalation DL be reduced for a given cohort.

Cohort DL escalations: Dose escalation will only continue if the safety and reactogenicity of the previous DL is considered acceptable by the IRC and no stopping/pausing rules were met.

In addition to the above triggers for dose modifications, other unplanned dose modifications, pausing (temporary halting) of trial treatment, or even discontinuation of trial treatment may be required. See Section 7 for guidance on criteria for such cases.

Statistics

No formal statistical hypotheses will be tested in this exploratory trial.

The sample size for each cohort is mainly driven by a telescoping dose escalation study in a limited number of subjects designed for early detection of potential safety and reactogenicity events, and is considered adequate to support the trial objectives, while minimizing the number of trial subjects exposed to a new IMP.

1.2 Schema (graphical representation of the trial)

Figure 2: Graphical representation of the trial

M0, M2, M6 represent the dosing schedule at Days 1, 57, and 183; D7 represents Internal Review Committee review after 7 days follow-up post-Dose 1.

1.3 Schedule of activities

The SoA provide an overview of the trial visits and procedures. The investigator may conduct unscheduled visits in addition to those listed in the SoA, in order to conduct evaluations or assessments required to protect the wellbeing of the trial subjects.

Table 1: Schedule of activities for three-vaccination schedule

Activity	Visit (V) 0	V 1	V 2	V 3	V S 1 (Call) [p]	V 4 (Call)	V 5	V 6	V 7	V S 2 (Call) [p]	V 8	V 9	V 10	V S 3 (Call) [p]	V 11	V 12	V 13	V 14
Visit description	**Screening**	**Dose (D) 1 (Day 1)**	**1 d FU post-D 1**	**7 d FU post-D 1**	**(14 d post-D 1)**	**28 d FU post-D 1**	**D 2 (Day 57)**	**1 d FU post-D 2**	**7 d FU post-D 2**	**(14 d post-D 2)**	**28 d FU post-D 2**	**D 3 (Day 183)**	**7 d FU post-D 3**	**(14 d post-D 3)**	**28 d FU post-D 3**	**84 d FU post-D 3**	**168 d FU post-D 3**	**365 d FU post-D 3 or ET**
Visit window	**-30 to -1 d**	**N/A**	**±4 h**	**+2 d**	**+1 d**	**±2 d**	**±2 d**	**±4 h**	**+2 d**	**+1 d**	**±2 d**	**±7 d**	**+2 d**	**+1 d**	**±2 d**	**±10 d**	**±10 d**	**±10 d**
Collect informed consent	X																	
Inclusion / exclusion criteria	X	X (review)																
Medical history incl. prior medication and COVID-19 vaccination	X	X (update)																
Physical exam.	X	X [a]		X [a]			X [a]		X [a]			X [a]	X [a]					
Height & body weight	X																	
Vital signs [c]	X	X [b]		X			X [b]		X			X [b]	X					
12-lead ECG	X	X [m]		X			X [m]		X			X [m]	X					
Nasal or oral swab for rapid SARS-CoV-2 antigen test	X																	

Activity	Visit (V) 0	V 1	V 2	V 3	V S 1 (Call) [p]	V 4 (Call)	V 5	V 6	V 7	V S 2 (Call) [p]	V 8	V 9	V 10	V S 3 (Call) [p]	V 11	V 12	V 13	V 14
Visit description	**Screening**	**Dose (D) 1 (Day 1)**	**1 d FU post-D 1**	**7 d FU post-D 1**	**(14 d post-D 1)**	**28 d FU post-D 1**	**D 2 (Day 57)**	**1 d FU post-D 2**	**7 d FU post-D 2**	**(14 d post-D 2)**	**28 d FU post-D 2**	**D 3 (Day 183)**	**7 d FU post-D 3**	**(14 d post-D 3)**	**28 d FU post-D 3**	**84 d FU post-D 3**	**168 d FU post-D 3**	**365 d FU post-D 3 or ET**
Visit window	**-30 to -1 d**	**N/A**	**±4 h**	**+2 d**	**+1 d**	**±2 d**	**±2 d**	**±4 h**	**+2 d**	**+1 d**	**±2 d**	**±7 d**	**+2 d**	**+1 d**	**±2 d**	**±10 d**	**±10 d**	**±10 d**
Blood draw for viral screen [d]	X 5 mL																	
Blood draw for clinical lab. [e]	X 15 mL	X [f] 15 mL		X 15 mL			X [f] 15 mL		X 15 mL			X [f] 15 mL	X 15 mL					
Pregnancy test for VOCBP [g]	X	X					X					X						
Allocation to trial treatment (Randomization)		X																
IMP or placebo injection		X					X					X						
Record pregnancies		X	=>	=>		=>	=>	=>	=>		=>	=>	=>		=>	=>	=>	End
Counsel / remind subjects to use contraception		X	X	X		X	X	X	X		X	X	X		X	X		
Record concomitant medication since last visit		X	X	X		X	X	X	X		X	X	X		X	X	X	X
Blood draws for humoral response assessments [h]		X [f] 30 mL					X [f] 30 mL		X 30 mL		X 30 mL	X [f] 30 mL	X 30 mL		X 30 mL	X 30 mL	X 30 mL	X 30 mL
CCI																		
Blood draw for genetics		X [f] 4 mL																

Activity	Visit (V) 0	V 1	V 2	V 3	V S 1 (Call) [p]	V 4 (Call)	V 5	V 6	V 7	V S 2 (Call) [p]	V 8	V 9	V 10	V S 3 (Call) [p]	V 11	V 12	V 13	V 14
Visit description	**Screening**	**Dose (D) 1 (Day 1)**	**1 d FU post-D 1**	**7 d FU post-D 1**	**(14 d post-D 1)**	**28 d FU post-D 1**	**D 2 (Day 57)**	**1 d FU post-D 2**	**7 d FU post-D 2**	**(14 d post-D 2)**	**28 d FU post-D 2**	**D 3 (Day 183)**	**7 d FU post-D 3**	**(14 d post-D 3)**	**28 d FU post-D 3**	**84 d FU post-D 3**	**168 d FU post-D 3**	**365 d FU post-D 3 or ET**
Visit window	**-30 to -1 d**	**N/A**	**±4 h**	**+2 d**	**+1 d**	**±2 d**	**±2 d**	**±4 h**	**+2 d**	**+1 d**	**±2 d**	**±7 d**	**+2 d**	**+1 d**	**±2 d**	**±10 d**	**±10 d**	**±10 d**
CCI [redacted]																		
Subject hotline availability	Start	=>	=>	=>		=>	=>	=>	=>		=>	=>	=>		=>	=>	=>	End
Issue, train and collect subject e-diaries		Issue, train [i]					Re-train [i]					Re-train [i]	Collect					
Subjects report reactogenicity (incl. oral body temperature) daily for 7 d after each IMP dose using an e-diary		Start after Dose 1	=>	End [n]			Start after Dose 2	=>	End [n]			Start after Dose 3	End [n]					
Investigators review e-diary data daily		Start	=>	End			Start	=>	End			Start	End					
Record AEs, MAAEs, and SAEs [j]		X	X	X		X	X	X	X		X	X	X		X	X	X	X
Wellbeing phone call		X [k]			X [o]		X [k]			X [o]		X [k]		X [o]				
Investigator local reaction assessment		X [l]					X [l]					X [l]						

Activity	Visit (V) 0	V 1	V 2	V 3	V S 1 (Call) [p]	V 4 (Call)	V 5	V 6	V 7	V S 2 (Call) [p]	V 8	V 9	V 10	V S 3 (Call) [p]	V 11	V 12	V 13	V 14
Visit description	Screening	Dose (D) 1 (Day 1)	1 d FU post-D 1	7 d FU post-D 1	(14 d post-D 1)	28 d FU post-D 1	D 2 (Day 57)	1 d FU post-D 2	7 d FU post-D 2	(14 d post-D 2)	28 d FU post-D 2	D 3 (Day 183)	7 d FU post-D 3	(14 d post-D 3)	28 d FU post-D 3	84 d FU post-D 3	168 d FU post-D 3	365 d FU post-D 3 or ET
Visit window	-30 to -1 d	N/A	±4 h	+2 d	+1 d	±2 d	±2 d	±4 h	+2 d	+1 d	±2 d	±7 d	+2 d	+1 d	±2 d	±10 d	±10 d	±10 d
Cumulative blood volume (mL)	20	164	10	70		0	150	10	160		140	155	155		140	140	140	140

a Brief (symptom-orientated) physical examination.

b Before (up to 1 h) dosing and at 1 h (±15 minutes) after dosing.

c Vital signs: systolic/diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature.

d Viral screen: screen for HIV 1, HIV 2, Hepatitis B, and Hepatitis C.

e Clinical laboratory tests: (Chemistry) alkaline phosphatase, alanine transaminase, creatinine, c-reactive protein, albumin, amylase, aspartate transaminase, gamma glutamyl transpeptidase, total bilirubin, blood urea nitrogen, glucose, lipase, sodium, potassium, calcium, troponin, IgG, IgM and IgA; (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 VOCBP (to confirm postmenopausal status): follicle stimulating hormone at Visit 0. Only for VOCBP: serum β-HCG at Visit 0.

f On days with dosing, blood draws should be done pre-dose.

g VOCBP: The serum β-HCG pregnancy test at Visit 0 is performed using the sample collected for clinical laboratory tests. Before each dosing, urine pregnancy tests will be performed using a commercial kit at the site and the trial subjects will be counseled about the need for consistent and correct use a highly effective method of contraception.

h If justified by the collected data, the listed blood draw days and the draw volumes may be adapted if not increasing the total number of draw days or the total volume drawn. Leftover blood after completion of the immunogenicity assessments may be used for additional biomarker analyses.

i Trial site personnel will remind the subjects to record the oral body temperature and the worst grade for each symptom in the e-diary at approximately the same time every evening on the day of IMP administration and then every day in the evening for a total of seven consecutive days. Ask/remind the subject to contact the site if they experience any severe or potentially life-threatening reactogenicity events.

j The AEs and MAAEs will be collected continuously until 28 d after each dose, and SAEs need to be recorded continuously until Visit 14.

k Trial subjects will be contacted by phone for non-leading wellbeing calls at 5 h, 24±4 h (after Dose 3 only), and 48±4 h after each IMP dose.

l Local reactogenicity assessed by the investigator pre-dose and up to 1 h after dosing.

m 12-lead ECG will be performed pre-dose.

n Subjects will make their last entries in the evening before the 7 d follow-up visit.

o Trial subjects will be contacted by phone for wellbeing calls at 14 (+1) d after each IMP dose and to solicit local injection site reactions starting after 7 d and through 14 d post-IMP administration.

p Local reactogenicity calls after 14 d.

Notes:

If, for any reason subjects are permanently discontinued from the trial before completing all scheduled visits, if possible, all assessments planned for the actual week or day of that visit as listed in the SoA, should be performed, at minimum, all assessments scheduled at Visit 14 should be performed. The only exception is pregnant women who will not have further research blood draws, but will otherwise complete planned assessments.

The total blood volume drawn over any 8-week period in any cohort will always be less than 550 mL. Additional blood samples may be taken, e.g., for safety assessments after AEs or SAEs. The total volume of blood drawn from each subject over 546 d will be up to ~1,594 mL.

Abbreviations: AE = adverse event; CCI COVID-19 = Coronavirus Disease 2019; d = day(s); ECG = electrocardiogram; ET = early termination; FU = follow-up (visit); h = hour(s); β-HCG = beta human chorionic gonadotropin; HIV = human immunodeficiency virus; IMP = investigation medicinal product; Ig = immunoglobulin; MAAE = medically attended adverse event; RNA = ribonucleic acid; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus type 2; SAE = serious adverse event; SoA = schedule of activities; VOCBP = volunteers of childbearing potential.

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ABBREVIATIONS/TERMS

Abbreviation/Term	Explanation
~	Approximately
AE	Adverse event
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CRO	Contract research organization
CSP	Circumsporozoite protein
D	Day(s)
ECG	Electrocardiogram
EDC	Electronic data capture (system)
EMA	European Medicines Agency
Enrolled subjects	Subjects who signed an informed consent form, i.e., who gave informed consent
EUA	Emergency use authorization
EU	European Union
H	Hour(s)
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRT	Hormonal replacement therapy
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IM	Intramuscular or intramuscularly
IMP	Investigational medicinal product
IRB/IEC	Institutional Review Boards/Independent Ethics Committees
IRC	Internal Review Committee
ISF	Investigator's site file
LNP	Lipid nanoparticle
NSAIDs	Non-steroidal anti-inflammatory drugs
ORF	Open reading frame
*Pf*CSP	*Plasmodium falciparum* circumsporozoite protein
RNA-LNP	RNA-lipid nanoparticle
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial master file

Abbreviation/Term	Explanation
VOCBP	"Volunteers" of childbearing potential is used instead of "women" of childbearing potential to encompass all volunteers born female
US FDA	United States Food and Drug Administration
WHO	World Health Organization

2 INTRODUCTION

2.1 Background

2.1.1 The medical need

Malaria is a serious and sometimes fatal disease caused by a parasite that commonly infects a certain type of mosquito (*Anopheles* mosquito) which feeds on humans. Typical symptoms of a malaria infection in humans are high fever, shaking chills, and flu-like illness. Compared to malaria caused by other *Plasmodium* species*, P. falciparum* malaria is the type that is most likely to result in severe infections and, if not promptly treated, may lead to death.

The WHO estimated that there were ~241 million cases of malaria and 627,000 malaria -associated deaths in 2020, of which 98% are caused by the parasite *P. falciparum*, and 95% of cases occur in the African region (WHO Malaria Report 2021). The WHO has stated the goal to reduce the incidence and mortality due to malaria by 90% until 2030.

Despite programmatic efforts, recent gains to decrease malaria morbidity and mortality have been partially reversed, underscoring the need for effective malaria vaccines and other new tools to prevent malaria and achieve the WHO goals. Medicines based on artemisinin have improved the treatment options for malaria and vector control and exposure control programs have led to large reductions in malaria incidence. However, progress has stalled recently, and has even reversed during the Coronavirus Disease 2019 (COVID-19) pandemic.

Additionally, there is a risk of development of biological resistance against insecticides and antimalarial treatments. Effective vaccines preventing malaria caused by *P. falciparum* are urgently needed to achieve the goal of malaria eradication and to reduce the physical and socioeconomic burden of malaria in highly endemic areas.

Children in highly malaria endemic countries may experience multiple malaria episodes in their lives – all associated with a risk of severe disease, chronic complications, or death. While effective treatment exists, this may not always be available in remote areas and travel to the next health center is often very cumbersome. Preventing these malaria episodes with highly effective vaccines would reduce the individual disease and economic burden on children and their families. Pregnant women and people living with human immunodeficiency virus (HIV) in endemic areas, are both special populations at higher risk of clinical malaria and malaria-associated complications while adults in endemic areas who can be parasitemic but asymptomatic, act as a reservoir for ongoing transmission. A highly effective vaccine preventing blood stage infection may therefore decrease disease and onward transmission.

In non-endemic countries, where the number of malaria cases are comparatively low, the vast majority of malaria cases are imported from malaria endemic areas by tourists, migrant workers or immigrants returning from visiting friends and relatives. Travelers can protect themselves from malaria by taking chemoprophylaxis (e.g., atovaquone/proguanil, doxycycline, mefloquine), however, this may be impractical for prolonged stays. Ultimately

over 90% of imported malaria cases occur in individuals who did not take or incorrectly applied chemoprophylaxis. A highly efficacious long-lasting malaria vaccine could also help prevent imported malaria cases.

The world's first approved malaria vaccine is an adjuvanted protein subunit vaccine that consists of the major repeat region and the C-terminus of the *Pf*CSP fused to the Hepatitis B surface antigen (HBsAg). The vaccine is a mix of this *Pf*CSP-HBsAg compound with HBsAg that forms virus-like particles (RTS,S/AS01; Mosquirix™). Phase III studies of RTS,S delivered as a 3-dose series with a booster after 1 year showed moderate vaccine efficacy in children aged 5 to 17 months preventing 36% of clinical malaria cases over the full study period with a median follow-up of 4 years, with a range of 20% in high to 66% in low transmission settings. Furthermore, published literature suggests that protection wanes over time including reports of potential negative efficacy after 5 years in children with high malaria exposure (Olotu et al. 2016).

2.1.2 Clinical development of a BioNTech multi-antigen vaccine

P. falciparum is transmitted when an infected *Anopheles* mosquito bites the human host and injects sporozoites into the skin. Within at most a few hours, the sporozoites travel via the bloodstream to the liver (pre-erythrocytic stage). After hepatocyte invasion the parasite multiplies over 7 to 10 d (liver stage), before the *P. falciparum* merozoites are released into the human host bloodstream and infect erythrocytes (blood stage).

Circumsporozoite protein (CSP) is the major surface antigen of sporozoites. Antibodies targeting CSP have been shown to neutralize sporozoites and to reduce malaria morbidity and mortality. The approved malaria vaccine RTS,S/A01 also consists of a fragment of CSP that includes 18 central NANP repeats as well as the C-terminus of CSP. A monoclonal antibody (CIS43LS) that binds preferentially to the junctional NPDP epitope has recently shown 100% protection in a human malaria challenge model (Gaudinski et al. 2021). Similarly, the monoclonal antibody L9 which in addition to binding to NANP repeats shows high avidity to NVDP repeats, mediates protection in a murine malaria challenge model (Wang et al. 2020). Vaccines eliciting antibodies similar to these monoclonal antibodies may therefore provide superior protection compared to RTS,S (Moon et al. 2020; RTS,S Clinical Trials Partnership 2015). Additionally, the durability of the anti-CSP immune response may be different when using an RNA-based approach and will be assessed.

A single sporozoite is sufficient to allow hepatocyte invasion and further development into the blood stage, at which point anti-CSP antibodies are not functional anymore. Targeting one or more other life cycle stages in addition to the sporozoites may therefore increase the likelihood of preventing blood stage infection and provide a higher vaccine efficacy, as parasites evading the anti-CSP response will face an additional immunological hurdle.

The rationale for the multi-antigen design is to build upon the success of RTS,S by (a) first improving the CSP antigen used in RTS,S and (b) adding additional antigens that target different parts of the *P. falciparum* life cycle to drive both B- and T-cell responses. The goal is to make a safe vaccine with higher efficacy, durability and suitability for use in different populations.

The BNT165 clinical development will begin with this FIH, dose escalation trial designed to assess the safety, tolerability, and immunogenicity of the vaccine component BNT165b1, that focuses on generating an immune response against a region of *Pf*CSP not included in RTS,S. Later other vaccine components that encode distinct regions of *Pf*CSP or the full length *Pf*CSP, or antigens associated with other *P. falciparum* life cycle stages and/or combinations thereof, will also be assessed. The final composition of the BNT165 multi-antigen vaccine will be defined based on aggregate data from pre-clinical studies and clinical testing of the components (used alone or in combination) before progressing into Phase II/III clinical development.

If vaccine components like BNT165b1 are well tolerated in the BNT165-01 clinical trial, BioNTech may investigate them alone or in combination in a Phase IIa proof of concept trial assessing protection against a human malaria (i.e., in a human malaria challenge model).

2.2 Trial rationale

The WHO estimated that there were ~241 million cases of malaria and 627,000 malaria-associated deaths in 2020, of which 98% were caused by the parasite *P falciparum* (WHO Malaria Report 2021). The WHO has stated the goal to reduce the incidence and mortality due to malaria by 90% until 2030. Despite programmatic efforts, recent gains to decrease malaria morbidity and mortality have been partially reversed, underscoring the need for effective malaria vaccines and other new tools to prevent malaria and achieve the WHO goals.

The world's first approved malaria vaccine (RTS,S/AS01; Mosquirix™) received favorable opinion from the EMA in 2015. It has a relatively low vaccine efficacy in preventing overall of clinical malaria cases (it prevented ~36% of cases of clinical malaria over a median follow-up of 48 months in children aged 5 to 17 months) and its efficacy also wanes over time (RTS,S Clinical Trials Partnership 2015). The WHO has therefore encouraged the development of new and improved next-generation malaria vaccines with higher efficacy and improved durability.

BioNTech seeks to develop a highly efficacious vaccine that prevents blood stage infection, thereby directly preventing clinical disease and on a population level, reduces the malaria incidence and secondary transmission. The planned malaria vaccine is intended to induce poly-specific humoral and cellular immune responses against multiple *P. falciparum* antigens expressed in different stages of its life cycle rather than relying on targeting sporozoites alone, as done by Mosquirix™.

For the development of this malaria vaccine, BioNTech will use the same RNA technology platform used for the BNT162b2, SARS-CoV-2 vaccine licensed as "COMIRNATY" (BLA 125742) and given emergency use authorization as "Pfizer-BioNTech COVID-19 vaccine" (EUA 27034). The lipid nanoparticle (LNP) carrier system, the chemistry (nucleoside-modified) and the sequence design of the RNA molecule's untranslated backbone elements (cap, untranslated regions, polyA tail) will remain unchanged. Only the encoded ORFs will change and will represent *P. falciparum* derived antigens. Also, the same well characterized manufacturing process, controls and possibly also manufacturing facilities, used for BNT162b2 will be utilized, as well as the same route of administration.

For this development, BioNTech plans to make reference to the platform data aggregated with development and marketing experience of BNT162b2, including toxicology data (e.g., RNA-LNP platform data from repeat-dose toxicity studies and pharmacokinetic studies) and the platform-intrinsic safety profile, to support FIH clinical trials for *P. falciparum* vaccine components.

The final multi-antigen malaria vaccine (designated BNT165) will consist of a single co-formulation of distinct RNAs encoding different *P. falciparum* antigens each encapsulated in LNP. Initially, the different RNAs planned for inclusion in the final vaccine formulation will be investigated separately or in combination as investigational vaccine candidates referred to as “components” throughout this document.

The BNT165 clinical development will begin with this FIH clinical trial, a dose escalation trial designed to assess the safety, tolerability, and exploratory immunogenicity of the vaccine component BNT165b1, that focuses on generating an immune response against a region of *Pf*CSP not included in RTS,S. Later other vaccine components that encode distinct regions of *Pf*CSP or the full length *Pf*CSP, or antigens associated with other *P. falciparum* life cycle stages and/or combinations thereof, will also be assessed. The final composition of the BNT165 multi-antigen vaccine will be defined based on aggregate data from pre-clinical studies and clinical testing of the components (used alone or in combination) before progressing into Phase II/III clinical development.

For a rationale for the trial design, see Section 4.2.

For the rationale for the dosing regimen, see Section 4.3.

2.3 Benefit/risk assessment

For further information on the expected benefits and risks connected with intramuscular (IM) administration of BNT165b1, including the reference safety information, see the current BNT165 investigator’s brochure (BNT165 IB).

2.3.1 Benefit assessment

Trial subjects will not benefit directly from participation in this trial, but by participating, they will be contributing to general knowledge of RNA-based malaria vaccines and potentially also help in development of a safe and effective prophylactic vaccine for the prevention of malaria.

The potential benefits of receiving BNT165b1 have not been demonstrated, but by undergoing laboratory tests and physical examinations in this trial, previously undiagnosed health problems may be uncovered.

2.3.2 Risk assessment

The potential risk to trial subjects is considered to be low. The general risks of vaccines are included in Section 6.2.1 of the BNT165 IB.

Potential risks related to trial procedures:

- Trial subjects will be required to attend healthcare facilities during the trial and thus there is a potential for increased exposure to SARS-CoV-2.
- Venipuncture will be performed during the trial. There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.

Potential risks of the BNT165b1:

Human experience with BNT165b1 is not available prior to this trial. The vaccine is made of RNA, is metabolized as RNA in humans and does not interfere with DNA of a cell. The RNA, which is delivered to and expressed in the antigen-presenting cells of the vaccinated host, then elicits an immune response that ideally disrupts the *Plasmodium* life cycle at different stages, and thus prevents clinical episodes of malaria caused by *P. falciparum* infection.

Based on risks observed with SARS-CoV-2 vaccine BNT162b2 (with the same LNP carrier system, the same nucleoside-modified RNA, and the same untranslated elements of the antigen-encoding RNA as in BNT165b1), some risks listed for BNT162b2 may also apply after vaccination with BNT165b1. For more details refer to Section 6.2.2 of the BNT165 IB.

2.3.3 Risk mitigation

General risks of vaccines and potential risks related to trial procedures are managed by working with qualified sites experienced in the conduct of such trials and that have suitably trained and experienced personnel.

For guidance on the management of risks associated with anemia related to the blood draws in this trial, see Section 12.2.

For guidance on the management of potential for increased exposure to SARS-CoV-2, and thus linked to the pandemic COVID-19, see Section 12.3.

For guidance on the management of potential risks related to BNT165b1 administration, see the following section:

- Toxicity management/mitigation plans for local and systemic reactogenicity (Section 12.1).

2.3.4 Overall benefit/risk conclusion

The potential risk to trial subjects is considered as low. The trial was designed to minimize risk to subjects by using sentinel dosing, close monitoring of subjects etc., thus the potential risks identified in association with the trial procedures and trial treatments are considered justified by the anticipated benefits if a vaccine for the prevention of clinical malaria is successfully developed. See Section 4.1 for further details on safety monitoring after each dose.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ESTIMANDS	ENDPOINTS
Primary objectives		
To describe the safety and tolerability of BNT165b1 vaccination in healthy adults.	For each DL cohort: • Frequency of solicited local reactions at the injection site recorded up to 7 d after each dose. • Frequency of solicited systemic reactions recorded up to 7 d after each dose. • Proportion of subjects with at least one AE occurring up to 28 d after each dose. • Proportion of subjects with at least one MAAE occurring up to 28 d after each dose. • Proportion of subjects in each cohort with at least one SAE occurring up to 24 weeks after Dose 3.	• Solicited local reactions (pain, erythema/redness, induration/swelling) • Solicited systemic reactions (vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, and fever) • AEs • SAEs • MAAEs
Exploratory objectives		
To describe the humoral immune responses induced by BNT165b1 vaccination at different DLs in healthy adults.	Not applicable	• Levels of antigen-specific serum and/or plasma antibodies (total IgG) measured using ELISA and/or similar assays CCI [redacted]

CCI [redacted]

Abbreviations: AE = adverse event; CCI d(s) = day; DL(s) = dose level(s); ELISA = enzyme-linked immunosorbent assay; IgG = immunoglobulin G; MAAE = medically attended adverse event; CCI SAE = serious adverse event.

4 TRIAL DESIGN

4.1 Overall design

The BNT165 multi-antigen vaccine clinical development will begin with this FIH clinical trial, a dose escalation multi-center trial designed to assess the safety, tolerability, and exploratory immunogenicity of the vaccine component. The vaccine component assessed in this trial will be BNT165b1, an RNA-LNP encoding for part of *Pf*CSP. Subsequently, multiple other vaccine components will be assessed (either individually or combinations) as well.

BNT165b1 will be evaluated at three DLs to select a safe and tolerable dose in a 3-dose schedule. A sponsor IRC will be used for the BNT165-01 clinical trial.

In total 60 healthy subjects divided into three cohorts by DL will be randomized 4:1 BNT165b1:placebo. Cohort 1 will receive 3 µg doses, Cohort 2 will receive 10 µg or lower doses, and Cohort 3 will receive 30 µg or lower doses.

For a flow diagram summary of the trial, see the schema in Section 1.2. For the planned assessments and visits, see the SoA in Section 1.3. This trial will use a staggered dose escalation schema with sentinel subjects in all cohorts (see Figure 1).

This trial will be initiated with Cohort 1 (3 µg), where two subjects (sentinel group) will be dosed. The randomization will be done at the same clinical site at least 1 hour (h) apart and the two subjects will complete 48 h of follow-up post-Dose 1 (sentinel dosing approach), making sure that at least one subject will receive the vaccine. If the investigator considers the vaccine reactogenicity is acceptable and no stopping/pausing rules are met, 18 more subjects will be dosed. Once these additional 18 subjects complete the 7 d follow-up post-Dose 1, all available clinical, laboratory and other relevant data of these 20 subjects will be reviewed by the IRC. If the IRC considers vaccine reactogenicity is acceptable and no stopping/pausing rules are met, dosing will be opened for the next DL cohort. Subsequent DL cohorts will dose under the same trial rules and will follow the same dose escalation/assessment process.

Provided no cohort trial treatment pausing rules are met throughout the dosing period and the IRC does not determine safety findings judged to be of clinical concern, subjects who received Dose 1 (Day 1) in each DL will proceed to receive Dose 2 (Week 8) and Dose 3 (Week 26). If a pausing rule is met, administration of Dose 2 and/or 3 for the affected and higher DL(s) will be halted, pending IRC review.

The trial Medical Monitor and Safety Physician will review the safety data in real time, interact with trial sites as needed, and assess whether any pausing rules are met.

4.1.1 Planned number of trial subjects

A total of 60 subjects are expected to enroll in the cohorts evaluating BNT165b1, such that there are 20 trial subjects for each of the cohorts as planned. Per cohort, trial subjects will

be randomized 4:1, using an online randomization tool to receive either vaccine or placebo (i.e., of 20 subjects, 16 subjects and 4 subjects will receive the vaccine or placebo, respectively).

4.1.2 Duration of all trial periods

The planned trial duration for each trial subject is ~19 months (up to 4 weeks screening, ~26 weeks treatment phase, and ~52 weeks follow-up phase).

4.2 Scientific rationale for the trial design

Because of the exploratory nature of the trial, no formal sample size calculation was performed. Based on prior experience with such type of trial, the sponsor considers the chosen sample size of 20 subjects per cohort to allow (i) detection of the most frequent systemic and local adverse events (AEs), thereby allowing dose escalation decisions, and (ii) immunogenicity analyses of sufficient scope to support dose selection decisions, to meet the trial objectives, while minimizing the number of trial subjects exposed to the investigational trial treatment BNT165b1. For further justification of the chosen sample size, see Section 9.2.

Since BNT165b1 will be evaluated for the first time, this trial uses a staggered, sequential approach for subject dosing. Dosing will proceed with an initial 2-subject sentinel group for each DL cohort, pause/stopping rules will be followed, and there will be ongoing monitoring by a trial IRC that may pause, permanently discontinue administration of trial treatment, or even permanently terminate the trial at any time.

This trial includes safety monitoring after each dose, including vital signs at ~1 h after each dose, investigator assessment of local reactions up to 1 h after each dose, site visits at ~24 h after Doses 1 and 2, wellbeing phone calls at 5 h, and ~48 h after Doses 1 and 2, wellbeing phone calls at 5 h, ~24 h, and ~48 h after Dose 3, daily investigator review of subject's e-diary data for 7 d after each dose. Also, wellbeing phone calls will be conducted at 14 (+1) d after each IMP dose and local injection site reactions will be solicited starting after 7 d and through 14 d post-IMP administration.

The monitoring focuses on the 48 h after each dose based on experience with the closely related BNT162b2 vaccine in clinical trials, where the most frequent adverse reactions in subjects 16 years of age and older who received two doses were injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%), and these adverse reactions were usually mild or moderate in intensity and resolved within a few days after vaccination.

This trial uses safety evaluations and vaccine-induced immune responses to assess if there is a dose-response. For further details refer to Section 8.8.

4.3 Justification for the trial treatment

The proposed starting DL for BNT165b1 in this trial (3 µg) is based on the safety and immunogenicity in non-clinical studies and on the safety data generated for other members of the same RNA technology platform such as the SARS-CoV-2 vaccine BNT162b2 licensed as "COMIRNATY" and given EUA as "Pfizer-BioNTech COVID-19 vaccine".

BNT162b2 and the BNT165b1 have the same LNP carrier system, the same nucleoside-modified RNA, and the same untranslated elements of the antigen-encoding RNA (the RNAs differ essentially in the encoded ORFs for antigen expression).

The starting dose for BNT165b1 in this trial is lower than the dose approved for BNT162b2 (3 µg versus 30 µg) and is also spread over a longer period of time, i.e., the injections in the BNT162b2 trials were given 3 weeks (Dose 2) and ~29 weeks (Dose 3) apart, and here will be given 8 weeks (Dose 2) and 26 weeks (Dose 3) apart.

The planned BNT165b1 DLs in this trial (3 µg, 10 µg or lower, and 30 µg or lower) are supported by the existing toxicology data from BNT162 vaccines that evaluated doses up to 100 µg in rats. Also, in the SARS-CoV-2 BNT162 Phase I trial BNT162-01 (NCT04380701), DLs of 50 µg BNT162b1 given twice 3 weeks apart were evaluated in humans and no serious adverse events (SAEs) were observed and documented related to the vaccine, while reactogenicity showed clear DL dependency.

Since its first marketing authorization in December 2020, more than 2.5 billion doses of 30 µg BNT162b2 (COMIRNATY) have been administered worldwide. Data is also available after dosing in children ≥6 months of age. Pharmacovigilance data on BNT162b2 continues to accumulate, and to date, continues to support a favorable safety profile with no specific safety concerns for the prevention of COVID-19 disease. For further details see the BNT165 IB.

For the above reasons, the planned trial treatments are considered to be justified.

5 TRIAL POPULATION

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

Investigators should always use good clinical judgment in considering a volunteer's overall fitness for trial participation. Some volunteers may not be appropriate for enrollment even if they meet all inclusion/exclusion criteria. Medical, psychiatric, occupational, or other conditions may make evaluation of safety and/or immunogenicity difficult, and some volunteers may be poor candidates for retention.

Determination of eligibility, considering all inclusion and exclusion criteria, must be made within 30 d before enrollment unless otherwise noted in the following sections.

There must be documentation supporting compliance with the following listed inclusion/exclusion criteria, e.g., interview feedback, outcomes of trial procedures, medical records, etc., that confirm volunteers are eligible for inclusion in this trial.

5.1 Inclusion criteria

Volunteers are eligible to be included in the trial if all of the following criteria apply:

1 Have given informed consent by signing and dating the informed consent form (ICF) before initiation of any trial-specific procedures.

2 Are willing and able to comply with scheduled visits, treatment schedule, laboratory tests, lifestyle restrictions (e.g., to follow good practices to reduce their chances of being infected or spreading COVID-19), and other requirements of the trial. This includes that they are able to understand and follow trial-related instructions.

3 Are aged 18 to 55 years, have a body mass index over 18.5 kg/m^2 and under 35 kg/m^2 and weigh at least 45 kg at Visit 0.

4 Are healthy, in the clinical judgment of the investigator based on volunteer-reported medical history data, and physical examination, 12-lead electrocardiogram (ECG), vital signs, and clinical laboratory test outcomes at Visit 0.

Note: Healthy volunteers with pre-existing stable disease (e.g., obesity, hypertension), defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 90 d before Visit 0, can be included.

5 Agree not to enroll in another trial with an IMP starting from Visit 0 and until 12 weeks after receiving Dose 3.

6 This inclusion criteria has been removed from the protocol version 4.0.

7 Agree not to travel to a malaria endemic region starting from Visit 0 and until 28 d after Dose 3, as defined per CDC (Centers for Disease Control and Prevention) (https://www.cdc.gov/malaria/travelers/country_table/a.html).

Virology

8 Negative HIV -1 and -2 blood test result at Visit 0.

9 Negative SARS-CoV-2 antigen test result at Visit 0.

10 Negative HbsAg test result at Visit 0 and negative anti-Hepatitis C virus (anti-HCV) antibodies, or negative HCV polymerase chain reaction test result if the anti-HCV is positive at Visit 0.

Reproductive status and contraception

11 Volunteers of childbearing potential (VOCBP) that have a negative serum β-HCG pregnancy test result at Visit 0 and negative urine pregnancy test results before each IMP administration. Volunteers born female who are postmenopausal or permanently sterilized will not be considered VOBCP (for definitions of postmenopausal or permanently sterilized, see Section 10.5).

12 VOCBP who agree to practice a highly effective form of contraception (for guidance on contraception, see Section 10.5) and to require their male sexual partners to use condoms with a spermicidal agent, starting at Visit 0 and continuously until 90 d after receiving Dose 3.

13 VOCBP who agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during trial, starting at Visit 0 and continuously until 90 d after receiving Dose 3.

14 Men who are sexually active with partners of childbearing potential and who have not had a vasectomy that agree to use condoms with a spermicidal agent and to practice a highly effective form of contraception with their sexual partners born female (for guidance on contraception, see Section 10.5) during the trial, starting at Visit 0 and continuously until 90 d after receiving Dose 3.

15 Men who are willing to refrain from sperm donation, starting at Visit 0 and continuously until 90 d after receiving Dose 3.

5.2 Exclusion criteria

Volunteers are not eligible to be included in the trial if any of the following criteria apply:

1 History of malaria infection (any species) based on volunteer-reported medical history.

2 Travel to a malaria endemic region starting 6 months before Visit 0 and continuously until 28 d after receiving Dose 3, as defined per CDC (https://www.cdc.gov/malaria/travelers/country_table/a.html).

3 Prior residence for ≥6 months in a malaria endemic region.

4 Breastfeeding or intending to become pregnant starting with Visit 0 and continuously until 90 d after receiving Dose 3 or to father children starting with Visit 0 and continuously until 90 d after receiving Dose 3.

5 History of any serious adverse reactions to vaccines or to vaccine components such as lipids, and including history of anaphylaxis and related symptoms such as hives, respiratory difficulty, angioedema, and/or abdominal pain. (Not excluded from participation: a volunteer who had an anaphylactic adverse reaction to pertussis vaccine as a child).

6 Current or history of the following medical conditions:

a) Uncontrolled or moderate or severe respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease); symptoms of asthma severity as defined in the US National Asthma Education and Prevention Program Expert Panel report, 2020 - e.g., exclude a volunteer who:

- Uses a short-acting rescue inhaler (typically a beta 2 agonist) daily, or
- Uses high dose inhaled corticosteroids (per American Academy of Allergy Asthma & Immunology), or
- In the past year has either of the following:
  - Greater than one exacerbation of symptoms treated with oral/parenteral corticosteroids;
  - Needed hospitalization, or intubation for asthma.

b) Diabetes mellitus type 1 or type 2, including cases controlled with diet alone (Not excluded: history of isolated gestational diabetes).

c) Hypertension:

- If a person has been found to have elevated blood pressure or hypertension during screening or previously, exclude for blood pressure that is not well controlled. Well controlled blood pressure is defined as consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic, with or without medication, with only isolated, brief instances of higher readings, which must be ≤150 mm Hg systolic and ≤100 mm Hg diastolic at enrollment.
- If a person does not have a history of elevated blood pressure or hypertension previously or during screening, also exclude for systolic blood pressure >150 mm Hg at enrollment or diastolic blood pressure ≥100 mm Hg at enrollment.

d) Malignancy within 5 years of screening, excluding localized basal or squamous cell cancer;

e) Any current or history of cardiovascular diseases, (e.g., myocarditis, pericarditis, myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias), unless such disease is not considered relevant for participation in this trial in the investigator's judgment;

f) Bleeding disorder diagnosed by a doctor (e.g., factor deficiency, coagulopathy, or platelet disorder requiring special precautions);

g) Seizure disorder: History of seizure(s) within past 3 years. Also exclude if volunteer has used medications in order to prevent or treat seizure(s) at any time within the past 3 years.

7 Documented major psychiatric illness, including bipolar disorder, major depressive disorder, schizophrenia, autism, and attention deficit-hyperactivity disorder that at the discretion of the investigator could interfere with participation and follow-up as outlined by the trial.

8 The following diseases associated with immune dysregulation:

- Primary immunodeficiencies.
- History of solid organ or bone marrow transplantation.
- Asplenia: any condition resulting in the absence of a functional spleen.
- Currently existing or history of autoimmune disease including and not limited to thyroid autoimmune disease, multiple sclerosis, psoriasis, etc.

Prior/concomitant therapy

9 Previous vaccination with an approved or investigational malaria vaccine at any time or having taken part in a human malaria challenge study.

10 Receipt of any investigational product within 28 d before Visit 0.

11 Any planned non-trial vaccinations starting at Visit 0 and continuously until Visit 11 (28 d after Dose 3).

Note: Seasonal influenza and COVID-19 vaccines are allowed; however, they should be administered at least 14 d before or after any IMP injection.

12 Received blood/plasma products or immunoglobulin (Ig) within 120 d before Visit 1 or planned administration starting at Visit 0 and continuously until Visit 12.

13 Received allergy treatment with antigen injections within 28 d before first IMP administration or that are scheduled within 14 d after Visits 1, 5 and 9.

14 Current or planned treatment with immunosuppressive therapy, including systemic corticosteroids (if systemic corticosteroids are administered for ≥14 d at a dose of ≥20 mg/d of prednisone or equivalent) starting at Visit 0 and continuously until Visit 11 (28 d after Dose 3). Intraarticular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

Additional exclusions

15 Have a history of alcohol abuse or drug addiction within 1 year before Visit 0 or have a history (within the past 5 years) of substance abuse which in the opinion of the investigator, could compromise their wellbeing if they participate as subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.

16 Any existing condition which may affect vaccine injection and/or assessment of local reactions assessment at the injection site, e.g., tattoos, severe scars, etc.

17 Are vulnerable individuals as per International Council for Harmonization (ICH) E6 definition, i.e., are individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.

18 Any screening hematology and/or blood chemistry laboratory value that meets the definition of a Grade ≥2 abnormality or of Grade 1 at the investigator's discretion at Visit 0. Individuals with abnormal but not clinically significant parameters not included in the toxicity guidance may be considered eligible at the discretion of the investigator.

19 Current febrile illness (body temperature ≥38.0°C/≥100.4°F) or febrile illness within 48 h of Visit 0.

5.3 Lifestyle considerations

The trial subjects will be required to remain at the site for ~1 h after each IMP administration. When at the trial site, trial subjects will be asked:

- To drink fluids (e.g., water) before each site visit and during the ~2 h after each IMP administration per trial site standard.
- To not smoke or to drink alcohol when on site.

Trial subjects will be asked to avoid strenuous exercise beyond their usual exercise routine for 6 d after each IMP administration after leaving the trial site.

Trial subjects will be required to follow the guidance from the trial site personnel on recommended social behaviors to avoid SARS-CoV-2 infection (e.g., mask wearing, social distancing) and to practice the prescribed forms of contraception (see Sections 5.3.1 and 10.5.2).

5.3.1 Contraception and donation or cryopreservation of germ cells

Currently, a risk of human teratogenicity/fetotoxicity CANNOT be excluded by available data. Therefore, all male and female trial subjects who, in the opinion of the investigator, are biologically capable of having children must agree to use a highly effective method of contraception consistently (see Section 10.5.2) and correctly as specified in the SoA (Section 1.3). In addition, pregnancy testing will be performed at screening and before each IMP administration.

When obtaining informed consent, the investigator or designee will inform the trial subject of the need to use highly effective contraception consistently and correctly, and will document the conversation. This will include advice about donation and cryopreservation of germ cells (see inclusion criteria 13 and inclusion criteria 14, Section 5.1). In addition, the investigator or designee will instruct the trial subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the trial subject or partner.

The investigator or his or her designee, in consultation with the trial subject, will confirm that the trial subject has selected an appropriate method of contraception for the individual trial subject and his or her partner(s) from the permitted list of contraception methods and will confirm that the trial subject has been instructed in its consistent and correct use.

VOCBP will only be administered trial treatment after negative pregnancy test outcome(s) at the time points indicated in the SoA (Section 1.3).

For definitions of VOCBP, postmenopausal female and fertile men, as well as guidance on how to collect pregnancy information, see Section 10.5.

5.4 Screen failures

Screen failures are defined as individuals who consent to participate in the trial but who are not subsequently allocated 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 demographic information, date the ICF was signed, the reasons for screen failures, and any SAEs, if applicable.

If agreed with the trial Medical Monitor, rescreening is allowed at the discretion of the investigators. Rescreened subjects will need to reconsent and will be assigned a new trial subject number.

6 TRIAL TREATMENTS

Trial treatment is defined as any investigational treatment(s) or marketed product(s) intended to be administered to a trial subject according to the trial protocol.

An “IMP” is any medicinal product which is being tested or used as a reference in a clinical trial (the tested product and its reference products, including placebos).

Concomitant therapy is not considered trial treatment.

6.1 Trial treatment administered

IMP name	BNT165b1
Type	Investigational
Route of administration	IM injection in the deltoid muscle of the non-dominant arm. Other injection sites may be used if necessary.
Dose levels	• 3 µg BNT165b1 or isotonic NaCl solution (0.9%) • 10 µg or lower BNT165b1 or isotonic NaCl solution (0.9%) • 30 µg or lower BNT165b1 or isotonic NaCl solution (0.9%)
Vaccination schedules	Three (one each on Days 1, 57, and 183) injections given at each dose level.
Packaging and labeling	IMP will be provided in glass vials. Each vial will be labeled as per country requirements. For details, see the Pharmacy Manual.

Abbreviations: IM = intramuscular; IMP = investigational medicinal product.

6.2 Preparation/handling/storage/accountability

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

Only trial subjects enrolled in the trial may receive trial treatment and only authorized site personnel may supply or administer trial treatment. All trial treatment 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 unblinded and authorized site personnel.

The investigator, site, or the head of the site (where applicable) is responsible for trial treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Any non-compliance with the provided storage conditions should be reported to the sponsor upon discovery along with any actions taken. Once non-compliance is identified, the trial treatment must be quarantined and not used until the sponsor provides permission to use/discard/return the trial treatment.

Further guidance and information for the storage, handling, and final disposition of trial treatment are provided in the Pharmacy Manual.

6.3 Measures to minimize bias: randomization and blinding

This is an observer-blind trial.

6.3.1 Allocation of IMP

Trial subjects will be randomized 4:1 to BNT165b1:placebo using an online randomization tool.

6.3.2 Blinding

This is a 3-dose cohort observer-blind trial. Further details relevant to blinding/unblinding procedures will be provided in the Blinding Plan.

6.3.2.1 Blinding of trial subjects

All randomized trial subjects will be blinded to their assigned trial treatments.

6.3.2.2 Blinding of trial site personnel

The trial personnel dispensing and administering the vaccine will be unblinded, but all other trial personnel, including the principal investigator, and the subject, will be blinded. The principal investigator will assign the responsibility of unblinded dispenser and unblinded administrator to persons who will not participate in the evaluation of any trial subject. More than one unblinded dispenser/administrator may be assigned. A member of

the trial site personnel or clinic pharmacy should fulfill this role. Contact between the unblinded dispenser/administrator and trial subjects should be kept to a minimum.

The investigator and any site personnel other than the unblinded dispenser/administrator must not be allowed to know the IMP assigned to any trial subject and must not be allowed to see the drug product containers.

Because BNT165b1 and placebo differ in their physical appearance, the trial treatment will be provided in a manner that maintains the blinding, e.g., syringes will be masked or colored. For details, see the Pharmacy Manual.

6.3.2.3 Unblinding of trial subject

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a trial subject's trial treatment assignment is warranted. Trial subject safety must always be the first consideration in making such a determination. Before trial start, the investigator will be provided with instructions for how to conduct emergency unblinding.

If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor before unblinding a trial subject's trial treatment assignment unless this could delay urgent medical management of the trial subject.

If a subject's trial treatment assignment is unblinded, the sponsor must be notified within 24 h after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF).

6.3.2.4 Blinding of laboratory personnel

In this observer-blind trial, laboratory personnel performing genetic (see Section 8.7) and immune response assays (see Section 8.8) will be blinded. However, sponsor laboratory personnel will be unblinded.

6.3.2.5 Blinding of IRC members

To enable the IRC to provide real time medical oversight of trial subject safety during the conduct of this trial, the IRC members will include unblinded sponsor personnel.

6.4 Trial treatment compliance

Trial subjects will receive trial treatment directly from the investigator or a designee under medical supervision. The date and time of each dose administered must be recorded in the source documents and in the CRF. The dose of trial treatment and subject identification number will be confirmed at the time of dosing by a member of the trial site personnel other than the person administering the trial treatment.

See Section 8.4 for guidance on the treatment of overdose or errors in drug administration.

6.5 Concomitant therapy

6.5.1 Prohibited concomitant therapies during the trial

Trial subjects should not receive any IMP within 28 d before Visit 0 and continuously until Visit 12 (12 weeks after receiving Dose 3) in this trial. See exclusion criteria 10 and inclusion criteria 5.

Trial subjects should not receive any non-trial vaccinations starting at Visit 0 and continuously until Visit 11 (28 d after Dose 3) in this trial unless medically indicated. See exclusion criteria 11.

Trial subjects should not receive blood/plasma products or Ig from 120 d before Dose 1 and continuously until Visit 12 (12 weeks after Dose 3). See exclusion criteria 12.

Trial subjects should not receive any allergy treatment with antigen injections within 28 d before first IMP administration or that are scheduled within 14 d after Visits 1, 5 and 9. See exclusion criteria 13.

Trial subjects should not receive any immunosuppressive therapy, including systemic corticosteroids (if systemic corticosteroids are administered for ≥14 d at a dose of ≥20 mg/d of prednisone or equivalent) starting at Visit 0 and continuously until Visit 11 (28 d after Dose 3). Intraarticular, intrabursal, or topical (skin or eyes) corticosteroids are permitted. See exclusion criteria 14.

Trial subjects should not receive prescription or nonprescription drugs (excluding vitamins and dietary or herbal supplements) starting at Visit 1 and continuously until Visit 11 (28 d after Dose 3), unless they are considered permitted medications (described in the next section) or medically indicated and that in the opinion of the investigator and sponsor will not interfere with the trial.

6.5.2 Permitted concomitant therapies during the trial

Trial subjects should not receive prophylactic antipyretics and other pain medication to prevent symptoms associated with IMP administration. However, if a trial subject is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to IMP administration in this trial.

Inhaled, topical, or localized injections of corticosteroids (e.g., intraarticular or intrabursal administration) are permitted.

The use of antipyretics and other pain medication to treat symptoms after IMP administration or for ongoing conditions is permitted, but not for prophylaxis (i.e., up to 12 h before each IMP administration).

Administration of standard therapeutic dose of acetaminophen (preferable), or a non-steroidal anti-inflammatory drug (NSAID) if acetaminophen is contraindicated is permitted (paracetamol / acetaminophen at doses of up to 4 g/d). See the guidance on antipyretics and other pain medication in Section 6.5.1.

For intercurrent infections e.g., urinary tract infections and sinusitis, a short course (up to 7 d) of oral antibiotics are permitted during the trial.

Other concomitant medication may be considered on a case by case basis by the investigator, if required after consultation with the trial Medical Monitor.

6.5.3 Recording of concomitant therapy during the trial

All concomitant medications permitted or prohibited (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the trial subject receives during the trial must be recorded along with:

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

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

The start and stop dates and name of the concomitant medication during the trial will be recorded in the CRF for the period defined in the SoA (Section 1.3).

6.6 Dose modifications

The trial design follows a structured dose escalation schema. For details, see Section 4.1.

Dose escalation decisions to the next DL and DL modifications (i.e., dropping the DL to the previous acceptable DL or to an 'in-between' DL) will be confirmed by the IRC.

Cohort DL reductions: The IRC may require that the planned escalation DL be reduced for a given cohort.

Cohort DL escalations: Dose escalation will only continue if the safety and reactogenicity of the previous DL is considered acceptable by the IRC and no stopping/pausing rules were met.

In addition to the above triggers for dose modifications, other unplanned dose modifications, pausing (temporary halting) of trial treatment, or even discontinuation of trial treatment may be required. See Section 7 for guidance on criteria for such cases.

6.7 Access to trial treatment after the end of the trial

Provision of access to trial treatment after the end of the trial is not planned.

7 DISCONTINUATION OF TRIAL TREATMENT AND TRIAL SUBJECT DISCONTINUATION/WITHDRAWAL

Any safety concerns of the investigators should be discussed with the sponsor immediately upon occurrence or awareness to determine if the trial subject should continue or discontinue trial treatment.

7.1 Discontinuation or pausing (temporary halting) of trial treatment

The following pausing rules are established within the trial based on reported AEs, e-diary reactogenicity data, ECG findings, and clinical laboratory results.

Safety data will be reviewed on ongoing basis by investigators and sponsor.

The sponsor will set up regular IRC meetings (as specified in the IRC Charter). In addition, *ad hoc* IRC meetings will be triggered by reported events contributing to pausing rules. The IRC may also schedule an *ad hoc* meeting in absence of any pausing rules being met to evaluate a specific AE/SAE or a safety signal.

The investigator should notify the sponsor within 24 h about any observed Grade 3 AE (Section 7.1.1) or above that is possibly related on an expedited timeline like that of an SAE. A paper form to collect SAE and Grade 3 or 4 AEs contributing to pausing rules will be used for collecting these events.

If the reported events fulfill pausing rules criteria:

- The IRC will review all related data.
- Randomization and trial treatment administration for the impacted DL cohort and any higher DL cohort will be paused until the IRC recommends that assignment to the cohort and administration of trial treatment may be resumed.

For all subjects who are vaccinated, all other routine trial conduct activities, including ongoing data entry, reporting of AEs, subject reactogenicity e-diary completion, blood sample collection, and subject follow-up, will continue during the pause.

7.1.1 Cohort trial treatment pausing rules

Grading scales for the intensity of AEs and SAE will be based on guidance from the US Food and Drug Administration "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

If any of the below is met in a given cohort and after any dose, no additional trial subjects will be assigned to the cohort and administration of trial treatment, including administration of Dose 2 and/or Dose 3 for affected cohorts and any higher DL(s), will be paused until the IRC reviews the event(s):

- Any SAE developed by subject administered with trial treatment (at any DL), for which there is no alternative, plausible, attributable cause and which is assessed by the investigator, or the sponsor as possibly related.
- Any severe (Grade 3) hypersensitivity or any anaphylactic AE that occurs within 7 d of vaccination without a clear alternative cause.

NOTE: Grade 3 hypersensitivity is defined as symptomatic bronchospasm with or without urticaria, parenteral intervention, allergy related edema/angioedema, or hypotension. Grade 4 hyposensitivity encompasses all life-threatening events and for which urgent intervention is indicated.

- Any Grade 4 AE after administration of trial treatment (at any DL) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.
- Any case of immune-related AE, including but not limited to myocarditis, pericarditis or myopericarditis, that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.
- Any case of fever >40.0°C (measured orally) persisting for over 6 h despite the use of antipyretics after administration of trial treatment (at any DL) that is assessed as possibly related by the investigator and/or sponsor, or for which there is no alternative, plausible, attributable cause.
- If two trial subjects develop the same or similar Grade 3 or higher AE at least possibly related to trial treatment (solicited injection site reactions, solicited systemic reactions, unsolicited AEs, and laboratory abnormalities considered at least possibly related to trial treatment).

NOTE:

- Reactogenicity e-diary data confirmed by the investigator as being entered by the subject in error will not contribute toward a pausing rule.
- Data from Control group/ placebo recipients will not support the pausing rules.

7.1.2 Individual trial subject trial treatment pausing rules

Trial treatment administration for an individual trial subject will be paused (if applicable), pending IRC review, if any of the below criteria are met:

- Safety concerns identified by an investigator or the IRC
- Subject request for medical reasons (e.g., severe local reaction)

A febrile illness (body temperature ≥38.0°C/≥100.4°F) or other acute illness within 48 h before any IMP administration is a reason for temporary deferral of a dose, until fever-free for at least 24 h without antipyretics.

7.1.3 Permanent discontinuation of trial treatment

Trial treatment administration will be permanently discontinued for an individual trial subject if any of the below criteria are met.

- Any Grade 4 reactogenicity event considered to be possibly related
- Pregnancy
- Any severe acute systemic hypersensitivity AE or anaphylactic reaction of Grade 3 or above assessed as possibly related to IMP
- Any suspected or confirmed immune-related AE, including but not limited to myocarditis or pericarditis assessed as possibly related to IMP

After pausing trial treatment according to Sections 7.1.1 and 7.1.2, the IRC may recommend a permanent discontinuation of trial treatment overall, in a cohort, or for a single trial subject.

A permanent discontinuation of trial treatment may also occur for non-medical reasons at the judgment of the investigator or the subject (i.e., subject moves to a new location).

Trial subjects permanently discontinued from trial treatment will complete all assessments planned for the actual week or day of that visit as listed in the SoA (Section 1.3), at minimum, all assessments scheduled at Visit 14 should be performed. The only exception is pregnant women who will not have further blood draws, but will otherwise complete planned assessments, if required including pregnancy follow-up until birth.

7.1.4 Criteria for temporarily delaying enrollment, randomization or administration of IMP

Enrollment or randomization into the dosing cohorts may be paused or delayed if the IRC recommends a pausing of trial treatment according to Sections 7.1.1 and 7.1.2.

7.2 Trial subject discontinuation or withdrawal from the trial

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

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.

For trial subjects who withdraw consent, the investigator must clarify whether consent for research sample storage/processing (if given) is also withdrawn. If yes, then they must be informed that any research samples collected will be destroyed. The investigator must document research sample destruction in the ISF and inform the sponsor about the withdrawal of consent immediately.

If possible, permanently discontinued trial subjects should complete all assessments planned for the Early Termination Visit according to Section 8.12.

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 are 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 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 not be replaced.

8 TRIAL ASSESSMENTS AND PROCEDURES

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

The investigator (or an appropriate delegate at the trial site) must obtain a signed and dated informed consent before performing any trial-specific procedures.

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

Protocol waivers or exemptions are protocol deviations, and are not allowed.

Any safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the trial subject should continue or discontinue trial treatment.

Procedures conducted as part of the trial subject's routine clinical management (e.g., blood count) and obtained before signing of the informed consent may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the time frame defined in the SoA (Section 1.3).

Adherence to the trial design requirements, including those specified in the SoA, is essential and required for trial conduct. Every effort should be made to ensure that protocol-required activities are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the activity as planned. In these cases, the investigator must take all steps necessary to ensure the safety and wellbeing of the trial subject. When a protocol-required activity cannot be performed, the investigator must document the reason for the missed activity and any corrective and preventive actions taken to ensure that required processes are adhered to as soon as possible. The sponsor must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the trial site before to initiation of the trial.

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 and symptom-orientated physical examinations will be performed at the time points listed in the SoA (Section 1.3).

- A (complete) physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- A brief (symptom-directed) physical examination. The brief physical examination includes an overall health judgment. In-depth physical examinations are required if obvious pathological signs are visible or in the case the subject states any signs or symptoms that indicate need for a physical exam based on investigator discretion.

8.2.2 Vital signs, height, and body weight

Vital signs (comprising systolic/diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature) will be assessed at the times given in the SoA (Section 1.3).

Vitals signs measurements should be preceded by at least 5 minutes of rest for the trial subject in a quiet setting without distractions (e.g., television, cell phones).

Vital signs will be measured with trial subjects in seated position.

Systolic/diastolic blood pressure, respiratory rate, and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Oral body temperature (in °C or °F) will be measured and recorded to one decimal place. Body temperature will be reported in °C.

Height and body weight will be measured in centimeters and kilograms and recorded at screening.

8.2.3 Electrocardiograms

A standard 12-lead ECG 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. The ECG should be performed in the standard supine position. All original ECG readings must be kept as source documents.

All ECGs will be judged by the investigator as clinically significant (yes/no); only the abnormal findings, investigator assessment and heart rate will be recorded in the CRF. If a clinically significant finding is identified, refer further to Section 8.5.1.

8.2.4 Clinical laboratory tests

See the SoA footnotes (Section 1.3) for the list of clinical laboratory tests to be performed at the times given in the SoA. Clinical laboratory tests will be performed at a local

laboratory. For details of all assessed blood clinical laboratory parameters, see Section 10.3.

All protocol-required clinical laboratory tests must be conducted in accordance with the local laboratory standard. The investigator must review the laboratory report, and document this review with their signature and date of signature.

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 trial 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.

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), then the results must be recorded in the CRF.

8.2.5 Viral screening

Viral screens will be performed at the visit given in the SoA (Section 1.3). The viral screen comprises a screen for HIV 1, HIV 2, Hepatitis B, and Hepatitis C. Viral screen testing will be performed at a local laboratory. In addition, nasal or oral swab for rapid SARS-CoV-2 antigen test will also be taken at the visit given in the SoA (Section 1.3).

8.2.6 Subject e-diaries for assessment of reactogenicity (local and systemic reactions)

Subject e-diaries will be issued, trained, and collected by trial site personnel at the visits given in the SoA (Section 1.3).

Subjects will be asked to:

- Report reactogenicity (incl. oral body temperature) daily for 7 d after each IMP dose using an e-diary.
- Report the use of antipyretic/analgesic medication to treat symptoms associated with IMP administration for 7 d after each IMP dose using an e-diary.
- Record the worst grade for each symptom at approximately the same time every evening.
- Contact the site if they experience any severe or potentially life-threatening reactogenicity events.

8.2.6.1 Assessments of intensity for local reactions

Pain (perceived) at the injection site will be assessed as absent, mild, moderate, severe, or potentially life-threatening, according to the grading scale in Table 2.

Erythema/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 2.

Any local reaction of Grade 3 or higher will be confirmed by the investigator along with an assessment if it meets the definition of Grade 4.

Table 2: Local reaction grading scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3) [c]	Potentially life-threatening (Grade 4) [c]
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
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 actual measurement.
c. Investigator or medically qualified person confirmation is required.

Source: Based on the US FDA "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

8.2.6.2 Assessments of intensity for systemic reactions

Symptoms of systemic reactions will be assessed as absent, mild, moderate, severe, or potentially life-threatening, according to the grading scale in Table 3.

Any systemic reaction of Grade 3 or higher will be confirmed by the investigator along with an assessment if it meets the definition of Grade 4.

Table 3: Systemic reaction grading scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3) [a]	Potentially life-threatening (Grade 4) [a]
Vomiting	1 to 2 times in 24 h	>2 times in 24 h	Requires intravenous 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
Myalgia – muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe muscle pain
Arthralgia – joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe joint pain
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
Fever (oral temperature of ≥38.0°C/≥100.4°F)	38.0°C/100.4°F to 38.4°C/101.1°F	38.5°C/101.2°F to 38.9°C/102.0°F	39.0°C/102.1°F to 40.0°C/104.0°F	>40.0°C/>104.0°F

a. Investigator or medically qualified person confirmation is required.

Source: Based on the US FDA "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

8.2.7 Subject e-diaries for assessment of reactogenicity (local and systemic reactions) – Trial site personnel and investigator tasks

Subject e-diaries will be issued, trained, and collected by trial site personnel at the visits given in the SoA (Section 1.3).

The trial site personnel will ask/remind the trial subjects to:

- Record the worst grade for each symptom in the e-diary at approximately the same time every evening on the day of IMP injection and then every day in the evening for a total of seven consecutive days.
- Measure their body temperature using the provided device and record their body temperature in the e-diary every day including the day of IMP injection.
- To assess any solicited local reactions at the injection site as described in Section 8.2.6.1 and solicited systemic reactions as described in Section 8.2.6.2.
- To contact the site immediately in case of severe or potentially life-threatening reactogenicity events.

Investigators will review subject-reported e-diary data at the times given in the SoA (Section 1.3).

Only an investigator or medically qualified person is able to confirm Grade 3 or a potentially life-threatening Grade 4 event for recording in the EDC system.

If a trial subject experiences confirmed Grade 4 reactogenicity, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of IMP, further IMP administration will be discontinued in that trial subject (see Section 7.1).

If a trial subject experiences a potential Grade 3 reactogenicity or higher, the subject must immediately notify the investigator or some other medically qualified person, who will then confirm the grading, the confirmed Grade 4 reactogenicity will be recorded by the investigator as an SAE. Data for solicited Grade 3 or lower events do not need to be reported separately by the investigator as AEs in the EDC system, unless they are reported as an unsolicited event or extends beyond the 7 d.

8.2.8 Assessment of local reactogenicity - Investigator tasks

Investigators will assess acute local reactogenicity at the visits given in the SoA (Section 1.3).

Investigators will grade and record acute local reactions as described in Section 8.2.6.1.

If any acute local reactions meet any SAE criteria, they must be recorded as an SAE.

8.2.9 Subject hotline

Trial 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 on the handling of specific adverse reactions, see Section 8.5.

8.2.10 Wellbeing phone calls

Subjects will be contacted by phone for non-leading wellbeing calls at the times given in the SoA (Section 1.3). Subjects will additionally be contacted by phone 14 d post-IMP administration to solicit potential delayed injection site reactions, as given in the SoA (Section 1.3). During this phone call, they will be asked to report on any new skin reaction at the site of injection in the last 7 d prior to the phone call (Day 8 to Day 14 post IMP-administration).

8.3 Adverse events and SAEs

Definitions of AEs and SAEs can be found in Section 10.4.

8.3.1 Time period and frequency for collecting AE and SAE information

All AE and SAE information will be collected at the time points specified in the SoA (Section 1.3).

Non-serious AEs will only be collected as of first IMP dose administered while SAEs need to be recorded upon awareness starting once informed consent is given.

Adverse events and medically attended adverse events will be collected until 28 d after each dose and SAEs need to be recorded continuously until Visit 14 (52 weeks post-Dose 3).

Medical occurrences that begin after obtaining informed consent but before the start of trial treatment administration must be recorded on the respective Medical History/Current Medical Conditions section of the CRF and not in the section of the AE unless they qualify as SAEs.

Medical occurrences meeting the criteria for an SAE (see Section 10.4.2) must be reported as SAEs (see Section 8.3.4).

8.3.2 Detecting and reporting AEs and SAEs

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up all AEs and SAEs. The investigator will record on the CRF all observed directly and all spontaneously reported AEs and SAEs reported by the trial subject.

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

Guidance for the recording, evaluating, and assessing of AEs and SAEs is provided in Section 10.4.

The US FDA "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" will be used to grade the severity of AEs and SAEs.

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 related (see Section 10.4, for guidance the assessment of causality) to the trial treatment or trial participation, the investigator must promptly notify the sponsor as described in Section 10.4.4.

The sponsor may request that the investigator obtain specific follow-up information in an expedited fashion.

All SAEs (initial and follow-up reports) will be recorded and reported to the sponsor or designee within 24 h after the site becomes aware of the event, as indicated in Section 10.4.4.

For real time monitoring of events which may contribute to the pausing rules criteria, all such AEs (Grade 3 or higher possibly related) need to be reported on an expedited timeline (within 24 h) like that of an SAE.

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 and SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the trial subject is lost to follow-up, or the trial subject withdraws consent (as defined in Section 7.3). If no final status is reached by the End of Trial Visit, the investigator must confirm the unavailability of a final status. Further information on follow-up procedures is provided in Section 10.4.2.

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 health care professionals.

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

If a trial subject dies during participation in the trial or during a predefined follow-up period (see the SoA in Section 1.3), the investigator will provide the sponsor a copy of any postmortem findings including histopathology.

The investigator will submit initial and follow-up AE/SAE reports to the sponsor within 24 h of receipt of the information, as indicated in Section 10.4.4.

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 End of Trial Visit, the investigator must confirm the unavailability of a final status.

8.3.4 Reporting requirements for SAEs including suspected unexpected serious adverse reactions (SUSARs)

Prompt notification of an SAE via an EDC system and the provided paper SAE form by the investigator to the sponsor within 24 h of the site's awareness is essential so that the ethical responsibilities to trial subjects, the safety standards of a trial treatment under clinical investigation, and regulatory reporting obligations can be met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies involved in the conduct of trials with the same IMP 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, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators. The execution of reporting to the different entities may be delegated as detailed in the trial-specific Safety Management Plan.

All serious adverse reactions, the nature, severity or outcome of which is not consistent with the reference safety information are “unexpected serious adverse reactions”. The expectedness assessment for all related SAEs is based on the reference safety information included in Section 6.1.5 of the BNT165 IB.

All suspected adverse reactions related to an IMP that occur in this trial, and that are both unexpected and serious qualify as SUSARs. SUSARs are subject to expedited reporting requirements according to applicable regulatory requirements and guidance (i.e., ICH E2A guidance). SUSARs are subject to expedited reporting following ICH E2A standard. Information about Analysis of Similar Events will be added to the SUSAR report. IRBs will receive SUSAR reports as applicable.

For the IMPs, it is the sponsor’s or delegate’s responsibility to perform expedited SUSAR reporting submission to the applicable regulatory authorities, the IRB/IECs within the timelines stipulated in the respective country regulations. Reporting to the investigators will follow country-specific regulatory requirements and applicable guidelines.

8.3.5 Pregnancy testing and handling of pregnancies

For VOCBP, pregnancy tests and counselling will be performed at the times given in the SoA (Section 1.3).

For all trial subjects, pregnancy information will be collected over the time period defined in SoA (Section 1.3).

Any female trial subject who becomes pregnant while participating in the trial will need to discontinue the IMP immediately.

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 the trial subjects’ partner).

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 10.5.3.

Pregnancy *per se* is not an AE (and hence not an SAE). 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, if not covered by the exemptions to the SAE definition as defined in Sections 8.3.7, 10.4.2, and 10.4.2.2, which do also apply for fatal cases. Date and cause of death will be recorded. If available, a copy of an autopsy report should be submitted if available upon request.

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 the outcome “fatal” (death) 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.

In addition to reporting as SAE, the death page of the CRF needs to be completed.

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

Not applicable.

8.3.8 Adverse events of special interest

No AEs of special interest are defined for this trial.

8.4 Actions in case of overdose or error in drug administration

For a definition of an overdose, see the subsection “AEs associated with an overdose or error in drug administration” in Section 10.4.1.3.3.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose or an error in drug administration, the investigator should:

- Contact the trial Medical Monitor immediately.
- (At the discretion of the investigator) Give symptomatic treatment.
- Closely monitor the trial subject for any AE/SAE and laboratory abnormalities (at least 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 trial Medical Monitor based on the clinical evaluation of the trial subject.

8.5 Treatment for specific adverse reactions

Expected adverse reactions are mostly reflective of mild to moderate local and systemic reactogenicity events. Additionally, anaphylaxis can occur after any vaccination. For further details see the BNT165 IB.

8.5.1 Myopericarditis

Any subject who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 6 weeks after an IMP dose must be specifically evaluated by a cardiologist for possible myocarditis or pericarditis.

The same applies for any subject in whom a new ECG abnormality (compared to baseline) consistent with probable or possible myocarditis or pericarditis or abnormal Troponin I level is observed within 6 weeks after each IMP dose administration. In addition to a clinical evaluation, the following should be performed:

- ECG and

- Measurement of the Troponin I level, if not already obtained (for cases where the abnormal Troponin I level is the initial reason for evaluation).

If myocarditis or pericarditis is suspected based upon the initial evaluation, the following should also be performed:

- Cardiac echocardiogram and/or
- Cardiac magnetic resonance study

Any case of myocarditis, pericarditis or myopericarditis, that is assessed as possibly related by the investigator will constitute a trial treatment pausing rule per Section 7.1.1, until the IRC reviews the event. The ECG abnormalities consistent with probable or possible myocarditis or pericarditis are those judged as such by a cardiologist, including:

- Sustained atrial or ventricular arrhythmias
- Second-degree Mobitz Type II or worse atrioventricular block, new bundle branch block
- Diffuse ST-segment elevation or PR-segment inversion, compatible with pericarditis

The investigators must followup on any case of clinically significant ECG abnormality with troponins and other relevant tests till resolution. If there are such abnormal tests after the first dose, then investigators must make all relevant assessments before the second dose in reasonable time.

8.5.2 Other specific reactions

Treatment of these adverse reactions is at the discretion of the investigators; the following suggestions are provided:

- After the first occurrence of flu-like symptomatology including fever, subjects can be treated with standard therapeutic dose of acetaminophen (preferable), or a NSAID if acetaminophen is contraindicated.
- Ensure adequate hydration of trial subjects on the day of vaccination, e.g., by asking trial subjects to drink water before each site visit and during the ~2 h after each IMP administration per trial site standard.

If subjects experience enhanced respiratory disease or progression of flu-like symptomatology (e.g., no improvement of the symptoms after 3 d, or symptom kinetics that are inconsistent with a relationship to RNA vaccination), additional diagnostic measures should be considered, and the trial Medical Monitor should be informed.

8.6 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this trial.

8.7 Genetics

A blood sample (blood and/or isolated peripheral blood mononuclear cells) will be taken to evaluate the association between the human leukocyte antigen (HLA) and the immune response elicited by BNT165b1[redacted]

CCI [redacted]

8.8 Immune responses

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

Instructions on the sample collection, handling, and shipping will be provided in a Laboratory Manual.

CCI [redacted]

Humoral immune response assessments will include:

- Characterization of kinetics of titers, CCI [redacted]

CCI [redacted]

CCI

Additional immunological assessments may be conducted with residual samples to further characterize the vaccine-induced immune response and/or support vaccine-specific assay development.

Biosamples for research will be retained for use for up to 15 years (or shorter if required by local regulations) after the end of the trial. The tube with the biosample will be labeled with a number (optionally also with a bar code) and will not include information that could be used to identify the subject. Results of the analyses will be linked to the clinical information collected during the trial using this specific number. The analysis will only be carried out on the basis of the label data and biosamples. Research biosamples and all data generated using the biosamples, will be handled in accordance with applicable laws and regulations; this includes requirements applicable for data protection and a potential withdrawal of consent.

8.9 Blood collection

The total blood volume drawn over any 8-week period in any cohort will always be less than 550 mL. Additional blood samples may be taken, e.g., for safety assessments after AEs or SAEs.

The total volume of blood drawn for subjects will be up to ~1,594 mL each.

8.10 Collection of demographic and other baseline characteristics

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

- Age
- Sex
- Ethnic group
- Race
- Body weight and height, derived body mass index

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

8.11 Unscheduled visits

In order to conduct evaluations or assessments required to protect the wellbeing of the trial subjects, the investigator may conduct unscheduled visits in addition to those listed in the SoA.

8.12 Early termination visit(s)

If, for any reason, subjects are permanently discontinued from the trial before completing all scheduled visits, subjects will complete an Early Termination Visit. If possible, all assessments planned for the actual week or day of that visit as listed in the SoA (Section 1.3) should be performed.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

No formal statistical hypotheses will be tested.

9.2 Sample size determination

The sample size for each cohort is mainly driven by a telescoping dose escalation study in a limited number of subjects designed for early detection of potential safety and reactogenicity events. The sample size of 16 subjects receiving the vaccine per cohort allow the detection of the most frequent AEs with high probability. For 20 subjects, the probability of detecting at least 1 AE is 88% if the underlying AE rate is 10% and if the AE rate is 15%, then the probability of detecting at least 1 AE is 96%.

9.3 Analysis sets

The following analyses sets are defined:

Analysis set	Description
Screened Set	All subjects who provided informed consent
Safety Set	All subjects who received at least one dose of the IMP

Abbreviation: IMP = investigational medicinal product

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 9.4 or higher, and/or other statistical software as required.

The statistical analysis plan (SAP) will be finalized before the first database lock, 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 identified and justified in the SAP and reported in the clinical trial report.

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

9.4.1 General considerations

In general, data will be summarized by DL.

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

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

Baseline is defined as last available value prior to first BNT165 administration.

9.4.2 Safety endpoints

The safety endpoints are defined in Section 3. All safety analyses will be based on the Safety Set, overall, by vaccine DL or placebo.

All AEs will be coded using the most recent version of MedDRA® coding system to get a system organ class and PT for each AE.

Reactogenicity - Subject-reported via the e-diary

Solicited local and systemic reactions (from the subject e-diary) will be summarized. In general, solicited reactions will be analyzed for each immunization, i.e.:

- Up to 7 d after each IMP injection

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

- Any local reactions or systemic reactions
- Grade 1, 2, or ≥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.

Unsolicited AEs

The number and percentage of subjects reporting at least one AE (defined in Section 10.4.1) will be summarized by PT nested within system organ class for each of the following AE types:

- Any AE
- Related AE
- Grade of AE
- Related Grade ≥3 AE
- Any solicited reactogenicity event that continues longer than 7 d post-IMP administration or is an SAE
- Any SAE
- Related SAE

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

Additional safety analyses may be described in the SAP.

9.4.3 Exploratory endpoints

The exploratory endpoints are defined in Section 3. Exploratory analyses will be described in the SAP, if relevant to the clinical trial report (CTR).

9.4.4 Other safety analyses

Details of the other safety analyses will be described in the SAP.

9.4.5 Other analyses

Other analyses, if relevant to the CTR will be described in the SAP.

9.5 Interim analyses

An interim report with safety and immunogenicity data may be prepared when subjects in any cohort have completed 28 d of follow-up after second or third injection to inform further clinical development. Also, interim reports at other time frames may be prepared.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, ethical, and trial oversight considerations

This trial will be conducted in accordance with this protocol, the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP guidelines, and applicable laws and regulations.

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 ICH GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents, will be submitted to the relevant regulatory authorities as required by applicable regulations. If required, approval for conducting the trial will be obtained from regulatory authorities in accordance with relevant regulatory requirements.

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

Any amendments to the protocol will be submitted for IRB/IEC approval and (if required) competent authority approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial subjects.

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

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 (if applicable), and all other applicable local regulations.
- Informing the sponsor immediately of about any urgent safety measures taken by the investigator to protect the trial subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

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.

Trial subjects must be informed that their participation is voluntary.

The investigator will explain the nature of the trial to the trial subject and answer all questions regarding the trial.

Trial subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations (e.g., 21 CFR 50), ICH GCP guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or trial site.

The medical record must include a statement that written informed consent was obtained 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 informed in a timely manner if new information becomes available that may impact their willingness to participate in the trial. If required, trial subjects will be re-consented to updated written information and consent forms.

Trial subjects who are rescreened must reconsent.

A copy of the ICF(s) must be provided to the trial subject.

10.1.4 Data protection

All data collected and processing during this trial will be performed in accordance with the applicable data protection requirements.

Trial subject personal data will be stored at the trial site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized trial personnel have access. The trial site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the trial site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

Trial subjects will be assigned a unique identifier. The trial site will maintain a confidential list of trial subjects who participated in the trial, linking each trial subject's unique identifier to his or her actual identity and medical record identification.

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.

The trial subject must be informed that their 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.

The trial subject 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 IRB/IEC members, and by inspectors from regulatory authorities.

If the trial subject withdraws from the trial and/or withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. When trial subject data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

10.1.5 Committees - IRC

The IRC will be established to provide medical oversight of trial subject safety during the conduct of this trial, with a focus on guidance, management of emergent safety issues, and decision making as outlined in the IRC Charter. It includes periodic in-depth review of

safety data by trial subject, cohort, and cumulatively, in order to confirm mechanism of action, identify potential off-target toxicities, and to understand the IMP's safety profile and feasibility for further clinical development. The IRC is also a forum for the discussion of other data which could impact the IMP benefit-risk assessment, thereby allowing the IRC to periodically assess the overall benefit-risk of the IMP.

The IRC will be constituted and act according to procedures described in the IRC Charter. The IRC will prepare written minutes of its meetings.

Ad hoc IRC meeting will be triggered if any of the stopping/pausing rules are met.

10.1.6 Dissemination of clinical trial data

A final ICH E3 conform report integrating all trial results will be prepared by the sponsor. The outcomes of exploratory research analyses will be reported according to the sponsor's standard operating procedures (SOP), i.e., independently of the clinical trial data.

In all cases, trial results will be reported in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the trial or the country in which the trial was conducted.

Clinical trial data and documentation will be disseminated as required per applicable laws and regulations, e.g., the European Union (EU) Regulation No 536/2014, EU Regulation 1049/2001, and the US Final Rule, which implements Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801). Clinical documents under such laws includes protocols and protocol amendments, SAPs, ICH E3 clinical study reports.

This trial will be registered, and trial results be publicly posted, on publicly accessible trial registries (e.g., ClinicalTrials.gov, EU Clinical Trials Register, etc.) as required per applicable laws and regulations.

If this clinical trial is used to support marketing authorization packages/submissions, the sponsor will comply with the EU Policy 0070, the proactive publication of clinical data on the EMA website. Clinical data, under Phase I of this policy, includes clinical overviews, clinical summaries, ICH E3 clinical study reports, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Under Phase II of this policy, "clinical data" includes the publishing of individual patient data.

Even if not required by applicable laws and regulations, this trial will be registered, and trial results be publicly posted on ClinicalTrials.gov. In addition, expert summaries of the outcomes for all primary outcome measures (irrespective of outcome) and lay summaries, will be posted on a publicly accessible website.

The results for all primary outcome measures, irrespective of outcome, will be submitted for publication in academic journals (for further details, see Section 10.1.9).

10.1.7 Data quality assurance

All trial subject data relating to the trial will be recorded on printed or electronic 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 physically or electronically 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, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

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

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

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

Ongoing source data verification will be performed 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, ICH 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 in accordance with relevant local requirements after trial completion unless 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 at the investigator's site.

Data reported on the CRF or 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, trial subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

10.1.9 Publication policy

The results for all primary outcome measures, irrespective of outcome, will be submitted by the sponsor for publication in academic journals. The results of this trial may also be presented by the sponsor at scientific meetings.

The results of this trial may be published or presented at scientific meetings by the investigator. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments. The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any trial treatment-related information necessary for the appropriate scientific presentation or understanding of the trial results.

Unless agreed in advance otherwise, site- or subpopulation-specific analyses may only be published after the outcomes of the primary endpoint analyses have been published.

The sponsor will comply with applicable requirements for publication of trial results. In accordance with standard editorial and ethical practice, including those established by the International Committee of Medical Journal Editors (ICMJE). 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 ICJME authorship requirements.

10.1.10 Protocol preparation and approval

This protocol has been prepared, reviewed and approved in accordance with the sponsor's SOPs. Documentation of this process is filed in the trial master file (TMF).

10.1.11 Investigators and trial administrative structure

10.1.11.1 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.

The responsibilities of principal investigator(s) must be documented before any trial-related procedure is performed. All persons assigned responsibility as principal investigator must sign a declaration of their responsibilities. They must also sign a declaration that they have read and understand the content of the protocol, that all questions have been adequately answered, and that they are qualified by experience and training to act as investigator for this trial.

The principal investigator at each trial site is responsible for ensuring that this trial is conducted in accordance with the protocol, the principles of GCP, and applicable regulatory requirements.

If the trial is conducted at multiple trial sites, a coordinating investigator must be assigned who is responsible for the coordination of investigators at different trial sites. The

responsibilities of the coordinating investigator must be documented before any trial-related procedure is performed.

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

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 medical care.

10.1.11.2 Trial site personnel assigned trial-related duties

The principal investigator may define appropriately qualified personnel at a trial site to perform significant trial-related procedures and/or to make trial-related decisions under their 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 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.

10.1.11.3 Contract research organizations

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

10.1.11.4 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 will 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, will be maintained.

Some sponsor tasks may be delegated, e.g., to CRO personnel. Documentation of any delegation of responsibilities will be maintained.

10.1.12 Premature termination or suspension of the trial

If the trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the

subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authorities. In addition:

- If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.
- If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.
- If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial, the investigator should inform the institution where applicable and the investigator should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

10.2 Data collection and management

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

10.2.1 Data management

The CRO 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 CRO will request data clarification from the trial sites, which the trial sites will resolve electronically in the EDC system.

The CRO 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.

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

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

10.2.2 Case report forms

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

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.

10.2.3 Subject-reported outcomes

Subject e-diaries will be used for the reporting of reactogenicity (local and systemic reactions) by the trial subjects. See Section 8.2.6 for details (for e-diaries).

10.2.4 Investigator's Site File and the Trial Master File

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

The principal investigator 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.

10.3 Clinical laboratory tests

The tests listed below will be performed at the time/days listed in SoA (Section 1.3). Additional tests may be performed (including the addition of parameters) at any time during the trial as determined necessary by the investigator or required by local regulations.

- Chemistry: alkaline phosphatase, alanine transaminase, creatinine, c-reactive protein, albumin, amylase, aspartate transaminase, gamma glutamyl transpeptidase, total bilirubin, blood urea nitrogen, glucose, lipase, sodium, potassium, calcium, troponin, IgG, IgM and IgA.
- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count.
- Serology: HIV 1 and 2, Hepatitis B and C.
- Only in volunteers born female who are not VOCBP (to confirm postmenopausal status): follicle stimulating hormone at Visit 0.
- Only for VOCBP (to check for pregnancy if urine test not performed): serum β-HCG.

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

10.4.1 Definition of AE

AE definition:

- An AE is any untoward medical occurrence in a trial subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Medically attended adverse event is an AE for which the subjects received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits.

10.4.1.1 Events meeting the AE definition:

- Any abnormal laboratory test results (hematology or clinical chemistry) or other safety assessments (e.g., ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or severity of the condition.
- Serious AEs occurring after the date informed consent was given (ICF signed and dated) and AEs (non-serious AEs) occurring after first IMP administration.
- 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.

10.4.1.2 Events not meeting the AE definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with an underlying disease, unless judged by the investigator to be more severe than expected for the trial subject's condition.
- 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 or continue (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.

10.4.1.3 Documentation of particular situations

10.4.1.3.1 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.

10.4.1.3.2 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.

10.4.1.3.3 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.

10.4.1.4 Suspected adverse reaction

Suspected adverse reactions are untoward and unintended responses to an IMP related to any dose administered.

The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

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.

10.4.2 Definition of SAE

A 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 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 outpatient 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.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity:
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly or 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. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- For real time monitoring of events which may contribute to the pausing rules criteria, all such AEs (Grade 3 or higher possibly related) need to be reported on an expedited timeline (within 24 h) like that of an SAE.

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate severe or potentially life-threatening, as described in the US FDA "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"); see Section 10.4.3 for guidance on the assessment of severity; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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 within 24 h after learning of the event; see Section 10.4.4 for reporting instructions.

10.4.2.2 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 10.4.2). 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 the end of the observation period must only be reported by the investigator to the sponsor if a relationship to trial treatment or trial procedure is suspected.
- Hospitalizations that were necessary solely because of trial subject requirement for care outside of normal outpatient clinic operating hours will not be considered as reportable SAE.
- Hospitalizations for procedures or interventions of a pre-existing condition of the trial subject (elective surgery = planned, non-emergency surgical procedure) will not be considered as a reportable SAE (unless the intervention/procedure is not caused by an acute worsening of the pre-existing condition during the time trial participation):
    - if it was planned and documented in trial subject record before the trial-specific trial subject informed consent was signed (ICF for trial participation, see Section 10.1.3), or
    - if it was scheduled during the trial when elective surgery became necessary, and the trial subject has not experienced an AE.
- Routine treatment or monitoring of an underlying disease not associated with any deterioration in the trial subject's condition.

10.4.3 Recording and follow-up of AEs and/or SAEs

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 (see Section 8.3.1).

- Data pertaining to AEs will be collected during each trial visit. 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:
  - Severity (see the section Assessment of severity)
  - Seriousness
  - Outcome
  - Causal relationship of the AE to the trial treatment/trial procedure
  - 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 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 severity

The assessment of AE and/or SAE intensity should be done consistently for all trial subjects treated with the same treatment and dose. In case of doubt, the trial Medical Monitor should be consulted.

The intensity of (serious) AEs will be graded by the investigator. For further guidance refer to the US FDA "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 trial subject's usual function.
- Grade 2 - Moderate; interferes to some extent with the trial subject's usual function.
- Grade 3 - Severe; interferes significantly with the trial subject's usual function.
- Grade 4 - Potentially life-threatening; life-threatening consequences, urgent intervention required.

With regards the intensity of an (serious) AE, the following needs to be documented and CRF:

- Initial intensity of the AE
- For each change of intensity:
    - New grade of intensity
    - Date of change (= start of new grade of intensity)
    - Time of change (only if relevant)
    - New action taken

A change of severity only needs to be documented if there is a clearly definable change in grading of the AE (e.g., a laboratory result changes from severe to moderate).

An event is defined as "serious" when it meets at least one of the predefined seriousness criteria as described in the definition of an SAE, independent from its intensity.

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 (= reduction of the trial treatment dosage *)
- Drug interrupted (i.e., trial treatment withdrawn temporarily, interruption and resumption); i.e.:
    - Delayed administration of IMP dose
    - Delayed start of the next IMP dose
    - Cancellation of IMP administration at a given visit
    - Interruption of IMP administration during a given visit
- Drug withdrawn (i.e., trial treatment permanently 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)

*If an increase of trial treatment dosage is intended according to the trial protocol and the dosage is kept in comparison to last administration of trial treatment, it needs to be documented as “Dose reduced.”

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

- None
- Initiation of a remedial (concomitant) therapy
- Other specific treatment(s) of AE (to be specified)

Investigator assessment of the outcome of an AE

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., decreases in severity 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 each occurrence of each SAE and trial treatment and/or trial procedure.

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)

The relationship or association of an AE or SAE to a trial treatment/trial procedure will be assessed 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 adverse reactions but not events caused by the procedure of trial treatment administration.

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). These events must be reported in the CRF on Adverse Event pages as “related to trial procedure” with the causing procedure specified.

Notes applicable for relationship to trial procedures including trial treatments

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 their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.4.4 Reporting of SAEs

All SAEs (defined in Section 10.4.2) 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 first 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 the sponsor using paper report forms

The investigator must ensure the respective paper report form is completed and transmitted to the sponsor via one of the following reporting lines:

- Safety Report Fax No.: PPD
- Safety Report E-Mail address: PPD

As of 01 MAR 2023, the following reporting lines apply:

- Safety Report Fax No.: PPD
- Safety Report E-Mail address:

In parallel the respective SAE should be recorded in EDC as soon as possible.

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

For SAEs, follow-up information should be sent to the sponsor (indicating that this is a "follow-up" report using the respective 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 date of birth) needs to be blackened before sending.

For SAEs in addition to a medical record, the investigator should complete an Additional Information and Follow-Up Form, which contains the event term and 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 IRB/IEC or authority and retain documentation of these submissions in the Site Trial File.

In case an investigator or any other trial team member has questions on safety reporting the sponsor may be contacted via:

- E-Mail: PPD

As of 01 MAR 2023, the following sponsor contact address applies:

- E-Mail: PPD

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

10.4.5 Assessment of laboratory abnormalities

Laboratory abnormalities will be graded according to the US FDA "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

10.5 Contraceptive guidance and collection of pregnancy information

The following definitions and guidance is based on the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials issued in 2020 (CTFG 2020).

10.5.1 Definitions

Volunteer of childbearing potential

For the purpose of this document, a volunteer born female is considered of childbearing potential, i.e., fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes or during cancer treatment), additional evaluation should be considered.

Women in the following categories are not considered VOCBP:

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

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

Postmenopausal female

For the purpose of this document, a postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

A high follicle stimulating hormone 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 follicle stimulating hormone measurement is required.

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

Fertile men

For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral vasectomy or orchidectomy.

10.5.2 Contraception guidance

The following guidance describe what is considered highly effective and acceptable methods of contraception.

The investigator or delegate should advise the trial subject how to achieve highly effective contraception.

The following birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly may be considered as highly effective:

- Combined estrogen and progestogen-based hormonal contraception associated with inhibition of ovulation [1], i.e., established use of (oral, intravaginal, or transdermal) hormonal methods of contraception.
- Progesterone-only based contraception associated with inhibition of ovulation [1], i.e., established use of (oral, injected, or implanted) hormonal methods of contraception. [2]
- Intrauterine device. [2]
- Intrauterine hormone-releasing system. [2]
- Bilateral tubal occlusion. [2]
- Bilateral vasectomy (for a male trial subject or male partner of a female trial subject). [2, 3]
- Sexual abstinence [4]

1 Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
2 Contraception methods that in the context of this guidance are considered to have low user dependency.
3 A vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the VOCBP trial subject and that the vasectomized partner has received medical assessment of the surgical success.
4 In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the trial subject.

10.5.3 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 subject's partner becomes pregnant, written informed consent from both).

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 and in the CRF. The completed form needs to be sent to the Safety Report Fax number or E-Mail given in Section 10.4.4. 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 (spontaneous abortion, bleeding, preeclampsia, etc.) 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 treatment by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former trial subjects, the investigator may learn of an SAE through spontaneous reporting.

10.6 Liver safety: Suggested actions and follow-up assessments

Not applicable.

10.7 Standard definitions

10.7.1 Trial site start/closure and trial discontinuation

The date of first site open (first act of recruitment of potential trial subjects for this trial) is the "trial start date".

The date when all trial sites are closed is the "date of trial closure".

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.

All trial sites will be closed upon trial completion.

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 trial site closure.

The sponsor reserves the right to close a trial site early or to terminate the whole trial or to suspend the whole trial (a temporary halt; an unplanned interruption of the conduct of a trial by the sponsor with the intention to resume it) at any time for any reason.

Reasons for the sponsor to close a trial site early may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of trial subjects by the investigator

Reasons for the sponsor to suspend the whole trial may include but are not limited to:

- When there are safety concerns (e.g., if there is an IRC recommendation)

Reasons for the sponsor to prematurely terminate the whole trial may include but are not limited to:

- When there are safety concerns (e.g., if there is an IRC recommendation)
- Discontinuation of further trial treatment development

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

10.7.2 Trial completer and end of trial definitions

A trial subject is considered to have completed the trial if they have completed the last scheduled procedure shown in the SoA (see Section 1.3).

The end of the trial is defined as the date of last scheduled procedure (final date on which data were or are expected to be collected) as shown in the SoA for the last trial subject in the trial globally.

For definitions of the trial and site start/closure, see Section 10.7.1.

10.8 Protocol amendments and updates

10.8.1 Update to protocol version 2.0

This amendment implements changes in the primary endpoint and pausing rules.

This update will be issued before the planned trial subjects will be enrolled into the trial.

A comparison of every new sponsor approved protocol version with the next approved version is filed together with the protocol in the TMF.

Detailed description of changes

Minor editorial changes, such as rewording or improvement of language for consistency, are not specifically listed.

See the table for a summary of the reasons for changes compared to the previous version:

Section	Reason for change
Section 1.1 Trial synopsis (Objectives), Section 3 Objectives and endpoints	Clarification on primary endpoint i.e., AEs will be collected continuously until 28 d after each dose and not up to 28 d post-Dose 3.
Section 7.1 Discontinuation or pausing (temporary halting) of trial treatment	Clarification on the reporting of AEs contributing to pausing rules i.e., Grade 3 AEs or above possibly related, contributing to pausing rules will be collected on an expedited timeline (within 24 h) like that of an SAE.
Section 10.4.4 Reporting of SAEs	Sponsor's email ID has been updated to PPD

10.8.2 Update to protocol version 3.0

This amendment implements changes in the pausing rules requested by the FDA.

This update will be issued before the planned trial subjects will be enrolled into the trial.

A comparison of every new sponsor approved protocol version with the next approved version is filed together with the protocol in the TMF.

Detailed description of changes

Minor editorial changes, such as rewording or improvement of language for consistency, are not specifically listed.

See the table for a summary of the reasons for changes compared to the previous version:

Section	Reason for change
7.1.1 Cohort trial treatment pausing rules	Changes in the pausing rules requested by the FDA.

10.8.3 Update to protocol version 4.0

This amendment implements changes in the primary and exploratory endpoints, SoA, trial treatment, exclusion criteria and treatment for specific adverse reactions requested by FDA, also includes update of the sponsor's new e-mail and fax number and sponsor's contact e-mail address. Other changes were clarifications (see the below tabular summary).

These changes have no impact on the planned trial objectives or trial conduct.

A comparison of every new sponsor approved protocol version with the next approved version is filed together with the protocol in the TMF.

Detailed description of changes

Minor editorial changes, such as rewording or improvement of language for consistency, are not specifically listed.

See the table for a summary of the reasons for changes compared to the previous version:

Section	Reason for change
1.1, 1.3, 3 and 8.3.1	Change in the MAAEs collection time
1.1, 3 and 8.8	Clarification on exploratory endpoints
1.1 and 6.1	Addition of isotonic NaCl solution (0.9%) as matching placebo in all instances as requested by FDA.
1.3	Removal of urine dipstick analysis and microscopic urinalysis, changes in blood volume and clarification on ECG timings
1.3	Change in non-leading wellbeing calls timings
1.3, 4.2 and 8.2.10	Addition of wellbeing calls at 14 (+1) d after each IMP dose and to solicit local injection site reactions starting after 7 d and through 14 d post-IMP administration as requested by FDA.

Section	Reason for change
5.2	Addition of exclusion criteria #19."Current febrile illness (body temperature ≥38.0°C/≥100.4°F) or febrile illness within 48 h of Visit 0" as requested by FDA.
8.5	Addition of two subsections 8.5.1 and 8.5.2. Section 8.5.1 includes guidance for investigators on myopericarditis as requested by FDA.
10.4.4	Addition of new sponsor e-mail and fax number, sponsor contact e-mail address valid as of 01 MAR 2023

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12 TOXICITY MANAGEMENT/MITIGATION PLANS

12.1 Toxicity management/mitigation plans for local and systemic reactogenicity

Based on experience with other BioNTech RNA-based vaccines and published data from other RNA-based vaccines, it is anticipated that subjects may experience local and systemic (flu-like) reactogenicity events of mostly mild to moderate severity following the administration of RNA vaccines within 1 to 3 d. Symptomology may include injection site pain, fever, chills, rigors, tachycardia, arthralgia, myalgia, lymphadenopathy, headache or nausea.

Treatment of these events is at the discretion of the investigators; however, the following management suggestions are provided:

- After the first occurrence of flu-like symptomatology, subjects can be treated with standard therapeutic dose of acetaminophen (preferable) rather than NSAIDs, according to local guidance after the immunization.
- Corticosteroids should be avoided as either prophylaxis or treatment as it counteracts the effects of immunization.
- Self-limited Grade 3 reactogenicity events may not require discontinuation of future trial injections, and the local investigator may discuss with the trial Medical Monitor.
- Grade 4 reactogenicity events will lead to discontinuation of future injections in the trial subject.

If subjects experience progression of flu-like symptomatology or non-resolution of the symptoms later than 7 d post-immunization, the trial Medical Monitor should be informed.

12.2 Management of risks associated with anemia

This trial limits the total volume drawn over each sequential 8 week period to less than 550 mL, however, if a trial subject develops anemia, they should be evaluated and treated with iron supplements if appropriate.

If the trial subject develops Grade 3 anemia, the volume of blood drawn at any visit will be kept to a minimum, i.e., may be reduced to only safety assessments, at the discretion of the investigator.

12.3 Management of risks linked to the pandemic COVID-19

Risks linked to the pandemic COVID-19 will be managed by requiring:

- Avoidance of contact with persons tested positive for SARS-CoV-2 or have an increased risk for infection during their participation in the trial.

- Practice of social distancing and follow good practices to reduce their chances of being infected or spreading COVID-19 during their participation in the trial.
- Completion of health status checks which include symptom-directed physical examinations, vital signs assessments, and clinical laboratory tests on visit days.

Use of 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.