CLINICAL TRIAL PROTOCOL

BNT162-14

Version: 4.0 **Date:** 20 JAN 2022

Sponsor: BioNTech SE

Trial title:	A Phase II, open-label, rollover trial to evaluate the safety and immunogenicity of one or two boosting doses of Comirnaty or one dose of BNT162b2s01 in BNT162-01 trial subjects, or two boosting doses of Comirnaty in BNT162-04 trial subjects
Brief title:	A trial investigating the safety and effects of one or two additional doses of Comirnaty or one dose of BNT162b2s01 in BNT162-01 or BNT162-04 trial subjects
Trial phase:	Phase II
Indication:	Prevention of COVID-19 disease
Vaccine:	BNT162 RNA-lipid nanoparticle (RNA-LNP) vaccine, either Comirnaty® or BNT162b2s01
Coordinating and Principal investigator:	Dr. Dr. med. Armin Schultz, CRS Clinical Research Services Mannheim GmbH, Germany (tel.: +49 621 150450)
Trial conducted by:	CRS Clinical Research Services Mannheim GmbH, Germany
Trial sites:	Multiple sites in Germany that participated in the trials BNT162-01 or BNT162-04. For details of the trial sites and site personnel, see the Trial Master File
Sponsor's medical representative:	Dr. Svetlana Shpyro, Director Clinical Development, BioNTech SE
Sponsor:	BioNTech SE, An der Goldgrube 12, 55131 Mainz, Germany
Regulatory identifiers:	EudraCT no.: 2021-002387-50
Medical Monitor:	Contact information will be provided separately

Document history	Date	Version number	Valid for
First approved version *	27 MAY 2021	1.0	Germany
Approved version * (implementing Paul-Ehrlich-Institute (PEI) feedback on version 1.0)	12 JUL 2021	2.0	Germany
Approved version * (implementing requests for clarifications on version 2.0)	12 AUG 2021	3.0	Germany
Approved version *	20 JAN 2022	4.0	Germany

* Approved by the sponsor

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

1 PROTOCOL SUMMARY

1.1 Trial synopsis

Trial number: BNT162-14

Trial title

A Phase II, open-label, rollover trial to evaluate the safety and immunogenicity of one or two boosting doses of Comirnaty or one dose of BNT162b2s01 in BNT162-01 trial subjects, or two boosting doses of Comirnaty in BNT162-04 trial subjects.

Trial rationale

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. The BNT162b platform uses modRNA. The BNT162b platform member BNT162b2 (Comirnaty®) has received emergency use authorization or conditional marketing authorization in numerous countries worldwide for the prevention of COVID-19 disease. As demonstrated by Comirnaty, LNP-formulated RNA-based vaccines provide one of the most flexible, scalable and fastest approaches to provide protection against the emerging viruses like SARS-CoV-2 (Mulligan et al. 2020; Rauch et al. 2018; Sahin et al. 2014; Walsh et al. 2020).

This rollover trial (BNT162-14) will enroll BNT162-01 or BNT162-04 trial subjects; the BNT162-01 or BNT162-04 trials are also referred to as parent trials. The trial subjects represent a unique group of BNT162 vaccinees because their antibody and T-cell responses to SARS-CoV-2 antigens have been longitudinally characterized in the parent trials. Longitudinal characterization of the continuum of antibody and T-cell responses to BNT162 vaccines given to outbred human populations where pressure on the virus from genetics and evolving immune responses is simultaneously occurring, provides an opportunity for new and prescient insights into how the virus may evolutionarily adapt. Studies have demonstrated that Comirnaty protects against severe COVID-19 disease caused by the first generation of SARS-CoV-2 viral strains (called “L strain”, reference, or “wild type”) at least 6 months (unpublished data). The trial provides the opportunity to assess vaccine and booster induced durability of immune responses in context of more recent data on natural infection and cross-neutralization immunity. For example, SARS-CoV-2 infection and RNA vaccines such as Comirnaty induce cross-neutralization to multiple, more recently identified viral variants, some of which are identified as variants of concern (VOC) (Liu et al. 2021; Widge et al. 2021). In addition, more recent data suggests that natural infection will induce sustained B and T cell memory responses for at least six months (Dan et al. 2021; Zuo et al. 2021).

Thus, the BNT162-14 trial proposes to evaluate the added value of booster injections of Comirnaty or a closely related BNT162 vaccine (BNT162b2s01 [also referred to as BNT162b2 (B.1.351)]), which targets the VOC strain B.1.351 originally identified in the Republic of South Africa. In addition, durability of immune responses will also be assessed

in a second group of subjects within Group B who received an alternative BNT162 vaccine in the BNT162-01 or BNT162-04 trial and who will be offered two injections of 30 µg Comirnaty as per the conditional marketing authorization as long as they have not received any COVID-19 vaccine independent of the parent trials. The selected subjects for in-depth immunologic assessments in Group B may provide additional insights (e.g., immuno-dominance, increasing breadth of responses to select antigens) because they were primed with differing antigen constructs (i.e., vaccine candidates other than Comirnaty) or differing doses of Comirnaty, where protection against COVID-19 disease was not evaluated and dosing may have been suboptimal.

BNT162-14 will also descriptively assess if a third vaccination may improve SARS-CoV-2 spike neutralizing antibodies in the BNT162-01 Cohort 13 transplant subjects. Based on published data collected from vaccinating transplant recipients with Comirnaty and data from the BNT162-01 trial, transplant subjects demonstrate poor neutralizing antibody responses to SARS-CoV-2 Spike epitopes (Boyarsky et al. 2021; Sattler et al. 2021; Rincon-Arevalo et al. 2021), not unexpectedly, given the known poor antibody responses induced by influenza vaccines in solid organ transplant patients. Safety data from Cohort 13 subjects in the parent trial and a 3rd and 4th vaccination of Comirnaty in healthy volunteers supports evaluation of three or four vaccinations in the Cohort 13 transplant subjects (per communication of Data Monitoring Committee reviewing trial BNT162-02/CA4591001 [NCT04368728], Amendment 14). While high levels of neutralizing antibodies elicited by viral vaccines are known to protect in many other viral diseases, to date, the titer amount/level of neutralizing antibodies correlating with a decreased risk of SARS-CoV-2 infection nor a bone fide vaccine-induced functional correlate of protection has been determined/published. This trial will enable Cohort 13 transplant subjects to receive their first immunization in this trial as soon as 3 months after their second injection in the parent trial. Based on the evaluation of ongoing safety and neutralizing antibody titer data after the 3rd vaccination (IMP injection 1 in this trial), using the methodology published by Khoury et al. 2021, a 4th vaccination (IMP injection 2) will be offered to this vulnerable population. The timeline will be 3 to 7 months after injection 1. Several breakthrough infections in transplant recipients have prompted a debate on how to provide additional protection to this vulnerable population (Tau et al. 2021; Qin et al. 2021). Therefore, this data will help support an evidence-based rationale for the safety and efficacy of a 4th vaccination in these recipients and will provide details of consistency and adequacy of antibody responses.

The safety and effectivity of Comirnaty has been demonstrated in more than 25,000 subjects in clinical trials. The available pharmacovigilance data after Comirnaty administration to millions of individuals worldwide has confirmed its favorable safety profile with no specific safety concerns identified to date. The sponsor has accumulated a significant experience on the safety of Comirnaty in BNT162-02/C4591001 (NCT04368728), which was the basis of the received Comirnaty authorization for emergency use or the conditional marketing authorization given in numerous countries.

BNT162b2s01 and Comirnaty have the same LNP formulation and RNA components except that the RNAs slightly differ in their encoded open reading frame. The RNA component in BNT162b2s01 leads to expression of a Spike protein with the amino acid changes seen in the SARS-CoV-2 strain B.1.351, a widely recognized SARS-CoV-2

variant originally identified in the Republic of South Africa. Based on the emerging reactogenicity and safety data from vaccine boosting of Phase III trial subjects in BNT162-02/C4591001 (NCT04368728), Amendment 14, with BNT162b2 or BNT162b2s01, no new safety concerns are anticipated with a 3rd or 4th vaccinations in this trial. Serious adverse events (SAEs) will be recorded throughout the trial and they will be reported in an expedited fashion if they meet Suspected Unexpected Serious Adverse Reactions (SUSAR) criteria. However, to further support development of multiple sequential vaccinations with this RNA-LNP platform, reactogenicity data will still be collected from subjects who are randomized to Comirnaty or BNT162b2s01 (Group A) and a selected subset of subjects who receive the conditionally authorized Comirnaty regimen (Group B).

Objectives and endpoints

OBJECTIVES	ENDPOINTS
Primary objectives	**Endpoints**
To determine the safety and tolerability of one or two boosting doses of Comirnaty or one dose of BNT162b2s01 in BNT162-01 trial subjects, or two boosting doses of Comirnaty in BNT162-04 trial subjects.	For all Group A and Group B subjects: • The proportion of subjects in each treatment group with at least one SAE or the proportion of AESIs occurring up to 26 weeks after the first IMP injection. For Group A and a selected subset of Group B subjects: • The frequency of solicited local reactions (pain, tenderness, erythema/redness, induration/swelling) at the injection site recorded up to 7 d after each IMP injection. • The frequency of solicited systemic reactions (vomiting, diarrhea, headache, fatigue/tiredness, fever, chills, nausea, new or worsened muscle pain, new or worsening joint pain) recorded up to 7 d after each IMP injection. • The proportion of subjects with at least one unsolicited TEAE occurring up to 28 d after IMP injection in each treatment group.
Secondary objectives	**Endpoints**
To describe changes in SARS-CoV-2 neutralizing antibody titers from baseline to reference and SARS-CoV-2 variant B.1.351.	For Group A and Group B subjects (except transplant subjects): • Antibody titers to recombinant S1 and RBD protein derived from reference and SARS-CoV-2 variant B.1.351** will be assessed at baseline (Day 1) and then Day 8, Weeks 3*, 4, 7*, 12, and 26: o Neutralizing antibody titers. o Antibody titers (ELISA). • SARS-CoV-2 functional cross-neutralization of variant B.1.351** to reference strain. *Group B only **Group A only For Group B transplant subjects only: • Antibody titers to recombinant S1 and RBD protein derived from SARS-CoV-2 will be assessed at baseline (Day 1) and then Day 8, Weeks 4, 12, and 26 post Dose 1, and at Dose 2 (Day 1) and then Day 8, Weeks 4, 12, and 26 post Dose 2: o Neutralizing antibody titers. o Antibody titers (ELISA).

OBJECTIVES	ENDPOINTS
Exploratory objectives	**Endpoints**
To describe B- and T-cell responses to SARS-CoV-2 S and RBD antigens after injection of Comirnaty or BNT162b2s01.	For Group A subjects: • Baseline (Day 1) and then at Day 8, and Weeks 12 and 26, CMI responses including B cell, CD4 and CD8 T-cell responses to S and RBD antigens of interest. For a selected subset of Group B subjects (except transplant subjects): • Baseline (Day 1) and then at Day 8 and Weeks 4, 12, and 26, CMI responses including B cell, CD4 and CD8 T-cell responses to S and RBD antigens of interest. For Group B transplant subjects only: • Baseline (Day 1) and then Day 8, Weeks 4 and 12 post Dose 1, and at Dose 2 (Day 1) and then Day 8, Weeks 4, 12, and 26 post Dose 2 CMI responses including B cell, CD4 and CD8 T-cell responses to S and RBD antigens of interest.
To evaluate SARS-CoV-2 viral sequences in trial subjects who become infected (with or without symptoms).	In subjects who become SARS-CoV-2 infected: • SARS-CoV-2 S antigen sequences or whole genome sequencing of interest.
To describe time course changes in antibody titers after IMP injection in this trial in relationship to titer time from the last IMP injection in the BNT162-01 or BNT162-04 trials.	In a selected subset of subjects in Groups A and B (except transplant subjects): • SARS-CoV-2 antibody titers to recombinant S1 assessed at baseline (Day 1), and then at Day 8 and Weeks 12 and 26 to describe any potential time dependency immune responses that may include data from BNT162-01 and BNT162-04 trials for: o Neutralizing antibody titers. o Antibody binding (ELISA titers) to SARS-CoV-2 antigens. For Group B transplant subjects only: • SARS-CoV-2 antibody titers to recombinant S1 assessed at baseline (Day 1), and then at Day 8 and Weeks 12 and 26 post Dose 1 and at Dose 2 (Day 1) and then Day 8, Weeks 4, 12, and 26 post Dose 2 to describe any potential time dependency immune responses that may include data from BNT162-01 trial for: o Neutralizing antibody titers. o Antibody binding (ELISA titers) to SARS-CoV-2 antigens.
To evaluate cross-neutralization of vaccine-induced antibodies to emerging SARS-CoV-2 variants.	In select subjects in Groups A and B: • Measure cross-neutralization of other SARS-CoV-2 VOCs (e.g., using pVNT).

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CD = cluster of differentiation; CMI = cell mediated immune response; d = day(s); ELISA = enzyme-linked immunosorbent assay; IMP = investigational medicinal product; pVNT = pseudovirus neutralization test; RBD = receptor binding domain; SA = Republic of South Africa; SAE = serious adverse event; S protein = SARS-CoV-2 spike protein; S1 = the subunit produced after the SARS-CoV-2 S protein is cleaved by host proteases; TEAE = treatment emergent adverse event; VOCs = variants of concern.

Trial design

This is a Phase II, open-label, rollover trial to evaluate the safety and immunogenicity of one or two boost injections of Comirnaty or one dose of BNT162b2s01 in BNT162-01 trial

subjects or two boosting doses of Comirnaty in BNT162-04 trial subjects. There will be two groups.

- Group A*: Trial subjects from BNT162-01 who received two injections of 30 µg Comirnaty will be randomized 2:1 to one booster injection (BNT162b2s01:Comirnaty). Day 1 (baseline in this trial) must occur ≥24 weeks after the last Comirnaty injection in the BNT162-01 trial.
- Group B: Trial subjects in either the trial BNT162-01 or BNT162-04 who did not receive the full two vaccinations of 30 µg Comirnaty will be offered two injections of 30 µg Comirnaty as per the conditional marketing authorization. Day 1 (baseline in this trial) must occur ≥12 weeks after receiving the last BNT162 candidate vaccine in the BNT162-01 or BNT162-04 trial.

*Group A excludes transplant subjects from Cohort 13 of the BNT162-01 trial; consenting transplant subjects will enroll into Group B immunology subgroup and will receive one injection, which will be followed 3 to 7 months afterward by a second injection of Comirnaty. Henceforth this group is referred to as Group B transplants.

All potential rollover volunteers must enroll in this trial within less than 18 months of their last injection of a BNT162 candidate vaccine in the parent BNT162-01 or BNT162-04 trials.

BNT162-01 or BNT162-04 trial subjects, including trial subjects who are still in the follow-up phase of their parent trial, will be actively informed about this rollover trial once it has received all necessary regulatory and ethical approvals. Depending on the timing of follow-up in the parent trial, data from the parent trial may be used to determine eligibility in this rollover trial after the trial subject has consented. Once the trial subject has enrolled into this rollover trial, all safety reporting will occur through this rollover trial, this includes the reporting of AEs that are unresolved from the parent trial, SAEs, and clinical events of special interest (AESIs).

A Safety Review Committee (SRC) will be reviewing emerging safety data at least every 16 weeks until the last enrolled subject in Group A has completed 28 d of follow-up. The SRC may then decide to decrease the frequency of its cumulative safety data reviews to a minimum of once a year. The SRC will also review data from Group B (e.g., SUSARS) on an as needed basis but also specifically data emerging from the Group B transplant subjects.

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

Duration of all trial periods

The planned trial duration for a subject in this trial is ~30 weeks (≤4 weeks of screening and ~26 weeks follow-up).

The estimated planned trial start (first subject enrolled) and trial end (last subject last visit) are JUN 2021 and Q4 2022.

Trial population

This trial will enroll subjects aged ≥18 years who received one or two previous injections of a BNT162 candidate vaccine in either the BNT162-01 trial or the BNT162-04 trial. Volunteers will not be enrolled if they have received any COVID-19 vaccine outside of the BNT162-01 trial or the BNT162-04 trial.

The maximum number of trial subjects in the Group A (BNT162-01 trial subjects in Cohorts 1 to 14 who received 2 x Comirnaty 30 µg) will be 90 and in Group B (all other BNT162-01 or BNT162-04 trial subjects) will be 459. A subset of Group B (n = 129) will be asked to participate in an immunologic subset evaluation.

Trial treatments

IMP name:	BNT162b2 (Comirnaty) or BNT162b2s01.
Type:	Vaccine (BNT162 RNA-LNP vaccine utilizing modRNA).
Administration route:	Intramuscular (IM); upper arm, musculus deltoideus. The same arm may be used for both immunizations. The non-dominant arm is preferred.
Dosing regimen:	Group A: One (at Day 1) IM injection with 30 µg of either Comirnaty or BNT162b2s01. Group B: Two (at Day 1 and Day 21) IM injections with 30 µg of Comirnaty, except Group B transplant subjects. Group B transplant subjects: Two IM injections of 30 µg of Comirnaty, with injection 2 administered 3 to 7 months after injection 1 (Day 1). The planned time points for injection of IMP for Groups A and B are provided in the SoA (Section 1.3).
Sourcing:	Provided centrally by the sponsor.
Packaging and labeling:	IMP will be provided in glass vials as open-label supply. Each vial will be labeled as required per country requirements. For details, see the Pharmacy Manual.

1.2 Schema (graphical representation of the trial)

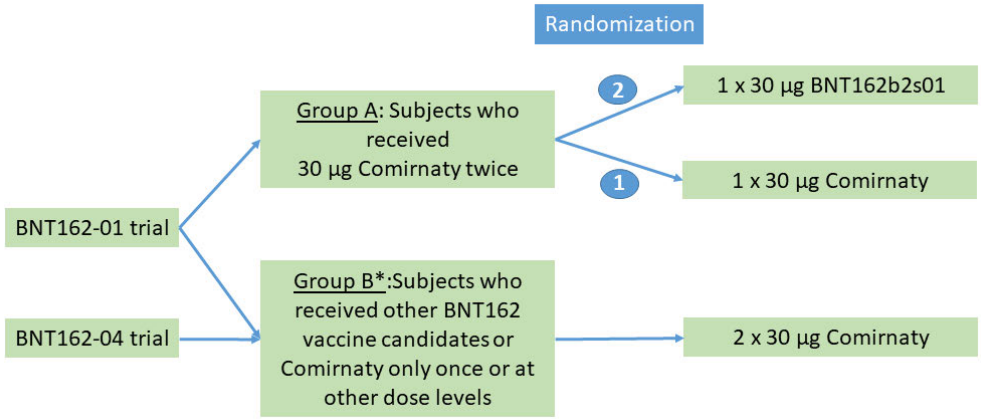

Figure 1: Open-label rollover trial for BNT162-01 or BNT162-04 trial subjects

* A subset of trial subjects will have in-depth immunological assessments, this will include the Group B transplant subjects (n = 15) who will receive their second injection based on SRC recommendation.

"2" and "1" Randomization ratio.

SRC = safety review committee.

1.3 Schedule of activities

The SoAs provide an overview of the protocol visits and procedures. The investigator may schedule visits (unplanned visits) in addition to those listed in the SoAs, in order to conduct evaluations or assessments required to protect the wellbeing of the trial subjects.

Table 1: Schedule of events for Group A (with one injection of either Comirnaty or BNT162b2s01)

Activity	Visit 0	Visit 1	Visit 2	Visit 4	Visit 5	Visit 6 [k]	Visit 7 [k]	Early termination
Week(s)			1	4	7	12	26	
Day	-30 to -1	1	8+2	29±7	50±7	85±10	182±20	
	(Screening)	(Day of inj. 1; pre-dose except IMP injection)	(~7 d post inj.)	(~28 d post inj.)	(~49 d post inj.)	(~84 d post inj.)	(~181 d post inj. EOT Visit)	
Collect informed consent	X							
Assess inclusion/exclusion criteria compliance	X	X (review)						
Collect demographic and medical history	X	X (update)						
Physical examination	X	X [a]	X [a]	X [a]			X [a]	X [a]
Vital signs, body weight [b]	X	X [c]	X	X			X	X
Urine pregnancy test for WOCBP	X	X					X	X
Urine for clinical laboratory [d]	X	X		X			X	X
Blood draws for clinical laboratory (15 mL) [e]	X	X		X			X	X
Allocation and randomization to IMP		X						
IMP injection, then observe subjects for ~1 h		X						
Subject hotline availability	Start	=>	=>	=>	=>	=>	End	(End)
Oral swabs for NAAT-based SARS-CoV-2 for screening [f]	X [g]	X [g]						
Oral swabs for NAAT-based SARS-CoV-2 for surveillance			X	X	X	X	X	X
Oral swabs for SARS-CoV-2 sequencing [h]	X [g]	X [g]	X	X	X	X	X	X

Activity	Visit 0	Visit 1	Visit 2	Visit 4	Visit 5	Visit 6 [k]	Visit 7 [k]	Early termination
Week(s)			1	4	7	12	26	
Day	-30 to -1	1	8+2	29±7	50±7	85±10	182±20	
	(Screening)	(Day of inj. 1; pre-dose except IMP injection)	(~7 d post inj.)	(~28 d post inj.)	(~49 d post inj.)	(~84 d post inj.)	(~181 d post inj. EOT Visit)	
Blood draws for NATAB and nucleocapsid protein testing (15 mL)		X	X	X		X	X	X
Blood draws for CMI (120 mL each)		X	X			X	X	X
Issue/collect subject diaries		X (issue)	X (collect)					
Subjects report daily reactogenicity (incl. body temperature) in their diary on Day 1 and for 7 d post each vaccination		X (post-dose) [j]	X					
Record AEs since last visit		X	X	X	X [i]	X [i]	X [i]	X [i]
Record pregnancies		Start	=>	=>	=>	=>	End	(End)
Record concomitant medication		X	X	X	X [l]	X [l]	X [l]	X [l]

Note: The SoA allows for *ad hoc* SARS-CoV-2 testing for symptomatic or asymptomatic subjects.

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

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

c Vital signs pre-dose and at 1 h (±15 minutes) on days with IMP injection.

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

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

f Will be tested within 24 h, either at a central laboratory or a "point of care" device at the trial site or a local laboratory of the trial site.

g Oral swab for SARS-CoV-2 testing either on Day -1 or at Visit 1 on Day 1.

h Swabs will only be analyzed (sequenced) if serum nucleocapsid protein ELISA testing and/or NAAT-based SARS-CoV-2 testing detects SARS-CoV-2 (with or without symptoms). Oral swabs for SARS-CoV-2 sequencing must be collected at the same day/time (±30 minutes) as the oral swabs for NAAT-based SARS-CoV-2 for screening/surveillance.

i Only AEs related to IMP, AESIs, and SAEs. All AEs linked to confirmed COVID-19 cases will be recorded. For trial subjects who receive non-trial SARS-CoV-2 vaccinations, the AEs expected to be captured after these vaccinations are within the frame of post-marketing safety data reporting (see Section 8.3.1) and should not be recorded in the CRF.

j Issue thermometer if not available from parent trial, for subjects to measure their body temperature each day and if they experience flu-like symptoms.

k For subjects who receive non-trial SARS-CoV-2 vaccinations there will be no sampling in subsequent visits. Information about these vaccinations may be received outside of a planned visit and can be collected remotely, e.g., by phone. In such cases information on physical examination and vital signs can be skipped. However, AEs that occurred prior to administration of non-trial vaccine must be enquired and should be recorded as stated in footnote “i”.

l Record any non-trial SARS-CoV-2 vaccinations that trial subjects receive during the trial in the CRF until the last trial visit.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CMI = cell mediated immunity; CRF = case report form; d = day; ELISA = enzyme-linked immunosorbent assay; EOT = end of trial; h = hour(s); IMP = investigational medicinal product; inj. = (IMP) injection; NAAT = nucleic acid amplification-based test; NATAB = neutralizing antibody titers and antibody binding; SAE = serious adverse event; SARS-CoV-2 = the virus leading to COVID-19; SoA = schedule of activities; WOCBP = women of childbearing potential.

Table 2: Schedule of events for Immunology Subgroup of Group B (with two injections of Comirnaty) [h]

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 [l, m]	Visit 7 [l, m, o]	Early termination
Week(s)			1	3	4	7	12	26	
Day	-30 to -1	1	8+2	22±3	29+7	50±7	85±10	182±20	
	(Screening)	(Day of inj. 1; pre-dose except IMP injection)	(~7 d post inj. 1)	(~21 d post inj. 1; pre-dose except IMP injection)	(~7 d post inj. 2)	(~28 d post inj. 2)	(~63 d post inj. 2)	(~161 d post inj. 2 EOT Visit)	
Collect informed consent	X						X [m]	X [m]	
Assess inclusion/exclusion criteria compliance	X	X (review)							
Collect demographic and medical history	X	X (update)							
Physical examination	X	X [a]	X [a]	X [a]	X [a]			X [a]	X [a]
Vital signs, body weight [b]	X	X [c]		X [c]					
Urine pregnancy test for WOCBP	X	X		X				X	X
Blood draw for clinical laboratory (15 mL) [d]	X								
Allocation to IMP		X							
IMP injection, then observe subjects for ~1 h		X		X [h]					
Subject hotline availability	Start	=>	=>	=>	=>	=>	=>	End	(End)
Oral swabs for NAAT-based SARS-CoV-2 for screening [f]	X [e]	X [e]							
Oral swab for NAAT-based SARS-CoV-2 testing for surveillance			X	X	X	X	X	X	X
Oral swab for SARS-CoV-2 sequencing [g]	X [e]	X [e]	X	X	X	X	X	X	X
Blood draws for NATAB and nucleocapsid protein testing (15 mL)		X	X	X	X	X	X	X	X
Blood draws for CMI (100 mL each)		X	X		X [h]		X	X	X
Issue/collect subject diaries		X (issue)	X (collect)	X (issue) [h]	X (collect) [h]				

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 [l, m]	Visit 7 [l, m, o]	Early termination
Week(s)			1	3	4	7	12	26	
Day	-30 to -1	1	8+2	22±3	29+7	50±7	85±10	182±20	
	(Screening)	(Day of inj. 1; pre-dose except IMP injection)	(~7 d post inj. 1)	(~21 d post inj. 1; pre-dose except IMP injection)	(~7 d post inj. 2)	(~28 d post inj. 2)	(~63 d post inj. 2)	(~161 d post inj. 2 EOT Visit)	
Subjects report daily reactogenicity (incl. body temperature) in their diary for 7 days post each vaccination		X (post-dose) [i]	X	X (post-dose) [h]	X [h]				
Record AEs since last visit		X	X	X	X	X [k]	X [j]	X [j]	X
Record pregnancies		=>	=>	=>	=>	=>	=>	End	(End)
Record concomitant medication		X	X	X	X	X [p]	X [n]	X [n]	X [n]

Note: The SoA allows for *ad hoc* SARS-CoV-2 testing for symptomatic or asymptomatic subjects.

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

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

c Vital signs pre-dose on days with IMP injection.

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

e Oral swab for SARS-CoV-2 testing either on Day -1 or at Visit 1 on Day 1.

f Will be tested within 24 h either at a central laboratory or a "point of care" device at the trial site or a local laboratory of the trial site.

g Swabs will only be analyzed (sequenced) if serum nucleocapsid protein ELISA testing and/or NAAT-based SARS-CoV-2 testing detects SARS-CoV-2 (with or without symptoms). Oral swabs for SARS-CoV-2 sequencing must be collected at the same day/time (±30 minutes) as the oral swabs for NAAT-based SARS-CoV-2 for screening/surveillance.

h Group B transplant subjects (Cohort 13 of the BNT162-01 trial) will be followed according to this SoA; BUT they will NOT receive their second vaccination on Visit 3 and no diaries will be distributed; their second vaccination will be administered based on SRC recommendation. Thereafter Group B transplant subjects (Cohort 13 of the BNT162-01 trial) will be followed according to the SoA in Table 2a.

i Issue thermometer if not available from parent trial, for subjects to measure their body temperature each day and if they experience flu-like symptoms.

j Only AEs related to IMP, AESIs, SAEs, and all AEs linked to confirmed COVID-19 cases will be recorded until the end of trial. For trial subjects who receive non-trial SARS-CoV-2 vaccinations, the AEs expected to be captured after these vaccinations are within the frame of post-marketing safety data reporting (see Section 8.3.1) and should not be recorded in the CRF.

k Only for Group B transplant subjects: only AEs related to IMP, AESIs, SAEs, and all AEs linked to confirmed COVID-19 cases will be recorded until the end of trial. For trial subjects who receive non-trial SARS-CoV-2 vaccinations, the AEs expected to be captured after these vaccinations are within the frame of post-marketing safety data reporting (see Section 8.3.1) and should not be recorded in the CRF.

l For subjects who receive non-trial SARS-CoV-2 vaccinations there will be no sampling in subsequent visits. Information about these vaccinations may be received outside of a planned visit and can be collected remotely, e.g., by phone. In such cases information on physical examination and vital signs can be skipped. However, AEs that occurred prior to administration of non-trial vaccine must be enquired and should be recorded as stated in footnotes “j” and “k”.

m If applicable, Visit 7 or Visit 6 should be used to inform Group B transplant subjects (Cohort 13 of the BNT162-01 trial) on Dose 2 and informed consent must be collected. If Visit 6 is applicable, then Visit 7 must be skipped. Thereafter the SoA in Table 2a is applicable.

n Record any non-trial SARS-CoV-2 vaccinations that trial subjects receive during the trial in the CRF until the last trial visit.

o If a transplant subject consents to receive a second vaccination (i.e., 4th dose since the parent trial), the SoA in Table 2a is then applicable, there will be no blood sampling for CMI testing at the visit of consent (Visit 6 or Visit 7).

p Only for Group B transplant subjects: record any non-trial SARS-CoV-2 vaccinations that trial subjects receive in the CRF.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CMI = cell mediated immunity; CRF = case report form; d = day; ELISA = enzyme-linked immunosorbent assay; EOT = end of trial; h = hour(s); IMP = investigational medicinal product; inj. = (IMP) injection; NAAT = nucleic acid amplification-based test; NATAB = neutralizing antibody titers and antibody binding; SAE = serious adverse event; SRC = safety review committee; SARS-CoV-2 = the virus leading to COVID-19; SoA = schedule of activities; WOCBP = women of childbearing potential.

Table 2a: Schedule of events for Immunology Subgroup of Group B transplant subjects (injection 2)

Activity	Visit 8	Visit 9	Visit 10	Visit 11 [g]	Visit 12 [g]	Early termination
Week(s) (post-Dose 2)		1	4	12	26	
Day (post-Dose 2)	1	8+2	29±7	85±10	182±20	
	(3 to 7 months post inj. 1; pre-dose except inj. 2)	(~7 d post inj. 2)	(~28 d post inj. 2)	(~3 months post inj. 2)	(~6 months post inj. 2 EOT Visit)	
Collect informed consent						
Assess inclusion/exclusion criteria compliance						
Collect demographic and medical history						
Physical examination	X [a]	X [a]			X [a]	X [a]
Vital signs, body weight [b]	X [c]					
Urine pregnancy test for WOCBP	X					X
Blood draw for hematology testing (up to 3 mL) [d]	X	X	X			
Allocation to IMP						
IMP injection, then observe subjects for ~1 h	X					
Subject hotline availability	=>	=>	=>	=>	End	(End)
Oral swab for NAAT-based SARS-CoV-2 testing for surveillance	X	X	X	X	X	X
Oral swab for SARS-CoV-2 sequencing [e]	X	X	X	X	X	X
Blood draws for NATAB and nucleocapsid protein testing (15 mL)	X	X	X	X	X	X
Blood draws for CMI (100 mL each)	X	X	X	X	X	X
Issue/collect subject diaries	X (issue)	X (collect)				
Subjects report daily reactogenicity (incl. body temperature) in their diary for 7 days post each vaccination	X (post-dose)	X (post-dose)				
Record AEs since last visit	X	X	X	X [f]	X [f]	X [f]
Record pregnancies	=>	=>	=>	=>	End	(End)
Record concomitant medication	X	X	X	X [h]	X [h]	X [h]

Note: The SoA allows for *ad hoc* SARS-CoV-2 testing for symptomatic or asymptomatic subjects.

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

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

c Vital signs pre-dose on days with IMP injection.

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

e Swabs will only be analyzed (sequenced) if serum nucleocapsid protein ELISA testing and/or NAAT-based SARS-CoV-2 testing detects SARS-CoV-2 (with or without symptoms). Oral swabs for SARS-CoV-2 sequencing must be collected at the same day/time (±30 minutes) as the oral swabs for NAAT-based SARS-CoV-2 for screening/surveillance.

f Starting 28 d post injection 2, only AEs related to IMP, AESIs, SAEs, and all AEs linked to confirmed COVID-19 cases will be recorded until the end of trial. For trial subjects who receive non-trial SARS-CoV-2 vaccinations, the AEs expected to be captured after these vaccinations are within the frame of post-marketing safety data reporting (see Section 8.3.1) and should not be recorded in the CRF.

g For subjects who receive non-trial SARS-CoV-2 vaccinations there will be no sampling in subsequent visits. Information about these vaccinations may be received outside of a planned visit and can be collected remotely, e.g., by phone. In such cases information on physical examination and vital signs can be skipped. However, AEs that occurred prior to administration of non-trial vaccine must be enquired and should be recorded as stated in footnote “f”.

h Record any non-trial SARS-CoV-2 vaccinations that trial subjects receive during the trial in the CRF until the last trial visit.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CMI = cell mediated immunity; COVID-19 = corona virus disease 2019CRF = case report form; d = day; ELISA = enzyme-linked immunosorbent assay; EOT = end of trial; h = hour(s); IMP = investigational medicinal product; inj. = (IMP) injection; NAAT = nucleic acid amplification-based test; NATAB = neutralizing antibody titers and antibody binding; SAE = serious adverse event; SARS-CoV-2 = the virus leading to COVID-19; SoA = schedule of activities; WOCBP = women of childbearing potential.

Table 3: Schedule of events for Group B (with two injections of Comirnaty) and no additional CMI or reactogenicity assessments

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 [i]	Early termination
Week(s)			1	3	4	7	12	26	
Day	-30 to -1	1	8±2	22±3	29±7	50±7	85±10	182±20	
	(Screening)	(Day of inj. 1; pre-dose except IMP injection)	(~7 d post inj. 1)	(~21 d post inj. 1; pre-dose except IMP injection)	(~7 d post inj. 2)	(~28 d post inj. 2)	(~63 d post inj. 2)	(~161 d post inj. 2 EOT Visit)	
Collect informed consent	X								
Assess inclusion/exclusion criteria compliance	X	X (review)							
Collect demographic and medical history	X	X (update)							
Physical examination	X	X [a]		X [a]				X [a]	X [a]
Vital signs, body weight [b]	X	X [c]		X [c]					
Urine pregnancy test for WOCBP	X	X		X				X	X
Blood draws for clinical laboratory (15 mL) [d]	X								
Allocation to IMP		X							
IMP injection, then observe subjects for ~1 h		X		X					
Subject hotline availability	Start	=>	=>	=>	=>	=>	=>	End	(End)
Oral swabs for NAAT-based SARS-CoV-2 for screening [f]	X [e]	X [e]							
Oral swab for NAAT-based SARS-CoV-2 testing for surveillance			X	X	X	X	X	X	X
Oral swab for SARS-CoV-2 sequencing [g]	X [e]	X [e]	X	X	X	X	X	X	X
Blood draws for NATAB and nucleocapsid protein testing (15 mL)		X	X	X	X	X	X	X	X
Record AEs since last visit [h]		X	X	X	X	X	X	X	X

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 [i]	Early termination
Week(s)			1	3	4	7	12	26	
Day	-30 to -1	1	8+2	22±3	29+7	50±7	85±10	182±20	
	(Screening)	(Day of inj. 1; pre-dose except IMP injection)	(~7 d post inj. 1)	(~21 d post inj. 1; pre-dose except IMP injection)	(~7 d post inj. 2)	(~28 d post inj. 2)	(~63 d post inj. 2)	(~161 d post inj. 2 EOT Visit)	
Record pregnancies		Start	=>	=>	=>	=>	=>	End	(End)
Record non-trial SARS-CoV-2 vaccinations [j]		X	X	X	X	X	X	X	X

Note: The SoA allows for *ad hoc* SARS-CoV-2 testing for symptomatic or asymptomatic subjects.

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

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

c Vital signs pre-dose on days with IMP injection.

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

e Oral swab for SARS-CoV-2 testing either on Day -1 or at Visit 1 on Day 1.

f Will be tested within 24 h either at a central laboratory or a "point of care" device at the trial site or a local laboratory of the trial site.

g Swabs will only be analyzed (sequenced) if serum nucleocapsid protein ELISA testing and/or NAAT-based SARS-CoV-2 testing detects SARS-CoV-2 (with or without symptoms). Oral swabs for SARS-CoV-2 sequencing must be collected at the same day/time (±30 minutes) as the oral swabs for NAAT-based SARS-CoV-2 for screening/surveillance.

h Only, AESIs, SAEs, and all AEs linked to confirmed COVID-19 cases will be recorded until the end of trial. For subjects who receive non-trial SARS-CoV-2 vaccinations, the AEs expected to be captured after these vaccinations are within the frame of post-marketing safety data reporting (see Section 8.3.1).

i For subjects who receive non-trial SARS-CoV-2 vaccinations there will be no sampling in subsequent visits. Information about these vaccinations may be received outside of a planned visit and can be collected remotely, e.g., by phone. In such cases information on physical examination and vital signs can be skipped. However, AEs that occurred prior to administration of non-trial vaccine must be enquired and should be recorded as stated in footnote "i".

j Record any non-trial SARS-CoV-2 vaccinations that trial subjects receive during the trial in the CRF until the last trial visit.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CMI = cell mediated immunity; CRF = case report form; d = day; ELISA = enzyme-linked immunosorbent assay; EOT = end of trial; h = hour(s); IMP = investigational medicinal product; inj. = (IMP) injection; NAAT = nucleic acid amplification-based test; NATAB =

neutralizing antibody titers and antibody binding; SAE = serious adverse event; SARS-CoV-2 = the virus leading to COVID-19; SoA = schedule of activities; WOCBP = women of childbearing potential.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS/TERMS

Abbreviation	Explanation
AE	Adverse Event
AESI	Adverse Event of Special Interest
BCR	B-cell receptor
BMI	Body Mass Index
CMI	Cell mediated immune (response)
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
d	Day(s)
EDC	Electronic Data Capture (system)
ELISA	Enzyme-Linked Immunosorbent Assay
EOT	End Of Trial
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
h	Hour(s)
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HRT	Hormonal Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation (of technical requirements for registration of pharmaceuticals for human use)
IEC	Independent Ethics Committee
IM	Intramuscular(ly)
IMP	Investigational Medicinal Product
ISF	Investigator's Site File
LNP	Lipid nanoparticle
min	Minute(s)
mRNA	Messenger RNA
NAAT	Nucleic Acid Amplification-based Test
NATAB	Neutralizing antibody titers and antibody binding
PBMC	Peripheral Blood Mononuclear Cells
pVNT	Pseudo viral neutralization test
PT	Preferred Term
RBD	Receptor Binding Domain
RNA-LNP	RNA-lipid nanoparticle
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Abbreviation	Explanation
SARS-CoV-2	The virus leading to COVID-19
SRC	Safety Review Committee
SoA	Schedule of Activities
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCR	T-cell receptor
TEAE	Treatment Emergent Adverse Event
US(A)	United States (of America)
VOC	Variant Of Concern
VOI	Variant Of Interest
WHO	World Health Organization
WOCBP	Women Of Childbearing Potential

NOTES FOR THE READER

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

BNT162b2s01 is also referred to as BNT162b2 (B1.351).

2 INTRODUCTION

2.1 Background

2.1.1 Overview of the disease

By November 2019, the Severe Acute Respiratory Syndrome (SARS) -CoV-2 infection responsible for Coronavirus Disease 2019 (COVID-19) was documented in humans. By March 2020, the World Health Organization (WHO) characterized the COVID-19 outbreak as a pandemic.

Since the SARS-CoV-2 viral sequence was first determined, studies demonstrate how it continues to evolve in humans (through recombination, suboptimal immune control, etc.), resulting in a variety of VOC. In addition to mutations, additions or deletions near the receptor binding domain (RBD) of the Spike protein, which is responsible for attaching to the human angiotensin cell receptor 2 and resulting in host infection, other key changes (e.g., deletions) circumventing antibody detection (e.g., around Y144 in the N terminal domain) are increasingly recognized. More specifically, newer mutations of the Spike protein not only provide the virus with greater transmissibility and affinity/avidity for cellular attachment but may also render the VOC less susceptible to virus neutralization, thus allowing increases in overall infection rates. Because successful prophylactic COVID-19 vaccines are designed to primarily work by inducing neutralizing antibodies, an increased sense of urgency has again risen to anticipate and combat SARS-CoV-2 evolution through numerous tactics including characterization of the evolving sequences of SAR-CoV-2 with respect to vaccine-induced immune response breadth and durability with respect to key functional immune responses.

An overview to the more widely recognized SARS-CoV-2 variants of concern and interest is provided in Table 4.

Table 4: Representative SARS-CoV-2 variants tracked by the WHO

Variant of concern or interest	WHO label	Pango lineage	GISAID clade / lineage	Next strain clade
VOC	Alpha	B.1.1.7	GRY	20I (V1)
VOC	Beta	B.1.351	GH/501Y.V2	20H (V2)
VOC	Gamma	P.1	GR/501Y.V3	20J (V3)
VOC	Delta	B.1.617.2	G/478K.V1	21A
VOC	Omicron	B.1.1.529	GRA	21K, 21L 21M
VOI	Lambda	C.37	GR/452Q.V1	21G
VOI	Mu	B.1.621	GH	21H

VOC = A SARS-CoV-2 variant that meets the definition of a VOI (see below) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance: Increase in transmissibility or detrimental change in COVID-19 epidemiology; or increase in virulence or change in clinical disease presentation; or decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.

VOI = A SARS-CoV-2 variant with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; AND identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.

Abbreviations: GISAID = Global Initiative on Sharing Avian Influenza Data; VOC = variant of concern; VOI = variant of interest; WHO = World Health Organization.
Source: WHO webpage https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/, accessed 27 DEC 2021.

2.1.2 Introduction to the trial treatment

The development of an RNA-based vaccine encoding a viral antigen that is translated to protein by the vaccinated organism to induce a protective immune response provides significant advantages over more conventional vaccine approaches. RNA-based vaccines have advantages over DNA, protein subunit, inactivated or live attenuated virus vaccines. First, safety: The RNA is degraded by normal cellular processes, is non-infectious, non-integrating, and poses no risk of insertional mutagenesis. Second, efficiency: Delivery of RNA results in transient translation that can be controlled by modifications in the untranslated regions (UTRs), cap, poly(A) tail, and coding sequences. These modifications can make the RNA more stable and highly translatable. Efficient *in vivo* delivery can be achieved by formulating RNA into carrier LNPs that promote rapid uptake and enable RNA expression in the cytoplasm. Third, production: Manufacturing of conventional protein subunits, inactivated virus or replication-defective virus vaccines is time consuming and involves multiple pieces of manufacturing equipment. Protein vaccine production and purification require optimization for each mammalian or insect cell culture system. In addition, each production system introduces the potential for improper folding and altered glycosylation patterns of the protein, particularly when produced in insect cells. In contrast, RNA-based vaccine production does not require individualized cell culture systems and unique purification systems for each vaccine antigen. Uniformly optimized transcription and purification techniques can be used to produce any RNA sequence. Furthermore, because RNA sequences are processed *in vivo* as would occur during viral infection, glycosylation patterns of the antigens are similar to those seen after natural infection.

As demonstrated by the SARS-CoV-2 RNA-LNP-based vaccine Comirnaty, LNP-formulated RNA-based vaccines provide one of the most flexible, scalable and fastest approaches to provide protection against the emerging viruses like SARS-CoV-2 (Mulligan et al. 2020; Rauch et al. 2018; Sahin et al. 2014; Walsh et al. 2020). The safety and effectivity of Comirnaty has been demonstrated in more than 25,000 subjects in clinical trials. The available pharmacovigilance data after Comirnaty administration to millions of individuals worldwide has confirmed its favorable safety profile with no specific safety concerns identified to date.

BNT162b2s01 and Comirnaty have the same LNP formulation and RNA components except that the RNAs differ slightly in their encoded open reading frame. The RNA component in BNT162b2s01 leads to expression of a Spike protein with the amino acid changes seen in the SARS-CoV-2 strain B.1.351, a widely recognized SARS-CoV-2 variant originally identified in the Republic of South Africa (Table 4).

Please see Section 2.3 for a detailed benefit/risk analysis. For further details on the BNT162 family of RNA-based vaccines, see the current BNT162 investigator's brochure (IB).

2.2 Trial rationale

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. The BNT162b platform uses modRNA. The BNT162b platform member BNT162b2 (Comirnaty) has received emergency use authorization or conditional marketing authorization in numerous countries worldwide for the prevention of COVID-19 disease. As demonstrated by Comirnaty, LNP-formulated RNA-based vaccines provide one of the most flexible, scalable and fastest approaches to provide protection against the emerging viruses like SARS-CoV-2 (Mulligan et al. 2020; Rauch et al. 2018; Sahin et al. 2014; Walsh et al. 2020).

This rollover trial (BNT162-14) will enroll BNT162-01 or BNT162-04 trial subjects; the BNT162-01 or BNT162-04 trials are also referred to as parent trials. The trial subjects represent a unique group of BNT162 vaccinees because their antibody and T-cell responses to SARS-CoV-2 antigens have been longitudinally characterized in the parent trials. Longitudinal characterization of the continuum of antibody and T-cell responses to BNT162 vaccines given to outbred human populations where pressure on the virus from genetics and evolving immune responses is simultaneously occurring, provides an opportunity for new and prescient insights into how the virus may evolutionarily adapt. Studies have demonstrated that Comirnaty protects against severe COVID-19 disease caused by the first generation of SARS-CoV-2 viral strains (called “L strain”, reference, or “wild type”) at least 6 months (unpublished data). The trial provides the opportunity to assess vaccine and booster induced durability of immune responses in context of more recent data on natural infection and cross-neutralization immunity. For example, SARS-CoV-2 infection and RNA vaccines such as Comirnaty induce cross-neutralization to multiple, more recently identified viral variants, some of which are identified as variants of concern (VOC) (Liu et al. 2021; Widge et al. 2021). In addition, more recent data suggests that natural infection will induce sustained B and T cell memory responses for at least six months (Dan et al. 2021; Zuo et al. 2021).

Thus, the BNT162-14 trial proposes to evaluate the added value of booster injections of Comirnaty or a closely related BNT162 vaccine (BNT162b2s01 [also referred to as BNT162b2 (B.1.351)]), which targets the VOC strain B.1.351 originally identified in the Republic of South Africa. In addition, durability of immune responses will also be assessed in a second group of subjects within Group B who received an alternative BNT162 vaccine in the BNT162-01 or BNT162-04 trial and who will be offered two injections of 30 µg Comirnaty as per the conditional marketing authorization as long as they have not received any COVID-19 vaccine independent of the parent trials. The selected subjects for in-depth immunologic assessments in Group B may provide additional insights (e.g., immuno-dominance, increasing breadth of responses to select antigens) because they were primed with differing antigen constructs (i.e., vaccine candidates other than Comirnaty) or differing doses of Comirnaty, where protection against COVID-19 disease was not evaluated and dosing may have been suboptimal.

BNT162-14 will also descriptively assess if a third vaccination may improve SARS-CoV-2 spike neutralizing antibodies in the BNT162-01 Cohort 13 transplant subjects. Based on published data collected from vaccinating transplant recipients with Comirnaty and data

from the BNT162-01 trial, transplant subjects demonstrate poor neutralizing antibody responses to SARS-CoV-2 Spike epitopes (Boyarsky et al. 2021; Sattler et al. 2021; Rincon-Arevalo et al. 2021), not unexpectedly, given the known poor antibody responses induced by influenza vaccines in solid organ transplant patients. Safety data from Cohort 13 subjects in the parent trial and a 3rd and 4th vaccination of Comirnaty in healthy volunteers supports evaluation of three or four vaccinations in the Cohort 13 transplant subjects (per communication of Data Monitoring Committee reviewing trial BNT162-02/CA4591001 [NCT04368728] Amendment 14). While high levels of neutralizing antibodies elicited by viral vaccines are known to protect in many other viral diseases, to date, the titer amount/level of neutralizing antibodies correlating with a decreased risk of SARS-CoV-2 infection nor a bone fide vaccine-induced functional correlate of protection has been determined/published. This trial will enable Cohort 13 transplant subjects to receive their first immunization in this trial as soon as three months after their second injection in the parent trial.

While monitoring transplant subject safety and reviewing immunogenicity data at 50 days after the third vaccination, an SRC decision was made to further evaluate the possibility of enhancing antibody response and monitoring the sustainability of antibody titers. The interim analysis post 50 days, using an evidence-based model (Khoury et al. 2021), demonstrated safety and protective efficacy (4-fold of convalescent) in up to 70% of the recipients. However, the response was inconsistent and heterogenous. There was also a limitation due to lack of CD4 counts or hypogammaglobulinemia information in low, negative, and/or inconsistent responders. Recently published evidence (Alejo et al. 2021) demonstrated that the fourth dose of vaccine in transplant recipients boosted immunologic response in low responders as well as non-responders. Another recently published data also from Kamar et al. 2021 suggested significant improvement of antibody titers 4 weeks after Dose 4 in solid organ transplant recipients who received the fourth dose 65 days after the third dose. Therefore, safety and efficacy data post-injection 2 in this trial will help support evidence-based rationale for the safety and efficacy of a 4th vaccination in this vulnerable population.

The safety and effectivity of Comirnaty has been demonstrated in more than 25,000 subjects in clinical trials. The available pharmacovigilance data after Comirnaty administration to millions of individuals worldwide has confirmed its favorable safety profile with no specific safety concerns identified to date. The sponsor has accumulated a significant experience on the safety of Comirnaty in BNT162-02/C4591001 (NCT04368728), which was the basis of the received Comirnaty authorization for emergency use or the conditional marketing authorization given in numerous countries.

BNT162b2s01 and Comirnaty have the same LNP formulation and RNA components except that the RNAs slightly differ in their encoded open reading frame. The RNA component in BNT162b2s01 leads to expression of a Spike protein with the amino acid changes seen in the SARS-CoV-2 strain B.1.351, a widely recognized SARS-CoV-2 variant originally identified in the Republic of South Africa. Based on the emerging reactogenicity and safety data from vaccine boosting of Phase III trial subjects in BNT162-02/C4591001 (NCT04368728), Amendment 14, with BNT162b2 or BNT162b2s01, no new safety concerns are anticipated with a 3rd or 4th vaccinations in this trial. Serious adverse events (SAEs) will be recorded throughout the trial and they will be

reported in an expedited fashion if they meet Suspected Unexpected Serious Adverse Reactions (SUSAR) criteria. However, to further support development of multiple sequential vaccinations with this RNA-LNP platform, reactogenicity data will still be collected from subjects who are randomized to Comirnaty or BNT162b2s01 (Group A) and a selected subset of subjects who receive the conditionally authorized Comirnaty regimen (Group B).

2.3 Benefit/risk assessment

Typically, healthy trial volunteers participating in clinical trials can expect no direct health benefits; however, subjects in this trial are offered a conditionally authorized SARS-CoV-2 vaccine or boosters of the same or similar vaccine, which may or may not provide benefit in continuing to protect against COVID-19 disease (see Benefit assessment Section 2.3.2). This trial is also designed to minimize the risks to trial subjects while maximizing the potential value of knowledge it is designed to provide.

For further information on the expected benefits and risks for injection with Comirnaty, including the reference safety information, see the current BNT162 IB.

2.3.1 Risk assessment

General risks of vaccines:

- The vaccines used in this trial may have side effects, some of which are listed below. Please note that these lists do not include all individual side effects ever seen with these vaccines. The more serious or common side effects with a known or possible relationship to the vaccine are listed.
- Rarely, a vaccine may cause an allergic reaction such as rash or difficulty breathing. Allergic reactions may be life-threatening. All trial subjects will be queried for a history of reactions to vaccines and this vaccine's excipients.
- Side effects seen from giving a vaccine by injection into the muscle include local reactions at the injection site such as redness, itchiness, tenderness, pain, and swelling.
- All vaccines can cause fever, chills, rash, aches and pains in the muscles or joints, nausea and loss of appetite, headache, dizziness, and feeling tired. Most people are still able to do their planned activities after getting a vaccine. Rarely, people experience side effects that limit their normal activities or make them go to their doctor.
- Very rarely, a vaccine may cause an autoimmune disease in a person or may make an autoimmune disease worse.
- For other known risks related to Comirnaty and anticipated risks related to BNT162b2s01, refer to the current BNT162 IB.

- BNT162b2 has received temporary authorization for emergency supply in 46 countries and licenses or conditional marketing authorizations in 46 countries globally under the tradename Comirnaty. Full approval of a 2-dose regimen of BNT162b2 30 µg in individuals ≥16 years of age was granted by the US Food and Drug Administration (FDA) on 23 AUG 2021. The safety profile of BNT162b2 based on available data in the ongoing Phase II/III trial BNT162-02 / C4591001 is favorable. Since its first marketing authorization in December 2020, BNT162b2 has been administered to hundreds of millions of individuals worldwide.
- The safety of BNT162b2 after two doses was evaluated in subjects 5 years of age and older. The trial BNT162-02 / C4591001 enrolled ~46,000 subjects 12 years of age or older. The trial BNT162-07 / C4591007 (NCT048166443) enrolled ~2,300 subjects 5 through less than 12 years of age. Additionally, 306 existing Phase III subjects at least 18 through 55 years of age received a booster dose (third dose) of BNT162b2 ~6 months after the second dose. The overall safety profile for the booster dose (third dose) was similar to that seen after two doses.
- The safety of BNT162b2 was evaluated in subjects 16 years of age and older after 2 doses. In the trial BNT162-02 / C4591001, a total of 22,026 subjects 16 years of age or older received at least one dose of BNT162b2 and a total of 22,021 subjects 16 years of age or older received placebo (as of the data cutoff date of 13 MAR 2021). The most frequent adverse reactions in subjects 16 years of age and older that 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 were usually mild or moderate in intensity and resolved within a few days after vaccination. A lower frequency of reactogenicity events was associated with greater age. The safety profile in 545 subjects receiving BNT162b2, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population. The trial BNT162-02 / C4591001 also included 200 subjects with confirmed stable human immunodeficiency virus (HIV) infection. The safety profile of the subjects receiving BNT162b2 (n = 100) in the individuals with stable HIV infection was similar to that seen in the general population.
- The safety of BNT162b2 was evaluated in subjects 18 years of age and older after booster dose (third dose). A subset from trial BNT162-02 / C4591001 Phase II/III subjects of 306 adults at least 18 through 55 years of age who completed the primary BNT162b2 2-dose course, received a booster dose (third dose) of BNT162b2 ~6 months (range of 4.8 to 8.0 months) after receiving Dose 2. The most frequent adverse reactions in subjects 18 through 55 years of age were injection site pain (>80%), fatigue (>60%), headache (>40%), myalgia (>30%), chills and arthralgia (>20%).

- The most common adverse reactions (seen ≥1/10) were headache, diarrhea, arthralgia, myalgia, injection site pain, fatigue, chills, pyrexia, and injection site swelling, and (seen ≥1/10 to <1/10) were vomiting, nausea, and injection site redness.
- Special warnings and precautions for use have been defined for anaphylaxis, myocarditis and pericarditis, acute severe febrile illness, coagulation disorders, for immunocompromised individuals, and for stress-related responses associated with the process of vaccination itself. For details see the current BNT162 IB.
- Hypersensitivity to the BNT162b2 active substance and/or to any of the excipients is a contraindication.
- Although not seen to date, it cannot yet be ruled out that the trial IMPs could make a later COVID-19 illness more severe.

Risks associated with trial-specific procedures:

- There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site. To minimize this risk, only appropriately qualified personnel will draw blood.
- The volume of blood drawn at any visit is kept to the amounts required to support the objectives of this trial, and the total blood volume drawn over any 28 d period will remain less than that drawn when donating blood (i.e., less than 450 mL, a typical blood donation volume).

Mitigations for vaccine-related and trial risks:

- In general, the listed risks of IM injection can be managed using routine symptom-driven standard of care. Treatment of these events is dependent on the discretion of the investigators. As Comirnaty has received conditional marketing authorization and been provided to millions of people without new or significant safety signals, procedures routine for monitoring Phase I trials are not planned.
- All trial-specific procedures will be performed by qualified trial site personnel.
- Trial subjects will be observed at the site for ~1 h after each IMP injection.
- Equipment to treat anaphylaxis will be readily available.
- To minimize the risk to trial subjects, the Medical Monitor and the SRC will regularly review and evaluate the safety data including any emerging SAEs or AESIs. For details, see Section 10.1.5.
- Human reproductive safety data are limited for Comirnaty. Therefore, although human teratogenicity is not suspected based on the intended pharmacology of the compound, the use of one highly effective method of contraception is required in this trial (see Section 10.4). For further details, see in the current BNT162 IB.

The risks and mitigations linked to the COVID-19 pandemic while participating in the trial include the following:

- The risk of becoming SARS-CoV-2 infected or unknowingly spreading the virus during participation in the trial; therefore, trial subjects will continue to be required to practice social distancing and infection prevention practices.
- Use of a Subject hotline for subjects to contact the trial site during their participation should they require guidance or experience symptoms suggestive of SARS-CoV-2 infection. If the subject reports symptoms of illness, e.g., enhanced respiratory disease or flu-like symptoms, the subject will be asked to return to the site for diagnostic measures. More specifically, respiratory disease or progression of flu-like symptomatology, such as non-resolution of the symptoms after 3 d, i.e., symptom kinetics that are inconsistent with SARS-CoV-2 RNA immunization, will trigger diagnostic measures, i.e., antigen and diagnostic nucleic acid SARS-CoV-2 testing with reflexive viral sequencing.

2.3.2 Benefit assessment

The vaccine Comirnaty has been given conditional marketing authorization in numerous countries worldwide for the prevention of COVID-19 disease. Thus, if subjects entering this trial did not receive injections of Comirnaty in their previous trial, they will be offered two injections of Comirnaty in this trial, and thus should have protection against severe COVID-19 disease.

If two injections of 30 µg Comirnaty were received in the parent trial, a booster injection with Comirnaty or BNT162b2s01 (a similar vaccine targeting a different SARS-CoV-2 strain) will be given in this trial. A booster injection could potentially enhance the durability of protection against COVID-19 disease or hypothetically help with protection from COVID-19 disease resulting from other circulating viral strains.

Participation in this trial could also help the trial subject indirectly. Clinical laboratory tests, physical exams and other safety assessments received while participating in this trial could uncover previously undiagnosed health problems. The trial subject will have access to real-time SARS-CoV-2 diagnostic testing. Also, by participating in this trial, trial subjects may better understand of how vaccines can help protect against COVID-19 disease.

2.3.3 Overall benefit/risk conclusion

Overall, the sponsor considers the benefit/risk ratio to be acceptable.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary objectives	**Endpoints**
To determine the safety and tolerability of one or two boosting doses of Comirnaty or one dose of BNT162b2s01 in BNT162-01 trial subjects, or two boosting doses of Comirnaty in BNT162-04 trial subjects.	For all Group A and Group B subjects: • The proportion of subjects in each treatment group with at least one SAE or the proportion of AESIs occurring up to 26 weeks after the first IMP injection. For Group A and a selected subset of Group B subjects: • The frequency of solicited local reactions (pain, tenderness, erythema/redness, induration/swelling) at the injection site recorded up to 7 d after each IMP injection. • The frequency of solicited systemic reactions (vomiting, diarrhea, headache, fatigue/tiredness, fever, chills, nausea, new or worsened muscle pain, new or worsening joint pain) recorded up to 7 d after each IMP injection. • The proportion of subjects with at least one unsolicited TEAE occurring up to 28 d after IMP injection in each treatment group.
Secondary objectives	**Endpoints**
To describe changes in SARS-CoV-2 neutralizing antibody titers from baseline to reference and SARS-CoV-2 variant B.1.351.	For Group A and Group B subjects (except transplant subjects): • Antibody titers to recombinant S1 and RBD protein derived from reference and SARS-CoV-2 variant B.1.351** will be assessed at baseline (Day 1) and then Day 8, Weeks 3*, 4, 7*, 12, and 26: o Neutralizing antibody titers. o Antibody titers (ELISA). • SARS-CoV-2 functional cross-neutralization of variant B.1.351** to reference strain. *Group B only **Group A only For Group B transplant subjects only: • Antibody titers to recombinant S1 and RBD protein derived from SARS-CoV-2 will be assessed at baseline (Day 1) and then Day 8, Weeks 4, 12, and 26 post Dose 1, and at Dose 2 (Day 1) and then Day 8, Weeks 4, 12, and 26 post Dose 2: o Neutralizing antibody titers. o Antibody titers (ELISA).
Exploratory objectives	**Endpoints**
To describe B- and T-cell responses to SARS-CoV-2 S and RBD antigens after injection of Comirnaty or BNT162b2s01.	For Group A subjects: • Baseline (Day 1) and then at Day 8, and Weeks 12 and 26, CMI responses including B cell, CD4 and CD8 T-cell responses to S and RBD antigens of interest. For a selected subset of Group B subjects (except transplant subjects): • Baseline (Day 1) and then at Day 8 and Weeks 4, 12, and 26, CMI responses including B cell, CD4 and CD8 T-cell responses to S and RBD antigens of interest. For Group B transplant subjects only: • Baseline (Day 1) and then Day 8, Weeks 4 and 12 post Dose 1, and at Dose 2 (Day 1) and then Day 8, Weeks 4, 12, and 26 post

OBJECTIVES	ENDPOINTS
	Dose 2 CMI responses including B cell, CD4 and CD8 T-cell responses to S and RBD antigens of interest.
To evaluate SARS-CoV-2 viral sequences in trial subjects who become infected (with or without symptoms).	In subjects who become SARS-CoV-2 infected: • SARS-CoV-2 S antigen sequences or whole genome sequencing of interest.
To describe time course changes in antibody titers after IMP injection in this trial in relationship to titer time from the last IMP injection in the BNT162-01 or BNT162-04 trials.	In a selected subset of subjects in Groups A and B (except transplant subjects): • SARS-CoV-2 antibody titers to recombinant S1 assessed at baseline (Day 1), and then at Day 8 and Weeks 12 and 26 to describe any potential time dependency immune responses that may include data from BNT162-01 and BNT162-04 trials for: o Neutralizing antibody titers. o Antibody binding (ELISA titers) to SARS-CoV-2 antigens. For Group B transplant subjects only: • SARS-CoV-2 antibody titers to recombinant S1 assessed at baseline (Day 1), and then at Day 8 and Weeks 12 and 26 post Dose 1 and at Dose 2 (Day 1) and then Day 8, Weeks 4, 12, and 26 post Dose 2 to describe any potential time dependency immune responses that may include data from BNT162-01 trial for: o Neutralizing antibody titers. o Antibody binding (ELISA titers) to SARS-CoV-2 antigens.
To evaluate cross-neutralization of vaccine-induced antibodies to emerging SARS-CoV-2 variants.	In select subjects in Groups A and B: • Measure cross-neutralization of other SARS-CoV-2 VOCs (e.g., using pVNT).

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CD = cluster of differentiation; CMI = cell mediated immune response; d = day(s); ELISA = enzyme-linked immunosorbent assay; IMP = investigational medicinal product; pVNT = pseudovirus neutralization test; RBD = receptor binding domain; SA = Republic of South Africa; SAE = serious adverse event; S protein = SARS-CoV-2 spike protein; S1 = the subunit produced after the SARS-CoV-2 S protein is cleaved by host proteases; TEAE = treatment emergent adverse event; VOCs = variants of concern.

4 TRIAL DESIGN

4.1 Overall design

This is a Phase II, open-label, rollover trial to evaluate the safety and immunogenicity of one or two boost injections of Comirnaty or one dose of BNT162b2s01 in BNT162-01 trial subjects or two boosting doses of Comirnaty in BNT162-04 trial subjects. There will be two groups.

- Group A*: Trial subjects from BNT162-01 who received two injections of 30 µg Comirnaty will be randomized 2:1 to one booster injection (BNT162b2s01:Comirnaty). Day 1 (baseline in this trial) must occur ≥24 weeks after the last Comirnaty injection in the BNT162-01 trial.

- Group B: Trial subjects in either the trial BNT162-01 or BNT162-04 who did not receive the full two vaccinations of 30 µg Comirnaty will be offered two injections of 30 µg Comirnaty as per the conditional marketing authorization. Day 1 (baseline in this trial) must occur ≥12 weeks after receiving the last BNT162 candidate vaccine in the BNT162-01 or BNT162-04 trial.

*Group A excludes transplant subjects from Cohort 13 of the BNT162-01 trial; consenting transplant subjects will enroll into Group B immunology subgroup and will receive one injection, which will be followed 3 to 7 months afterward by a second injection of Comirnaty. Henceforth this group is referred to as Group B transplants.

All potential rollover volunteers must enroll in this trial within less than 18 months of their last injection of a BNT162 candidate vaccine in the parent BNT162-01 or BNT162-04 trials.

BNT162-01 or BNT162-04 trial subjects, including trial subjects who are still in the follow-up phase of their parent trial, will be actively informed about this rollover trial once it has received all necessary regulatory and ethical approvals. Depending on the timing of follow-up in the parent trial, data from the parent trial may be used to determine eligibility in this rollover trial after the trial subject has consented. Once the trial subject has enrolled into this rollover trial, all safety reporting will occur through this rollover trial, this includes the reporting of AEs that are unresolved from the parent trial, SAEs, and clinical events of special interest (AESIs).

A Safety Review Committee (SRC) will be reviewing emerging safety data at least every 16 weeks until the last enrolled subject in Group A has completed 28 d of follow-up. The SRC may then decide to decrease the frequency of its cumulative safety data reviews to a minimum of once a year. The SRC will also review data from Group B (e.g., SUSARS) on an as needed basis but also specifically data emerging from the Group B transplant subjects.

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

This trial will enroll healthy volunteers aged ≥18 years who received one or two previous injections of a BNT162 candidate vaccine in either the BNT162-01 trial or the BNT162-04 trial. Volunteers will not be enrolled if they have received any COVID-19 vaccine outside of their parent trial.

The maximum number of trial subjects in the Group A (BNT162-01 trial subjects in Cohorts 1 to 14 who received 2 x Comirnaty 30 µg) will be 90 and in Group B (all other BNT162-01 or BNT162-04 trial subjects) will be 459. A subset of Group B (n = 129) will be asked to participate in an immunologic subset evaluation.

Group A (previous 2 x Comirnaty 30 µg recipients from BNT162-01): n = 90

- BNT162-01 trial Cohorts 2 and 10: n = 24
- BNT162-01 trial Cohort 12: n = 31 (of 90)
- BNT162-01 trial Cohort 13: n = 15 HIV-infected subjects
- BNT162-01 trial Cohort 14: n = 20

The immunology subset of Group B (BNT162-01 or BNT162-04 trial subjects who did not receive 2 x Comirnaty 30 µg and Cohort 13 transplant patients) whom will be asked to participate in reactogenicity and detailed immunologic assessments: n = 129

- BNT162-01 trial - BNT162b1 Cohorts 2, 5 and 1: n = 36 (of 120)
- BNT162-01 trial - BNT 162b2 Cohort 11: n = 30
- BNT162-01 trial - BNT 162b2 Cohort 13: n = 15 transplant subjects
- BNT162-04 trial - BNT162b3 younger Cohorts 1, 2, 5, 7: n = 48 (of 96)

4.2 Scientific rationale for the trial design

The scientific rationale for this open-label trial is the following:

- to describe changes in vaccine-induced durability and T cell, B cell and antibody breadth to SARS-CoV-2 antigens before and after booster vaccines;
    - to assess if booster vaccines improve immune responses against variant B.1.351;
    - to describe changes in vaccine-induced correlates of protection (if identified from other BNT162 vaccine studies);
- to assess safety of additional BNT162 booster vaccines;
- to describe sequences of SARS-CoV-2 infections to increase understanding of the current SARS-CoV-2 strains in circulation and document if potential signs of immune pressure from vaccines, genetics, etc. on the virus are observed; and
- to assess changes in immune responses in transplant subjects with 3rd and 4th vaccinations.

4.3 Justification for dose

Trial subjects from the BNT162-01 and BNT162-04 trials who did not receive two injections with 30 µg Comirnaty will be offered the Comirnaty dose and injection schedule that received conditional marketing authorization. This is the same dose evaluated in the Phase III trial (BNT162-02/C4591001) and the dose for which the available pharmacovigilance data after Comirnaty administration to millions of individuals worldwide has confirmed a favorable safety profile with no specific safety concerns.

Trial subjects from the BNT162-01 trial who did receive two injections of 30 µg Comirnaty will be offered a single 30 µg Comirnaty or BNT162b2s01 booster injection. The safety and immunogenicity of the candidate vaccine BNT162b2s01 is not anticipated to be any different than for the prototype vaccine Comirnaty.

4.4 Trial completer and end of trial definitions

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

The end of the trial is defined as the date of the last visit of the last subject in the trial.

5 TRIAL POPULATION

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 in the rollover trial even if they meet all inclusion/exclusion criteria.

5.1 Inclusion criteria

Volunteers are eligible for enrollment into this trial if all of the following criteria apply:

1. Have given informed consent by signing the informed consent form (ICF) before initiation of any trial-specific procedures.
2. Willing and able to comply with scheduled visits, treatment schedule, laboratory tests, lifestyle restrictions (including those requested by the German and federal Governments, e.g., to follow good practices to reduce chances of spreading COVID-19), and other requirements of the trial.
3. Have received BNT162 vaccine candidates in the BNT162-01 or BNT162-04 trials.
4. Remain overall healthy (i.e., has not medically deteriorated significantly since participation in the parent trial, is not anticipated to die in the next 26 weeks, and is able to provide blood as specified by the trial without anticipated, deleterious medical consequences) in the clinical judgment of the investigator based on medical history and physical examination. Screening clinical laboratory tests are to assess the subjects "new baseline" unless required for eligibility (e.g., platelets).

   Note: In particular, caution should be used with a subject who has a history of cardiovascular disease, e.g., myocarditis, pericarditis, myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmia.
5. Agree not to enroll in another trial of an IMP, starting after Visit 0 and continuously until Visit 5 (Day 50).
6. Less than 18 months have passed since their last IMP injection in their parent trial.
7. If they received 30 µg Comirnaty twice in the BNT162-01 trial, Visit 1 in this trial is ≥24 weeks after their last IMP injection, unless the subject is a Cohort 13 transplant subject of the BNT162-01 trial.
8. If they received any other BNT162 vaccine candidate than Comirnaty in the BNT162-01 or BNT162-04 trial or are a Cohort 13 transplant subject, Visit 1 in this trial is ≥12 weeks after their last IMP injection.
9. Have not been diagnosed with SARS-CoV-2 infection in the 12 weeks prior to Day 1 (baseline). Subjects who screen-fail on this criterion may be rescreened.

Laboratory inclusion values

Hemogram/complete blood count (CBC):

10. Platelets = 125,000 to 550,000/mm^3.

Chemistry:

11. Chemistry panel: the following apply: alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) are <3.0 times the upper limit of normal, and glomerular filtration rate (GFR) is ≥ 40 mL/min/1.73 m^2.

    Note: Other collected chemistries per the SoA are considered “baseline” values should serious adverse events occur in this trial.

Immunocompromised subjects/BNT162-01 Cohort 13:

12. Immunocompromised subjects may be included if their clinical laboratory values are stable in the context of their disease, and if there is no acute deterioration present with the expected need to change their therapy within the 2 weeks after the anticipated trial vaccination.

Reproductive status

13. Women of childbearing potential (WOCBP) must test negative in a urine beta-human chorionic gonadotropin (β-HCG) test at Visits 0 and 1. Women that are post-menopausal or permanently sterilized will be considered as not having reproductive potential.
14. WOCBP must agree to practice a highly effective form of contraception during the trial, starting at screening and continuously until Visit 5 (Day 50). For guidance on what is considered a “highly effective form of contraception”, see Section 10.4.2.
15. WOCBP must confirm that they practiced one highly effective form of contraception for the 14 d prior to screening.
16. WOCBP must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the trial, starting after Visit 0 and continuously until Visit 5 (Day 50).
17. Men who are sexually active with a WOCBP and have not had a vasectomy must agree to use a highly effective form of contraception with their female partner of childbearing potential during the trial, starting after Visit 0 and continuously until Visit 5 (Day 50).
18. Men must be willing to refrain from sperm donation, starting after Visit 0 and continuously until Visit 5 (Day 50).

5.2 Exclusion criteria

Volunteers are not eligible for enrollment if any of the following criteria apply:

1. Have received any SARS-CoV-2 vaccine outside of the BNT162-01 or BNT162-04 trials.
2. Have a known allergy, hypersensitivity, or intolerance to the planned IMP including any excipients of the IMP.
3. Have a current febrile illness (body temperature ≥38.0°C) or other acute illness within 48 h prior to Day 1/IMP injection in this trial. Subjects who screen-fail on this criterion may be rescreened.

4. Have received a live or live attenuated vaccine within 30 d prior to Day 1/IMP injection, or any other vaccination within 14 d prior to Day 1/IMP injection. Subjects who screen-fail on this criterion may be rescreened.
5. Have an ongoing AE assessed as related to any BNT162-01 or BNT162-04 trial vaccine.

5.3 Lifestyle considerations

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

The trial subjects will be required to remain at the site for ~1 h after each IMP injection.

Subjects will be asked to avoid strenuous exercise beyond their usual exercise routine for 7 d after each IMP administration.

Trial subjects will be updated on the most recent local guidance on recommended social behaviors for people who have been vaccinated, e.g., continued social distancing because of an increasing number of more infectious variants and following good practices to reduce their chances of being infected or asymptomatically spreading COVID-19.

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.

For subjects who may not have passed all of the screening requirements such as one of the following:

- diagnosis of SARS-CoV-2 infection within 12 weeks prior to Day 1,
- febrile illness within 48 hours prior to Day 1, or
- required (clinically indicated) vaccine within its exclusion time period (i.e., 2 or 4 weeks) prior to Day 1

medical judgement may be used to decide if and when to rescreen as long as the subject is <18 months from their last IMP injection of the parent trial prior to Day 1.

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

6 TRIAL TREATMENTS

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

6.1 IMPs administered

IMP name:	BNT162b2 (Comirnaty) or BNT162b2s01.
Type:	Vaccine (BNT162 RNA-LNP vaccine utilizing modRNA).
Administration route:	Intramuscular (IM); upper arm, musculus deltoideus. The same arm may be used for both immunizations. The non-dominant arm is preferred.
Dosing regimen:	Group A: One (at Day 1) IM injection with 30 µg of either Comirnaty or BNT162b2s01. Group B: Two (at Day 1 and Day 21) IM injections with 30 µg of Comirnaty, except Group B transplant subjects. Group B transplant subjects: Two IM injections of 30 µg of Comirnaty, with injection 2 administered 3 to 7 months after injection 1 (Day 1). The planned time points for injection of IMP for Groups A and B are provided in the SoA (Section 1.3).
Sourcing:	Provided centrally by the sponsor.
Packaging and labeling:	IMP will be provided in glass vials as open-label supply. Each vial will be labeled as required per country requirements. For details, see the Pharmacy Manual.

6.2 Preparation/handling/storage/accountability

The principal investigator is responsible for IMP (and any components thereof) accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

For instructions on IMP preparation, handling, and storage, see the Pharmacy Manual.

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

The preparation of solution for injection will be performed by aseptic handling procedures by pharmaceutical personnel or other trained personnel at the trial site. Further guidance and information for the final disposition of unused IMP (and any components thereof) is provided in the Pharmacy Manual.

6.3 Measures to minimize bias: randomization and blinding

This is an open-label trial but:

- Group A trial subjects will be randomized 2:1 to BNT162b2s01:Comirnaty using an online randomization tool.
- Group B trial subjects will be allocated to trial treatment without active randomization and selected subjects will be asked to participate in the detailed immunogenicity assessment based on their parent trial cohort.

6.4 Trial treatment compliance

All IMP injections will be administered by a trial site physician.

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

6.5 Concomitant therapy

Trial subjects should not receive any live or live attenuated vaccination within 30 d before or after any trial injection e.g., measles, mumps, and rubella (MMR); oral polio vaccine (OPV); varicella; yellow fever unless medically indicated e.g., rabies.

Trial subjects should not receive any other vaccines within 14 d before or after any trial injection, e.g., influenza, tetanus, pneumococcal, hepatitis A or B. When possible standard or care vaccinations should be planned with the trial injections in mind.

Recording of concomitant therapy for Group A: any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest), that the trial subject receives starting after Visit 0 until Visit 5, and any medications due to medical history started before Visit 0 must be recorded in the CRF along with the:

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

Concomitant therapy recording is not required for Group B but will be recorded on the SAE or AESI report.

Any non-trial SARS-CoV-2 vaccine, that trial subjects receive starting after Visit 0 until the last trial visit (at the times listed in the SoA, Section 1.3) must be recorded in the CRF.

6.6 Dose modifications

Not applicable to this trial.

6.7 Access to trial treatment after the end of the trial

Not applicable.

7 DISCONTINUATION OF TRIAL TREATMENT AND TRIAL SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of trial treatment

7.1.1 Criteria to permanently discontinue IMP administration for Group B

Note that discontinuation from IMP does not represent withdrawal/discontinuation from the trial. Trial subjects permanently discontinued from IMP administration should still complete all assessments planned in the SoA (Section 1.3).

Reasons for definitive discontinuation from IMP include the following:

- SAEs warranting discontinuation;
- other trial-related safety concerns;
- subject or investigator request;
- pregnancy;
- deterioration in trial subject health at the time of IMP injection (at the discretion of the investigator).

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

7.1.2 Criteria for temporarily delaying enrollment, randomization for Group A, or administration of IMP

The are no criteria defined which trigger temporarily delaying trial subject enrollment or randomization.

There are medical conditions or situations which may delay administration of IMP as follows:

- Current febrile illness (body temperature ≥38.0°C) or other acute illness within 48 h before IMP administration.
- Confirmed SARS-CoV-2 infection; vaccination should still proceed as soon as medically indicated but ideally no later than 12 weeks after resolution of any serious COVID-19 symptoms at the discretion of the investigator.
- The second Comirnaty injection (injection 2) may also be delayed for medical reasons (e.g., influenza vaccination) and such delays should be as short as possible, e.g., ≤3 weeks for non-live or attenuated vaccines, ≤5 weeks for live attenuated vaccines, ≤12 weeks if SARS-CoV-2 infection is confirmed, etc., with the exception of Group B transplant subjects who will receive their injection 2 based on SRC recommendation.

- The circumstances leading to the delay and the resulting delay should be discussed with the sponsor's Medical Monitor.

7.2 Trial subject discontinuation or withdrawal from the trial

A trial subject may withdraw 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. Withdrawals are expected to be uncommon.

Reasons for discontinuation from the trial include the following:

- Refused further trial procedures
- Lost to follow-up
- Death
- Trial terminated by sponsor
- SAEs thought related to the vaccine
- Trial subject request
- Investigator request
- Important protocol deviation per the investigator after consultation with the Medical Monitor
- A Group B transplant subject who receives a non-trial SARS-CoV-2 vaccination

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 Investigator's Site File (ISF) and inform the sponsor about the withdrawal of consent immediately.

If possible, permanently discontinued trial subjects will complete all assessments planned for the Early Termination Visit.

7.3 Lost to follow-up

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

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

- The trial site must attempt to contact the trial subject and reschedule the missed visit as soon as possible and counsel the trial subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the trial subject wishes to 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

Trial subjects must have given informed consent (i.e., have signed the ICF) before initiation of any trial-specific procedures are performed.

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

Protocol waivers or exemptions are not allowed.

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

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

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

For the baseline assessments (demographics, medical history), see Section 10.11.

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).

The trial site personnel will remind the subject to record the worst grade for each symptom in their diary at approximately the same time every evening on the day of IMP injection and then every day at the same time until the day of the next planned site visit. The trial site personnel will remind the subject to measure their body temperature using the provided thermometer and record their body temperature in the diary every day including the day of IMP injection.

8.2.1 Physical examinations

Complete physical examinations will be performed at screening.

Brief physical examinations will be performed at later time points listed in the SoA in 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.

8.2.2 Vital signs including body weight

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

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

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

8.2.3 Clinical laboratory tests

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

The investigator must review the laboratory report, document this review with signature and date.

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.

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

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

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

8.2.4 Subject diaries

For Group A and Group B Immunology Subgroup trial subjects, subject diaries will be issued and collected by trial site personnel at the visits given in the SoA (Section 1.3).

Trial subjects will be asked to record any solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling), and solicited systemic reactions (vomiting, diarrhea, headache, fatigue/tiredness, fever [oral temperature of ≥38.0°C], chills, nausea, new or worsened muscle pain, new or worsening joint pain). Data will be recorded on the reactogenicity CRF, NOT on the AE CRF/log unless the reactogenicity AE extends past Day 8. If one of the solicited reactogenicity adverse events from the subject diary fulfills SAE criteria, additional CRF SAE data must be provided.

For Group B transplant subjects, a subject diary should be distributed when they receive their second vaccination.

8.2.5 Assessment of solicited local and systemic reactions

Group A and Group B Immunology Subgroup trial subjects will be asked to assess their local and systemic reactions daily until 7 d after each injection. Trial subject assessments will be recorded in the diary provided to the subject by the trial site (Section 1.3). The trial site personnel will remind the subject to record in the subject diary the worst grade for each symptom every day including the day of IMP injection.

The reporting on the CRF of local and systemic reactions will be based on the subject's assessments only. Reactions will be graded based on the guidance given in the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (see Section 10.3.2).

8.2.6 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.

8.2.7 Oral swabs for NAAT-based SARS-CoV-2 testing for screening and surveillance

Oral swabs for (nucleic acid amplification-based test [NAAT]-based) SARS-CoV-2 testing will be collected by trial site personnel at the time points provided in the SoA (Section 1.3).

For screening (Visit 0 on Day-1 or pre-dose on Day 1), the NAAT-based analysis of oral swabs for SARS-CoV-2 can be performed by either a central laboratory or a "point of care" device at the trial site or a local laboratory of the trial site to ensure rapid results.

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

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

For surveillance (Visits 2 and later), the NAAT-based analysis of oral swabs for SARS-CoV-2 will be conducted in the central laboratory.

Additionally, any potentially SARS-CoV-2 - infected and symptomatic trial subjects will be asked to return to the site for SARS-CoV-2 diagnostics as soon as possible. Oral swabs for SARS-CoV-2 genomic sequencing will also be collected and analyzed at a later time point. If subject tests SARS-CoV-2 positive outside of the trial site, then the site will request the information from the subject.

Instructions on the sample handling and shipping to the analysis site will be provided in a Laboratory Manual. The methodology used for the NAAT-based analysis will be documented in the Biomarker Manual.

8.2.8 Serum for nucleocapsid protein testing

Blood will be drawn by trial site personnel for nucleocapsid ELISA SARS-CoV-2 testing at the time points provided in the SoA (Section 1.3); this will use blood draw for Neutralizing antibody titers and antibody binding (NATAB) (see Section 8.10.1).

Nucleocapsid ELISA SARS-CoV-2 testing will be performed at a central laboratory.

8.2.9 Triggered SARS-CoV-2 genomic sequencing

Swabs for triggered SARS-CoV-2 genomic sequencing storage will be collected by trial site personnel at the time points provided in SoA (Section 1.3).

The swabs will be inserted into collection tubes pre-filled with RNAlater stabilizer solution. The swabs must be stored in the central laboratory at a minimum -70°C until the end of the trial.

There are two triggers for SARS-CoV-2 genomic sequencing:

- Serum-based nucleocapsid ELISA SARS-CoV-2 testing using one of the samples collected for NATAB.
- Oral swab-based NAAT testing for surveillance conducted in the central laboratory.

SARS-CoV-2 genomic sequencing will be initiated if any of the above tests are positive (with or without symptoms).

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

The outcome of triggered SARS-CoV-2 genomic sequencing would be SARS-CoV-2 S antigen sequences and/or whole genome sequences and assigned (where possible) to known viral variants.

8.3 Adverse events and serious adverse events

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

The detection of AE or SAE or AESI is unsolicited.

Solicited AEs that are recorded from the subject diaries on the reactogenicity CRFs should not be reported as AEs unless the solicited AE meets criteria for SAE or begins after Day 8 or started before Day 8 and continues past Day 8.

8.3.1 Time period and frequency for collecting AE, AESI, and SAE information

For trial subjects enrolled in this clinical trial, i.e., after transfer from the parent trial to this trial, all AEs, AESI, and SAEs (including a death) will be recorded at the time points listed in the SoA in Section 1.3. All safety reporting will occur through this rollover trial; this includes the reporting of non-vaccine related AEs that are unresolved from the parent trial.

For subjects who receive a non-trial SARS-CoV-2 vaccination, AEs/SAEs will be collected as specified above until the date when the subject was vaccinated with the non-trial SARS-CoV-2 vaccine. The AEs expected to be captured after non-trial SARS-CoV-2 vaccination are within the frame of post-marketing safety data reporting.

Investigators are not obligated to actively seek AEs or SAEs at any time after a trial subject has been discharged from the trial, however, if the investigator learns of any SAE (including a death), that they consider to be reasonably related to the IMP administration or trial participation, the investigator must promptly notify the sponsor.

8.3.2 Method of detecting AEs and SAEs

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

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

8.3.3 Follow-up of AEs and SAEs

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

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

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

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

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

8.3.4 Regulatory reporting requirements for SAEs

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

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

Safety reports will be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

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

8.3.5 Pregnancy

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

Pregnancy information (information on trials subjects who become pregnant or information for female partners of male trial subjects who become pregnant) will be collected for pregnancies that occurred after the date of the first injection of IMP until the subject terminates or completes the study.

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

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

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

8.3.6 Death events

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

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

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

Not applicable.

8.3.8 Adverse events of special interest

The following will be reported as AESIs:

- Myocarditis (all Levels of Certainty including ''Possible cases'' (1 to 3) as per Brighton Collaboration Case Definition) 1 to 3 (Possible case), Myocarditis_Version_1.0_15 July 2021_FINAL_for Posting)
- Pericarditis (all Levels of Certainty including ''Possible cases'' (1 to 3) as per Brighton Collaboration Case Definition) 1 to 3 (Possible case), Pericarditis_Version_1.0_15 July 2021_FINAL_for Posting)
- Anaphylaxis
- Thromboembolic events (e.g., deep vein thrombosis, stroke, myocardial infarction)
- Immune thrombocytopenia
- Immune based neurologic events (e.g., optic neuropathy, Guillain-Barré syndrome)

8.4 Treatment of overdose

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

- Closely monitor the trial subject for any AE/SAE and laboratory abnormalities (at least for 7 d).
- (At the discretion of the investigator) Give symptomatic treatment.

- Inform the sponsor's Medical Monitor as soon as possible; the sponsor's Medical Monitor should agree with the investigator regarding any action triggered, e.g., trial subject withdrawal from the trial or (if applicable) trial treatment.
- Document the quantity of the excess dose overdose in the CRF.

8.5 Treatments for specific adverse reactions

The adverse reactions determined for Comirnaty from the available unblinded clinical trial data (from BNT162-02/C4591001 [NCT04368728]) are mostly reflective of mild to moderate local and systemic reactogenicity events. The most frequent adverse reactions in trial subjects 16 yrs of age and older were injection site pain, fatigue, headache, myalgia and chills, arthralgia, pyrexia and injection site swelling, and were usually mild or moderate in intensity and resolved within a few days after vaccination. Additional adverse reactions determined from the clinical trial data are lymphadenopathy, nausea and malaise. Since authorization of Comirnaty, anaphylaxis has been reported and determined to be an adverse reaction. For details see the BNT162 IB.

Treatment of these adverse reactions is at the discretion of the investigators, however, 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 nonsteroidal anti-inflammatory drug if acetaminophen is contraindicated.
- Corticosteroids should be avoided as either prophylaxis or treatment as it counteracts the effects of immunization.
- Ensure adequate hydration of trial subjects on the day of immunization. Consider administering fluids (e.g., water for drinking, 0.5 to 1.0 L) within ~2 h following the immunization per trial site standard.

If subjects experience enhanced respiratory disease symptom kinetics that are inconsistent with a relationship to RNA immunization, additional diagnostic measures should be considered, and the Medical Monitor should be informed.

If subjects report symptoms that could represent myocarditis or pericarditis, in addition to any medically indicated evaluations at the discretion of the investigators, the following United States Center for Disease Control (CDC) clinical recommendations for myocarditis and pericarditis following COVID-19 vaccination published on 28 May 2021 (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html) should be considered:

- For initial evaluation, consider an ECG, troponin level, and inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate. In the setting of normal ECG, troponin, and inflammatory markers, myocarditis or pericarditis are unlikely.
- Consider consultation with:
    - Cardiology for assistance with cardiac evaluation and management.
    - Infectious disease and/or rheumatology to assist in this evaluation.

- Where available, evaluate for potential etiologies of myocarditis and pericarditis, particularly acute COVID-19 infection (e.g., PCR testing), prior SARS-CoV-2 infection (e.g., detection of SARS-CoV-2 nucleocapsid-binding antibodies), and other viral etiologies (e.g., enterovirus PCR and comprehensive respiratory viral pathogen testing).

8.6 Safety stopping criteria

The SRC will review and evaluate the collected safety data for Group A and all reported SAEs from the trial at a minimum every 16 weeks during the trial and any emerging data concerns from Group B (e.g., SUSARs, Group B transplant data, etc.). A decision to stop treatment for an individual subject or to terminate the trial may be taken by the sponsor and investigator if safety concerns are identified by the SRC.

All SAEs will be reviewed by the SRC and all SUSARs as soon as possible. Any trial SAE but specifically a SUSAR in Group A may trigger a temporary stop of IMP administration to new subjects in Group A until the SRC has reviewed and discussed the relevant data and come to a recommendation to continue or permanently stop trial injections for Group A.

8.7 Pharmacokinetics

Not applicable.

8.8 Pharmacodynamics

Not applicable.

8.9 Genetics

After completion of the planned investigations of the immune response, residual blood and/or isolated PBMCs may be used for genetic analysis.

If not already done as part of the parent trial, blood and/or isolated PBMCs may be used for human leukocyte antigen (HLA) typing of a subject to allow additional analysis, e.g., characterization of T-cell receptor (TCR) repertoire and/or phenotypic characterization of antigen-specific T cells. Data generated with these additional analyses may provide information about the HLA dependency of immune response (e.g., if distinct HLA types have stronger/better immune response towards SARS-CoV-2).

Further, residual blood may also be used for profiling (e.g., by use of next generation sequencing) of B-cell receptor (BCR) and/or TCR variants in peripheral blood after vaccination.

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

8.10 Immune responses

Neutralizing antibody titers, antibody binding and CMI 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. The methodology used for these assessments will be documented in the Biomarker Manual.

Leftover blood after completion of the serology assessments will be used for the analyses as described in Section 8.10.3 (i.e., for explorative biomarker/immunogenicity research purposes).

Trial subjects will be asked if leftover blood may also be used for research purposes, e.g., to develop methods, assays, etc., related to BNT162 vaccine candidates. The use of leftover blood for these purposes will require a separate informed consent.

8.10.1 Neutralizing antibody titers and antibody binding (NATAB)

Neutralizing antibody titers and antibody binding assessment comprise of:

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

8.10.2 Cell mediated immune responses

Cell mediated immune responses assessments comprise:

- CMI/responses mediated by immune cells such as CD4 and CD8 T cells and their functional phenotypic subset by, e.g., ELISpot, ICS, multimer analyses, cytokine secretion assays, flow cytometry, and other tests.
- CMI analysis will include among others CD4 and CD8 T cells, Th1-specific cytokines (e.g., IFN-gamma, TNF-alpha, IL-2, or IL-12) and Th2-specific cytokines (e.g., IL-4, IL-5, IL-10, IL-13) to analyze the induction of either balanced Th1/Th2 responses, or of unbalanced Th1-dominant or Th2-dominant immune responses, respectively.

8.10.3 Explorative biomarker/immunogenicity research

After completion of the planned investigations of the immune response, residual blood samples may be used for explorative biomarker/immunogenicity research.

This research may include investigation of vaccine-induced immune responses by use of, but not limited to, phenotypic or functional characterization of antigen-specific B cells and

T cells (e.g., by flow cytometry-based phenotyping including multimer staining), analysis of BCR/TCR repertoire (e.g., by next generation sequencing) and multiplex-cytokine analysis.

In addition, residual blood samples may be stored and analysis may be performed on biomarker variants thought to play a role in the mechanism of action of BNT162 vaccine candidates to evaluate their association with observed clinical responses to BNT162 vaccine candidates

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

8.11 Blood collection

Up to ~615 mL (Group A) or ~620 mL (Immunology Subgroup of Group B) or ~120 mL (Group B no additional CMI or reactogenicity assessments) blood will be drawn per subject over the course of the trial. In the first 7 to 8 weeks, a maximum of 390 mL amount of blood is drawn in any group.

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

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

There is no formal statistical hypothesis under test.

9.2 Sample size determination

No formal sample size calculations were performed as this rollover trial is based on the trials BNT162-01 and BNT162-04.

9.3 Analysis sets

The following analyses sets are defined:

Analysis set	Description
Screened Set	All subjects who signed informed consent.
Safety Set	All subjects who received at least one dose of IMP.
Immunogenicity Set (IMM)	All subjects who received at least one dose of IMP and have at least one post-baseline functional antibody titer immunogenicity assessment.

Analysis set	Description
Immunogenicity Per-Protocol set (IMMPP)	All subjects included in the IMM set that have no major protocol deviations as determined by the clinician.

9.4 Statistical analyses

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

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

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

9.4.1 General considerations

In general, data will be summarized by groups (i.e., two randomized subgroups in Group A and non-randomized Group B with an immunology subset). Data may be pooled with trials BNT162-01 and BNT162-04.

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

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

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

9.4.2 Primary endpoints

The primary endpoints are defined in Section 3.

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

Reactogenicity

Solicited local and systemic reactions (from the subject diary) will be summarized using the Safety Set. 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 diaries) will be summarized for each of the following types using the Safety Set:

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

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

Unsolicited TEAEs

For Group A and Group B immunology subset, the number and percentage of subjects reporting at least one TEAE (defined in Section 10.3.1) will be summarized by PT nested within SOC for each of the following AE types using the Safety Set:

- Any AE
- Related AE
- Grade of AE
- Related Grade ≥3 AE
- Any solicited AE that continues past 7 d post-trial injection or is an SAE, or AE that fits the definition of a solicited AE but starts after Day 8
- Any SAE
- Related SAE
- AESI

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

For Group B, AESIs and SAEs will be analyzed.

Additional AE analyses may be described in the SAP.

9.4.3 Secondary endpoints

The secondary endpoints are defined in Section 3.

All secondary immunogenicity analyses will be performed first with the IMM population (see Section 9.3) as this is an exploratory hypothesis-generating trial. However, the Immunogenicity Per Protocol set (IMMPP) population will also be analyzed.

The scheduled time points for assessment are given in the SoA (see Section 1.3).

The binary secondary endpoints will be summarized by group presenting absolute and relative frequencies (n and %) of subjects in each category for each assessment. The continuous secondary endpoints will be summarized by group using summary statistics.

For each subject and each time point, antibody titers will be defined based on the calculated geometric mean of antibody titers assessed in duplicate. Additionally, GMT with 95% CI will be presented.

Change in antibody titers to recombinant S1 and RBD protein derived from reference and B.1.351 strains will be assessed from baseline to time points as identified in the endpoints (see Section 3) and SoA (see Section 1.3). In addition to analysis of changes in

neutralizing antibody and binding antibody titers, functional cross-neutralization of vaccine-induced antibodies to B.1.351 in relationship to reference strain will be analyzed at time points identified in the secondary endpoints.

9.4.4 Exploratory endpoints

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

9.4.5 Other safety analyses

Safety data other than AEs that will be summarized includes clinical laboratory parameters and vital signs for Group A and the Immunology Subgroup of Group B only. All safety analyses will be based on the Safety Set and will be summarized descriptively by group unless otherwise stated.

Clinical laboratory parameters for Group A and the Immunology Subgroup of Group B

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

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

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

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

Abnormal laboratory results will be graded using criteria based on the guidance given in FDA Guidance for Industry “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (see Section 10.3.2).

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

Clinical laboratory analysis details will be described in the SAP.

Vital signs for Group A and the Immunology Subgroup of Group B

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

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

9.4.6 Other analyses

Other analyses will be described in the SAP.

9.5 Interim analyses

No formal interim statistical analysis will be performed. However, preliminary analyses may be performed after completion of Visit 5 for any group (i.e., Group A or Group B).

9.6 Data monitoring committee

No Data Monitoring Committee is planned. An SRC is planned, for details see Section 10.1.5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, ethical, and trial oversight considerations

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

10.1.1 Regulatory and ethical considerations

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

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

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

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

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

- Providing written summaries of the status of the trial to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC.
- Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures.

- Providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IEC, European regulation 536/2014 (if applicable), and all other applicable local regulations.

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

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

10.1.2 Financial disclosure

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

10.1.3 Informed consent process

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

Trial subjects must be informed that their participation is voluntary.

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

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

The medical record must include a statement that written informed consent was obtained 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, subjects will be re-consented to updated written information and consent forms.

Separate informed consent will be obtained for the use of samples for genetics, i.e., testing of HLA type, BCR and TCR variants (see Section 8.9), and for the use of leftover blood for research purposes e.g., to develop methods, assays, etc. (see Section 8.10).

10.1.4 Data protection

Trial subjects will be assigned a unique identifier by the investigator according to the sponsor specifications on unique identifier assignment. Any trial subject records or datasets that are transferred to the sponsor will contain the identifier only; trial subject

names or any information which would make the trial subject identifiable will not be transferred.

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

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

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

10.1.5 Committees - SRC

Safety reviews of the unblinded data will be conducted by an SRC every 16 weeks and *ad hoc* basis. The SRC will review all safety data, including AESIs, and SAEs, as well as laboratory data and other relevant safety data.

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

The SRC will at least comprise a sponsor medical representative, the Medical Monitor, a statistician, coordinating investigator, a sponsor-independent investigator, and on an *ad hoc* basis, a representative for the respective trial site depending on the trial subject in question.

10.1.6 Dissemination of clinical trial data

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

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

10.1.7 Data quality assurance

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

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

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

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of non-compliance issues

and monitoring techniques (central, remote, or on site monitoring) are provided in the Monitoring Plan.

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

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

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

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

10.1.8 Source documents

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

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

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

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

10.1.9 Trial and site start and closure

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

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

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

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

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

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

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

10.1.10 Publication policy

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

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

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

10.1.11 Protocol preparation and approval

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

10.2 Clinical laboratory tests

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

Hematology

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

Clinical chemistry

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

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

Urinalysis

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

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

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

10.3.1 Definition of AE and TEAE

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

10.3.1.1 Events meeting the AE definition

- Any abnormal laboratory test results or other safety assessments (e.g., vital signs measurements), including those that worsen from baseline, and which are considered clinically significant in the medical and scientific judgment of the investigator, may be considered as AEs.
- New conditions or (at the discretion of the investigator) any worsening of a pre-existing condition detected or diagnosed after Visit 0.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE.

10.3.1.2 Events not meeting the AE definition

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

10.3.1.3 Suspected adverse reaction

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

- The definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the IMP.
- The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship and an alternative etiology is not apparent.

10.3.1.4 Definition of SAE

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

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

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or a birth defect.
- Other situations:
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the trial subject or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

10.3.1.5 Suspected unexpected serious adverse reactions

All suspected adverse reactions related to an IMP that occur in this trial and that are both unexpected and serious are SUSARs. SUSARs are subject to expedited reporting.

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

Severity (intensity or grade) and seriousness need to be assessed independently for each AE and be recorded in the CRF. For a definition of the terms “severe” and “serious” for AEs, see:

- Section 10.3.1.7 for AEs.
- Section 10.3.1.4 for SAEs (see Section 10.3.1.10 for SAE reporting instructions).

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

AE and SAE recording

The investigator needs to assess and document any AE regardless of association with the use of the trial treatment during the period of observation as defined in Section 8.3.1.

Data pertaining to AEs will be collected during each trial visit and the 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.
- AEs that are related to one clinical event should be subsumed under that event when recorded on the CRF. For example, elevated creatinine, nausea, vomiting, hypercalcemia should be subsumed under renal failure if that explains the etiology for the subsumed signs and symptoms.
- The investigator will then record AE information in the CRF and perform an assessment on:
  - Intensity, see the section “Assessment of intensity” in Section 10.3.2 for guidance on the assessment of intensity,
  - Seriousness,

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

Assessment of AE and/or SAE intensity

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

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

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

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

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

Actions taken by the investigator

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

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

- Dose not changed (= continuation of trial treatment administration according to the trial protocol)

- Drug withdrawn
- Not applicable (e.g., in case treatment with trial treatment has not yet started or event starts after last trial treatment administration)

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

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

Outcome

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

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

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

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

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

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

Assessment of causality

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

The investigator will use clinical judgment to determine the relationship.

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

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

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

Relationship to trial treatment

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

Relationship to trial procedures including trial treatments

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

10.3.1.8 SAE exemptions

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

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

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

10.3.1.9 Documentation of particular situations

AEs that are secondary to other events:

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

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

Abnormal clinical 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 clinical 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 clinical laboratory/vital signs abnormality is not a sign of a disease or syndrome and does not result in specific symptoms but leads to a change in trial treatment or in a medical intervention, the laboratory/vital signs abnormality is clinically significant and must be documented as AE.
- If a clinical laboratory/vital signs abnormality is not considered clinically significant by the investigator, then an AE does not need to be documented.

AEs associated with an overdose or error in drug administration:

- An overdose or incorrect administration of a drug is not itself an AE, but it may result in an AE. For a definition of an overdose, see Section 8.4.
- All AEs associated with an overdose or incorrect administration should be documented as AE in source data and CRF and reported as SAE if applicable.

AEs of proven COVID-19 disease:

Any case of proven COVID-19 disease occurring until the last FU visit should be reported as an SAE/AE.

10.3.1.10 Reporting of SAEs and AESIs

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

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

SAE and AESI reporting to sponsor

For the period of observation, see Section 8.3.1.

For any SAE or AESI (even if the AESI is non-serious), the investigator needs to complete the applicable paper Report Form which must be sent to the sponsor via one of the following reporting methods:

- Safety Report Fax No.: [redacted]
- Safety Report Email Address: [redacted]

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

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

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

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

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

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

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

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

10.3.2.1 Local reactions

Redness and swelling/induration will be measured and recorded in centimeters and then categorized during analysis as absent, mild, moderate, severe or potentially life-threatening, based on the grading scale in Table 5. Likewise, pain (perceived) and tenderness (elicited) at the injection site will be assessed by the trial subject as absent, mild, moderate, severe, or potentially life-threatening, according the grading scale in Table 5.

Table 5: Local reaction grading scale

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

a. In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
b. Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

10.3.2.2 Systemic reactions (signs and symptoms)

Symptoms of systemic reactions

Symptoms of systemic reactions will be assessed by the participant as absent, mild, moderate, severe, or potentially life-threatening, according to the grading scale in Table 6.

Table 6: Systemic reaction grading scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
Vomiting	1 to 2 times in 24 h	>2 times in 24 h	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 h	4 to 5 loose stools in 24 h	6 or more loose stools in 24 h	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue / tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Fever (oral temperature of ≥38.0°C)	38.0 to 38.4°C	38.5 to 38.9°C	39.0 to 40.0°C	>40.0°C
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
Nausea	No interference with activity or 1 to 2 episodes/24 h	No interference with activity or >2 episodes/24 h	Prevents daily activity, requires outpatient IV hydration	Emergency room visit or hospitalization for hypotensive shock
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsening joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

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

Laboratory abnormalities

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

Table 7: Laboratory abnormality grading scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
Hematology				
Hemoglobin (female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (female) change from baseline value - g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
Hemoglobin (male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hemoglobin (male) change from baseline value - g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	>25,000
WBC decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1,500	1,501 – 5,000	>5,000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
Chemistry				
BUN - mg/dL	23 – 26	27 – 31	>31	Requires dialysis
Creatinine - mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	>2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST - increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

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

10.4 Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

Women of childbearing potential

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

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

Women in the following categories are not considered WOCBP:

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

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

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

Post-menopausal female

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

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

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

Male trial subjects

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

10.4.2 Contraception guidance

Trial subjects must meet the “Reproductive status” inclusion criteria, including contraception requirements, as listed in Section 5.1.

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

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

* Contraception methods that in the context of this guidance are considered to have low user dependency.

** 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 assessed in relation to its maintenance until Visit 5 (Day 50) and the preferred and usual lifestyle of the subject.

10.4.3 Collection of pregnancy information

Pregnancy information will only be collected after obtaining written informed consent from the pregnant trial subject/trial subject’s pregnant partner.

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

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-trial pregnancy related SAE considered reasonably related to the trial

intervention by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former trial subjects, he or she may learn of an SAE through spontaneous reporting.

10.4.4 Sperm donation

Trial subjects must comply with the “Reproductive status” inclusion criteria prohibiting sperm donation listed in Section 5.1.

10.5 Genetics

Not applicable.

10.6 Liver safety: Suggested actions and follow-up assessments

Not applicable.

10.7 Investigators and trial administrative structure

10.7.1 Investigators and trial site personnel

There must be an investigator at each trial site.

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

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

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

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

10.7.2 Trial site personnel assigned trial-related duties

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

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

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

10.7.3 Contract research organizations

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

10.7.4 The sponsor and sponsor's personnel

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

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

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

10.8 Country-specific requirements

Not applicable.

10.9 Protocol amendments and updates

10.9.1 Protocol amendment 01 (update from protocol version 1.0 to 2.0)

Update rationale

This update describes changes made in response to feedback from the German Paul-Ehrlich-Institute (PEI) on version 1.0 (July 1st, 2021).

This update was issued before any trial subjects were enrolled into the trial. This change had no impact on the planned trial objectives or trial conduct.

Detailed description of changes

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	**Rationale**
Section 2.3.1 Risk assessment • Reports of AEs following use of the RNA-based vaccine Comirnaty (BNT162b2) suggest increased risks of myocarditis and pericarditis, particularly following the second dose. Typically, onset of symptoms has been within a few days following receipt of the vaccine.	PEI feedback
Section 8.3.8 Adverse events of special interest Any events of myocarditis or pericarditis regardless of grade will be considered AESIs.	PEI feedback

Changed text (inserted text is blue/underlined; deleted text is red/struck out) Where appropriate, a simple description of the changes is given.	Rationale
Section 8.5: Treatment for specific adverse reactions If subjects report symptoms that could represent myocarditis or pericarditis, in addition to any medically indicated evaluations at the discretion of the investigators, the following United States Center for Disease Control (CDC) clinical recommendations for myocarditis and pericarditis following COVID-19 vaccination published on 28 May 2021 (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html) should be considered: • For initial evaluation, consider an ECG, troponin level, and inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate. In the setting of normal ECG, troponin, and inflammatory markers, myocarditis or pericarditis are unlikely. • Consider consultation with: ○ Cardiology for assistance with cardiac evaluation and management. ○ Infectious disease and/or rheumatology to assist in this evaluation. • Where available, evaluate for potential etiologies of myocarditis and pericarditis, particularly acute COVID-19 infection (e.g., PCR testing), prior SARS-CoV-2 infection (e.g., detection of SARS-CoV-2 nucleocapsid-binding antibodies), and other viral etiologies (e.g., enterovirus PCR and comprehensive respiratory viral pathogen testing).	PEI feedback
Section 10.3.1.9: Documentation of particular situations **Myocarditis/pericarditis as AESI:** Any case of myocarditis/pericarditis occurring until the last planned visit (Visit 7) should be reported as AESI as defined by the protocol (regardless of grade). In addition to completion of a CRF, an SAE form should be completed fulfilling SAE criteria (e.g., hospitalization for severe disease), including follow-up information, as detailed in Section 10.3.1.10.	PEI feedback

10.9.2 Protocol amendment 02 (update from protocol version 2.0 to 3.0)

Update rationale

This update describes changes made in response to requests for clarification on version 2.0 (July 12th, 2021).

This change had no impact on the planned trial objectives.

Detailed description of changes

Minor editorial changes, such as the correction of typing errors, are not specifically listed. In the table below, deleted text is crossed out and red; new text is underlined and blue.

Updated text	Brief Rationale
Title page **(Title):** A Phase II, open-label, rollover trial to evaluate the safety and immunogenicity of one or two boosting doses of Comirnaty™ or one dose of BNT162b2s01 in BNT162-01 trial subjects, or two boosting doses of Comirnaty™ in BNT162-04 trial subjects **(Vaccine):** BNT162 RNA-lipid nanoparticle (RNA-LNP) vaccine, either Comirnaty™® or BNT162b2s01	Sponsor decision to not include trademark in the title and correction of trademark vaccine name

<table>
<tr><th>Updated text</th><th>Brief Rationale</th></tr>
<tr><td>

Section 1.1 (Trial synopsis) and Section 3 (Objectives and endpoints)

<table>
<tr><th>OBJECTIVES</th><th>ENDPOINTS</th></tr>
<tr><td>Primary objectives</td><td>Endpoints</td></tr>
<tr><td>To determine the safety and tolerability of one or two boosting doses of Comirnaty or one dose of BNT162b2s01 in BNT162-01 trial subjects, or two boosting doses of Comirnaty in BNT162-04 trial subjects.</td><td>For all Group A and Group B subjects:
The proportion of subjects in each treatment group with at least one SAE or the proportion of AESIs occurring up to 26 weeks after the first IMP injection.
For Group A and a selected subset of Group B subjects:
The frequency of solicited local reactions (pain, tenderness, erythema/redness, induration/swelling) at the injection site recorded up to 7 d after each IMP injection.
The frequency of solicited systemic reactions (vomiting, diarrhea, headache, fatigue/tiredness, fever, chills, nausea, new or worsened muscle pain, new or worsening joint pain) recorded up to 7 d after each IMP injection.
~~For Group A subjects only:~~
The proportion of subjects with at least one unsolicited TEAE ~~or at least one AE related to IMP~~ occurring up to 28 d after IMP injection in each treatment group.</td></tr>
</table>

</td><td>Deletion of redundancy</td></tr>
<tr><td>

Section 1.1 Trial synopsis and Section 4.1 Overall design

Trial design

*Group A excludes transplant subjects from Cohort 13 of the BNT-01 trial; consenting transplant subjects will ~~may~~ enroll into Group B immunology subgroup and will receive one injection; their potential second injection will be delayed indefinitely. Henceforth this group is referred to as Group B transplants.

All potential rollover volunteers must enroll in this trial within less than 18 months of their last injection of a BNT162 candidate vaccine in the parent BNT162-01 or BNT162-04 trials. ~~Subjects may be rescreened if they are discovered to have been infected with SARS-CoV-2 within 24 weeks of the first scheduled trial injection.~~

</td><td>Updates for clarity and deletion to avoid confusion on overall timing of screening</td></tr>
<tr><td>

Section 1.1: Trial synopsis

Trial population

This trial will enroll ~~healthy volunteers~~ subjects aged ≥18 years who received one or two previous injections of a BNT162 candidate vaccine in either the BNT162-01 trial or the BNT162-04 trial.

</td><td>Change in wording of trial population</td></tr>
<tr><td>

Section 1.3: Schedule of activities (Table 1)

<table>
<tr><th>Activity</th><th>Visit 0</th><th>Visit 1</th><th>…</th><th>Visit 6</th><th>…</th></tr>
<tr><td>Week(s)</td><td></td><td></td><td>…</td><td>12</td><td>…</td></tr>
<tr><td>Day</td><td>-30 to -1</td><td>1</td><td>…</td><td>85±10</td><td>…</td></tr>
<tr><td></td><td>(Screening)</td><td>(Day of inj. 1; pre-dose except IMP injection)</td><td>…</td><td>(~84 d post inj.)</td><td>…</td></tr>
<tr><td>…</td><td>…</td><td>…</td><td>…</td><td></td><td>…</td></tr>
<tr><td>Urine for clinical laboratory [d]</td><td>X</td><td>X ~~(pre-dose)~~</td><td>…</td><td></td><td>…</td></tr>
<tr><td>Blood draws for clinical laboratory (15 mL) [e]</td><td>X</td><td>X ~~(pre-dose)~~</td><td>…</td><td></td><td>…</td></tr>
<tr><td>…</td><td>…</td><td>…</td><td>…</td><td></td><td>…</td></tr>
<tr><td>Oral swabs for SARS-CoV-2 sequencing [h]</td><td>X[g]</td><td>X[g]</td><td>…</td><td>X</td><td>…</td></tr>
<tr><td>Blood draws for NATAB and nucleocapsid protein testing (15 mL)</td><td></td><td>X ~~(pre-dose)~~</td><td>…</td><td>X</td><td>…</td></tr>
<tr><td>Blood draws for CMI (120 mL each)</td><td></td><td>X ~~(pre-dose)~~</td><td>…</td><td>X</td><td>…</td></tr>
</table>

</td><td>Update to clarify schedule of activities</td></tr>
</table>

Updated text

…		…	…		…
Subjects report daily reactogenicity (incl. body temperature) in their ~~Record local and systemic reactions into subject~~ diary ~~from~~ on Day 1 and for 7 d post each vaccination ~~through Day 8~~		X (post-dose) [i]	…		…
Record AEs since last visit		X	…	X [i]	…
…		…			…

…

h Swabs will only be analyzed (sequenced) if serum nucleocapsid protein ELISA testing and/or NAAT-based SARS-CoV-2 testing detects SARS-CoV-2 (with or without symptoms). Oral swabs for SARS-CoV-2 sequencing must be collected at the same day/time as the oral swabs for NAAT-based SARS-CoV-2 for screening/surveillance.

i Only AEs related to IMP, AESIs, and SAEs. All AEs linked to confirmed COVID-19 cases will be recorded.

j Issue thermometer if not available from parent trial, for subjects to measure their body temperature each day and if they experience flu-l ke symptoms.

Brief Rationale

Update to clarify schedule of activities

Section 1.3: Schedule of activities (Table 2)

Activity	Visit 0	Visit 1	Visit 2	Visit 3	…	Visit 5	Visit 6	Visit 7
Week(s)			1	3	…	7	12	26
Day	-30 to -1	1	8+2	22±3	…	50±7	85±10	182±20
	(Screening)	(Day of inj. 1; pre-dose except IMP injection)	(~7 d post inj. 1)	(~21 d post inj. 1; pre-dose except IMP injection)	…		(~63 d post inj. 2)	(~161 d post inj 2 EOT Visit)
…	…	…	…	…	…		…	…
Urine pregnancy test for WOCBP	X	X ~~(pre-dose)~~		X ~~(pre-dose)~~	…			X
…	…	…	…	…	…		…	…
Oral swab for SARS-CoV-2 sequencing [g]	X [g]	X [g]	X	X	…	X	X	X
Blood draws for NATAB and nucleocapsid protein testing (15 mL)		X ~~(pre-dose)~~	X	X ~~(pre-dose)~~	…	X	X	X
Blood draws for CMI (100 mL each)		X ~~(pre-dose)~~	X		…		X	X
…	…	…	…	…	…		…	
Subjects report daily reactogenicity (incl. body temperature) in their ~~Record local and systemic reactions into subject~~ diary for 7 days post each vaccination		X (post-dose) [i]	X	X (post-dose) [h]	…		…	
Record AEs since last visit		X	X	X	…	X [k]	X [j]	X [j]

Updated text	Brief Rationale

~~AESIs/SAEs only~~								
…	…	…	…	…	…		…	…

…

g Swabs will only be analyzed (sequenced) if serum nucleocapsid protein ELISA testing and/or NAAT-based SARS-CoV-2 testing detects SARS-CoV-2 (with or without symptoms). Oral swabs for SARS-CoV-2 sequencing must be collected at the same day/time as the oral swabs for NAAT-based SARS-CoV-2 for screening / surveillance.

…

i Issue thermometer if not available from parent trial, for subjects to measure their body temperature each day and if they experience flu-l ke symptoms.

j Only AEs related to IMP, AESIs, SAEs, and all AEs linked to confirmed COVID-19 cases will be recorded until the end of trial.

k Only for Group B transplant subjects: only AEs related to IMP, AESIs, SAEs, and all AEs linked to confirmed COVID-19 cases will be recorded until the end of trial.

Section 1.3: Schedule of activities (Table 3)

Update to clarify schedule of activities

Activity	Visit 0	Visit 1	Visit 2	Visit 3	…	Visit 6	…
Week(s)			1	3	…	12	…
Day	-30 to -1	1	8+2	22±3	…	85±10	…
	(Screening)	(Day of inj. 1; pre-dose except IMP injection)	(~7 d post inj. 1)	(~21 d post inj. 1; pre-dose except IMP injection)	…	(~63 d post inj. 2)	…
…	…	…	…	…	…	…	…
Urine pregnancy test for WOCBP	X	X ~~(pre-dose)~~		X ~~(pre-dose)~~	…		…
…	…	…	…	…	…	…	
Oral swab for SARS-CoV-2 sequencing [g]	X[e]	X[e]	X	X	…	X	…
Blood draws for NATAB and nucleocapsid protein testing (15 mL)		X ~~(pre-dose)~~	X	X ~~(pre-dose)~~	…	X	…
Record AEs ~~AESIs/SAEs~~ since last visit [h]		X	X	X	…	X	…

…

g Swabs will only be analyzed (sequenced) if serum nucleocapsid protein ELISA testing and/or NAAT-based SARS-CoV-2 testing detects SARS-CoV-2 (with or without symptoms). Oral swabs for SARS-CoV-2 sequencing must be collected at the same day/time as the oral swabs for NAAT-based SARS-CoV-2 for screening / surveillance.

h Only, AESIs, SAEs, and all AEs linked to confirmed COVID-19 cases will be recorded until the end of trial.

Section 2.3.1: Risk assessment

Deletion and updates to reflect more recent information

- Very rarely, a vaccine may cause~~s~~ an autoimmune disease in a person or may make an autoimmune disease worse.
- For other known risks related to Comirnaty and anticipated risks related to BNT162b2s01, refer to the current BNT162 IB.
  - ~~More than 25,000 people have received the RNA-based vaccine Comirnaty (BNT162b2) in clinical trials including Phase III. The most frequent AEs were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), and fever (14.2%). Solicited local and systemic reactions (reactogenicity) were most often reported as mild to moderate and lasting less than 2 to 3 d. Among reported unsolicited AEs, lymphadenopathy~~

Updated text	Brief Rationale
~~occurred more frequently in the vaccine group compared to placebo group.~~ ~~o Hypersensitivity related AEs were slightly higher in the vaccine group compared to the placebo groups (137 [0.63%] vs 111 [0.51%]). Severe adverse reactions occurred in 0.0 to 4.6% of subjects, were more frequent after dose 2 than after dose 1 and were generally less frequent in older adults (>55 years of age) (<2.8%) as compared to in younger subjects (≤4.6%). SAEs (<1.0%) represented medical events that occur in the general population at similar frequencies as observed in the Phase III trial.~~ ~~o Reports of AEs following use of the RNA-based vaccine Comirnaty (BNT162b2) suggest increased risks of myocarditis and pericarditis, particularly following the second dose. Typically, onset of symptoms has been within a few days following receipt of the vaccine.~~ ~~o Since both BNT162b2s01 and Comirnaty use the same RNA platform and LNP formulation, they are expected to share the same formulation based risks.~~ ~~o BNT162b2s01 and Comirnaty differ slightly in the RNA encoded open reading frame. Despite this difference, the safety and immunogenicity of BNT162b2s01 is not anticipated to be any different than for the prototype vaccine Comirnaty.~~ o Up until June 2021, the safety of BNT162b2 has been studied in clinical trials that have included about 28,500 people who have received at least one dose of BNT162b2. In addition, since BNT162b2 has been approved for emergency use or received a conditional marketing authorization in many countries, by the end of April 2021 about 400 million doses have been distributed. Based on the available data, the following risks have been determined to be caused by BNT162b2: Injection site pain, injection site swelling, fatigue, fever, chills, headache, diarrhea, joint aches, muscle aches, nausea, vomiting, injection site redness, enlarged lymph glands, allergic reactions (symptoms may include rash, itching, hives, and swelling of the face or lips), decreased appetite, lethargy, sweating and night sweats, pain in arm, feeling weak or unwell, and severe allergic reactions (anaphylaxis). o Myocarditis and pericarditis have occurred in some people who have received BNT162b2. Cases have mainly been reported in males under 30 years of age and following the second vaccination, however, there have been some cases reported in older males and females as well as following the first vaccination. Symptoms may include: Chest pain, shortness of breath, or feelings of having a fast-beating, fluttering, pounding heart, presyncope and syncope. The chance of having myocarditis or pericarditis occur is very low.	
Section 5.1: Inclusion criteria 3. Have received BNT162 vaccine candidates in the BNT162-01 or BNT162-04 ~~trials and do not have an ongoing IMP related AE~~. 4. …Note: In particular, caution should be used with a subject who has a history of cardiovascular disease, e.g., myocarditis, pericarditis, myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmia. 9. Have not been diagnosed with SARS-CoV-2 infection in the 12 weeks prior to Day 1 (baseline). Subjects who screen-fail on this criterion ~~only~~ may be rescreened. 11. Chemistry panel: the following apply: alkaline phosphatase (ALP), alanine aminotransferase (ALT), ~~or~~ and aspartate aminotransferase (AST) are <3.0 times the upper limit of normal, and~~/or~~ glomerular filtration rate (GFR) is ≥ 40 mL/min/1.73 m^2.	Deleted to avoid repetition with exclusion criteria 5, to provide guidance on history of cardio-vascular disease and to correct error
Section 5.2: Exclusion criteria 3. Have a current febrile illness (body temperature ≥38.0°C) or other acute illness within 48 h prior to Day 1/IMP injection in this trial. Subjects who screen-fail on this criterion may be rescreened. 4. Have received a live or live attenuated vaccine within 30 d prior to Day 1/IMP injection, or any other vaccination within 14 d prior to Day 1/IMP injection. Subjects who screen-fail on	Sponsor decision based on site feedback

Updated text	Brief Rationale
this criterion may be rescreened.	
Section 5.3: Lifestyle considerations Subjects will be asked to avoid strenuous exercise beyond their usual exercise routine for 7 d after each IMP administration.	Insertion for clarity
Section 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. ~~Subjects who have failed screening due to diagnosis of SARS-CoV-2 infection within 12 weeks prior to Day 1 may be rescreened.~~ For subjects who may not have passed all of the screening requirements such as one of the following: • diagnosis of SARS-CoV-2 infection within 12 weeks prior to Day 1, • febrile illness within 48 hours prior to Day 1, or • required (clinically indicated) vaccine within its exclusion time period (i.e., 2 or 4 weeks) prior to Day 1 medical judgement may be used to decide if and when to rescreen as long as the subject is <18 months from their last IMP injection of the parent trial prior to Day 1.	Change to clarify timing of rescreening
Section 7.2: Trial subject discontinuation or withdrawal from the trial Reasons for discontinuation from the trial include the following: • Refused further ~~IMP injections or~~ trial procedures	Correction of an error
Section 7.3: Lost to follow-up • The trial site must attempt to contact the trial subject and reschedule the missed visit as soon as possible and counsel the trial subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the trial subject wishes to ~~and/or should~~ continue in the trial.	Correction of an error
Section 8.2 Safety assessments The trial site personnel will remind the subject to record the worst grade for each symptom in their diary at approximately the same time every evening on the day of IMP injection and then every day at the same time until the day of the next planned site visit. The trial site personnel will remind the subject to measure their body temperature using the provided thermometer and record their body temperature in the diary every day including the day of IMP injection.	Sponsor decision to include instructions to the site.
Section 8.3.2: Method of detecting AEs and SAEs Care will be taken not to introduce bias when detecting AEs ~~and/~~or SAEs. Open-ended and non-leading verbal questioning of the trial subject is the preferred method to inquire about AE occurrences.	Change for clarity
Section 8.3.7: Disease-related events/outcomes not qualifying as AEs or SAEs Not applicable~~, this trial will only enroll healthy trial subjects~~.	Deletion for clarity
Section 8.3.8: Adverse events of special interest ~~Reports of enhanced respiratory disease or progression of flu like symptomatology, such as non-resolution of the symptoms after 3 d, symptom kinetics that are inconsistent with a relationship to RNA immunization will be considered AESIs.~~ ~~Also, any case of proven COVID-19 disease occurring after Visit 1 until the last planned trial visit will be considered an AESI (regardless of grade).~~ ~~Any events of myocarditis or pericarditis regardless of grade will be considered AESIs.~~ The following will be reported as AESIs: • Myocarditis (all Levels of Certainty including "Possible cases" (1 to 3) as per Brighton Collaboration Case Definition) 1 to 3 (Possible Case), Myocarditis_Version_1.0_15 July 2021_FINAL_for Posting) • Pericarditis (all Levels of Certainty including "Possible cases" (1 to 3) as per Brighton Collaboration Case Definition) 1 to 3 (Possible case), Pericarditis_Version_1.0_15 July	Sponsor decision to modify AESIs for clarity.

Updated text	Brief Rationale
2021_FINAL_for Posting) • Anaphylaxis • Thromboembolic events (e.g., deep vein thrombosis, stroke, myocardial infarction) • Immune thrombocytopenia • Immune based neurologic events (e.g., optic neuropathy, Guillain-Barré syndrome)	
Section 8.5: Treatments for specific adverse reactions If subjects experience enhanced respiratory disease ~~or progression of flu like symptomatology, such as non resolution of the symptoms after 3 d,~~ symptom kinetics that are inconsistent with a relationship to RNA immunization, additional diagnostic measures should be considered, and the Medical Monitor should be informed.	Deletion for clarity
Section 9.4.2: Primary endpoints Unsolicited TEAEs • For Group A and Group B immunology subset, the number and percentage of subjects reporting at least one TEAE (defined in Section 10.3.1) will be summarized by PT nested within SOC for each of the following AE types using the Safety Set:	Update to match wording change in Endpoints
Section 10.3.1.9: Documentation of particular situations ~~**Proven COVID-19 disease as an AESI:**~~ ~~Any case of COVID-19 disease occurring until the last planned visit (Visit 7) should be reported as an AESI as defined by the protocol (regardless of grade). In addition to completion of a CRF, an SAE form should be completed for COVID-19 disease fulfilling SAE criteria (e.g., hospitalization for severe disease), including follow-up information, as detailed in Section 10.3.1.10.~~ ~~**Myocarditis or pericarditis as AESI:**~~ ~~Any case of myocarditis or pericarditis occurring until the last planned visit (Visit 7) should be reported as AESI as defined by the protocol (regardless of grade). In addition to completion of a CRF, an SAE form should be completed fulfilling SAE criteria (e.g., hospitalization), including follow-up information, as detailed in Section 10.3.1.10.~~	Sponsor decision to not document proven COVID-19 disease as an AESI and deletion of Myocarditis / Pericarditis to avoid duplication with section 8.3.8
Section 10.3.1.10: Reporting SAEs and AESIs All SAEs and AESI (even if the AESI is non-serious) ~~(even if non-serious)~~ which occur in a trial subject during the observation period, whether considered to be associated with trial medication or not, must be reported by the investigator to the sponsor within 24 h following knowledge of the event. **SAE and AESI reporting to sponsor** ~~**using a paper form (SAE report)**~~ For the period of observation, see Section 8.3.1. For any SAE or AESI (even if the AESI is non-serious), the investigator needs to complete the applicable paper ~~Serious Adverse Event~~ Report Form which must be sent to the sponsor via one of the following reporting methods: … All SAE/AESI follow-up information should be sent to the sponsor (indicating that this is a "follow-up" report using the SAE Form or the Additional Information and Follow-Up Form) without delay as described above and accompanied by appropriate anonymous supporting documentation (e.g., discharge letters, medical reports or death certificates), until a final outcome and date are available. … A copy of the submitted SAE/AESI report must be retained on file by the investigator.	Sponsor decision to update AESI reporting
Section 10.3.2.2: Systemic reactions (signs and symptoms) Table 6: Systemic reaction grading scale	Change to correct error

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
…	…	…	…	…

Updated text					Brief Rationale
Nausea	No interference with activity or 1 to 2 episodes/24 h	No interference with activity or ~~1to~~ >2 episodes/24 h	Prevents daily activity, requires outpatient IV hydration	Emergency room visit or hospitalization for hypotensive shock	
...	...	...	...	...	
Section 10.4.2: Contraception guidance • Sexual abstinence. ** ** 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 assessed in relation to maintenance until Visit 5 (day 50) and the preferred and usual lifestyle of the subject.					Sponsor decision based on site feedback

10.9.3 Protocol amendment 03 (update from protocol version 3.0 to 4.0)

Overall amendment rationale

This update describes changes made to allow administration of Dose 2 to Group B transplant subjects (Cohort 13 of the BNT162-01 trial) based on an SRC recommendation and for a reduction of the recruitment period.

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 the correction of typing errors, are not specifically listed. See the table for a summary of the reasons for major changes compared to the previous version.

Section	Reason for change
Title page	Change in sponsor's medical representative
1.1 Trial synopsis (Trial rationale), 2.2 Trial rationale	Updates to describe rationale for allowing administration of Dose 2 to Group B transplant subjects.
1.1 Trial synopsis (Trial design, Duration of all trial periods)	Reduction in recruitment period as no subjects from parent trial left for rollover.
1.3 Schedule of activities	A separate SoA table for Group B transplant subjects was added to allow administration of Dose 2. Updates of footnotes in existing tables made to accommodate subjects receiving non-trial SARS-CoV-2 vaccinations.
Throughout	Updating the representative SARS-CoV-2 variants tracked by the WHO, deletion of "SA" from variant B.1.351 (Pango lineage) for clarity of variant names.
2.3.1 Risk assessment	Deletion and updates to reflect more recent information.
3 Objectives and endpoints	Updates to secondary and exploratory endpoints related to Group B transplant subjects due to administration of Dose 2.
6.1 IMPs administered	Addition of dosing regimen for the Group B transplant subjects
6.5 Concomitant therapy	Addition to accommodate subjects receiving non-trial SARS-CoV-2 vaccinations.
7.2 Trial subject discontinuation or withdrawal from the trial	Addition to accommodate subjects receiving non-trial SARS-CoV-2 vaccinations.
8.3.1 Time period and frequency for collecting AE, AESI, and SAE information	Addition to accommodate subjects receiving non-trial SARS-CoV-2 vaccinations.

Section	Reason for change
9.4.5 Other safety analyses	Addition of the Immunology Subgroup of Group B to clinical laboratory parameters and vital signs.
10.3.1 Definition of AE and TEAE	Addition for clarity: AEs with an onset date more than 28 d after the last administration of IMP will be considered as treatment-emergent only if assessed as related to IMP by the investigator
10.3.1.9 Documentation of particular situations	Addition for clarity: Any case of proven COVID-19 disease occurring until the last FU visit should be reported as an SAE/AE

10.10 Data collection and management

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

10.10.1 Case report forms

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

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

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

10.10.2 Trial subject reported outcomes

Not applicable.

10.10.3 Data management

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

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

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

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

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

10.10.4 Investigator's Site File and the Trial Master File

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

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

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

10.11 Other data

10.11.1 Demographic data

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

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

10.11.2 Medical history

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

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