CLINICAL TRIAL PROTOCOL
Trial number: BNT162-21

Document version:	8.0	**Date:**	16 SEP 2024
Sponsor name:	BioNTech SE 55131 Mainz, Germany		

Trial title:	An exploratory Phase I, randomized, observer-blind, active-controlled, dose-escalation trial evaluating the safety, tolerability, and immunogenicity of an investigational RNA-based SARS-CoV-2 vaccine in COVID-19 vaccine experienced healthy adults
Brief lay title:	Safety and effects of an investigational COVID-19 vaccine as booster in healthy people
Trial phase:	Phase I
Indication:	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Investigational medicinal products:	BNT162b4, BNT162b2 Bivalent (WT/OMI BA.4/BA.5), BNT162b2 Monovalent (OMI XBB.1.5)
Regulatory identifiers:	BB-IND 28877, ClinicalTrials.gov ID: NCT05541861
Trial sites:	Sites are planned in the United States (US)
Trial Medical Monitor:	For the name and contact details, see the Medical Monitoring Plan

A list of key sponsor personnel involved in the preparation of this protocol and the conduct of the trial, including their full names, titles, roles, and responsibilities, will be maintained. These personnel include the sponsor's medical expert for the trial and the person authorized to sign (approve) the protocol and any protocol amendment(s) for the sponsor.

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

Document history	Date	Version number
First sponsor approved version	01 SEP 2022	1.0
Second sponsor approved version	07 SEP 2022	2.0
Third sponsor approved version	11 NOV 2022	3.0
Fourth sponsor approved version	16 FEB 2023	4.0
Fifth sponsor approved version	12 JUN 2023	5.0
Sixth sponsor approved version	17 AUG 2023	6.0
Seventh sponsor approved version	05 MAR 2024	7.0
Eighth sponsor approved version	16 SEP 2024	8.0

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

PROTOCOL UPDATE SUMMARY OF CHANGES

Update from protocol version 7.0 to 8.0

Update rationale

This amendment was prepared to include an update on timepoint prioritization for analysis of the secondary immunogenicity objective (geometric mean titers at 28 days after every IMP dose, geometric mean fold rises, and seroresponses), in order to focus analyses and expedite testing for Cohorts 1 to 4. In addition, CCI [redacted]

Description of changes

See the table below for a summary of the reasons for major changes compared to the previous version. Minor editorial changes, such as the correction of typing errors, are not specifically listed here.

Section	Reason for change
Protocol update summary of changes	Addition of section after the title page that summarizes the latest protocol update
1.1	Updates including to reflect the updated timepoints of analysis for the secondary objective and CCI [redacted] for Cohorts 1 to 4 and clarification on the approval status of the BNT162b2 (OMI XBB.1.5) vaccine in the US
1.1 and 2.2	Updates for clarifications on the BNT162b2 Monovalent (OMI XBB.1.5) vaccine approval status and updated COVID-19 vaccine recommendations
1.1 and 13.6	Insertions for CCI [redacted] CCI [redacted] study in an exploratory endpoint CCI [redacted]
2.1.1	Insertion to include updated SARS-CoV-2 lineage information
2.3.2	Deletion for clarification on the BNT162b2 Monovalent (OMI XBB.1.5) approval status
3	Updates including clarifications and to reflect the updated timepoints of analysis for the secondary objective CCI [redacted] for Cohorts 1 to 4
8.7	Updates including to reflect the updated timepoints of analysis for the secondary objective and CCI [redacted] for Cohorts 1 to 4
8.7.1	Insertion to include CCI [redacted] as exploratory research
9.4.2	Updates for clarification, including to reflect that reactogenicity data may be collected from AEs in the CRF in addition to the e-diary

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

1 PROTOCOL SUMMARY

1.1 Synopsis

Trial title

An exploratory Phase I, randomized, observer-blind, active-controlled, dose-escalation trial evaluating the safety, tolerability, and immunogenicity of an investigational RNA-based SARS-CoV-2 vaccine in COVID-19 vaccine experienced healthy adults

Trial rationale

Vaccines targeting the spike glycoprotein (S protein) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been used as a mitigation strategy of the Coronavirus disease 2019 (COVID-19) pandemic. BNT162b2 has received authorization for emergency supply, conditional marketing authorization, and/or full authorization in more than 100 countries globally under the tradename "COMIRNATY" for the prevention of COVID-19 caused by SARS-CoV-2. BNT162b2, a N1-methylpseudouridine-nucleoside-modified RNA encoding the S protein that is encapsulated in lipid nanoparticles (LNPs), has demonstrated potent immunogenicity, high vaccine efficacy, and a favorable safety profile in Phase I//II/III trials, as well as in real world usage. Considering the increase in the number of variants of concern (VOCs), as well as the number of new mutations in the S protein in these variants, a long term and durable immune response targeting conserved viral epitopes could help protect individuals from severe symptoms caused by emergent VOCs.

The value of T-cell responses against non-spike proteins has been emphasized by the rise of more antigenically diverse VOCs (e.g., Omicron sublineages, such as BA.1, BA.2, BA.4, BA.5, and XBB), which can avoid neutralization via mutations to the S protein. However, the rate of mutations in non-spike proteins is much lower than the mutation rate observed in the S protein. Epitopes eliciting potent T-cell responses have been reported to be largely variant-independent.

Based on the rationale of targeting conserved epitopes from multiple viral proteins that elicit potent T-cell responses, BioNTech is evaluating a vaccine candidate, BNT162b4, aimed at enhancing the breadth of T-cell responses and the protective capacity of spike-based vaccines, especially against severe disease and future VOCs.

BNT162b4 uses the same modRNA platform, processes, and LNP formulation as BNT162b2, with the RNA components comprising a single RNA encoding segments of the nucleocapsid and membrane proteins, as well as short segments containing CCI [redacted] CCI [redacted]

In this trial, BNT162b4 will either be combined with two selected spike-based RNA vaccines, i.e., BNT162b2 Bivalent (WT/OMI BA.4/BA.5), hereinafter referred to as "BNT162b2 Bivalent", and BNT162b2 Monovalent (OMI XBB.1.5), or given alone.

- BNT162b4 will be combined with BNT162b2 Bivalent for Doses 1 and 2 for Cohorts 1 and 2, and Dose 1 for Cohorts 3a, 3b, 4a, and 4b.
- BNT162b4 will be combined with BNT162b2 Monovalent (OMI XBB.1.5) for Dose 2 in Cohorts 3a, 3b, 4a and 4b.
- BNT162b4 alone will be given for Dose 1 and Dose 2 in Cohort 5.

BNT162b2 Bivalent is a BNT162b2-based vaccine with an RNA encoding the ancestral strain of the virus S protein in combination with an RNA encoding the S protein of the Omicron BA.4/BA.5 variant. BNT162b2 Bivalent uses the same modRNA platform, processes, and LNP formulation as licensed BNT162b2.

BNT162b2 Monovalent (OMI XBB.1.5) is a BNT162b2-based vaccine with an RNA encoding the S protein of the XBB.1.5 variant, a sub-lineage of Omicron XBB. BNT162b2 Monovalent (OMI XBB.1.5) uses the same modRNA platform, processes, and LNP formulation as licensed BNT162b2. Marketing approval of the BNT162b2 Monovalent (OMI XBB.1.5) vaccine has been granted. The supplemental biological license application for the BNT162b2 Monovalent (OMI XBB.1.5) vaccine was approved in the US on 11 SEP 2023.

The combination of BNT162b4 and BNT162b2 Bivalent or BNT162b2 Monovalent (OMI XBB.1.5) is intended to improve the protective capacity of spike-based vaccines, especially against severe disease, to make the protection less dependent on virus variants and to have durable T cells protective immunity. The addition of BNT162b2 Monovalent (OMI XBB.1.5) added to BNT162b4, is intended to address the most recent recommendations by World Health Organization (WHO) and is endorsed by the United States Food and Drug Administration (US FDA) for additional protection against the most widely circulating variant lineage XBB. The use of BNT162b4 alone is intended to characterize the induced T-cell immune response independent of spike co-administration.

Objectives, estimands and endpoints – Cohorts 1 to 4

OBJECTIVES	ESTIMAND *	ENDPOINTS
Primary objectives		
To describe the safety and tolerability of one and two doses of BNT162b4 + BNT162b2 Bivalent, one dose of BNT162b4 + BNT162b2 Monovalent (OMI XBB.1.5) as a booster, or one dose of BNT162b2 Bivalent alone at each applicable DL in healthy adults aged 18 years and older, with and without evidence of prior SARS-CoV-2 infection who previously received at least three prior doses of an authorized RNA-based COVID-19 vaccine.	For each DL cohort, the frequency of dosed subjects with: • Solicited local reactions at the injection site recorded up to 7 d after every IMP dose. • Solicited systemic events recorded up to 7 d after every IMP dose. • Subjects with at least one AE occurring up to 28 d after every IMP dose. • Subjects with at least one SAE occurring up to 6 months after every IMP dose.	• Solicited local reactions (pain, erythema / redness, induration / swelling) • Solicited systemic events (vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills and fever) • AEs • SAEs
	For each DL cohort, the percentage of dosed subjects with: • Abnormal hematology or chemistry laboratory values 3 d (Dose 1 sentinel group only) and 7 d after every IMP dose. • Grading shifts in hematology or chemistry laboratory assessments between baseline and 3 d (Dose 1 sentinel group only) and 7 d after every IMP dose.	• Hematology and chemistry laboratory parameters (see Section 10.3)
	For each DL cohort, the percentage of dosed subjects with: • New ECG abnormalities 3 d (Dose 1 sentinel group only) and 7 d after every IMP dose.	• ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in the protocol

OBJECTIVES	ESTIMAND *	ENDPOINTS
Secondary objectives		
To describe the humoral immune responses elicited by one and two doses of BNT162b4 + BNT162b2 Bivalent, one dose of BNT162b4 + BNT162b2 Monovalent (OMI XBB.1.5) as a booster, or one dose of BNT162b2 Bivalent alone at each applicable DL in healthy adults aged 18 years and older, with and without evidence of prior SARS-CoV-2 infection, who received at least three prior doses of an authorized RNA-based COVID-19 vaccine.	<u>For each DL cohort:</u> • GMTs at baseline and 28 d after every IMP dose. • GMFRs from baseline (pre-Dose 1) to 28 d after every IMP dose. • Percentages of subjects with seroresponse at 28 d after every IMP dose.	• SARS-CoV-2 ancestral strain neutralizing titers • SARS-CoV-2 Omicron neutralizing titers (viral strains matching the antigen encoded by BNT162b2)
Exploratory objectives		
CCI [redacted]		

Abbreviations: AE = adverse event; CCI [redacted]
CCI [redacted] COVID-19 = coronavirus disease 2019; d = day; DL = dose level; ECG = electrocardiogram; CCI [redacted]
CCI [redacted] GMFR = geometric mean fold rises; GMT = geometric mean titer; CCI [redacted]

CCI IMP = investigational medicinal product; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; CCI

* All assessments as described in the estimands will be conducted within the schedule of visits window.

Objectives, estimands and endpoints – Cohort 5

OBJECTIVES	ESTIMAND *	ENDPOINTS
Primary objectives		
To describe the safety and tolerability of two doses of 30 µg BNT162b4 alone in healthy adults aged 18 to 55 years, with and without evidence of prior SARS-CoV-2 infection, who received at least three prior doses of an authorized RNA-based COVID-19 vaccine.	The frequency of dosed subjects with: • Solicited local reactions at the injection site recorded up to 7 d after each IMP dose. • Solicited systemic events recorded up to 7 d after each IMP dose. • Subjects with at least one AE occurring up to 28 d after each IMP dose. • Subjects with at least one SAE occurring up to 3 months after last dose.	• Solicited local reactions (pain, erythema / redness, induration / swelling) • Solicited systemic events (vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills and fever) • AEs • SAEs
	The frequency of dosed subjects with: • Abnormal hematology or chemistry laboratory values 7 d after each IMP dose. • Grading shifts in hematology or chemistry laboratory assessments between baseline and 7 d after each IMP dose.	• Hematology and chemistry laboratory parameters (see Section 10.3)
	The frequency of dosed subjects with: • New ECG abnormalities 7 d after each IMP dose.	• ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in the protocol
Exploratory objectives		
CCI [redacted]		

OBJECTIVES	ESTIMAND *	ENDPOINTS
CCI		

Abbreviations: AE = adverse event; CCI COVID-19 = coronavirus disease 2019; d = day; ECG = electrocardiogram; CCI GMT = geometric mean titer; CCI IMP = investigational medicinal product CCI SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; CCI

* All assessments as described in the estimands will be conducted within the schedule of visits window.

Overall design

This is an exploratory Phase I, randomized, observer-blind, active-controlled, dose-escalation trial to evaluate four dose levels (DLs) of BNT162b4 given in combination with BNT162b2 Bivalent to select a safe and tolerable dose and to evaluate BNT162b4 + BNT162b2 Bivalent when given as Dose 1 and Dose 2 (booster) in Cohorts 1 and 2 and BNT162b4 + BNT162b2 Monovalent (OMI XBB.1.5) when given as Dose 2 (booster) in Cohorts 3a, 3b, 4a, and 4b, and 30 µg BNT162b4 when given alone as Dose 1 and Dose 2 in Cohort 5.

For flow diagram summaries of the trial, see Section 1.2. For the planned assessments and visits, see the schedules of activities (SoAs) in Section 1.3 and Section 13.5.

In total, up to ~380 healthy subjects aged 18 years (yrs) and older will be enrolled: up to 60 in each of Cohorts 1, 2, 3a, 3b, 4a, and 4b and ~20 in Cohort 5. For the trial populations (including the planned number of subjects per cohort), dosing regimens, and blinding in Cohorts 1 to 5, see Table 2.

Randomization for enrollment in Cohorts 1, 2, and 3a will be stratified based on N-binding antibody status and CCI

CCI

Randomization for enrollment in Cohort 3b will be stratified based on age and N-binding antibody status. Randomization for enrollment in Cohort 4b will be stratified based on age only. All subjects enrolled in Cohorts 4a and 4b, and all subjects giving consent for Dose 2 will be eligible CCI CCI Cohorts 1 to 4 are observer-blind and randomized; Cohort 5 is single arm and open-label.

To minimize heterogeneity between DL cohorts with regard to the baseline N-binding antibody status of subjects in Cohorts 1, 2, 3a, and 3b, the following subject distribution is planned for each DL cohort when possible: approximately 1/3 N-binding antibody negative subjects and 2/3 N-binding antibody positive subjects. However, this distribution can be modified based on the existing prevalence of N-binding antibody negative subjects or operational needs.

Subjects screened to the specific DL cohorts, but not enrolled due to reached N-binding subject distribution rate, will be allowed to be enrolled into the next cohort. Safety laboratory tests (except viral screening) will need to be repeated if performed >28 days (d) prior to the planned IMP vaccination day.

In addition, depending upon the observed safety and immunogenicity data, the sponsor may update Cohorts 1 to 4 to evaluate higher or additional DLs of BNT162b4 in combination with the selected spike-encoding RNA vaccine BNT162b2 Bivalent or BNT162b2 Monovalent (OMI XBB.1.5).

An Internal Review Committee (IRC) will be established and maintained for the entire trial to periodically review subject safety data and make decisions about dose escalations (for details about the IRC, see Section 10.1.5).

The staggered dosing process for Cohorts 1 to 4

The trial will use a staggered dosing process schema with sentinel subjects in Cohorts 1, 2, 3a, and 4a (see Figure 1).

The trial will be initiated with Cohort 1 where eight sentinel subjects will be randomized 3:1 to receive one dose of either BNT162b2 Bivalent + BNT162b4 or control BNT162b2 Bivalent followed by IRC review of 7 d post-Dose 1 data.

If the IRC considers the shown tolerability to be acceptable and no stopping/pausing rules are met, 52 additional trial subjects (expansion group) will be randomized 3:1 to the BNT162b2 Bivalent + BNT162b4 or control group BNT162b2 Bivalent (one dose). Following dosing of the expansion group (7 d post-Dose 1), all available clinical, laboratory and other relevant data from these 60 trial subjects (full cohort) will be reviewed by the IRC. If the IRC considers the shown tolerability is acceptable and no stopping/pausing rules are met for Cohort 1, enrollment will be opened for Cohort 2. Cohort 2 will follow the same dose escalation/assessment process. For a graphical depiction of the staggered dosing process for Cohorts 1 to 4, see Figure 1.

If the IRC considers the shown tolerability acceptable and no stopping/pausing rules are met for Cohort 2 (for the stopping/pausing rules, see Section 7.1), enrollment will be opened for Cohorts 3a and 3b which will follow the same dose escalation/assessment process as for Cohorts 1 and 2 with the following exception: enrollment for the Cohort 3b will be opened after 7 d post-dose data for Cohort 3a sentinel subjects has been reviewed by the IRC and approval is granted. There will be a safety review of 7 d post-dose data for the first 8 subjects in Cohort 3b. In addition to safety data being reviewed on an ongoing basis by investigators and sponsor, 7 d post-dose data for Cohort 3a expansion subjects and Cohort 3b subjects will be reviewed by the IRC.

If the IRC considers the shown tolerability acceptable and no stopping/pausing rules are met for Cohorts 3a and 3b (for the stopping/pausing rules, see Section 7.1), enrollment will be opened for Cohorts 4a and 4b which will follow the same IRC review process as for Cohorts 3a and 3b. In addition to safety data being reviewed on an ongoing basis by investigators and sponsor, 7 d post-dose data for Cohort 4a expansion subjects and Cohort 4b subjects will be reviewed by the IRC.

Dose escalation decisions to progress to the next DL and DL modifications (i.e., dropping the DL to the previous acceptable DL or to an ‘in-between’ DL) will be confirmed by the IRC. Dose escalation will only continue if the safety and tolerability of the previous DL was considered acceptable by the IRC and no stopping/pausing rules were met.

In addition to the above safety reviews for dose modifications, other unplanned dose modifications, pausing (temporary halting) of trial treatment, or discontinuation of trial treatment may be required. See Section 7.1 for guidance on criteria for such cases.

For Dose 2 recipients, IRC safety review will be performed for the first 8 subjects 7 d post-Dose 2 in all DL cohorts (see Table 1).

Based on the WHO’s recommendation, which has been endorsed by the FDA, and the FDA approval of BNT162b2 Monovalent (OMI XBB.1.5), Dose 2 for Cohorts 1 to 4 will be provided in line with current agency recommendations when available in the US. This will provide standard of care for vaccinees and carries a proven benefit for the current circulating XBB subvariants.

The dosing process for Cohort 5

For the dosing process schema for Cohort 5, see Figure 2. Cohort 5 trial subjects will not be randomized and will be administered two doses of 30 µg BNT162b4 alone. An IRC safety review will be performed after all subjects receive Dose 2 (see Table 1).

Table 1: Schedule of IRC and safety reviews

Dose 1	**Cohort 1**	**Cohort 2**	**Cohort 3a**	**Cohort 3b**	**Cohort 4a**	**Cohort 4b**	**Cohort 5**
IRC contingent review (Gated) *	First 8 sentinel 7 d PD1 review approval needed prior to cohort expansion	First 8 sentinel 7 d PD1 review approval needed prior to cohort expansion	First 8 sentinel 7 d PD1 review approval needed prior to cohort expansion and enrollment of Cohort 3b		First 8 sentinel 7 d PD1 review approval needed prior to cohort expansion and enrollment of Cohort 4b		
IRC contingent review (Gated) *	Cohort 7 d PD1 review / approval needed prior to DL increase	Cohort 7 d PD1 review / approval needed prior to DL increase		Cohort 7 d PD1 review / approval needed prior to DL increase			
IRC safety review (Non-Gated) **				First 8 subjects 7 d PD1 reviewed		First 8 subjects 7 d PD1 reviewed	
Dose 2	**Cohort 1**	**Cohort 2**	**Cohort 3a**	**Cohort 3b**	**Cohort 4a**	**Cohort 4b**	**Cohort 5**
IRC safety review (Non-Gated) **	First 8 subjects 7 d PD2	First 8 subjects 7 d PD2	First 8 subjects 7 d PD2		First 8 subjects 7 d PD2		All Cohort 5 subject data up to 7 d PD2 reviewed

* Gated review: trial dosing is paused until IRC approves.

** Non-Gated review: trial dosing is not paused while awaiting IRC approval.

Abbreviations: d = day; DL = dose level; IRC = Internal Review Committee; PD1 = post-Dose 1; PD2 = post-Dose 2.

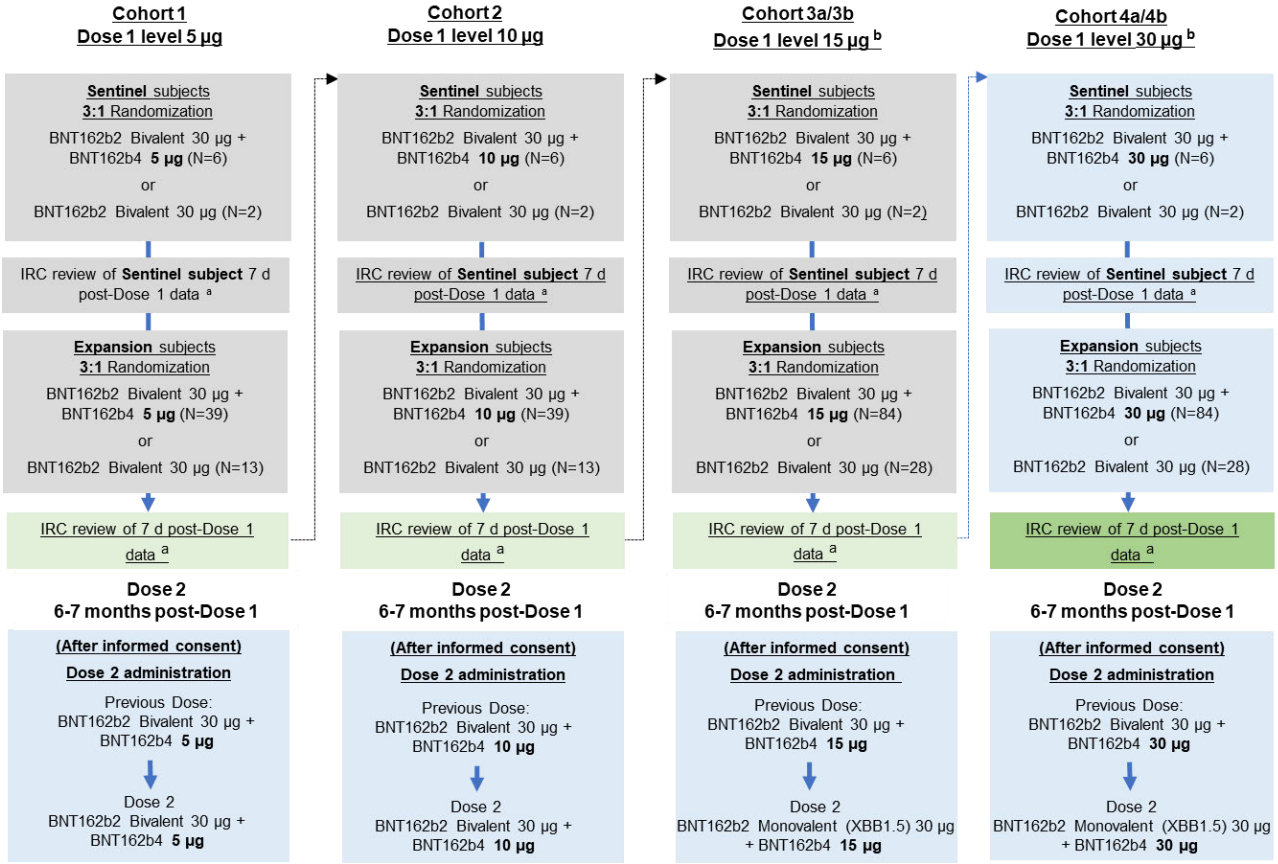

Figure 1: The staggered dosing process for Cohorts 1 to 4

a. Further dosing of subjects or opening of new cohorts will proceed if acceptable tolerability is shown and no stopping/pausing rules are met.

b. Enrollment for Cohort 3b and 4b will be opened after 7 d post-dose data for Cohort 3a and 4a (respectively) sentinel subjects have been reviewed by the IRC and approval for progression is granted.

Abbreviations: d = day(s); IRC = Internal Review Committee; N = number of subjects.

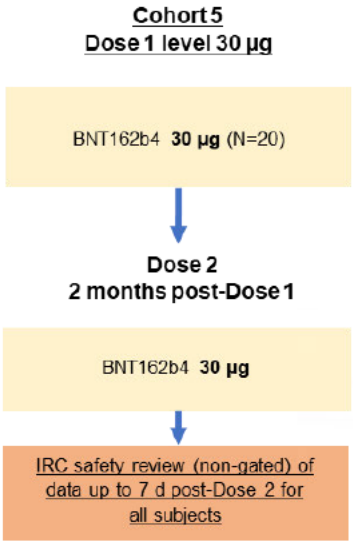

Figure 2: The dosing process for Cohort 5

Abbreviations: d = day(s); IRC = Internal Review Committee; N = number of subjects.

Trial treatments

IMP name	BNT162b4	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) referred to as "BNT162b2 Bivalent"	BNT162b2 Monovalent (OMI XBB.1.5)
Type	Investigational. Nucleoside-modified RNA vaccine which encodes non-spike protein antigens from SARS-CoV-2 (i.e., nucleocapsid protein, membrane protein CCI [redacted] CCI	Investigational and active comparator. Nucleoside-modified RNA vaccine which encodes spike protein antigens from SARS-CoV-2. BNT162b2 Bivalent is supplied as a co-formulated drug product of BNT162b2 Wild Type and BNT162b2 OMICRON [B.1.1.529 sublineages BA.4/BA.5] in a single vial.	Investigational. Nucleoside-modified RNA vaccine which encodes spike protein antigen from SARS-CoV-2. BNT162b2 Monovalent (OMI XBB.1.5) is supplied in a single vial.
Dose levels	5 µg, 10 µg, 15 µg, 30 µg	30 µg (15 µg BNT162b2 + 15 µg BNT162b2 OMI BA.4/BA.5)	30 µg
Allocation to IMP	Trial subjects in Cohorts 1 to 4 who receive BNT162b4 in combination with a BNT162b2-based vaccine will be randomized using an online randomization tool. Trial subjects in single arm Cohort 5 who are assigned to receive BNT162b4 alone in an unblinded fashion without a control/placebo group.	Trial subjects will be randomized using an online randomization tool. Randomization 3:1 for all cohorts: to BNT162b4 + BNT162b2 Bivalent: BNT162b2 Bivalent.	Trial subjects will receive BNT162b2 Monovalent (XBB.1.5) in an unblinded fashion without a control/placebo group (non-randomized).

Route of administration	Intramuscular injection in the mid-deltoid muscle of the non-dominant arm. For "BNT162b4 + BNT162b2 Bivalent" administration, BNT162b4 plus BNT162b2 Bivalent will be co-administered as a single injection. BNT162b4 alone will be administered as a single injection. For details regarding IMP preparation for administration, see the Pharmacy Manual.	Intramuscular injection in the mid-deltoid muscle of the non-dominant arm. For administration, BNT162b4 plus BNT162b2 Monovalent (OMI XBB.1.5) will be co-administered as a single injection. For details regarding IMP preparation for co-administration, see the Pharmacy Manual.
Vaccination schedules	IMP will be administered on Day 1 (Dose 1) and, for treatment groups administered BNT162b4 + BNT162b2 Bivalent: again 6 to 7 months after Day 1 (for Dose 2), or BNT162b4 + BNT162b2 Monovalent (OMI XBB.1.5): 6 to 7 months after Day 1 (for Dose 2), or BNT162b4 alone: 2 months after Day 1 (for Dose 2).	

Abbreviations: IMP = investigational medicinal product; OMI = Omicron [redacted]
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WT = Wild Type.

Statistics

Because of the exploratory nature of the trial, no formal sample size calculation will be performed. The chosen sample size per cohort allows, (i) detection of the most frequent systemic and local adverse events (AEs) thereby allowing dose escalation decisions, and (ii) immunogenicity analyses of sufficient scope to support dose selection decisions and the trial objectives, while minimizing the number of trial subjects exposed to the investigational trial treatment.

Trial population

This trial will enroll healthy volunteers aged 18 yrs and older, who have been previously vaccinated with at least three doses of any authorized COVID-19 RNA vaccine (the last COVID-19 RNA vaccine dose must have been administered at least 90 d before Visit 1). Subjects who have had SARS-CoV-2 infection 60 d or more prior to randomization are not excluded from the trial. All subjects must meet the eligibility criteria listed in Section 5 for Cohort 1 to 4 or Section 13.7 for Cohort 5.

Trial duration

The planned trial duration for each trial subject in Cohorts 1 to 4 who receives only one dose of IMP is up to ~7 months (up to ~1 month [28 d] screening and ~6 months follow-up after Dose 1 of IMP). The planned trial duration for each trial subject in Cohorts 1 to 4 who receives two doses of IMP is up to ~13 months (up to ~1 month [28 d] screening and ~6 months follow-up after Dose 1 of IMP, plus ~6 months follow-up after Dose 2 of IMP). The planned trial duration for each trial subject in Cohort 5 who receives two doses of IMP is up to ~6 months (up to ~1 month [28 d] screening and ~3 months follow-up after Dose 2 of IMP).

Number of trial subjects

Table 2: Number of trial subjects per trial treatment (total number of subjects enrolled = ~380)

Trial treatment – Dose 1 (Visit 1) [c]	Trial treatment – Dose 2 [d]	Number of trial subjects	Randomization ratio to treatment groups
Cohort 1 – Sentinel subjects aged 18-55 yrs	***Cohort 1 – Sentinel subjects aged 18-55 yrs***		
• BNT162b2 Bivalent 30 µg + BNT162b4 5 µg **or** • BNT162b2 Bivalent 30 µg (one dose)	• BNT162b2 Bivalent 30 µg + BNT162b4 5 µg [a]	6 2	3:1
Cohort 1 – Expansion subjects aged 18-55 yrs	***Cohort 1 – Expansion subjects aged 18-55 yrs***		
• BNT162b2 Bivalent 30 µg + BNT162b4 5 µg **or** • BNT162b2 Bivalent 30 µg (one dose)	• BNT162b2 Bivalent 30 µg + BNT162b4 5 µg [a]	39 13	3:1
Cohort 2 – Sentinel subjects aged 18-55 yrs	***Cohort 2 – Sentinel subjects aged 18-55 yrs***		
• BNT162b2 Bivalent 30 µg + BNT162b4 10 µg **or** • BNT162b2 Bivalent 30 µg	• BNT162b2 Bivalent 30 µg + BNT162b4 10 µg [a]	6 2	3:1
Cohort 2 – Expansion subjects aged 18-55 yrs	***Cohort 2 – Expansion subjects aged 18-55 yrs***		
• BNT162b2 Bivalent 30 µg + BNT162b4 10 µg **or** • BNT162b2 Bivalent 30 µg	• BNT162b2 Bivalent 30 µg + BNT162b4 10 µg [a]	39 13	3:1
Cohort 3a – Sentinel subjects aged 18-55 yrs	***Cohort 3a – Sentinel subjects aged 18-55 yrs***		
• BNT162b2 Bivalent 30 µg + BNT162b4 15 µg **or** • BNT162b2 Bivalent 30 µg	• BNT162b2 Monovalent (OMI XBB.1.5) 30 µg + BNT162b4 15 µg	6 2	3:1
Cohort 3a – Expansion subjects aged 18-55 yrs	***Cohort 3a – Expansion subjects aged 18-55 yrs***		
• BNT162b2 Bivalent 30 µg + BNT162b4 15 µg **or**	• BNT162b2 Monovalent (OMI XBB.1.5) 30 µg + BNT162b4 15 µg	39	3:1

Trial treatment – Dose 1 (Visit 1) [c]	Trial treatment – Dose 2 [d]	Number of trial subjects	Randomization ratio to treatment groups
• BNT162b2 Bivalent 30 µg		13	
Cohort 3b – Subjects aged >55 yrs [b]	***Cohort 3b – Subjects aged >55 yrs*** [b]		
• BNT162b2 Bivalent 30 µg + BNT162b4 15 µg **or** • BNT162b2 Bivalent 30 µg	• BNT162b2 Monovalent (OMI XBB.1.5) 30 µg + BNT162b4 15 µg	45 15	3:1
Cohort 4a – Sentinel subjects aged 18-55 yrs	***Cohort 4a – Sentinel subjects aged 18-55 yrs***		
• BNT162b2 Bivalent 30 µg + BNT162b4 30 µg **or** • BNT162b2 Bivalent 30 µg	• BNT162b2 Monovalent (OMI XBB.1.5) 30 µg + BNT162b4 30 µg	6 2	3:1
Cohort 4a – Expansion subjects aged 18-55 yrs	***Cohort 4a – Expansion subjects aged 18-55 yrs***		
• BNT162b2 Bivalent 30 µg + BNT162b4 30 µg **or** • BNT162b2 Bivalent 30 µg (one dose)	• BNT162b2 Monovalent (OMI XBB.1.5) 30 µg + BNT162b4 30 µg	39 13	3:1
Cohort 4b – Subjects aged >55 yrs [b]	***Cohort 4b – Subjects aged >55 yrs*** [b]		
• BNT162b2 Bivalent 30 µg + BNT162b4 30 µg **or** • BNT162b2 Bivalent 30 µg (one dose)	• BNT162b2 Monovalent (OMI XBB.1.5) 30 µg + BNT162b4 30 µg	45 15	3:1
Cohort 5 – Subjects aged 18-55 yrs	***Cohort 5 – Subjects aged 18-55 yrs***		
• BNT162b4 30 µg	• BNT162b4 30 µg	20	Not applicable

a) If the subject consents to a second dose of IMP as implemented using protocol version 5.0.
b) In Cohorts 3b and 4b, the age group distribution enrolled will be ~60% of subjects aged ≥65 yrs and ~40% of subjects aged >55 to <65 yrs.
c) Dose 1 is given observer-blind for Cohorts 1 to 4 and open-label for Cohort 5.
d) Dose 2 is given open-label for Cohorts 1 to 5. For Cohorts 1 to 4, Dose 2 is at 6 to 7 months post-Dose 1. For Cohort 5, Dose 2 is at 2 months post-Dose 1.

1.2 Schema of the trial (graphical representations of the trial)

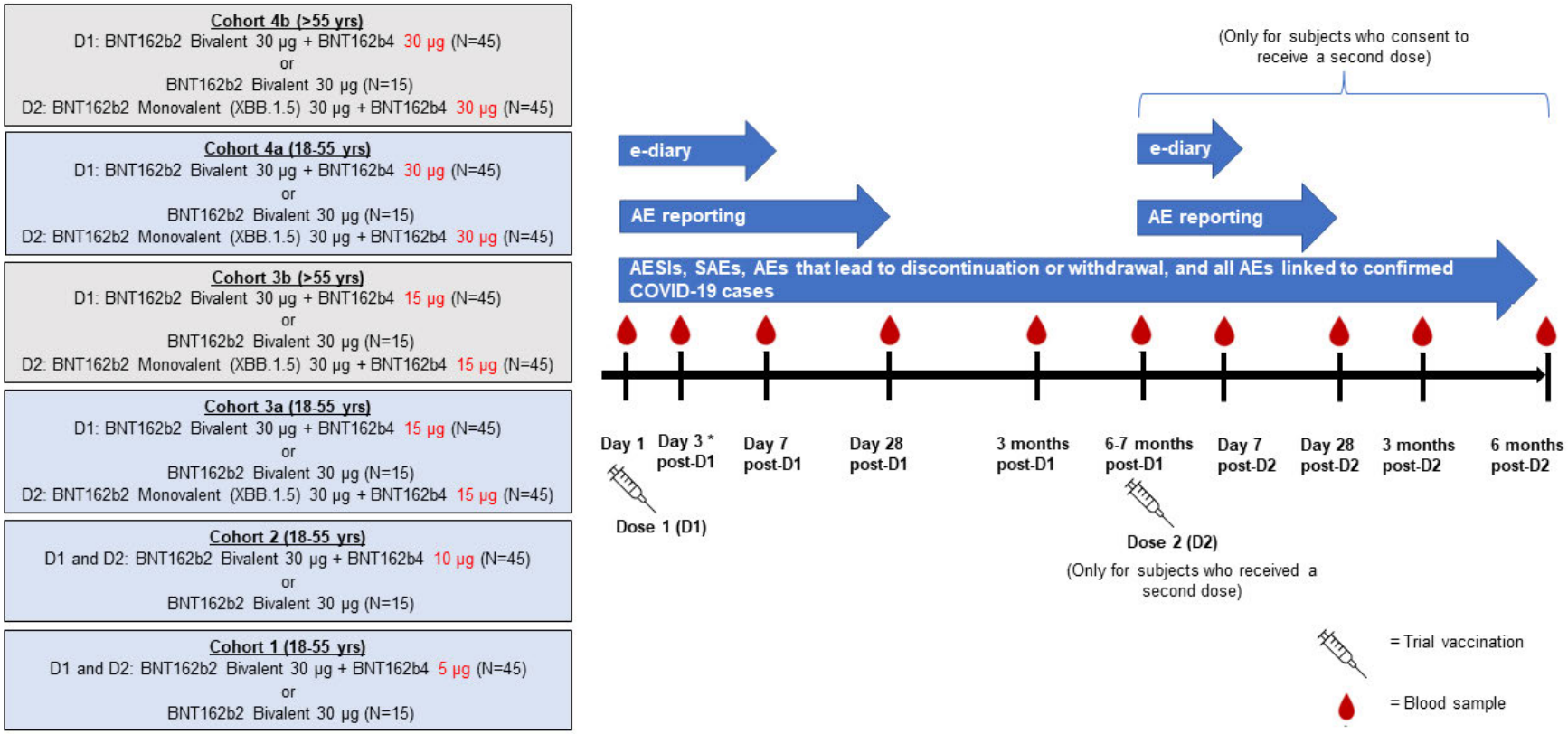

Figure 3: Schema for Cohorts 1 to 4

Abbreviations: * = sentinel subjects only; AE = adverse event; AESI = adverse event of special interest; COVID-19 = Coronavirus disease 2019; D1, D2 = dose 1, dose 2; N = number of subjects; SAE = serious adverse event; yrs = years.

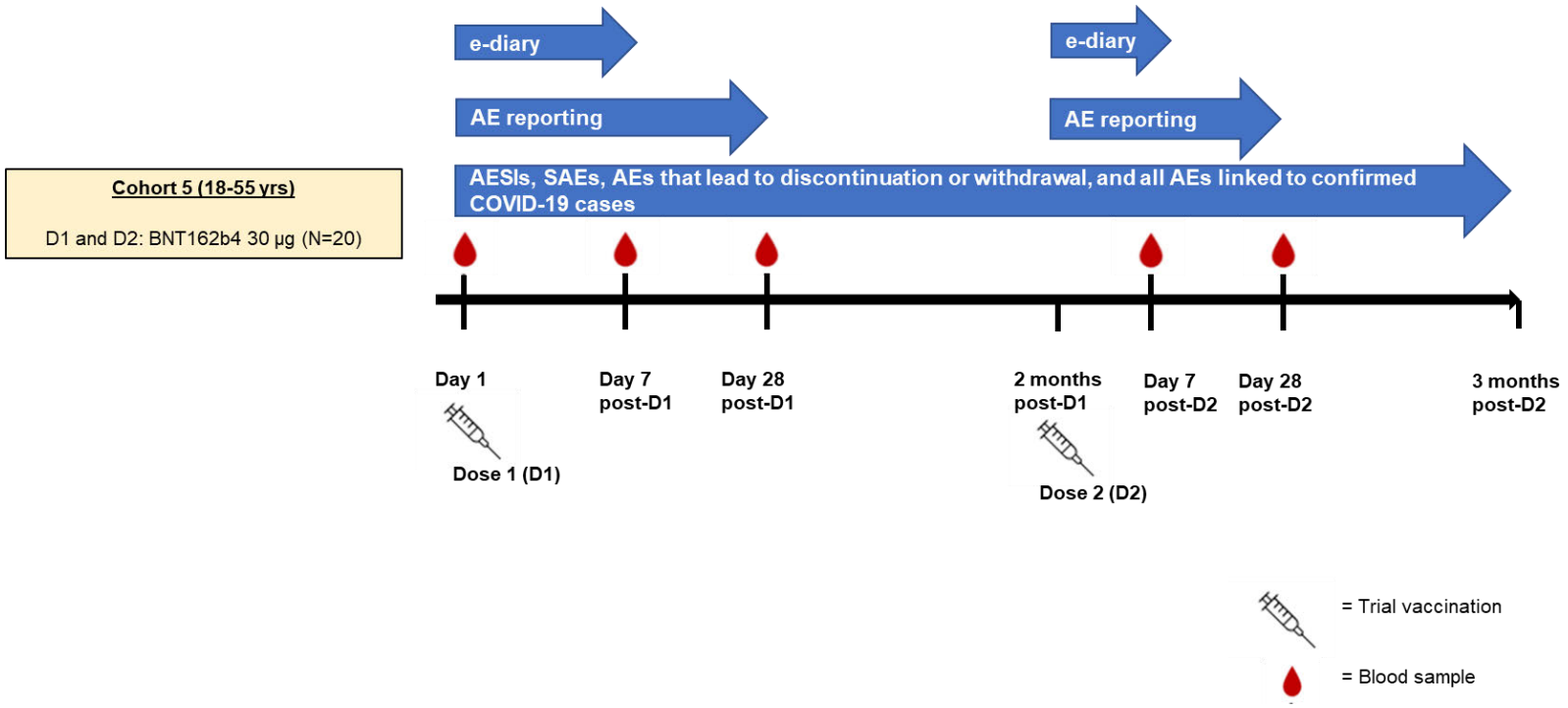

Figure 4: Schema for Cohort 5

Abbreviations: AE = adverse event; AESI = adverse event of special interest; COVID-19 = Coronavirus disease 2019; D1, D2 = dose 1, dose 2; N = number of subjects; SAE = serious adverse event; yrs = years.

1.3 Schedule of activities

The SoAs provide an overview of the trial visits and procedures. The investigator may conduct 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.

If, for any reason, subjects are permanently discontinued from the trial before completing all scheduled visits, if possible trial subjects should complete all assessments planned for the Early Termination Visit.

For the SoA for Cohort 5, see Section 13.5.

For Cohorts 1 to 4, Visit 0 to Visit 6 apply for all subjects, Visit 7 to Visit 11 only apply for subjects who consent to a second dose of IMP after issue of protocol version 5.0.

Table 3: Schedule of activities – Cohorts 1 to 4

Activity	Visit 0 (V0)	V1	V1	V2 [o]	V3	V4	V5	V6 [p]	V7 [p]	V8	V9	V10	V11	Early term. Visit	Unsche-duled [l]
Visit description	Screening at ≤28 d pre-V1	Pre-dose	Dose 1 (D1)	3 d post-D1	7 d post-D1	28 d post-D1	3 m FU post-D1	6 m FU post-D1	Dose 2 (6 to 7 m post-D1)	7 d post-D2	28 d post-D2	3 m FU post-D2	6 m FU post-D2		Potential COVID-19 Illness Visit
Days relative to Dose 1	N/A	1	1	3	8	29	90	180						N/A	N/A
Permitted visit window				+2 d	+2 d	±3 d	±7 d	-10 d to +30 d	+30 d post-V6	+2 d from 7 d post-D2	±3 d from 28 d post-D2	±7 d from 3 m post-D2	±10 d from 6 m post-D2		
Obtain informed consent	X						X	X	X [q, s]						
Inclusion / exclusion criteria	X	X (review)						X (re-confirm)	X [t] (re-confirm)						
Medical history incl. prior medication and COVID-19 vaccinations / SARS-CoV-2 infections	X	X (update)						X (change from V0)	X [s, t] (change from V0)						
Physical examination	X	X [a]		X [a]	X [a]	X [a]	X [a]	X [a]	X [a, s, t]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]
Height & body weight	X														

Activity	Visit 0 (V0)	V1	V1	V2 [o]	V3	V4	V5	V6 [p]	V7 [p]	V8	V9	V10	V11	Early term. Visit	Unsche-duled [l]
Visit description	**Screening at ≤28 d pre-V1**	**Pre-dose**	**Dose 1 (D1)**	**3 d post-D1**	**7 d post-D1**	**28 d post-D1**	**3 m FU post-D1**	**6 m FU post-D1**	**Dose 2 (6 to 7 m post-D1)**	**7 d post-D2**	**28 d post-D2**	**3 m FU post-D2**	**6 m FU post-D2**		**Potential COVID-19 Illness Visit**
Days relative to Dose 1	**N/A**	**1**	**1**	**3**	**8**	**29**	**90**	**180**						**N/A**	**N/A**
Permitted visit window				**+2 d**	**+2 d**	**±3 d**	**±7 d**	**-10 d to +30 d**	**+30 d post-V6**	**+2 d from 7 d post-D2**	**±3 d from 28 d post-D2**	**±7 d from 3 m post-D2**	**±10 d from 6 m post-D2**		
Vital signs [c]	X	X [b]	X [b]	X	X	X			X [b]	X	X				
12-lead ECG	X	X		X	X					X					
Urine sample for clinical laboratory [d]	X	X			X					X					
Blood draw for clinical laboratory [f]	X 15 mL	X 15 mL		X 15 mL	X 15 mL					X 15 mL					
Blood draw for viral screen [e]	X 5 mL														
Pregnancy test for VOCBP [g]	X	X				X		X	X [s, t]		X		X	X	
Counsel / remind subjects to use contraception		X		X	X				X [s]	X					
Record pregnancies		Start	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	End	End	
N-binding antibody test to detect prior SARS-CoV-2 infection	X [m] 5 mL														
Rapid antigen test for SARS-CoV-2 infection		X [m]													X

Activity	Visit 0 (V0)	V1	V1	V2 [o]	V3	V4	V5	V6 [p]	V7 [p]	V8	V9	V10	V11	Early term. Visit	Unsche-duled [l]
Visit description	Screening at ≤28 d pre-V1	Pre-dose	Dose 1 (D1)	3 d post-D1	7 d post-D1	28 d post-D1	3 m FU post-D1	6 m FU post-D1	Dose 2 (6 to 7 m post-D1)	7 d post-D2	28 d post-D2	3 m FU post-D2	6 m FU post-D2		Potential COVID-19 Illness Visit
Days relative to Dose 1	N/A	1	1	3	8	29	90	180						N/A	N/A
Permitted visit window				+2 d	+2 d	±3 d	±7 d	-10 d to +30 d	+30 d post-V6	+2 d from 7 d post-D2	±3 d from 28 d post-D2	±7 d from 3 m post-D2	±10 d from 6 m post-D2		
Oral swabs for NAAT-based SARS-CoV-2 [v] testing and sequencing for surveillance (central test site)	X	X			X	X	X	X	X [t]	X	X	X	X	X	X
Oral swab for NAAT-based SARS-CoV-2 (local test site)	X [u]	X [u]													X
Allocate to trial treatment (Randomization)		X													
IMP administration			X						X [r]						
Unblind subjects who proceed to Dose 2							X	X (if not done at V5)	X (if not done at V5)						
Investigator assessment of reactogenicity for up to 1 h after IMP administration			X						X [s]						
Issue thermometer/confirm subjects still have thermometer		Issue							Confirm						
Blood draws for humoral response assessments [h]		X 20 mL			X 20 mL	X 20 mL	X 20 mL	X 20 mL	X [s, t] 20 mL	X 20 mL	X 20 mL	X 20 mL	X 20 mL	X 20 mL	X 20 mL

Activity	Visit 0 (V0)	V1	V1	V2 [o]	V3	V4	V5	V6 [p]	V7 [p]	V8	V9	V10	V11	Early term. Visit	Unsche-duled [l]
Visit description	Screening at ≤28 d pre-V1	Pre-dose	Dose 1 (D1)	3 d post-D1	7 d post-D1	28 d post-D1	3 m FU post-D1	6 m FU post-D1	Dose 2 (6 to 7 m post-D1)	7 d post-D2	28 d post-D2	3 m FU post-D2	6 m FU post-D2		Potential COVID-19 Illness Visit
Days relative to Dose 1	N/A	1	1	3	8	29	90	180						N/A	N/A
Permitted visit window				+2 d	+2 d	±3 d	±7 d	-10 d to +30 d	+30 d post-V6	+2 d from 7 d post-D2	±3 d from 28 d post-D2	±7 d from 3 m post-D2	±10 d from 6 m post-D2		
Issue, train, or collect subject e-diaries; remind subjects [i]		Issue, train		Remind					Remind	Collect				Collect	
Subjects report reactogenicity (incl. oral body temperature) daily for 7 d after each IMP dose using an e-diary [i]			Start after Dose 1	=>	End				Start after Dose 2	End				End	
Investigators review e-diary data daily			Start	=>	End				Start	End				End	X
Record AEs since last visit		X		X	X	X			X	X	X			X	X
Record SAEs and specific AEs types since last visit [j]		X		X	X	X	X	X	X	X	X	X	X	X	X
Record medical occurrences since just before Dose 1		X													
Record medication since last visit		X	X	X	X	X	X	X	X	X	X	X [k]	X [k]	X	X
CCI [redacted]															
CCI [redacted]															
CCI [redacted]															

Activity	Visit 0 (V0)	V1	V1	V2 [o]	V3	V4	V5	V6 [p]	V7 [p]	V8	V9	V10	V11	Early term. Visit	Unsche-duled [l]
Visit description	Screening at ≤28 d pre-V1	Pre-dose	Dose 1 (D1)	3 d post-D1	7 d post-D1	28 d post-D1	3 m FU post-D1	6 m FU post-D1	Dose 2 (6 to 7 m post-D1)	7 d post-D2	28 d post-D2	3 m FU post-D2	6 m FU post-D2		Potential COVID-19 Illness Visit
Days relative to Dose 1	N/A	1	1	3	8	29	90	180						N/A	N/A
Permitted visit window				+2 d	+2 d	±3 d	±7 d	-10 d to +30 d	+30 d post-V6	+2 d from 7 d post-D2	±3 d from 28 d post-D2	±7 d from 3 m post-D2	±10 d from 6 m post-D2		
Maximum total blood volume (mL) drawn per visit	25	175	0	15	170	155	155	155		170	155	155	155	155	65

a. Brief (symptom-directed) physical examination as indicated.
b. At 1 h (±15 minutes) before and after dosing.
c. Vital signs: systolic/diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature.
d. Dipstick urine analysis: For details of all assessed urine clinical laboratory parameters, see Section 10.3.
e. Viral screen: screen for human immunodeficiency virus (HIV)-1 and HIV-2, Hepatitis B, and Hepatitis C.
f. Clinical laboratory tests: Chemistry and hematology. Only in women who are not VOCBP (to confirm postmenopausal status): follicle stimulating hormone at Visit 0. Only for VOCBP: serum β-HCG at Visit 0. For details of all assessed blood clinical laboratory parameters, see Section 10.3.
g. In VOCBP: The serum β-HCG pregnancy test at Visit 0 will be performed using the sample collected for clinical laboratory tests. Before each dosing, urine pregnancy tests will be performed using a commercial kit at the site and the trial subjects will be counseled about the need for consistent and correct use of a highly effective method of contraception.
h. Leftover blood after completion of the assessments may be used for additional biomarker analyses and/or development of analytical methods.
i. Trial site personnel will remind the subjects to record the oral body temperature and the worst grade for each symptom in the e-diary at approximately the same time every evening on the day of IMP administration and then every day in the evening for a total of seven consecutive days. Ask/remind the subject to contact the site if they experience any severe or potentially life-threatening reactogenicity events. Trial site personnel will remind the subjects to record the use of antipyretic/analgesic medication to treat symptoms associated with IMP administration for 7 d after each IMP dose using the e-diary.
j. Only SAEs, adverse event(s) of special interest, AEs that lead to discontinuation or withdrawal, and AEs linked to confirmed COVID-19 cases will be recorded. SAEs must be recorded upon awareness.
k. For FU visits, only any prohibited medication (including SARS-CoV-2 non-trial vaccinations) will be recorded.
l. Optimally within 3 d after potential COVID-19 illness onset. All known NAAT-based SARS-CoV-2 positive subjects, from randomization until end of trial, will be asked for an additional unscheduled visit to define the COVID-19 illness as per Section 8.2.8. The COVID-19 illness visit will define the illness as either confirmed COVID-19, unconfirmed COVID-19, or confirmed severe COVID-19.
m. The results must be available prior to administration of trial treatment at Visit 1.
n. Blood samples for CCI assessment at "Potential COVID-19 Illness Visit" should only be collected if the visit occurs more than 2 months after the last IMP dose.
o. This visit will apply to sentinel subjects only.
p. Visit 6 and Visit 7 can (should ideally) occur on the same day.

q. Informed consent can be obtained for Dose 2 at either Visit 5, 6 or Visit 7.
r. Only for subjects that received BNT162b2 Bivalent + BNT162b4 for Dose 1 and who consented to a second (Dose 2).
s. To be completed before administration of Dose 2.
t. In case of a combined Visit 6+7 all assessments/samplings listed for both visits, only need to be done once. Blood draw for CCI assessments must be obtained prior to Dose 2.
u. Not for Cohorts 4a and 4b.
v. Obtained locally for central laboratory testing.

Notes

The total blood volume drawn over any 8-week period in any cohort will always be less than 550 mL. Additional blood samples may be taken, e.g., for safety assessments after AEs or SAEs. Assuming there are no unplanned visits, the total volume of blood drawn from each subject during trial participation will be up to ~1,860 mL.

Abbreviations: AE = adverse event; CCI COVID-19 = coronavirus disease 2019; d = day(s); D = dose; Early term. = early termination (visit); ECG = electrocardiogram; FU = follow-up (visit); h = hour(s); β-HCG = beta human chorionic gonadotropin; CCI IMP = investigational medicinal product; m = month(s); NAAT = nucleic acid amplification-based test; N/A = not applicable; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VOCBP = volunteers of childbearing potential.

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ABBREVIATIONS/TERMS

Abbreviation/Term	Explanation
~	Approximately
AE	Adverse event Note: All reactogenicity events derived from the subject e-diaries are solicited events. All AEs recorded by the investigator are unsolicited events.
AESI	Adverse event of special interest
CCI	[redacted]
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
d	Day(s)
DL	Dose level
ECG	Electrocardiogram
EDC	Electronic data capture (system)
EMA	European Medicines Agency
EU	European Union
FSH	Follicle stimulating hormone
h	Hour(s)
GCP	Good clinical practice
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IM	Intramuscular or intramuscularly
IMP	Investigational medicinal product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRC	Internal Review Committee
ISF	Investigator's site file
LNP	Lipid nanoparticle
NAAT	Nucleic acid amplification-based test
NCT	National Clinical Trial number
ORF	Open reading frame
CCI	[redacted]
PCR	Polymerase chain reaction
PT	Preferred term
RNA-LNP	RNA lipid nanoparticle

Abbreviation/Term	Explanation
SAE	Serious adverse event
S (protein)	Spike glycoprotein
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reaction
US FDA	United States Food and Drug Administration
VOC	Variant of concern
VOCBP	"Volunteers" of childbearing potential is used instead of "women" of childbearing potential to encompass all volunteers born female
WHO	World Health Organization
yr(s)	Year(s)

2 INTRODUCTION

2.1 Background

2.1.1 The medical need

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In February 2020, the virus was officially named SARS-CoV-2, and the WHO officially named the disease caused by SARS-CoV-2 as COVID-19. SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, and in March 2020, the WHO characterized the COVID-19 outbreak as a pandemic. To date, there have been >584 million confirmed cases of COVID-19 and >6.4 million have died, demonstrating an urgent need for efficacious vaccines (WHO Coronavirus [COVID-19] Dashboard, accessed 10 AUG 2022).

Numerous COVID-19 vaccines are currently in development globally, and several COVID-19 vaccines (e.g., RNA-based vaccines and adenovirus-vectored vaccines expressing the S protein) have been shown to be efficacious in the prevention of COVID-19 in clinical trials and are now available under emergency authorizations. For a list of such vaccines, see the WHO website “COVID-19 Vaccines with WHO Emergency Use Listing” at: (https://extranet.who.int/pqweb/vaccines/vaccinescovid-19-vaccine-eul-issued).

Recently a number of new SARS-CoV-2 viral variants has emerged with multiple mutations in the S protein. These variants might be associated with the lower efficacy of some of the current vaccines. Therefore, there is a need to continue research including new approaches to overcome waning immunity and/or the development of modified vaccines.

The SARS-CoV-2 Omicron variant continues its rapid evolution, with significant mutational changes noted in late 2022, resulting in a fast changing epidemiological landscape. This evolution has given rise to the XBB variants, derived from a recombination between Omicron BA.2.75 and BA.2.10.1.4-7 (European Centre for Disease Prevention and Control [ECDC] update).

At present, Omicron and its sublineages continue to cause most SARS-CoV-2 infections. Omicron XBB.1 descendent sublineages (i.e., XBB.1.5, XBB.1.16, XBB.1.9, JN.1) that predominate in the US and globally are more antigenically distant from prior Omicron strain sublineages (e.g., BA.1, BA.5); more so than the distance of these early Omicron sublineages from the ancestral Wuhan-Hu-1 strain. They also show the greatest magnitude of immune escape that has been observed to date.

2.1.2 Background to the trial treatments

Vaccines targeting the S protein of SARS-CoV-2 have been used as an important mitigation strategy of the COVID-19 pandemic. There are currently three vaccines, including BNT162b2, that target the S protein authorized or approved for use in the US. BNT162b2 includes a nucleoside-modified RNA encapsulated in RNA-LNP, whereby the RNA encodes the stabilized trimeric wild type S protein. BNT162b2 has been granted emergency use authorization (EUA) for individuals 6 months of age and above (Pfizer/BioNTech COVID-19 Vaccine), and has been licensed for individuals 16 yrs of age

and above (COMIRNATY [COVID-19 Vaccine, mRNA]) for the prevention of severe symptoms of COVID-19 caused by SARS-CoV-2.

BNT162b2 has demonstrated potent immunogenicity, high vaccine efficacy and a favorable safety profile in Phase I to III trials (Polack et al. 2020). Many studies have shown that BNT162b2 induces antibody and T-cell responses against the S protein after vaccination and that it has been highly effective against many variants. However, mutations in the S protein in some variants of interest and VOCs can increase viral transmission and have allowed partial evasion of neutralizing antibodies (Muik et al. 2022). In light of the increase in the number of VOCs, particularly the Omicron variant which has a large number of mutations in the S protein, an immune response targeting conserved viral epitopes, in addition to those targeting the S protein, may provide further protection against COVID-19 caused by emergent and potentially more antigenically diverse VOCs. In addition, it is anticipated that future additional modification of the S protein may increase the level of induced neutralizing antibodies and thus may contribute to longer lasting protection against SARS-CoV-2.

Studies in SARS-CoV-2 and SARS-CoV, a closely related coronavirus which caused the 2003 SARS pandemic, demonstrated that effective protection could be achieved through spike specific antibodies. In addition to humoral immunity driven by S protein recognition, cellular immune responses also play a significant role in the control of viral infection and disease. T-cell responses are important in the control and clearance of SARS-CoV-2 infected cells, are not limited to the S protein, and can provide more durable immunity particularly against more severe outcomes of COVID-19. While neutralizing antibody levels are known to decrease after infection or vaccination thus reducing protection against infection over time (Cohen et al. 2021; Dan et al. 2021), virus-specific T cell memory persists for over a decade following convalescence from SARS-CoV-2 (Ng et al. 2016). A recent study reported nucleocapsid-specific T cells persisting for 17 yrs post SARS infection, highlighting the potential for durable T-cell responses against SARS-CoV-2 (Le Bert et al. 2020). Additionally, monitoring of subjects given BNT162b2 over 6 months show a substantial decline in neutralizing antibodies, but stability in memory T cell populations over time (Zhang et al. 2022). CCI [redacted] CCI [redacted] CCI [redacted] Together, this evidence confirms the important and durable nature of the cell-mediated immune response in control of SARS-CoV-2.

The potential benefit of T-cell responses against non-spike proteins has been emphasized by the rise of more antigenically diverse VOCs (e.g., Omicron), which require higher neutralization titers than other variants because of larger numbers of mutations in the

S protein. However, the rate of mutations in non-spike SARS-CoV-2 proteins is much lower than the mutation rate observed in S protein. Epitopes eliciting potent T-cell responses have been reported to be largely variant-independent (Tarke et al. 2021b). As the virus continues to acquire more mutations with potentially greater impact on humoral and cellular responses, raising T-cell responses through vaccination against both spike and conserved non-spike antigens could provide more stable and durable T cell protective immunity.

The selection of epitopes conserved across SARS-CoV-2 variants that are predicted to bind multiple alleles, combined with knowledge of the epitope protein expression, is known to be crucial when designing therapeutics providing long lasting T cell immunity (Poran et al. 2020). In addition, in order to face the challenge of partial protection, the use of vaccines targeting a combination of B and T cell epitopes may provide long lasting immunity.

Based on this rationale, this trial will evaluate a vaccine candidate, composed of BNT162b4 and BNT162b2 Bivalent drug products. BNT162b4 is an RNA vaccine component targeting nucleocapsid, membrane CCI The membrane and CCI within BNT162b4 have been largely conserved across different viral variants (i.e., Omicron). BNT162b4 will be either mixed with BNT162b2 Bivalent or BNT162b2 Monovalent (OMI XBB.1.5) drug product, an RNA vaccine targeting the SARS-CoV-2 spike protein, or given alone. On 31 AUG 2022, the US FDA issued an emergency use authorization (EUA) for a booster vaccination (30 µg) with the BNT162b2 Bivalent (BNT162b2 WT/OMI BA.4/BA.5) for individuals 12 yrs of age and older.

Data supporting clinical investigation of BNT162b4 and BNT162b2 Bivalent or BNT162b2 Monovalent (OMI XBB.1.5)

Non-clinical studies in mice with BNT162b4 and BNT162b2 co-administration showed a similar immunogenicity, as measured by neutralization titers in a pseudovirus neutralization assay, to that seen with BNT162b2 alone when mice are given a prime/boost regimen. In preclinical mouse models, BNT162b4 has been shown to provide increased T-cell responses to the antigen components. For further details, see the BNT162b4 (COVID-19 Vaccine) investigator's brochure (IB, BNT162b4 IB) and data on file. The supplemental biological license application for the BNT162b2 Monovalent (OMI XBB.1.5) vaccine was approved in the US on 11 SEP 2023.

2.2 Trial rationale

Vaccines targeting the spike glycoprotein (S protein) of SARS-CoV-2 have been used as a mitigation strategy of the COVID-19 pandemic. BNT162b2 has received authorization for emergency supply, conditional marketing authorization, and/or full authorization in more than 100 countries globally under the tradename "COMIRNATY" for the prevention of COVID-19 caused by SARS-CoV-2. BNT162b2, a N1-methylpseudouridine-nucleoside-modified RNA encoding the S protein that is encapsulated in LNPs, has demonstrated potent immunogenicity, high vaccine efficacy, and a favorable safety profile in Phase I//II/III trials, as well as in real world usage. In light of the increase in the number of VOCs, as well as the number of new mutations in the S protein in these variants, a long term and durable immune response targeting conserved viral epitopes could help protect individuals from severe symptoms caused by emergent VOCs.

The value of T-cell responses against non-spike proteins has been emphasized by the rise of more antigenically diverse VOCs (e.g., Omicron sublineages, such as BA.1, BA.2, BA.4, BA.5, and XBB), which can avoid neutralization via mutations to the S protein. However, the rate of mutations in non-spike proteins is much lower than the mutation rate observed in the S protein. Epitopes eliciting potent T-cell responses have been reported to be largely variant-independent.

Based on the rationale of targeting conserved epitopes from multiple viral proteins that elicit potent T-cell responses, BioNTech is evaluating a vaccine candidate, BNT162b4, aimed at enhancing the breadth of T-cell responses and the protective capacity of spike-based vaccines, especially against severe disease and future VOCs.

BNT162b4 uses the same modRNA platform, processes, and LNP formulation as BNT162b2, with the RNA components comprising a single RNA encoding segments of the nucleocapsid and membrane proteins, as well as short segments containing CCI [redacted] CCI [redacted].

In this trial, BNT162b4 will either be combined with two selected spike-based RNA vaccines i.e., BNT162b2 Bivalent (WT/OMI BA.4/BA.5), hereinafter referred to as "BNT162b2 Bivalent", and BNT162b2 Monovalent (OMI XBB.1.5), or given alone.

- BNT162b4 will be combined with BNT162b2 Bivalent for Doses 1 and 2 for Cohorts 1 and 2, and Dose 1 for Cohorts 3a, 3b, 4a, and 4b.
- BNT162b4 will be combined with BNT162b2 Monovalent (OMI XBB.1.5) for Dose 2 in Cohorts 3a, 3b, 4a, and 4b.
- BNT162b4 alone will be given for Dose 1 and Dose 2 in Cohort 5.

BNT162b2 Bivalent is a BNT162b2-based vaccine with an RNA encoding the ancestral strain of the virus S protein in combination with an RNA encoding the S protein of the Omicron BA.4/BA.5 variant. BNT162b2 Bivalent uses the same modRNA platform, processes, and LNP formulation as licensed BNT162b2.

BNT162b2 Monovalent (OMI XBB.1.5) is a BNT162b2-based vaccine with an RNA encoding the S protein of the XBB.1.5 variant, a sub-lineage of Omicron XBB. BNT162b2 Monovalent (OMI XBB.1.5) uses the same modRNA platform, processes, and LNP formulation as licensed BNT162b2. Marketing approval of the BNT162b2 Monovalent (OMI XBB.1.5) vaccine has been granted. The supplemental biological license application for the BNT162b2 Monovalent (OMI XBB.1.5) vaccine was approved in the US on 11 SEP 2023.

The combination of BNT162b4 and BNT162b2 Bivalent or BNT162b2 Monovalent (OMI XBB.1.5) is intended to improve the protective capacity of spike-based vaccines, especially against severe disease, to make the protection less dependent on virus variants and to have durable T cells protective immunity. The addition of BNT162b2 Monovalent (OMI XBB.1.5) added to BNT162b4, is intended to address the most recent recommendations by WHO and endorsed by the US FDA for additional protection against the most widely circulating variant lineage XBB. The use of BNT162b4 alone is intended to characterize the induced T-cell immune response independent of spike co-administration.

For the rationale for the dosing regimen, see Section 4.3. For the rationale for the implemented updates to this protocol, see Section 10.8.

2.3 Benefit/risk assessment

See the BNT162b4 IB for further information on the expected benefits and risks connected with intramuscular (IM) administration of BNT162b4, including the reference safety information included in IB Section 6.1.5.

See the BNT162 IB for further information on the expected benefits and risks connected with IM administration of BNT162b2 Bivalent or BNT162b2 Monovalent (OMI XBB.1.5), including the reference safety information included in IB Section 7.8.2.

Clinical investigation of BNT162b4, BNT162b2 Bivalent, and BNT162b2 Monovalent (OMI XBB.1.5) is justified given:

- The threat posed by the antigenically diverse VOCs (e.g., Omicron) emerging worldwide.
- The potential need for enhancing immune responses to overcome waning immunity.
- The potential of the sponsor platform of RNA-based vaccines to deliver high numbers of vaccine doses rapidly in a single production campaign.

2.3.1 Benefit assessment

Benefits to individual trial subjects enrolled in this trial may be:

- Receipt of a further dose of an efficacious and a potentially efficacious COVID-19 vaccine that may convey a longer duration of protection.
- Access to COVID-19 diagnostic testing.
- Contributing to research potentially supporting development of an improved vaccine for the prevention of COVID-19 caused by SARS-CoV-2.

Also, by undergoing the clinical laboratory tests and physical examinations in this trial, previously undiagnosed health problems may be uncovered.

2.3.2 Risk assessment

Potential risks related to trial procedures:

- Trial subjects will be required to attend healthcare facilities during the trial and thus there is a potential for increased exposure to SARS-CoV-2.
- Venipuncture will be performed during the trial. There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.
- General risks of vaccines and IM injection of vaccines apply here, for details see Section 6.2.1 in the BNT162b4 IB.

Potential/identified risks of BNT162b4, BNT162b2 Bivalent, and BNT162b2 Monovalent (OMI XBB.1.5)

For BNT162b2:

- Identified risks for BNT162b2 based on clinical and post-authorization data include local reactions, such as injection site redness, injection site swelling, and injection site pain, and systemic events, such as fever, fatigue, headache, chills, muscle pain, and joint pain.
- Key risks identified for BNT162b2 are myocarditis and pericarditis.

For BNT162b2 Monovalent (OMI XBB.1.5):

- BNT162b2 Monovalent (OMI XBB.1.5) has the same modRNA platform (with sequence changes that are XBB.1.5 specific) and LNP formulation as BNT162b2; therefore, the safety profile is expected to be similar to that of BNT162b2. Marketing approval of the BNT162b2 Monovalent (OMI XBB.1.5) vaccine has been granted.

For BNT162b2 Bivalent:

- BNT162b2 Bivalent has the same modRNA platform and LNP formulations as BNT162b2, thus a similar safety profile is expected (for further details of the BNT162b2, see the BNT162 IB).
- A clinical trial to evaluate the safety and tolerability of BNT162b2 Bivalent is ongoing (C4591044). This trial is an interventional, randomized, active-controlled, Phase II observer-blind investigation of the safety, tolerability, and immunogenicity of BNT162b2 Bivalent as a 30 µg booster dose in healthy COVID-19 vaccine experienced subjects 12 yrs of age and older.

For BNT162b4:

- BNT162b4 has not been studied in humans. This is the first clinical trial to evaluate the safety and tolerability of BNT162b4 in combination with BNT162b2 Bivalent or BNT162b2 Monovalent (OMI XBB.1.5) or given alone. Since BNT162b4 uses the same modRNA platform and LNP formulation as BNT162b2, a similar safety profile to BNT162b2 is expected with regards to local and systemic reactogenicities.
- Myocarditis and pericarditis are considered an important identified risk for BNT162b2 vaccines based on post-authorization reports. Based on risks identified for other members of the same RNA-based vaccine platform, the risks listed for BNT162b2 may apply for BNT162b4. Thus, myocarditis and pericarditis are considered a key potential risk for BNT162b4 and are therefore monitored as AESIs, see Section 8.3.8.
- Any potential risks that might be associated with the new non-spike antigens encoded by BNT162b4 will be closely monitored throughout the trial.
- As of 20 Dec 2023, no safety concerns have been identified for the combination of BNT162b2 and BNT162b4. Therefore, no new risks or safety concerns are expected for BNT162b4 when administered as monotherapy.

- Potential risks linked to first-in-human (FIH) administration of BNT162b4 will be managed by the planned use of a staggered dosing process with sentinel subjects in Cohorts 1, 2, 3a, and 4a. In addition, the trial IRC will assess whether the tolerability shown up to 7 d post-dose in the sentinel subjects was acceptable and whether any stopping/pausing rules were met. Only when safety and tolerability is confirmed by the IRC will dosing of all other subjects per DL cohort be continued. The IRC will also assess whether the tolerability shown up to 7 d post-dose in all cohort subjects was acceptable and that no stopping/pausing rules were met, before allowing progression to the next higher DL cohort. For Cohort 5, an IRC safety review of available data for Dose 1 and Dose 2 will be performed after all subjects receive Dose 2. For details, including a graphical depiction of the process, see Section 1.1.

For the combination of BNT162b4 and BNT162b2 Bivalent or BNT162b2 Monovalent (OMI XBB.1.5):

- Taking into the account that the total dose of vaccines given in this trial (35, 40, 45, and 60 µg) is higher than the authorized BNT162b2 dose (30 µg), a higher frequency and/or severity of local and systemic reactions cannot be ruled out. However, the trial-specific dose escalation process which includes sentinel subjects at each DL, usage of e-diaries which allows real time control of entered data and defined stopping rules will support appropriate risks minimization measures.

2.3.3 Overall benefit/risk conclusion

Taking into account the measures taken to minimize the risks to subjects in this trial (see Section 2.3.2), the potential risks identified in association with administration of the investigational BNT162 RNA-based COVID-19 vaccines and the planned trial procedures are considered justified by the anticipated benefits that may be afforded to trial subjects.

3 OBJECTIVES AND ENDPOINTS

Objectives, estimands and endpoints – Cohorts 1 to 4

OBJECTIVES	ESTIMAND *	ENDPOINTS
Primary objectives		
To describe the safety and tolerability of one and two doses of BNT162b4 + BNT162b2 Bivalent, one dose of BNT162b4 + BNT162b2 Monovalent (OMI XBB.1.5) as a booster, or one dose of BNT162b2 Bivalent alone at each applicable DL in healthy adults aged 18 years and older, with and without evidence of prior SARS-CoV-2 infection who previously received at least three prior doses of an authorized RNA-based COVID-19 vaccine.	<u>For each DL cohort, the frequency of dosed subjects with:</u> • Solicited local reactions at the injection site recorded up to 7 d after every IMP dose. • Solicited systemic events recorded up to 7 d after every IMP dose. • Subjects with at least one AE occurring up to 28 d after every IMP dose. • Subjects with at least one SAE occurring up to 6 months after every IMP dose.	• Solicited local reactions (pain, erythema / redness, induration / swelling) • Solicited systemic events (vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills and fever) • AEs • SAEs
	<u>For each DL cohort, the percentage of dosed subjects with:</u> • Abnormal hematology or chemistry laboratory values 3 d (Dose 1 sentinel group only) and 7 d after every dose. • Grading shifts in hematology or chemistry laboratory assessments between baseline and 3 d (Dose 1 sentinel group only) and 7 d after every IMP dose.	• Hematology and chemistry laboratory parameters (see Section 10.3)
	<u>For each DL cohort, the percentage of dosed subjects with:</u> • New ECG abnormalities 3 d (Dose 1 sentinel group only) and 7 d after every IMP dose.	• ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in the protocol
Secondary objectives		
To describe the humoral immune responses elicited by one and two doses of BNT162b4 + BNT162b2 Bivalent, one dose of BNT162b4 + BNT162b2 Monovalent (OMI XBB.1.5) as a booster, or one dose of BNT162b2 Bivalent alone at each applicable DL in healthy adults aged 18 years and older, with and without evidence of prior SARS-CoV-2 infection, who received at least three prior doses of an authorized RNA-based COVID-19 vaccine.	<u>For each DL cohort:</u> • GMTs at baseline and 28 d after every IMP dose. • GMFRs from baseline (pre-Dose 1) to 28 d after every IMP dose. • Percentages of subjects with seroresponse at 28 d after every IMP dose.	• SARS-CoV-2 ancestral strain neutralizing titers • SARS-CoV-2 Omicron neutralizing titers (viral strains matching the antigen encoded by BNT162b2)

OBJECTIVES	ESTIMAND *	ENDPOINTS
Exploratory objectives		
CCI [redacted]		

Abbreviations: AE = adverse event; CCI [redacted] COVID-19 = coronavirus disease 2019; d = day; DL = dose level; ECG = electrocardiogram; CCI [redacted] GMFR = geometric mean fold rises; GMT = geometric mean titer; CCI [redacted] IMP = investigational medicinal product; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; CCI [redacted]

* All assessments as described in the estimands will be conducted within the schedule of visits window.

For the objectives and endpoints for Cohort 5, see Section 13.6.

4 TRIAL DESIGN

4.1 Overall design

This is an exploratory Phase I, randomized, observer-blind, active-controlled, dose-escalation trial to evaluate four DLs of BNT162b4 given in combination with BNT162b2 Bivalent to select a safe and tolerable dose and to evaluate BNT162b4 + BNT162b2 Bivalent when given as Dose 1 and Dose 2 (booster) in Cohorts 1 and 2 and

BNT162b4 + BNT162b2 Monovalent (OMI XBB.1.5) when given as Dose 2 (booster) in Cohorts 3a, 3b, 4a, and 4b, and 30 µg BNT162b4 when given alone as Dose 1 and Dose 2 in Cohort 5.

For flow diagram summaries of the trial, see Section 1.2. For the planned assessments and visits, see the SoAs in Section 1.3 and Section 13.5.

In total, up to ~380 healthy subjects aged 18 yrs and older will be enrolled: up to 60 in each of Cohorts 1, 2, 3a, 3b, 4a, and 4b and ~20 in Cohort 5. For the trial populations (including the planned number of subjects per cohort), dosing regimens, and blinding in Cohorts 1 to 5, see Table 2.

Randomization for enrollment in Cohorts 1, 2, and 3a will be stratified based on N-binding antibody status and CCI

Randomization for enrollment in Cohort 3b will be stratified based on age and N-binding antibody status. Randomization for enrollment in Cohort 4b will be stratified based on age only. All subjects enrolled in Cohorts 4a and 4b, and all subjects giving consent for Dose 2 will be eligible CCI Cohorts 1 to 4 are observer-blind and randomized; Cohort 5 is single arm and open-label.

To minimize heterogeneity between DL cohorts with regard to the baseline N-binding antibody status of subjects, the following subject distribution is planned for each DL cohort when possible: approximately 1/3 N-binding antibody negative subjects and 2/3 N-binding antibody positive subjects in Cohorts 1, 2, 3a, and 3b. However, this distribution can be modified based on the existing prevalence of N-binding antibody negative subjects or operational needs.

Subjects screened to the specific DL cohorts, but not enrolled due to reached N-binding subject distribution rate, will be allowed to be enrolled into the next cohort. Safety laboratory tests (except viral screening) will need to be repeated if performed >28 d prior to the planned IMP vaccination day.

In addition, depending upon the observed safety and immunogenicity data, the sponsor may update Cohorts 1 to 4 to evaluate higher or additional DLs of BNT162b4 in combination with the selected spike-encoding RNA vaccine BNT162b2 Bivalent or BNT162b2 Monovalent (OMI XBB.1.5).

An IRC will be established and maintained for the entire trial to periodically review subject safety data and make decisions about dose escalations (for details about the IRC, see Section 10.1.5).

The staggered dosing process for Cohorts 1 to 4

The trial will use a staggered dosing process schema with sentinel subjects in Cohorts 1, 2, 3a, and 4a, see Figure 1.

The trial will be initiated with Cohort 1 where eight sentinel subjects will be randomized 3:1 to receive one dose of either BNT162b2 Bivalent + BNT162b4 or control BNT162b2 Bivalent followed by IRC review of 7 d post-Dose 1 data.

If the IRC considers the shown tolerability to be acceptable and no stopping/pausing rules are met, 52 additional trial subjects (expansion group) will be randomized 3:1 to the BNT162b2 Bivalent + BNT162b4 or control group BNT162b2 Bivalent (one dose). Following dosing of the expansion group (7 d post-Dose 1), all available clinical, laboratory

and other relevant data from these 60 trial subjects (full cohort) will be reviewed by the IRC. If the IRC considers the shown tolerability is acceptable and no stopping/pausing rules are met for Cohort 1, enrollment will be opened for Cohort 2. Cohort 2 will follow the same dose escalation/assessment process. For a graphical depiction of the staggered dosing process for Cohorts 1 to 4, see Figure 1.

If the IRC considers the shown tolerability acceptable and no stopping/pausing rules are met for Cohort 2 (for the stopping/pausing rules, see Section 7.1), enrollment will be opened for Cohorts 3a and 3b which will follow the same dose escalation/assessment process as for Cohorts 1 and 2 with the following exception: enrollment for the Cohort 3b will be opened after 7 d post-dose data for Cohort 3a sentinel subjects has been reviewed by the IRC and approval is granted. There will be a safety review of 7 d post-dose data for the first 8 subjects in Cohort 3b. In addition to safety data being reviewed on an ongoing basis by investigators and sponsor, 7 d post-dose data for Cohort 3a expansion subjects and Cohort 3b subjects will be reviewed by the IRC.

If the IRC considers the shown tolerability acceptable and no stopping/pausing rules are met for Cohorts 3a and 3b (for the stopping/pausing rules, see Section 7.1), enrollment will be opened for Cohorts 4a and 4b which will follow the same IRC review process as for Cohorts 3a and 3b. In addition to safety data being reviewed on an ongoing basis by investigators and sponsor, 7 d post-dose data for Cohort 4a expansion subjects and Cohort 4b subjects will be reviewed by the IRC.

Dose escalation decisions to progress to the next DL and DL modifications (i.e., dropping the DL to the previous acceptable DL or to an ‘in-between’ DL) will be confirmed by the IRC. Dose escalation will only continue if the safety and tolerability of the previous DL was considered acceptable by the IRC and no stopping/pausing rules were met.

In addition to the above safety reviews for dose modifications, other unplanned dose modifications, pausing (temporary halting) of trial treatment, or discontinuation of trial treatment may be required. See Section 7.1 for guidance on criteria for such cases.

For Dose 2 recipients, IRC safety review will be performed for the first 8 subjects 7 d post-Dose 2 in all DL cohorts (see Table 1).

Based on the WHO’s recommendation, which has been endorsed by the FDA, and the FDA approval of BNT162b2 Monovalent (OMI XBB.1.5), Dose 2 for Cohorts 1 to 4 will be provided in line with current agency recommendations when available in the US. This will provide standard of care for vaccinees and carries a proven benefit for the current circulating XBB subvariants.

The dosing process for Cohort 5

For the dosing process schema for Cohort 5, see Figure 2. Cohort 5 trial subjects will not be randomized and will be administered two doses of 30 µg BNT162b4 alone. An IRC safety review will be performed after all subjects receive Dose 2 (see Table 1).

4.1.1 Duration of all trial periods

The planned trial duration for each trial subject in Cohorts 1 to 4 who receives only one dose of IMP is up to ~7 months (up to ~1 month [28 d] screening and ~6 months follow-up after Dose 1 of IMP).

The planned trial duration for each trial subject in Cohorts 1 to 4 who receives two doses of IMP is up to ~13 months (up to ~1 month [28 d] screening and ~6 months follow-up after Dose 1 of IMP, plus ~6 months follow-up after Dose 1 of IMP).

See Section 13.3.2 for the planned trial duration for trial subjects in Cohort 5.

4.1.2 Planned number of trial subjects

See Table 2 for the planned number of trial subjects.

4.2 Scientific rationale for the trial design

The trial design is based on the sponsor's experience with trials of this type and other similar published trials for vaccine development following EMA 2017 guidance "Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products" and US FDA 2020 guidance "Development and Licensure of Vaccines to Prevent COVID-19".

No formal sample size calculations have been performed as the trial size is not based on any formal hypothesis test. The sample size for each cohort is mainly driven by typical small dose escalation designs for early detection of potential safety and reactogenicity events. The proposed number of subjects per cohort allows (i) detection of the most frequent systemic and local events (AEs and reactogenicity events), thereby allowing dose escalation decisions, and (ii) immunogenicity analyses of sufficient scope to support dose selection decisions and the trial objectives, while minimizing the number of trial subjects exposed to the investigational trial treatment.

Since the trial treatments are investigational and will be evaluated for the first time in this trial, this trial uses a staggered, sequential approach for subject dosing. Dosing will proceed with an initial sentinel group of subjects for each DL cohort (Cohorts 1 to 4), and for all cohorts pause/stopping rules (see Section 7.1 for details) will be followed, and there will be ongoing monitoring by a trial IRC that may pause, permanently discontinue administration of trial treatment, or even permanently terminate the trial at any point in time.

Cohorts 3b and Cohort 4b aim to investigate if BNT162b2 Bivalent + BNT162b4 is well tolerated and immunogenic in an older population.

Cohort 5 will evaluate the BNT162b4 component alone to characterize the induced T-cell immune response independent of spike co-administration and to inform on potential interactions between the components.

Safety evaluations and vaccine-induced immune responses will be used to assess if there is a dose-response, for further details see Section 8.7.

For the rationale for the implemented updates to this protocol, see Section 10.8.

4.3 Justification for the trial treatment

The proposed starting DL for BNT162b4 in this trial (5 µg) is based on the immunogenicity and safety observed in non-clinical studies and on the safety, immunogenicity, and efficacy data generated for other members of the same RNA technology platform such as the SARS-CoV-2 vaccine BNT162b2 licensed as "COMIRNATY". BNT162b2 and the BNT162b4 and BNT162b2 Bivalent or BNT162b2 Monovalent (OMI XBB.1.5) use the

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

BNT162b2 is authorized for IM administration as a series of two 30 µg IM doses at greater than or equal to 21 d (preferably 3 weeks) apart in individuals aged 12 yrs of age or older. A booster dose (third dose) of BNT162b2 may be administered ~6 months after the second dose in individuals 16 yrs of age and older.

Since its first marketing authorization in December 2020, BNT162b2 (COMIRNATY) has been administered to billions of individuals worldwide. Administration of BNT162b2 in the post-authorization setting has confirmed a favorable benefit-risk profile. Pharmacovigilance data on BNT162b2 to date continues to support a favorable safety profile. For more information about the completed non-clinical studies and the ongoing clinical trials with BNT162b2 and the other candidate BNT162b2-based variant vaccines under development, see the BNT162 IB.

The starting dose for BNT162b4 in this trial is lower than what was approved for BNT162b2 (5 µg versus 30 µg). The highest BNT162b4 dose planned in this trial (30 µg) is the same as that authorized for BNT162b2. The highest cumulative RNA-based vaccine dose in this trial will be 60 µg, but the sponsor considers this dose to be acceptable given the data listed below which includes good tolerability of cumulative RNA-based vaccine doses of up to 60 µg.

To date, there is very limited clinical experience with vaccine candidates aimed at eliciting broader T-cell response against SARS-CoV-2. However, the sponsor considers all planned BNT162b4 DLs in this trial (5 µg, 10 µg, 15 µg, and 30 µg) as safe because of:

- The available non-clinical safety data for the BNT162 vaccine candidates, including BNT162b2, support the clinical investigation of the BNT162 vaccine candidates in this trial (see the BNT162 IB). This data includes repeat-dose toxicology data for doses up to 100 µg in rats.
- Both vaccine candidates in this trial are derived from the same RNA technology platform as the widely used BNT162b2 (COMIRNATY) vaccine that has been administered as a series of two 30 µg IM doses to billions of individuals worldwide. Administration of BNT162b2 in the post-authorization setting has confirmed a favorable benefit-risk profile.
- The existing clinical data for BNT162b2 has demonstrated that vaccination with BNT162b2 as a series of two 30 µg IM doses is safe.
- Preliminary safety and tolerability data from a 60 µg BNT162b2 booster dose to adults 18 yrs of age and older who have received three prior doses of BNT162b2 (30 µg) at least ≥4 months prior to the booster dose is under investigation in the clinical trial C4591031. Based on the currently available data, a 60 µg BNT162b2 booster dose shows acceptable tolerability.
- Based on safety data within 7 d post-Dose 4, BNT162b2 Bivalent (BNT162b2 + BNT162b2 Omicron BA.4/BA.5) at the 30 µg and 60 µg DLs was generally well tolerated across subjects 18 yrs of age and older in the trial C4591044.

- The Phase I trial BNT162-01 with DLs of up to 50 µg BNT162b1 (another member of the same RNA technology platform where the RNA differs essentially in the encoded ORFs for antigen expression) given twice 3 weeks apart, there were no SAEs related to the vaccine, while reactogenicity showed clear DL dependency.

Therefore, the planned BNT162b4, BNT162b2 Bivalent, and BNT162b2 Monovalent (OMI XBB.1.5) doses in this trial are considered safe for use in this trial.

5 TRIAL POPULATION

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

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

Determination of eligibility, considering all inclusion and exclusion criteria, must be made within 28 d prior to allocation to trial treatment unless otherwise noted in the following sections.

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

5.1 Inclusion criteria

5.1.1 Inclusion criteria – Cohorts 1 to 4

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

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

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

3 Are aged 18 yrs and older at randomization, have a body mass index over 18.5 kg/m^2 and under 35 kg/m^2, and weigh at least 50 kg at Visit 0.

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

Note: Healthy volunteers with pre-existing stable disease (e.g., obesity), defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 84 d before Visit 0, can be included.

5 Agree not to enroll in another trial with an IMP starting from Visit 0 and until 168 d after receiving the last IMP dose.

Inclusion criteria pertaining to Dose 2: If 168 d after the subject's first IMP dose had passed before they consent to Dose 2, they should agree to not enroll in another trial from the time of consent to Dose 2 until 168 d after receiving Dose 2 of the IMP.

6 Agree not to be vaccinated with:

- Non-trial vaccines (except COVID-19 vaccines, as per next sub-bullet) starting 28 d prior to the Dose 1 and until 28 d after receiving of the last IMP dose. Seasonal influenza vaccine is allowed; however, it should be given at least 14 d before or after any administration of IMP.
  Inclusion criteria pertaining to Dose 2: If 28 d after the subject's first IMP dose had passed before they consent to continue Dose 2, they should not have been vaccinated with non-trial vaccines starting from the time of consent to Dose 2 and until 168 d after receiving the Dose 2 of the IMP.
- Non-trial COVID-19 vaccines starting at least 90 d prior to the Visit 1 and until completion of the subject's last trial visit.

7 Have been vaccinated with at least three doses of an RNA-based COVID-19 vaccine authorized in the US before Visit 0. The last COVID-19 RNA vaccine dose must have been administered at least 90 d before Visit 1.

Note: Documented confirmation of prior COVID-19 vaccine receipt must be obtained prior to randomization.

Virology

8 Have negative human immunodeficiency virus (HIV)-1 and HIV-2 test results at Visit 0.

9 Have negative Hepatitis B surface antigen (HBsAg) test results at Visit 0.

10 Have negative anti-Hepatitis C virus (HCV) antibodies, or negative HCV polymerase chain reaction (PCR) test results if the anti-HCV is positive at Visit 0.

Reproductive status and contraception

11 Volunteers of childbearing potential (VOCBP) that have a negative serum β-HCG pregnancy test result at Visit 0 and negative urine pregnancy test results prior to receiving Dose 1. Volunteers born female that are postmenopausal or permanently sterilized (verified by medical records) will not be considered VOCBP (for definitions of postmenopausal or permanently sterilized, see Section 10.5).

Inclusion criteria pertaining to Dose 2: VOCBP that have a negative urine pregnancy test results prior to receiving Dose 2.

12 VOCBP who agree to practice a highly effective form of contraception (for guidance on contraception, see Section 10.5) and to require their male sexual partners to use condoms with a spermicidal agent, starting at Visit 0 and continuously until 28 d after receiving the last IMP dose.

Inclusion criteria pertaining to Dose 2: If 28 d after the subject's first IMP dose had passed before they consent to continue Dose 2, they should have a negative urine β-HCG pregnancy test result at Visit 7 and agree to practice a highly effective form of contraception and to require their male sexual partners to use condoms with a spermicidal agent, starting from the time they consent to Dose 2 and continuously until 28 d after receiving Dose 2 of IMP.

13 VOCBP who agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during trial, starting at Visit 0 and continuously until 28 d after receiving the last IMP dose.

Inclusion criteria pertaining to Dose 2: If 28 d after the subject's first IMP dose had passed before they consent to continue Dose 2, they should agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during trial, starting from the time they consent to Dose 2 and continuously until 28 d after receiving Dose 2 of IMP.

14 Men who are sexually active with partners of childbearing potential and who have not had a verified vasectomy (documented in medical records) that agree to use condoms with a spermicidal agent and to practice a highly effective form of contraception with their sexual partners born female (for guidance on contraception, see Section 10.5) starting at Visit 0 and continuously until 28 d after receiving the last IMP dose.

Inclusion criteria pertaining to Dose 2: If 28 d after the subject's first IMP dose had passed before they consent to continue Dose 2, they should agree to use condoms with a spermicidal agent and to practice a highly effective form of contraception with their sexual partners born female starting from the time they consent to Dose 2 and continuously until 28 d after receiving Dose 2 of IMP.

15 Men who are willing to refrain from sperm donation, starting at Visit 0 and continuously until 28 d after receiving the last IMP dose.

Inclusion criteria pertaining to Dose 2: If 28 d after the subject's first IMP dose had passed before they consent to continue Dose 2, they should agree to refrain from sperm donation, starting from the time they consent to Dose 2 and continuously until 28 d after receiving Dose 2 of IMP.

5.1.1.1 Inclusion criteria (Dose 2 groups) – Cohorts 1 to 4

Volunteers are eligible to receive Dose 2 of BNT162b4 + BNT162b2 Bivalent or BNT162b4 + Monovalent (OMI XBB.1.5) and complete Visits 7 to 11 if all of the following criteria (in addition to inclusion criteria 1 to 15) apply:

16 Have given informed consent by signing and dating the ICF reflecting protocol version 5.0 before administration of Dose 2.

17 Have enrolled in a dose cohort and received Dose 1 of BNT162b4 + BNT162b2 Bivalent in this trial.

18 Are healthy in the opinion of the investigator based on a brief (symptom-directed) physical examination as described in Section 8.2.1.

5.1.2 Inclusion criteria – Cohort 5

For the inclusion criteria for Cohort 5, see Section 13.7.1.

5.2 Exclusion criteria

5.2.1 Exclusion criteria – Cohorts 1 to 4

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

1 Breastfeeding or intending to become pregnant starting with Visit 0 until 28 d after receiving the last dose of trial IMP or intending to father children starting with Visit 0 until 28 d after receiving the last trial IMP dose.

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

3 Current or history of the following medical conditions:

a) Uncontrolled or moderate or severe respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease); symptoms of asthma severity as defined in the most recent US National Heart, Lung, and Blood Institute asthma management guidelines - e.g., exclude a volunteer who:
   - Uses a short-acting rescue inhaler (typically a beta 2 agonist) daily, or
   - Uses high dose inhaled corticosteroids (per National Heart, Lung, and Blood Institute asthma management guidelines [Tables 4–8b]), or
   - In the past year has either of the following:
     - Greater than one exacerbation of symptoms treated with oral/parenteral corticosteroids;
     - Needed emergency care, urgent care, hospitalization, or intubation for asthma.

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

c) Hypertension:

- If a person has been found to have elevated blood pressure or hypertension during screening or previously, exclude for “blood pressure that is not well controlled”. Well controlled blood pressure is defined as consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic, with or without medication, with only isolated, brief instances of higher readings, which must be ≤150 mm Hg systolic and ≤90 mm Hg diastolic at Visit 0.
- If a person does not have a history of elevated blood pressure or hypertension previously or during screening, also exclude for systolic blood pressure ≥150 mm Hg at Visit 0 or diastolic blood pressure ≥100 mm Hg at Visit 0.

Exclusion pertaining to Dose 2: Subjects who have new onset of worsening hypertension since enrollment, that, in the opinion of the investigator would constitute an increased risk to the subject’s participation in Dose 2.

d) Any current or history of cardiovascular diseases such as myocarditis, pericarditis, myocardial infarction, symptomatic congestive heart failure, cardiomyopathy or clinically significant arrhythmias.

   Exclusion pertaining to Dose 2: Subjects who have new onset of cardiovascular disease since enrollment, that, in the opinion of the investigator would constitute an increased risk to the subject’s participation in Dose 2.

e) A diagnosed bleeding disorder (e.g., factor deficiency, coagulopathy, or platelet disorder requiring special precautions).

   Exclusion pertaining to Dose 2: Subjects who have new onset of a bleeding disorder since enrollment, that, in the opinion of the investigator, would constitute an increased risk to the subject’s participation in Dose 2.

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

g) Screening 12-lead ECG that is consistent with probable or possible myocarditis or pericarditis, or demonstrates clinically relevant abnormalities that may affect subject safety or interpretation of the trial results.

   Exclusion pertaining to Dose 2: Only symptomatic subjects or whose clinical picture, in the opinion of the investigator, warrant ECG will have a repeat 12-lead ECG prior to Dose 2.

   Note for exclusion criteria 3g: ECG changes including but not limited to: paroxysmal or sustained atrial or ventricular arrhythmias, atrioventricular (AV) block (grade 2-3) or bundle branch block, diffuse ST-segment elevation or PR-segment inversion, QTcF interval (QT interval corrected by the Fridericia formula) >450 ms in men and >460 ms in women, changes supporting myocardial infarction and/or myocardial ischemia.

Exclusion pertaining to Dose 2: Subjects who have an ECG prior to Dose 2 and have a change or new onset that, in the opinion of the investigator, should not receive Dose 2.

4 Current or history of major psychiatric illness, including but not limited to bipolar disorder, major depressive disorder, schizophrenia, autism, and attention deficit-hyperactivity disorder that could interfere with participation and follow-up as required by the trial protocol.

Exclusion pertaining to Dose 2: Subjects who have a change or new onset psychiatric illness.

5 Current or history of the following diseases associated with immune dysregulation:

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

Exclusion pertaining to Dose 2: Subjects who have a change or new onset immunodeficiency.

Prior/concomitant therapy

6 Received any non-trial IMP within 28 d before Visit 0 or Visit 7.

7 Received or planned treatment throughout the entire trial with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 d at a dose of ≥20 mg/d of prednisone or equivalent), e.g., for cancer or an autoimmune disease, or planned receipt throughout this trial. Inhaled/nebulized (except high doses as per exclusion criteria 3a), intraarticular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

8 Blood/plasma products and/or immunoglobulin containing therapy (including monoclonal antibodies) received within 120 d before Visit 1 or Visit 7 or administration is planned starting at Visit 0 or prior to Visit 7 until 120 d after the last IMP administration in this trial.

Exclusion pertaining to Dose 2: if 28 d after the subject's last IMP dose had passed before they consent to continue Dose 2, blood/plasma products and/or immunoglobulin containing therapy (including monoclonal antibodies) received within 120 d before Dose 2 of IMP (Visit 7) continuously until 120 d after receiving Dose 2 of IMP.

9 Received allergy treatment with antigen injections within 28 d before Visit 1 or Visit 7 or where allergy treatment with antigen injections are scheduled within 14 d after any visit with IMP administration in this trial.

10 Subjects with a history of SARS-CoV-2 infection (symptomatic or asymptomatic) <60 d prior to randomization.

11 Have received any non-RNA or unauthorized COVID-19 vaccine, aside from Dose 1 of the current trial.

Additional exclusions

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

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

14 Any screening hematology and/or blood chemistry laboratory value that meets the definition of a Grade ≥1 abnormality at Visit 0, or an abnormal C-reactive protein (identified by any method) or troponin I value.

Note: Volunteers with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: “stable” Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same volunteer).

Gilberts disease, in and of itself, is not considered exclusionary.

Exclusion pertaining to Dose 2: Only symptomatic subjects or whose clinical picture, in the opinion of the investigator, warrant laboratory investigation, will have a repeat lab(s) prior to Dose 2.

15 History of alcohol abuse or drug addiction within 1 yr before Visit 0, or a history (within the past 5 yrs) of substance abuse or known medical, psychological, or social conditions which, in the opinion of the investigator, could compromise their wellbeing if they participate as subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.

5.2.2 Exclusion criteria – Cohort 5

For the exclusion criteria for Cohort 5, see Section 13.7.2.

5.3 Lifestyle considerations

The trial subjects will be required to remain at the site for ~1 hour (h) after each administration of trial treatment. When at the trial site, trial subjects will be asked to drink fluids (e.g., water) per trial site standard for visits with blood draws.

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

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

Trial subjects will be advised to avoid donating blood or blood products during their participation in this trial.

5.3.1 Contraception and donation or cryopreservation of germ cells

Currently, the risk of human teratogenicity/fetotoxicity can NOT be excluded by available data. Therefore, all male and female trial subjects who, in the opinion of the investigator, are biologically capable of having children must agree to use of a highly effective method of contraception consistently (see Section 10.5.2) and correctly (as specified in the SoAs, see Section 1.3 and Section 13.5). In addition, pregnancy testing will be performed at screening and before each IMP administration.

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

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

VOCBP will only be administered trial treatment after negative pregnancy test outcome(s) at the timepoints indicated in the SoAs (Section 1.3 and Section 13.5).

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

5.4 Screen failures

Screen failures are defined as individuals who consent to participate in the trial, but did not meet one or more eligibility criteria, and therefore were not eligible for randomization (allocated to IMP).

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

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

6 TRIAL TREATMENTS

Trial treatment is defined as any investigational treatment intended to be administered to a trial subject according to the trial protocol. An “IMP” is any medicinal product which is

being tested or used as a reference in a clinical trial (the tested product and its reference products, including placebos). Concomitant therapy is not considered trial treatment.

6.1 Trial treatments administered

IMP name	BNT162b4	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) referred to as "BNT162b2 Bivalent"	BNT162b2 Monovalent (OMI XBB.1.5)
Type	Investigational. Nucleoside-modified RNA vaccine which encodes non-spike protein antigens from SARS-CoV-2 (i.e., nucleocapsid protein, membrane protein CCI [redacted]	Investigational and active comparator. Nucleoside-modified RNA vaccine which encodes spike protein antigens from SARS-CoV-2. BNT162b2 Bivalent is supplied as a co-formulated drug product of BNT162b2 Wild Type and BNT162b2 OMICRON [B.1.1.529 sublineages BA.4/BA.5] in a single vial.	Investigational. Nucleoside-modified RNA vaccine which encodes spike protein antigen from SARS-CoV-2. BNT162b2 Monovalent (OMI XBB.1.5) is supplied in a single vial.
Dose levels	5 µg, 10 µg, 15 µg, 30 µg	30 µg (15 µg BNT162b2 + 15 µg BNT162b2 OMI BA.4/BA.5)	30 µg
Allocation to IMP	Trial subjects in Cohorts 1 to 4 who receive BNT162b4 in combination with a BNT162b2-based vaccine will be randomized using an online randomization tool. Trial subjects in single arm Cohort 5 who are assigned to receive BNT162b4 alone in an unblinded fashion without a control/placebo group.	Trial subjects will be randomized using an online randomization tool. Randomization 3:1 for all cohorts: to BNT162b4 + BNT162b2 Bivalent: BNT162b2 Bivalent.	Trial subjects will receive BNT162b2 Monovalent (XBB.1.5) in an unblinded fashion without a control/placebo group (non-randomized).
IMP administration	Intramuscular injection in the mid-deltoid muscle of the non-dominant arm. For "BNT162b4 + BNT162b2 Bivalent" administration, BNT162b4 plus BNT162b2 Bivalent will be co-administered as a single injection. BNT162b4 alone will be administered as a single injection. For details regarding IMP preparation for administration, see the Pharmacy Manual.		Intramuscular injection in the mid-deltoid muscle of the non-dominant arm. For administration, BNT162b4 plus BNT162b2 Monovalent (OMI XBB.1.5) will be co-administered as a single injection. For details regarding IMP preparation for co-administration, see the Pharmacy Manual.
Vaccination schedules	IMP will be administered on Day 1 (Dose 1) and, for treatment groups administered BNT162b4 + BNT162b2 Bivalent, again 6 to 7 months after Day 1 (for Dose 2), or BNT162b4 + BNT162b2 Monovalent (OMI XBB.1.5) 6 to 7 months after Day 1 (for Dose 2), or BNT162b4 alone: 2 months after Day 1 (for Dose 2).		
Packaging and labeling	IMP will be provided in glass vials. Each vial will be labeled as per country requirements. For details of the IMP packaging, labeling, and IMP sourcing, see the Pharmacy Manual.		

Abbreviations: IMP = investigational medicinal product; OMI = Omicron CCI [redacted]
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WT = Wild Type.

6.2 Preparation/handling/storage/accountability

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

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

The investigator is accountable for trial treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

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

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

6.3 Measures to minimize bias: randomization and blinding

Cohorts 1, 2, 3a, 3b, 4a, and 4b are observer-blind for Dose 1, through Visit 5 only. Since only prior recipients of BNT162b4 will receive Dose 2, Dose 2 will be open-label. Trial subjects will be permitted to be unblinded from Visit 5.

Cohort 5 is single arm and open-label for Dose 1 and Dose 2.

6.3.1 Allocation of IMP

Treatment allocation will be done using an online randomization tool for Cohorts 1 to 4, and online open-label kit allocation will be used for Cohort 5.

Randomization for enrollment in Cohorts 1, 2, and 3a will be stratified based on N-binding antibody status and CCI [redacted]

Randomization for enrollment in Cohort 3b will be stratified based on age and N-binding antibody status. Randomization for enrollment in Cohort 4b will be stratified based on age only. All subjects enrolled in Cohorts 4a and 4b, and all subjects giving consent for Dose 2 will be eligible CCI [redacted]

For Cohorts 3b and 4b, the age group distribution enrolled will be ~60% of subjects aged ≥65 yrs and ~40% of subjects aged >55 to <65 yrs.

All subjects in Cohort 5 will be allocated to a single arm.

6.3.2 Blinding

For Cohorts 1 to 4, this is an observer-blind trial until Visit 5 (or later, if subjects only consent to Dose 2 later). Individuals will be unblinded as described in the SoA in Section 1.3. Further details relevant to blinding/unblinding procedures will be provided in the Blind Management Plan.

Cohort 5 is open-label.

6.3.2.1 Blinding of trial subjects

All trial subjects in Cohorts 1 to 4 will be blinded to their assigned trial treatments as described in the SoA in Section 1.3.

6.3.2.2 Blinding of trial site personnel

The trial staff dispensing and administering the vaccine will be unblinded, but all other trial personnel, including the principal investigator, will be blinded as described in the SoA in Section 1.3. The principal investigator will assign the responsibility of unblinded dispenser and unblinded administrator to persons who will not participate in the evaluation of any trial subject. More than one unblinded dispenser/administrator may be assigned. A member of the trial site personnel or clinic pharmacy should fulfill this role. Contact between the unblinded dispenser/administrator and trial subjects should be kept to a minimum.

The investigator, trial coordinator, and any site staff other than the unblinded dispenser/administrator must not be allowed to know the investigational product assigned to any trial subject and must not be allowed to see the investigational product containers.

BNT162b4 and BNT162b2 Bivalent do not differ in physical appearance but the trial treatments differ slightly in volume (and thus could lead to unblinding, e.g., when administering the IMP or recording the administered IMP volume), details of the trial treatment blinding measures will be provided in the Blind Management Plan.

The trial may be unblinded to site personnel at timepoints as decided by the sponsor.

6.3.2.2.1 Unblinding of trial subjects

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

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

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

6.3.2.3 Blinding of laboratory personnel

In this trial, the laboratory personnel at internal or external laboratories may be unblinded to support rolling snapshot analyses. For further details relevant to the unblinding of these laboratory personnel, see the Blind Management Plan.

6.3.2.4 Blinding of IRC members

To enable the IRC to provide real time medical oversight of trial subject safety during the conduct of this trial, the IRC members will include unblinded sponsor staff. For further details about the IRC, see Section 10.1.5.

6.3.2.5 Blinding of sponsor personnel

Relevant sponsor personnel will be unblinded to trial treatment allocation for the subjects. However, sponsor personnel who routinely have contact with blinded site personnel and the functions responsible for the daily CRO oversight will be blinded. Further details, see the Blind Management Plan.

6.4 Trial treatment compliance

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

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

6.5 Concomitant therapy

6.5.1 Prohibited concomitant therapies during the trial

(See #6 in the inclusion criteria for Cohorts 1 to 4 and #6 in the inclusion criteria for Cohort 5) Trial subjects should not have been vaccinated with:

- Non-trial vaccines (except COVID-19 vaccines) starting 28 d prior to Dose 1 and until 28 d after receiving of the last IMP dose (Dose 2). Seasonal influenza vaccine is allowed, however it should be given at least 14 d before or after any administration of IMP.
- Non-trial COVID-19 vaccines until 6 months (168 d) post last IMP dose for Cohorts 1 to 4 and until 28 d post last IMP dose for Cohort 5.
  Subjects in Cohorts 1 to 4 that continue to Dose 2 should not have been vaccinated with non-trial COVID-19 vaccines, starting at least 90 d prior to Visit 1 and until completion of the subject's last trial visit.

(See #7 in the exclusion criteria for Cohorts 1 to 4 and #7 in the exclusion criteria for Cohort 5) Throughout the entire trial, trial subjects should not receive radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 d at a dose of ≥20 mg/d of prednisone or equivalent), e.g., for cancer or an autoimmune disease, or planned receipt throughout this trial. Inhaled/nebulized (except high doses as per #3a in the exclusion criteria for Cohorts 1 to 4 and #3a in the exclusion criteria for Cohort 5), intraarticular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

(See #8 in the exclusion criteria for Cohorts 1 to 4 and #8 in the exclusion criteria for Cohort 5) Trial subjects should not receive any blood/plasma products and/or immunoglobulin containing therapy (including monoclonal antibodies) from Visit 0 or prior to Dose 2 until 120 d after the last IMP administration for Cohorts 1 to 4, or until 90 d after the last IMP administration for Cohort 5.

(See #9 in the exclusion criteria for Cohorts 1 to 4 and #9 in the exclusion criteria for Cohort 5) Trial subjects should not receive allergy treatment within 14 d after any visit with IMP administration in this trial.

6.5.2 Permitted concomitant therapies during the trial

Seasonal influenza vaccine is allowed; however, it should be given at least 14 d before or after any administration of trial IMP.

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

Administration of standard therapeutic dose of acetaminophen (preferable), or a non-steroidal anti-inflammatory drug (NSAID) if acetaminophen is contraindicated is permitted (paracetamol / acetaminophen at doses of up to 4 g/d).

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

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

6.5.3 Recording of concomitant therapy during the trial

All concomitant medications used (permitted or prohibited, including over the counter or prescription medicines, vitamins, and/or herbal supplements) during the periods defined in the SoAs (Section 1.3 and Section 13.5) 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

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

6.6 Dose modifications

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

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

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

Other unplanned dose modifications, pausing (temporary halting) of trial treatment, or even discontinuation of trial treatment may be required. See Section 7.1 for guidance on criteria for such cases.

6.7 Access to trial treatment after the end of the trial

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

7 DISCONTINUATION OF TRIAL TREATMENT AND TRIAL SUBJECT DISCONTINUATION/WITHDRAWAL

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

7.1 Discontinuation (stopping) or pausing (temporary halting) of trial treatment

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

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

The sponsor will set up regular IRC meetings (as specified in the IRC Charter). In addition, *ad hoc* IRC meetings will be triggered by reported events that contribute to pausing rules (see Section 7.1.1).

If the sponsor confirms reported events fulfill pausing rules criteria:

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

For all trial subjects who are vaccinated, all other routine trial procedures and assessments, including ongoing data entry, reporting of AEs, subject-reporting of reactogenicity in e-diaries, blood draws, and subject follow-up, will continue during the pause.

7.1.1 Cohort trial treatment pausing rules

In this trial AEs and SAEs will be graded for the intensity using scales based on guidance from the US FDA "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (for further details, see Section 10.4.3):

If any of the below situations is observed in a given cohort, no further trial subjects will be assigned to the cohort and administration of trial treatment in the affected cohort and any higher DLs will be paused until IRC reviews the event(s):

- Any SAE developed by a subject administered the combination BNT162b4 + BNT162b2 Bivalent or BNT162b4 + BNT162b2 Monovalent (OMI XBB.1.5), or BNT162b4 alone (at any DL), for which there is no alternative, plausible, attributable cause and which is assessed by the investigator, or the sponsor as possibly related.
- Any Grade 4 AEs (solicited and/or unsolicited) after administration of combination BNT162b4 + BNT162b2 Bivalent or BNT162b4 + BNT162b2 Monovalent (OMI XBB.1.5), or BNT162b4 alone (at any DL) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

- Any case of fever >40.0°C/>104.0°F for at least one daily measurement persisting for over 6 h despite the use of antipyretic after administration of combination BNT162b4 + BNT162b2 Bivalent or BNT162b4 + BNT162b2 Monovalent (OMI XBB.1.5), or BNT162b4 alone (at any DL) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.
- If the IRC determines that >20% of trial subjects administered the combination BNT162b4 + BNT162b2 Bivalent or BNT162b4 + BNT162b2 Monovalent (OMI XBB.1.5), or BNT162b4 alone in the same cohort experienced the same or similar ≥Grade 3 or above unsolicited AE (including laboratory abnormalities) considered related, and/or for which there is no alternative, plausible, attributable cause.
- Any severe acute systemic hypersensitivity AE or anaphylactic reactions of Grade 3 that occurs within 7 d of trial treatment administration for which there is no alternative, plausible, attributable cause.
- Any case of myocarditis or pericarditis documented within 28 d after BNT162b4 + BNT162b2 Bivalent, BNT162b4 + BNT162b2 Monovalent (OMI XBB.1.5), or BNT162b4 alone administration with ECG or clinical laboratory findings supporting probable or possible myocarditis or pericarditis as per Brighton Collaboration Case Definition (see Section 8.3.8).

NOTE:

- Reactogenicity e-diary data confirmed by the investigator as being entered by the subject in error will not contribute toward a pausing rule.
- Data from recipients of BNT162b2 Bivalent alone will not support the pausing rules.

7.1.2 Individual trial subject trial treatment pausing rules

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

- Safety concerns are identified by an investigator or the IRC.
- Permanent discontinuation (stopping) of trial treatment.

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

- Any Grade 4 reactogenicity event considered to be related.
- Pregnancy.
- If a subject's trial treatment assignment is unblinded prior to Visit 5.

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

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

Trial subjects permanently discontinued from trial treatment will not be discontinued from the trial (i.e., will continue with trial visits and be evaluated for safety). The only exception is pregnant women who will not have further blood draws, but will otherwise complete all

planned assessments, if required including pregnancy follow-up as described in Section 10.5.3.

7.1.3 Criteria for temporarily delaying enrollment or randomization

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

7.2 Trial subject discontinuation or withdrawal from the trial

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

If the trial subject withdraws consent for data processing, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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

If possible, permanently discontinued trial subjects should complete all assessments planned for the Early Termination Visit as given in the respective SoAs (Section 1.3 and Section 13.5).

7.3 Lost to follow-up

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

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

- The trial site must attempt to contact the trial subject and reschedule the missed visit as soon as possible and counsel the trial subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the trial subject wishes to continue in the trial.
- Before a trial subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the trial subject (where possible, three telephone calls and, if necessary, a certified letter to the trial subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the trial subject's medical record.
- If the trial subject continues to be unreachable, they will be considered to have withdrawn from the trial.

7.4 Replacement of permanently discontinued trial subjects

Permanently discontinued trial subjects will not be replaced.

8 TRIAL ASSESSMENTS AND PROCEDURES

See the SoAs (Section 1.3 for Cohorts 1 to 4 and Section 13.5 for Cohort 5) for all planned timepoints for assessments.

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

All screening evaluations must be completed and reviewed to confirm that a trial subject meets all eligibility criteria before allocation to IMP (randomization). For Cohorts 1 to 4, subject eligibility for receipt of Dose 2 must be confirmed prior to administration of Dose 2. Subjects in Cohort 5 are eligible to receive Dose 1 and Dose 2 per protocol. The investigator will maintain a screening log to record details of all volunteers screened and to confirm eligibility or record reasons for screening failure (as applicable), and to avoid duplicate inclusion.

Procedures conducted as part of the trial subject's routine clinical management (e.g., blood count) and obtained before signing of the informed consent may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the time frame defined in the SoAs (Section 1.3 and Section 13.5).

Adherence to the trial design requirements, including those specified in the SoAs (see Section 1.3 and Section 13.5), is essential and required for trial conduct. Every effort should be made to ensure that protocol-required activities are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the planned activity. In these cases, the investigator must take all steps necessary to ensure the safety and wellbeing of the trial subject. When a protocol-required activity cannot be performed, the investigator must document the reason for the missed activity and any corrective and preventive actions taken to ensure that required processes are adhered to as soon as possible. The sponsor must be informed of these incidents in a timely manner.

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

8.1 Efficacy assessments

Not applicable.

8.2 Safety assessments

8.2.1 Physical examinations

Complete and symptom-orientated physical examinations will be performed at the timepoints listed in the SoAs (Section 1.3 and Section 13.5).

- A (complete) physical examination will include, at a minimum, assessments of the skin, lymphatic nodes, 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 and height and body weight

Vital signs (comprising systolic/diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature) will be assessed at the times given in the SoAs (Section 1.3 and Section 13.5).

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

Oral body temperature will be measured and recorded to one decimal place.

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

Height and body weight will be measured and recorded at screening. Height and body weight will be reported in cm and kg for results reporting in the ICH E3 clinical study report (CSR).

8.2.3 Electrocardiograms

Standard 12-lead ECGs will be recorded at the times given in the SoAs (Section 1.3 and Section 13.5) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc; according to Bazett) intervals. All original ECG readings must be kept as source documents subject to review as needed.

All ECGs will be judged by the investigator in terms of clinical significance.

Any post-dose new ECGs changes which may support myocarditis/pericarditis following Brighton Collaboration definition such as:

- Paroxysmal or sustained atrial or ventricular arrhythmias,
- AV block (grade 1-3) or new bundle branch block,
- Diffuse ST-segment elevation or PR-segment inversion, compatible with pericarditis,

will trigger additional actions as described Section 12.2 and will require evaluation of the ECG by a cardiologist.

Also, if a clinically significant finding is identified (including, but not limited to events listed above) at/or after receipt of at least one dose of trial treatment, the investigator should forward the ECG for evaluation by a cardiologist. This forwarding must be documented.

For guidance on the management of symptoms that could represent myocarditis or pericarditis, see Section 12.2.

8.2.4 Clinical laboratory tests

Urine collection and blood draws for clinical laboratory tests will be performed at the times given in the SoAs (Section 10.3 and Section 13.5). For details of all assessed urine and blood clinical laboratory parameters, see Section 10.3.

All protocol-required clinical laboratory tests must be conducted in accordance with the laboratory standard. The investigator must review the laboratory report and document this review with their 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 or the trial Medical Monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

If laboratory values from non-protocol-specified laboratory assessments performed at the laboratory constitute an SAE or AE, it must be recorded as such.

Clinical laboratory tests results will be categorized in accordance with US FDA guidance for industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

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

Subject e-diaries will be issued to trial subjects, trained, and collected by trial site personnel at the visits given in the SoAs (Section 1.3 and Section 13.5).

Subjects will be asked to:

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

If a local and/or systemic reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the trial subject will be requested to report that information to the investigator. Solicited local and systemic events that are recorded in the subject e-diaries should not be reported as AEs unless they meet criteria for an SAE or starts at Days 1 to 7 and continues past Day 7.

Note: in case an e-diary entry was missed, or the e-diary did not work, the site personnel will ask if any reactogenicity event occurred. The site will record reported events that were not entered in the e-diary on the AE page of the CRF.

8.2.5.1 Assessments of intensity for local reactions

Pain (perceived) at the injection site will be assessed as absent, mild, moderate, or severe according to the grading scale in Table 4.

Erythema/redness and induration/swelling will be measured and recorded and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 4.

Table 4: Local reaction grading scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4) [c]
Pain	Does not interfere with activity	Interferes with activity	Prevents daily activity	Requires attendance at an emergency room or hospitalization for severe pain
Erythema / redness [a]	2.5 cm to 5.0 cm (0.98 in to 1.96 in)	>5.1 cm to 10.0 cm (>1.96 in to 3.94 in)	>10 cm (>3.94 in)	Necrosis or exfoliative dermatitis
Induration / swelling [b]	2.5 cm to 5.0 cm	>5.1 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 actual measurement.
c. Investigator or medically qualified person confirmation is required for all reactogenicity graded as Grade 4.

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

8.2.5.2 Assessments of intensity for systemic reactions

Symptoms of systemic reactions will be assessed as absent, mild, moderate, or severe according to the grading scale in Table 5.

Table 5: Systemic reaction grading scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4) [a]
Vomiting	1 to 2 times in 24 h	>2 times in 24 h	Requires intravenous hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 h	4 to 5 loose stools in 24 h	6 or more loose stools in 24 h	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Myalgia	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe muscle pain
Arthralgia	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe joint pain
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
Fever (oral temperature of ≥38.0°C/≥100.4°F)	38.0°C/100.4°F to 38.4°C/101.1°F	38.5°C/101.2°F to 38.9°C/102.0°F	39.0°C/102.1°F to 40.0°C/104.0°F	>40.0°C/>104.0°F

a. Investigator or medically qualified person confirmation is required for all reactogenicity graded as Grade 4.
Source: Based on the US FDA guidance for industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

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

Subject e-diaries will be issued, trained, and collected by trial site personnel at the visits given in the SoAs. Subject e-diaries will be issued, trained, and collected by trial site personnel at the visits given in the SoAs (Section 1.3 and Section 13.5).

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

- Record the worst grade for each symptom in the e-diary at approximately the same time every evening on the day of IMP injection and then every day in the evening for a total of seven consecutive days.
- Measure their oral body temperature using the provided device and record their body temperature in the e-diary every day including the day of IMP injection.
- To assess any solicited local reactions at the injection site as described in Section 8.2.5.1 and solicited systemic reactions as described in Section 8.2.5.2.
- To contact the site immediately in case of severe or potentially life-threatening reactogenicity events.

- To report if an e-diary entry was missed or if the e-diary did not work; if any such events occurred, the site will record them (e.g.) on the AE page of the CRF.

Investigators will review subject e-diary data daily as indicated in the SoAs (Section 1.3 and Section 13.5).

Only an investigator or medically qualified person is able to confirm a trial subject's fever as >40.0°C/>104.0°F (a potentially life-threatening Grade 4 event) for recording in the electronic data capture (EDC) system.

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

If a trial subject experiences a potential Grade 4 reactogenicity, and the grading is confirmed by the investigator or some other medically qualified person, the confirmed Grade 4 reactogenicity will be recorded by the investigator as an SAE.

8.2.7 Assessment of local reactogenicity – Investigator tasks

Investigators will assess acute local and systemic reactogenicity at the visits given in the SoAs (Section 1.3 and Section 13.5). If any acute local reactions meet any SAE criteria, they must be recorded as an SAE.

8.2.8 COVID-19 surveillance

Surveillance of asymptomatic SARS-CoV-2 cases and "confirmed COVID-19" cases will be implemented in this trial.

If a trial subject experiences symptoms consistent with COVID-19 illness they should be advised to contact the site immediately. If confirmed to be a potential COVID-19 illness, the site should schedule an unscheduled "Potential COVID-19 visit" (see the SoAs in Section 1.3 and Section 13.5) as soon as possible and optimally within 3 d after symptom onset (and at the latest after symptom resolution).

The definition of "confirmed COVID-19" cases is based on the US FDA guidance for industry "Development and Licensure of Vaccines to Prevent COVID-19".

Confirmed COVID-19: presence of one or more of the below symptoms and SARS-CoV-2 nucleic acid amplification-based test (NAAT) positive test outcome during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using a certified test):

- Fever or chills
- New or increased cough
- New or increased shortness of breath or difficulty breathing
- Fatigue
- Headache
- New or increased muscle or body aches (pain)
- New loss of taste or smell

- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

Confirmed severe COVID-19 (US FDA definition): SARS-CoV-2 NAAT positive (based on central or local certified tests) and presence of at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg)
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation)
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to an intensive care unit
- Death

Note that:
The US Centers for Disease Control and Prevention (CDC) list of COVID-19 symptoms can be found at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. The symptoms listed by the CDC should not trigger a “Potential COVID-19 Illness Visit” unless, in the opinion of the investigator, deemed necessary.

If new symptoms are reported within 4 d after resolution of all previous symptoms, they will be considered to be part of a single illness and a second illness visit is not required;

Surveillance of potential COVID-19 symptoms should continue even if a trial subject has a positive SARS-CoV-2 test earlier in the trial.

During the 7 d following the vaccination, potential COVID-19, symptoms that overlap with specific systemic events similar to COVID-19 infection, should not trigger a “Potential COVID-19 Illness Visit” unless, in the investigator’s opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator’s opinion, the symptoms are considered more likely to be vaccine reactogenicity, or if the symptoms are equivocal, the investigator may conduct a local SARS-CoV-2 rapid test. If the test result is positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms that overlap with systemic events should be recorded in the reactogenicity e-diary or as AEs, if not captured in the reactogenicity e-diary.

The trial subject is also instructed to contact the site should they receive a positive SARS-CoV-2 test (NAAT or rapid antigen) to inform the site of the result and the date the test was conducted.

Potential COVID-19 Illness Visit:

This visit should be conducted in person. Telehealth visits are not advised unless the investigator has sufficient justifications with no safety concerns for the trial subject. At minimum, the following details should be recorded by the investigator during "Potential COVID-19 Illness Visits":

- Any concomitant treatments (if any)
- Confirmation that the trial subject does not require emergent medical care
- Method of COVID-19 diagnosis
- Any AEs, SAEs, AESIs, AEs leading to subject withdrawal/discontinuation
- Outcome of the brief (symptom-directed) physical examination
- Outcome of the rapid antigen test for SARS-CoV-2 infection

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

Oral swabs for (NAAT-based) SARS-CoV-2 testing will be collected by trial site personnel and analyzed at a local or central laboratory as listed in the SoAs (Section 1.3 and Section 13.5).The devices used most commonly at trial sites come with predefined 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. For test performed at trial sites, 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.

Additionally, any potentially SARS-CoV-2-infected and/or symptomatic trial subjects will be asked to return *ad hoc* 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 timepoint at a central laboratory.

8.2.8.2 Serological testing for SARS-CoV-2 N-binding antibodies

Blood will be drawn by trial site personnel for serological testing for SARS-CoV-2 N-binding antibodies by serum SARS-CoV-2 nucleocapsid protein-specific antibody immunoassay at screening.

SARS-CoV-2 nucleocapsid protein serological testing will be performed at a central laboratory.

8.2.8.3 SARS-CoV-2 sequencing

Swabs for SARS-CoV-2 genomic sequencing storage will be collected by trial site personnel at the timepoints provided in SoAs (Section 1.3 and Section 13.5).

The swabs will be inserted into collection tubes pre-filled with stabilizer solution. The swabs must be stored in the central laboratory at least at -70°C/-94°F until the end of the trial.

Instructions on the sample handling and shipping to the analysis site will be provided in a Laboratory Manual.

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

8.3 Adverse events and SAEs

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

8.3.1 Time period and frequency for collecting AE and SAE information

All AE related information will be collected at the timepoints specified in the SoAs (Section 1.3 and Section 13.5).

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

For Cohorts 1 to 4, AE collection will start from Visit 0 and continue until Visit 4 (i.e., until 1 month follow-up post-Dose 1), and (for subjects who consent to a second dose of IMP after issue of protocol version 5.0) restart from Visit 7 and continue until Visit 9 (i.e., until 1 month follow-up post-Dose 2).

For Cohort 5, AE collection will start from Visit 0 and continue until Visit 9 (1 month post-Dose 2).

AESIs, SAEs, AEs that lead to trial subject discontinuation or withdrawal, and all AEs linked to confirmed COVID-19 cases will be recorded up to the last planned visit for subjects who consent to a second dose of IMP. For subjects in Cohorts 1 to 4 completing Dose 1 only, recording will continue until Visit 6 (6 months post-Dose 1). For subjects in Cohort 5 completing Dose 1 only, recording will continue until the last scheduled visit (5 months post-Dose 1).

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

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

8.3.2 Detecting and reporting AEs and SAEs

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

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

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

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

Investigators are not obligated to actively seek AE or SAE after conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a trial subject has been discharged from the trial, and he/she considers the event to be related (see Section 10.4) to the trial treatment or trial participation, the investigator must promptly notify the sponsor as described in Section 10.4.4.

The investigator may be requested by the sponsor to obtain specific follow-up information in an expedited fashion.

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

For real time monitoring of events which contribute to pausing rule criteria (see Section 7.1.1), all such events (even if non-serious) need to be reported on the SAE form within 24 h of awareness as described in Section 10.4.4.

AESIs have been defined in this trial. For how to report AESIs, see Section 8.3.8.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow up with each trial subject at subsequent visits/contacts.

All AEs and SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the trial subject is lost to follow-up, or the trial subject withdraws consent (as defined in Section 7.3). If no final status is reached by the last planned follow-up visit, the investigator must confirm the unavailability of a final status. Further information on follow-up procedures is provided in Section 10.4.2.2.

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

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

If a trial subject dies during participation in the trial or during a predefined follow-up period (see the SoAs in Section 1.3 and Section 13.5), the investigator will provide the sponsor a copy of any postmortem findings including histopathology.

The investigator will submit initial and follow-up SAE reports to the sponsor or designee within 24 h after the site becoming aware of the event, as indicated in Section 10.4.4.

8.3.4 Reporting requirements for SAEs including SUSARs

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

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

All serious adverse reactions where the nature, severity or outcome is not consistent with the reference safety information are “unexpected serious adverse reactions”. The expectedness assessment for all related SAEs is based on the reference safety information included in Section 6.1.5 of the BNT162 IB and the BNT162b4 IB.

All suspected adverse reactions related to an IMP (the tested drugs and comparators) that occur in this trial, and that are both unexpected and serious, qualify as SUSARs. SUSARs are subject to expedited reporting by the sponsor according to applicable regulatory requirements and guidance (i.e., ICH E2A guidance). Information about analysis of similar events will be added to the SUSAR report. IRBs/IECs will receive SUSAR reports as applicable.

8.3.5 Pregnancy testing and handling of pregnancies

For VOCBP, pregnancy tests will be performed at the times given in the SoAs (Section 1.3 and Section 13.5).

For all trial subjects, pregnancy information will be collected over the time period defined in SoAs (Section 1.3 and Section 13.5).

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

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

If a pregnancy is reported, the investigator should inform the sponsor within 24 h of learning of the pregnancy and should follow the procedures outlined in Section 10.5.3.

Pregnancy *per se* is not an AE (and hence not an SAE). Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

As described in Section 7.1.2, trial subjects who become pregnant will be permanently discontinued from trial treatment and will not have further blood draws, but will otherwise complete all planned assessments, if required including pregnancy follow-up as described in Section 10.5.3.

8.3.6 Death events

Any death that occurs within the observation period will be reported as an SAE, if not covered by the exemptions to the SAE definition as defined in Sections 8.3.7, 10.4.2, and 10.4.2.2, which do also apply for fatal cases. Date and cause of death will be recorded. If available, a copy of an autopsy report should be submitted upon request.

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

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

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

Not applicable.

8.3.8 Adverse events of special interest (AESIs)

An AESI, serious or non-serious, is one of scientific and medical concern specific to the sponsor’s product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor are appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.

The following will be reported as AESIs:

- Anaphylaxis
- Thromboembolic events (e.g., deep vein thrombosis, stroke, myocardial infarction)
- Immune thrombocytopenia
- Immune-based neurologic events (e.g., optic neuropathy, Guillain-Barré syndrome)
- Myocarditis (all Levels of Certainty including “Possible cases” (1 to 3) as per Brighton Collaboration Case Definition), https://brightoncollaboration.org/myocarditis/
- Pericarditis (all Levels of Certainty including “Possible cases” (1 to 3) as per Brighton Collaboration Case Definition), https://brightoncollaboration.org/myocarditis/

All symptoms that could represent myocarditis or pericarditis should be reported within 24 h of awareness using the dedicated Myocarditis or Pericarditis AESI Report Form and reporting to the contact details provided in Section 10.4.4. For guidance on the management of symptoms that could represent myocarditis or pericarditis, see Section 12.2.

All other AESIs, excluding myocarditis and pericarditis, (even if non-serious), should be reported within 24 h of awareness as well, using the AESI Report Form and reporting to the contact details provided in Section 10.4.4. However, if such AESI meets the serious criteria, it must be reported on the SAE form within 24 h of awareness as described in Section 10.4.4.

All AESIs will be followed up until resolution, stabilization, the event is otherwise explained, or the trial subject is lost to follow-up (as defined in Section 7.3).

8.4 Procedures in case of overdose or errors in IMP administration

For a definition of an overdose and errors in IMP administration, see Section 10.4.1.3.3. For the reporting of these events, see Section 10.4.1.3.3.

The sponsor does not recommend specific treatment for an overdose.

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

- Contact the trial Medical Monitor immediately.
- (At the discretion of the investigator) Give symptomatic treatment.
- Closely monitor the trial subject for any AE/SAE and laboratory abnormalities (at least 7 d).
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
- Document the error in IMP administration.

For cases of errors in IMP administration, the trial Medical Monitor, in coordination with the trial safety team, will decide on how the events should be captured in the database, and suggest appropriate corrective and/or preventive actions.

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

8.5 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this trial.

8.6 Genetics

For subjects for whom a CCI sample is obtained, a blood sample for genetic research will be drawn at the times listed in the SoAs (Section 1.3 and Section 13.5). CCI

CCI

8.7 Immune responses

Humoral and cellular immune responses will be assessed as planned in Section 3; see also the SoAs (Section 1.3 and Section 13.5).

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

Humoral immune response assessments will include:

- GMTs at baseline and 28 d after every IMP dose and seroresponses. Other timepoints may be assessed (see the CCI
- Characterization of titers and kinetics of antigen-binding antibodies and functionality of antigen-specific serum antibodies using ligand-binding- and virus neutralization tests.

CCI

8.7.1 Exploratory research

Biosamples for research will be retained for use for up to 15 yrs (or shorter if required by local regulations) after the end of the trial. The tubes with the biosamples will be labeled

with a number (optionally also with a bar code) and will not include information that could be used to identify the subject. Results of the analyses will be linked to the clinical information collected during the trial using this specific number. The analysis will only be carried out on the basis of the label data and biosamples. Research biosamples and all data generated using the biosamples will be handled in accordance with applicable laws and regulations; this includes requirements applicable for data protection and a potential withdrawal of consent.

8.8 Collection of demographic and other baseline characteristics

At screening, the following data will be recorded for all trial subjects: age, sex, ethnic group, race, body weight and height, derived body mass index.

Medical history information will be recorded as listed in the SoAs (see Section 1.3 and Section 13.5).

8.9 Unscheduled visit(s)

In order to conduct evaluations or assessments required to protect the wellbeing of the trial subjects, the investigator may conduct unscheduled visits in addition to those listed in the SoAs (Section 1.3 and Section 13.5).

8.10 Early termination visit(s)

If subjects are permanently discontinued from the trial before completing all scheduled visits, they will be asked to complete an Early Termination Visit as listed in the SoAs (Section 1.3 and Section 13.5).

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

No formal statistical hypotheses will be tested in this trial.

9.2 Sample size determination

The sample size for each cohort is mainly driven by typical small dose escalation designs for early detection of potential safety and reactogenicity events. The sample size is not based on any formal hypothesis test.

For safety outcomes, Table 6 shows the probability of observing at least 1 AE for a given true event rate of a particular AE. For example, if the true AE rate is 2%, with approximately 90 subjects in a vaccine group, there is 84% probability of observing at least 1 AE. Cohort 5 has a lower N, however, the dose given to Cohort 5 will have already been tested within Cohort 4.

Table 6: Probability of observing at least 1 AE, by assumed true event rate

Assumed true event rate of an AE	N=20 (Cohort 5)	N=45 (Cohorts 1,2)	N=90 (Cohorts 3,4)
1%	0.18	0.36	0.60

Assumed true event rate of an AE	N=20 (Cohort 5)	N=45 (Cohorts 1,2)	N=90 (Cohorts 3,4)
2%	0.33	0.60	0.84
3%	0.46	0.75	0.94
4%	0.56	0.84	0.97
5%	0.64	0.90	0.99

Abbreviations: AE = adverse event; N = number of subjects.

9.3 Analysis sets

The following analyses sets are defined:

Analysis set	Description
Screened Set	All subjects who provided informed consent.
Safety Set	All subjects who received at least one dose of IMP.
Dose 2 Safety Set	All subjects who received two doses of IMP.
Randomized/Assigned Set	All subjects who were randomized/assigned with a subject number using the online randomization tool.
Immunogenicity Analysis Set	All subjects who received the planned dose of the IMP on Day 1 and who have at least one valid viral neutralization titer assessment within an appropriate window of the target day.
Immunogenicity Per Protocol Set	All subjects included in the Immunogenicity Analysis Set that have no major protocol deviations that can confound immunogenicity data.

9.4 Statistical analyses

This section gives a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. The SAP, with more details of statistical analyses, will be finalized prior to database snapshot for the primary analysis.

Unless otherwise specified, all statistical analysis will be performed by vaccine group. Safety analyses will be performed on the Safety Set. Immunogenicity analyses will be performed on the Immunogenicity Per Protocol Set; the Immunogenicity Analysis Set may be used for additional analyses.

9.4.1 General considerations

In general, data will be summarized by DL.

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

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

Analysis of antibody titers will be performed on natural log scale and the results will be exponentiated back to original scale.

9.4.2 Primary safety endpoints

The safety endpoints are defined in Sections 3 and 13.6. All safety analyses will be based on the Safety Set.

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 and PT for each AE.

Reactogenicity

Solicited local reactions and systemic events (from the subject e-diary or the AE CRF) will be summarized. In general, solicited reactions will be analyzed for each IMP administration, i.e.:

- Up to 7 d after each IMP injection

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

- Any local reactions or systemic events
- Local reactions or systemic events by maximum severity

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Adverse events

All AEs recorded by the investigator are unsolicited events. The number and percentage of subjects reporting at least one AE from Dose 1 will be summarized by PT nested within system organ class for each of the following AE types (for subjects with at least one AE occurring up to 28 d after each IMP administration, and for subjects in Cohorts 1 to 4 with at least one SAE occurring up to 6 months after each IMP administration and for subjects in Cohort 5 with at least one SAE occurring up to 3 months after last IMP administration):

- Any AE
- Grade of AE
- Related AE
- Related Grade ≥3 AE
- Any SAE
- Related SAE
- Any AESI
- Related AESI

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

Additional safety analyses may be described in the SAP.

9.4.3 Secondary immunogenicity endpoints

The secondary endpoints are defined in Sections 3 and 13.6.

Cohorts 1 to 4

Geometric mean titers (GMTs) of SARS-CoV-2 ancestral strain and Omicron neutralizing antibody with associated 95% confidence interval (CI) will be calculated at each timepoint as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transformations of assay results, calculating the 95% CI with reference to the Student t distribution, and then exponentiating the confidence limits.

Geometric mean fold rises (GMFR) of SARS-CoV-2 ancestral strain and Omicron neutralizing antibody with associated 95% CI will be calculated at each timepoint. GMFRs are defined as ratios of the results after vaccination to the results before vaccination (pre-Dose 1). GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later timepoint minus earlier timepoint) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using the Student t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

Seroresponse is defined as achieving ≥4-fold rise from baseline (pre-Dose 1). If the baseline measurement is below lower limit of quantitation (LLOQ), the postvaccination measure of ≥4 × LLOQ is considered seroresponse. The counts, percentages and associated Clopper-Pearson 95% CI of subjects with seroresponse at each timepoint will be provided.

Further details of the secondary immunogenicity analyses will be described in the SAP.

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9.4.5 Other safety analyses

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

9.4.6 Other analyses

Other analyses will be described in the SAP.

9.5 Interim analyses

As this is an observer-blind Phase I trial, the sponsor may conduct unblinded reviews of the data during the course of the trial (e.g., at 7 d and 28 d after each IMP administration) for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development. For further details, see the SAP.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, ethical, and trial oversight considerations

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

10.1.1 Regulatory and ethical considerations

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

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

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

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

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

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

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 (if applicable), and all other applicable local regulations.
- Informing the sponsor immediately about any urgent safety measures taken by the investigator to protect the trial subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of (see Section 10.1.13).

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 yr after completion of the trial.

10.1.3 Informed consent process

Informed consent must be obtained before any trial-specific screening procedure is performed. For subjects in Cohorts 1 to 4 consenting to a second dose of IMP and trial procedures as implemented by protocol version 5.0, informed consent must also be obtained before any procedures implemented by protocol version 5.0 are performed.

Trial subjects must be informed that their participation is voluntary.

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

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

The medical record must include a statement that written informed consent (including version and type of ICF) was obtained before the trial subject was enrolled in the trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Trial subjects must be informed in a timely manner if new information becomes available that may impact their willingness to participate in the trial. If required, trial subjects will be reconsented to updated written information and consent forms.

Trial subjects who are rescreened must re-consent.

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

10.1.4 Data protection

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

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

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

Any trial subject records or datasets that are transferred to the sponsor will contain the identifier only; trial subject names or any information which would make the trial subject identifiable will not be transferred.

The trial subject must be informed that their personal trial-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be

explained to the trial subject who will be required to give consent for their data to be used as described in the informed consent.

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

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

10.1.5 Committees – IRC

A trial IRC will be established to provide medical oversight of trial subject safety during the conduct of this trial, with a focus on guidance, management of emergent safety issues, and decision making as outlined in the IRC Charter. It includes periodic in-depth review of safety data by trial subject, cohort, and cumulatively, in order to confirm mechanism of action, identify potential off-target toxicities, and to understand the IMP's safety profile and feasibility for further clinical development. The IRC is also a forum for the discussion of other data which could impact the IMP benefit-risk assessment, thereby allowing the IRC to periodically assess the overall benefit-risk of the IMP.

All SAEs considered related either by the investigator or the sponsor will trigger an *ad hoc* review by the IRC.

The IRC will be constituted and act according to procedures described in the IRC Charter. The charter will define suitable measures to maintain the blinding described in Section 6.3.2. The IRC will prepare written minutes of its meetings. Documentation of IRC activities will be filed in the trial master file.

10.1.6 Dissemination of clinical trial data

A final ICH E3 conform report integrating all trial results will be prepared by the sponsor.

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

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

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

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

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

The sponsor may provide researchers secure access to subject-level data, expert summaries, lay summaries, and CSRs for the purposes of “bona fide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. In these cases, all trial patient level data will be anonymized in accordance with applicable privacy laws and regulations.

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

10.1.7 Data quality assurance

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

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

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

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

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

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

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

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

10.1.8 Source documents

Source documents provide evidence for the existence of the trial subject and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

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

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

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

10.1.9 Publication policy

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

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

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

The sponsor will comply with applicable requirements for publication of trial results. In accordance with standard editorial and ethical practice, including those established by the International Committee of Medical Journal Editors (ICJME). The sponsor will generally support publication of multi-site trials only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with ICJME authorship requirements.

10.1.10 Protocol preparation and approval

This protocol has been prepared, reviewed and approved in accordance with the sponsor's standard operating procedures. Documentation of this process is filed in the trial master file.

10.1.11 Investigators and trial administrative structure

10.1.11.1 Investigators and trial site personnel

There must be an investigator at each trial site.

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

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

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

If the trial is conducted at multiple trial sites, a coordinating investigator must be assigned who is responsible for the coordination of investigators at different trial sites. The responsibilities of the coordinating investigator must be documented before any trial-related procedure is performed.

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

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

10.1.11.2 Trial site personnel assigned trial-related duties

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

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

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

10.1.11.3 Contract research organizations

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

10.1.11.4 The sponsor and sponsor’s personnel

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

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

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

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

10.1.12 Premature termination or suspension of the trial

If the trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authorities. In addition:

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, applicable sponsor procedures, or the ICH GCP guidelines.
- Inadequate recruitment of trial subjects by the investigator.
- Discontinuation of further IMP development based on sponsor decision.
- If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator should promptly inform the trial subject and should assure appropriate therapy and/or follow-up (if applicable).

If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial, the investigator should inform the institution where applicable and the investigator should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

10.1.13 Reporting of serious breaches

A serious breach is any deviation from the approved protocol version that is likely to affect to a significant degree the safety of a trial subject and/or the rights of trial subjects and/or the reliability and robustness of the data generated in the clinical trial.

Trial sites, including pharmacists, CROs and other designees of the sponsor, must report any suspected serious breaches promptly to the sponsor. Suspected serious breaches, as well as any communication related to suspected serious breaches, must be reported to the sponsor by e-mail using the following e-mail address within 24 hours of knowledge:

- [redacted]

The sponsor will assess each suspected serious breach to decide whether it should be reported as a serious breach. The sponsor will comply with country-specific regulatory requirements relating to the reporting of serious breaches to regulatory authorities and IRBs/IECs.

10.2 Data collection and management

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

10.2.1 Data management

The CRO will be responsible for data management of this trial, including quality checking of the data.

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

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

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

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

10.2.2 Case report forms

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

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

10.2.3 Subject-reported outcomes

Subject e-diaries will be used for the reporting of reactogenicity (local and systemic reactions) by the trial subjects. See Section 8.2.5 for details (for e-diaries).

10.2.4 Investigator's Site File and the Trial Master File

The principal investigator is responsible for the filing of all essential documents in an ISF. The sponsor is responsible for the timely filing of all essential documents in the 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 must ensure that all source data/documentation related to the trial is recorded, handled, and stored in a way that

allows its accurate reporting, interpretation and verification. The principal investigator must take measures to prevent accidental or premature destruction of these documents.

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

10.3 Clinical laboratory tests

Blood/urine sampling for clinical laboratory tests will be performed at the time/days listed in the SoAs (Section 1.3 and Section 13.5).

The clinical laboratory tests are:

- Chemistry: alkaline phosphatase, alanine transaminase, creatinine, C-reactive protein, albumin, amylase, aspartate transaminase, gamma glutamyl transpeptidase, total bilirubin, indirect and direct bilirubin, blood urea nitrogen, glucose, lipase, cardiac troponin I.
- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (absolute and %; neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count.
    - Women who are VOCBP will be measured for serum β-HCG at Visit 0.
    - Women who are not VOCBP will be measured for follicle stimulating hormone (FSH) at Visit 0 (to confirm postmenopausal status).
- 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.

Additional tests may be performed (including the addition of parameters) at any time during the trial as determined necessary by the investigator or required by local regulations.

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

10.4.1 Definition of AEs

- An AE is any untoward medical occurrence in a trial subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment.

    - NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

10.4.1.1 Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- New conditions diagnosed after the date informed consent was given (ICF signed and dated) but before the first administration of trial treatment, that meet the criteria for SAEs.
- New conditions diagnosed after the first administration of trial treatment.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or severity of the condition.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial treatment or a concomitant medication. Overdose *per se* will not be reported as an AE/SAE.

10.4.1.2 Events not meeting the AE definition

- (This trial will allow enrollment of healthy volunteers with pre-existing stable disease) Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the trial subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur or continue (social and/or convenience admission to a hospital).
- New conditions diagnosed after the date informed consent was given (ICF signed and dated) but before the first administration of trial treatment that does not meet the criteria for an SAE.
- (This trial will allow enrollment of healthy volunteers with pre-existing stable disease) Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.
- (This trial will allow enrollment of healthy volunteers with pre-existing stable disease) Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are further specified in Section 8.3.7.

10.4.1.3 Documentation of particular situations

10.4.1.3.1 AEs that are secondary to other events

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

If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be documented as AE.

If vomiting results in severe dehydration, both events should be documented as AEs separately.

10.4.1.3.2 Abnormal laboratory results and vital signs values

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

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

10.4.1.3.3 AEs associated with an overdose or error in drug administration

An overdose is the accidental or intentional use of a drug in an amount (per administration or cumulatively) higher than the dose being studied (for the trial treatment) or higher than the maximum recommended dose according to the authorized product information (for approved concomitant medications).

An error in drug administration is any administration outside what is foreseen in the protocol (higher or lower), including misuse and abuse of the product.

An overdose or incorrect administration of a drug is not itself an AE, but it may result in an AE.

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

As of issue of protocol version 5.0, all cases of overdose or incorrect administration of a drug with or without AEs must be captured as AEs in the CRF as follows:

- If without an associated AE, as non-serious, related, Grade 1 AEs.
- If with an associated AE, as related with seriousness and grade corresponding to the associated AE.

10.4.1.4 Suspected adverse reactions

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

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

The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

10.4.2 Definition of SAEs

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 hospitalization or prolongation of existing hospitalization:
- In general, hospitalization signifies that the trial subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity:
- The term disability means a substantial disruption of a person’s ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly or birth defect.
- Other situations:
- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the trial subject or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE); see Section 10.4.2.2 for guidance on the assessment of severity; the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be assessed independently for each AE recorded on the CRF.

SAEs must be reported by the investigator to the sponsor within 24 h after learning of the event; see Section 10.4.4 for reporting instructions.

10.4.2.2 SAE exemptions

In general, SAEs are defined according to ICH Topic E2A (CPMP/ICH/377/95), EU Directive 2001/20/EC and ENTR/CT-3 (see Section 10.4.2). In the present trial, some events are excluded from the SAE definition. The following events do not need to be reported as SAEs:

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

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

AE and SAE recording

The investigator needs to assess and document any AE regardless of association with the use of the trial treatment during the period of observation (see Section 8.3.1).

- Data pertaining to AEs will be collected during each trial visit. Based on the trial subject’s spontaneous description or investigator’s inquiry or discovered in the course of examinations done during the visit, clinical significance of any sign or symptom needs to be evaluated by the investigator. For the handling of reactogenicity reported by the trial subjects, see Section 8.2.5.1.

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

Assessment of severity

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

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

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

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

- Initial intensity of the AE

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

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

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

Actions taken by the investigator

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

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

- Dose not changed (= continuation of trial treatment administration according to the trial protocol)
- Dose reduced (= reduction of the trial treatment dosage *)
- Drug interrupted (i.e., trial treatment withdrawn temporarily, interruption and resumption); i.e.:
    - Drug withdrawn (i.e., trial treatment permanently withdrawn)
- Unknown (e.g., in case the trial subject is lost to follow-up)
- Not applicable (e.g., in case treatment with trial treatment has not yet started or event starts after last trial treatment administration)

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

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

- None
- Initiation of a remedial (concomitant) therapy

Investigator assessment of the outcome of an AE

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

- Recovered/resolved* (= complete resolution of the AE)
- Recovering/resolving (= AEs which are improving but not yet resolved completely, e.g., decreases in severity grade)
- Not recovered/not resolved (= AEs which are ongoing without improving or still present when the trial subject deceases due to another cause)

- Recovered/resolved with sequelae * (= trial subject recuperated but retained pathological conditions resulting from the AE; the sequelae should be indicated)
- Fatal ** (= death due to the AE)
- Unknown (e.g., in case the trial subject is lost to follow-up)

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

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

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

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

Assessment of causality

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

The investigator will use clinical judgment to determine the relationship.

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

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

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

The relationship or association of an AE or SAE to a trial treatment/trial procedure will be assessed by the investigator after having evaluated all accessible data and, if necessary, he/she will re-evaluate the case as new information becomes available.

Events caused by the procedure of trial treatment administration should be differentiated from events caused by the trial treatment itself. Only events suspected to be caused by the IMPs itself should be documented as suspected adverse reactions but not events caused by the procedure of trial treatment administration.

In this trial, it cannot be excluded that during the course of the trial some procedures give rise to AEs which are related to the trial procedure and not to the trial treatment. Procedure-related AEs occur during or after trial-specific procedure (e.g., discomfort after blood drawing) must be reported in the CRF on AE pages as “related to trial procedure” with the causing procedure specified. These procedure-related AEs should not include

events which correspond to solicited local reactions captured by subject e-diaries (these reactions, see Section 8.2.5.1).

Notes applicable for relationship to trial procedures including trial treatments

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

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

10.4.4 Reporting of SAEs

All SAEs (defined in Section 10.4.2) which occur in a trial subject during the observation period, whether considered to be associated with trial medication or not, must be reported by the investigator to the sponsor within 24 h following first knowledge of the event.

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

SAE reporting to the sponsor using paper report forms

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

- Safety Report Fax No.: +49 (0) 6131 908 [redacted]
- Safety Report E-Mail address: [redacted]

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

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

For SAEs follow-up information should be sent to the sponsor (indicating that this is a “follow-up” report using the respective SAE Form or the Additional Information and Follow-Up Form) within 24 h after the site becoming aware of the update as described above and accompanied by appropriate anonymous supporting documentation (e.g., discharge letters, medical reports or death certificates), until a final outcome and date are available. All confidential information (name, address, full date of birth) needs to be blackened before sending.

For SAEs, in addition to a medical record, the investigator should complete an Additional Information and Follow-Up Form, which contains the event term and subject number.

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

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

- E-Mail: [redacted]

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

10.4.5 Assessment of laboratory abnormalities

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

10.5 Contraceptive guidance and collection of pregnancy information

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

10.5.1 Definitions

Volunteer of childbearing potential

A trial subject born female is considered of childbearing potential, i.e., fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Documentation for sterilization can come from the trial site personnel's review of the trial subject's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the subject's medical record for the trial.

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

Postmenopausal female

For the purpose of this document, a postmenopausal state is defined as no menses for 12 months without an alternative medical cause (verified by high FSH levels).

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

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

Fertile men

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

10.5.2 Contraception guidance

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

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

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

- Combined estrogen and progestogen-based hormonal contraception associated with inhibition of ovulation [1], i.e., established use of (oral, intravaginal, or transdermal) hormonal methods of contraception.
- Progesterone-only based contraception associated with inhibition of ovulation [1], i.e., established use of (oral, injected, or implanted) hormonal methods of contraception. [2]
- Intrauterine device. [2]
- Intrauterine hormone-releasing system. [2]
- Bilateral tubal occlusion. [2, 5]
- Bilateral vasectomy (for a male trial subject or male partner of a female trial subject). [2, 3]
- Sexual abstinence. [4]

1 Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

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

3 A vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the VOCBP trial subject and that the vasectomized partner has received medical assessment of the surgical success.

4 In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the trial subject.

5 Includes bilateral tubal ligation.

10.5.3 Collection of pregnancy information

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

The initial and follow-up information must be documented on the paper-based Pregnancy Reporting Form and submitted to the sponsor within 24 h of learning of a trial subject's pregnancy/partner's pregnancy and in the CRF. The completed form needs to be sent to the Safety Report Fax number or E-Mail given in Section 10.4.4. Completed pregnancy forms must be signed by an investigator before faxing/mailing them to the sponsor. Blank

reporting forms are provided to the investigator during the site initiation visit and are filed in the ISF.

The investigator will collect follow-up information on the trial subject/trial subject's partner and the child (at least two times, i.e., at the time of expected date of delivery and around the time of the child's first birthday), 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.

Pregnancy *per se* is not an AE (and hence not an SAE). Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Any post-trial pregnancy-related SAE considered reasonably related to the trial treatment by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former trial subjects, the investigator may learn of an SAE through spontaneous reporting.

10.6 Liver safety: Suggested actions and follow-up assessments

Not applicable.

10.7 Standard definitions

10.7.1 Trial site start/closure and trial discontinuation

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

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

A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

All trial sites will be closed upon trial completion.

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

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

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

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

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

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

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

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

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

10.7.2 Trial completer and end of trial definitions

A trial subject is considered to have completed the trial if they have completed the last scheduled procedure shown in the SoAs (see Section 1.3 and Section 13.5).

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

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

10.8 Protocol amendments and updates

10.8.1 Update from protocol version 1.0 to 2.0

The second sponsor approved version was issued to correct two instances where the IMP dose was incorrectly listed and potentially misleading descriptions of some trial treatments. Since related to trial treatment, it was decided to update and re-issue the document (which had not been submitted to any regulatory or ethical body). Minor editorial changes, such as the correction of typing errors, are not specifically listed.

10.8.2 Update from protocol version 2.0 to 3.0

The third sponsor approved version was issued to reflect the decision to use BNT162b2 Bivalent and not BNT162b5 Bivalent, to correct potentially misleading wording in the trial objectives, to eliminate some text duplication in the description of the overall trial design. At the same time, other updates for clarification and alignment with developing sponsor standards were implemented. See the table below for a summary of the reasons for major changes compared to the previous version. Minor editorial changes, such as the correction of typing errors, are not specifically listed here. A redline draft showing all content updates is available upon request.

Section	Reason for change
All sections	Update to reflect the decision to use BNT162b2 Bivalent and not BNT162b5 Bivalent.
1	Update to correct potentially misleading wording in the trial objectives. Update to eliminate some text duplication in the description of the overall trial design.
2.1, 2.2	Update to reflect the decision to use BNT162b2 Bivalent and not BNT162b5 Bivalent.
2.3	Update to mention general risks only in the IB. Update to delete the potential risks linked to use of BNT162b5 Bivalent.
3	Update to correct potentially misleading wording in the trial objectives.
4.1	Update to eliminate some text duplication in the description of the overall trial design.

Section	Reason for change
5.3	Update to add guidance for blood or blood products donations during trial participation.
6.3.2.4	Update to clarify ambiguous text regarding blinding.
6.3.2.5	Update to add guidance regarding blinding of sponsor personnel.
6.5.2	Update to repeat guidance on the sue of seasonal influenza vaccines given in Section 5 also in this section.
7.1.2	Content deleted since not a relevant for a 1-dose trial.
8.2.5	Additional guidance was added for subject e-diaries for assessment of reactogenicity (local and systemic reactions). The local reaction grading scale was updated to align with other infectious disease protocols.
8.3.2	Additional guidance was added for clarification regarding the reporting method for AEs and SAEs.
8.3.8	Additional guidance was added for clarification regarding the reporting method for AESIs.
8.7	Updated to refine the description of the planned immune response assessments.
9.3	Updated to refine the description of the immunogenicity analysis set.
9.4.2	Detail was added regarding how the number and percentage of subjects reporting at least one AE from Dose 1 will be summarized.
9.5	Updated to refine the description of the interim analyses.
10.1.1	Updated to clarify principal investigator responsibilities.
10.5	Content for acceptable methods of contraception was deleted, since not an option in this trial. Content was updated to clarify the timing for follow-up following pregnancy.

10.8.3 Update from protocol version 3.0 to 4.0

The fourth sponsor approved version was issued to reflect the decision to add Cohort 3b that comprises subjects aged >55 yrs. See the table below for a summary of the reasons for major changes compared to the previous version. Minor editorial changes, such as the correction of typing errors, are not specifically listed here. A redline draft showing all content updates is available upon request.

Section	Reason for change
All sections	Update to reflect the decision to add Cohort 3b that comprises subjects aged >55 yrs.
1.1	Correction to align with inclusion criteria 7, whereby the last COVID-19 RNA vaccine dose must have been administered at least 90 d before Visit 1.
1.3	Update to visit windows for Visits 2 and 4 to allow flexibility, with no impact on primary endpoints; addition to footnote “m” to allow SARS-CoV-2 repeat testing (N-binding antibody testing); update to clarify that blood volumes for CCI can be approximately 5 mL.
4.3	Update to include safety data from the trial C4591044.
5.2	Deletion in exclusion criteria 2 for clarification: drug product has no detectable levels of antibiotics; update to include exclusion criteria 3a definition of high dose inhaled corticosteroids per most recent national guidelines; update to exclusion criteria 3d to provide investigators guidance on congestive heart failure exclusion due to change in cohort enrollment; update to exclusion criteria 3g to provide clarity around exclusion parameters relevant to ECG interpretation.
1.1, 6.1	Update to provide clarity on position of injection to avoid shoulder injury related to vaccine administration (SIRVA).
8.2.4	Update for clarification.
9.4.3	Update for clarification.
9.5	Update to correct that this is an observer-blind, not open-label, trial.
10.3	Update to restructure for clarity.
10.4.4	Update to add new fax number and e-mail addresses for safety reporting.
10.5.2	Insertion of footnote for clarification on tubal occlusion and tubal ligation.

Section	Reason for change
11	Update to references that were preprints and are now published, and addition of US National Heart, Lung, and Blood Institute Guidance 2007. Expert Panel Report 3.

10.8.4 Update from protocol version 4.0 to 5.0

The fifth sponsor approved protocol version was issued to reflect the decision to add a 30 µg BNT162b4 dose level with the addition of Cohorts 4a and 4b that comprise subjects respectively aged 18 to 55 yrs of age and >55 yrs of age dosed with 30 µg BNT162b2 Bivalent plus 30 µg of BNT162b4 or one dose of 30 µg BNT162b2 Bivalent alone. In addition, this update allows administration of a second dose of BNT162b4 + BNT162b2 Bivalent to subjects who received one dose of BNT162b4 + BNT162b2 Bivalent, with Dose 2 being the same BNT162b4 dose level as Dose 1, i.e., 5 µg, 10 µg, 15 µg, or 30 µg.

See the table below for a summary of the reasons for major changes compared to the previous version. Minor editorial changes, such as the correction of typing errors, are not specifically listed here. A redline draft showing all content updates is available upon request.

Section	Reason for change
All sections	Update to reflect the additions of Cohorts 4a and 4b for a 30 µg BNT162b4 DL and of a second dose of BNT162b4 + BNT162b2 Bivalent to subjects who had previously received a dose of BNT162b4 + BNT162b2 Bivalent. The addition of Cohort 4 is to investigate the dose related difference in immunogenicity from an increase in BNT162b4, and based on the current safety assessment, as well as the safety and tolerance of increased BNT162b+b4 + BNT162b2. The addition of Dose 2 is to investigate the immunogenicity and safety of a second dose of BNT162b2+b4. Both additions are based on the assessment of interim data of the study regarding immunogenicity and safety, as well as consideration of lifecycle asset planning and management in addition to current VOC dynamics.
1.1 and 3	Additions for clarifications and to reflect this update.
1.1 and 4.1	Additions for clarifications on randomization and N-binding antibody status and to reflect this update. The proposed 56 d between Dose 1 and a Dose 2 will be extended to 6 to 7 months because immunogenicity data obtained from the 5 µg dose group suggests a prolonged interval between first dose and a booster would be advantageous immunologically.
1.1 and 6.1	Additions for clarifications and to reflect this update.

10.8.5 Update from protocol version 5.0 to 6.0

The sixth sponsor approved protocol version was issued to reflect the decision to add BNT162b2 Monovalent (OMI XBB.1.5) for Cohorts 3 and 4, which will be administered for Dose 2 (booster):

- 30 µg BNT162b2 Monovalent (OMI XBB.1.5) plus 15 µg BNT162b4 for Cohorts 3a and 3b.
- 30 µg BNT162b2 Monovalent (OMI XBB.1.5) plus 30 µg BNT162b4 for Cohorts 4a and 4b.

See the table below for a summary of the reasons for major changes compared to the previous version. Minor editorial changes, such as the correction of typing errors, are not specifically listed here. A redline draft showing all content updates is available upon request.

Section	Reason for change
All sections	Update to reflect the addition of BNT162b2 Monovalent (OMI XBB.1.5) for Cohorts 3a, 3b, 4a, and 4b.
1.1	Table 1 was updated for clarification.
1.1 and 3	Objectives/endpoints - Updates to reflect addition of BNT162b2 Monovalent (OMI XBB.1.5) and for clarification.
1.1 and 4.1	Overall design - Updates to reflect addition of BNT162b2 Monovalent (OMI XBB.1.5) and for clarification. The description of the overall design was simplified for improved comprehension.
1.1, 4.1, and 6.3.1	Updates for clarification on randomization.
1.1 and 6.1	Trial treatments - Updates to reflect addition of BNT162b2 Monovalent (OMI XBB.1.5) and for clarification.
1.3	Schedule of activities – updated for further clarification of the required AE recording.
2	Updates to reflect the addition of BNT162b2 Monovalent (OMI XBB.1.5).
8.2.8	Updates for clarification and harmonization of COVID-19 surveillance with other sponsor trials investigating BNT162b2, BNT162b4, and BNT162b2-based variant vaccines.
8.3.1	Updates for clarification on AEs that are collected after 28 d after IMP administration.
8.6	Updated to expand the subjects for whom samples for genetics will be drawn.
8.10	Updated for clarification.
9.3	Insertion describing the Randomized Set.
9.4.3	Insertion describing the secondary immunogenicity endpoint analyses.
10.8.5	Insertion to describe this update.
11	Addition of references reflecting the addition of BNT162b2 Monovalent (OMI XBB.1.5).

10.8.6 Update from protocol version 6.0 to 7.0

The seventh sponsor approved protocol version was issued to reflect the decision to add an additional cohort. Healthy subjects (N=20) aged 18 to 55 yrs in Cohort 5 will receive two doses of 30 µg BNT162b4 alone, 2 months apart.

See the table below for a summary of the reasons for major changes compared to the previous version. Minor editorial changes, such as the correction of typing errors, are not specifically listed here. A redline draft showing all content updates is available upon request.

Section	Reason for change
All relevant sections	Updates to reflect the addition of Cohort 5 that comprises healthy subjects aged 18 to 55 yrs who will receive two doses of 30 µg BNT162b4 alone.
Title page	Addition of ClinicalTrials.gov identifier.
1.1	Updates for clarity and to include that BNT162b2 Monovalent (OMI XBB.1.5) has marketing authorization.
1.1 and 3	Updates for clarity.
1.1 and 4.1	Updates for clarity.
1.1 and 6.1	Updates for clarity.
1.3	Updates for clarity, including that sites are not requested to collect thermometers at the end of the trial.
2.1.2	Updates for clarity and to include that BNT162b2 Monovalent (OMI XBB.1.5) has marketing authorization.
2.2	Updates for clarity and to include that BNT162b2 Monovalent (OMI XBB.1.5) has marketing authorization.
2.3.2	Updates to include risk management plan content, for clarity, and to include that BNT162b2 Monovalent (OMI XBB.1.5) has marketing authorization.
2.3.3	Deletion of paragraph, and moved this paragraph to the more relevant Sections 1.1 and 4.1.
4.1	Updates for clarity and to include that BNT162b2 Monovalent (OMI XBB.1.5) has marketing authorization.

Section	Reason for change
5.1	Additions for clarity.
5.2	Updates for clarity.
6.3	Updates for clarity.
7.1.1	Additions for clarity and to include BNT162b4 + BNT162b2 Monovalent (OMI XBB.1.5) and BNT162b4 alone.
8.2.5	Updates for clarity.
8.2.8	Updates for clarity, including COVID-19 case definitions for reporting.
8.3	Updates for clarity.
8.7.1	Updates for clarity.
9.2	Updates for clarity including addition of sample sizes for AEs.
9.3	Extended to include Cohort 5, which is assigned and not randomized.
9.4	Updates for clarity.
10.1.13	Addition of new section to describe the reporting of serious breaches, including an e-mail address.
10.4.4	Updates for clarity.
10.8.6	Insertion to describe this update.
11	Updates for clarity.
13	Addition of new section to describe Cohort 5 specific information.

11 REFERENCES

BNT162 investigator's brochure, current edition.

BNT162b4 investigator's brochure, current edition.

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12 ADVERSE REACTION MANAGEMENT

12.1 Management of local and systemic reactogenicity events

The adverse reactions determined for BNT162b2 from the available unblinded clinical trial data (from BNT162-02 / C4591001) 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 1 to 3 d after BNT162b2 administration. Additional adverse reactions determined from the clinical trial data are lymphadenopathy, nausea and malaise. Since authorization of BNT162b2, anaphylaxis has been reported and determined to be an adverse reaction. For details see the BNT162 IB.

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

- After the first occurrence of flu-like symptomatology including fever, subjects can be treated with standard therapeutic dose of acetaminophen (preferable), or a non-steroidal anti-inflammatory drug if acetaminophen is contraindicated, according to local guidance after the immunization.
- Corticosteroids should be avoided as either prophylaxis or treatment as it counteracts the effects of immunization.

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 trial Medical Monitor should be informed.

12.2 Management of symptoms that could represent myocarditis or pericarditis

If any trial subjects report symptoms that could represent myocarditis or pericarditis, please follow the US CDC Clinical Considerations for myocarditis and pericarditis following COVID-19 (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html) which includes but not limits following:

- Consider myocarditis and pericarditis in persons with acute chest pain, shortness of breath, or palpitations.
- For suspected cases, consider consultation with cardiologists for assistance with cardiac evaluation and management. Evaluation and management may vary depending on the patient age, clinical presentation, potential causes, or practice preference of the provider.
- For follow-up of patients with myocarditis, consult the guidance from the American Heart Association and American College of Cardiology.
- It is important to rule out other potential causes of myocarditis and pericarditis. Consider consultation with infectious disease and/or rheumatology to assist in this evaluation.

Where available, evaluate for potential causes of myocarditis and pericarditis, particularly acute COVID-19 infection (such as PCR testing), current or prior SARS-CoV-2 infection (such as, detection of SARS-CoV-2 antibodies), and other viral causes (such as, enterovirus PCR and comprehensive respiratory viral pathogen testing).

12.3 Management of risks associated with anemia

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

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

12.4 Management of risks linked to the pandemic COVID-19

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

- Avoidance of contact with persons tested positive for SARS-CoV-2.
- Practice of social distancing and follow good practices to reduce their chances of being infected or spreading COVID-19 during their participation in the trial.
- Completion of health status checks which include symptom-directed physical examinations, vital signs assessments, and clinical laboratory tests as planned in the SoAs (see Section 1.3 and Section 13.5).
- Assessments planned at the predefined “Potential COVID-19 Illness Visit”.

Subjects will be asked to contact the trial site during their participation in the trial should they require guidance or should they experience any symptoms of illness. The reporting of any symptoms of illness, e.g., enhanced respiratory disease or flu-like symptoms, may trigger diagnostic measures at the discretion of the investigator.

13 COHORT 5 SPECIFIC INFORMATION

13.1 Summary – Cohort 5

See Section 1.1 for a synopsis of the overall trial.

See Figure 4 for a schema depicting Cohort 5.

See Section 13.5 for the SoA for Cohort 5.

13.2 Introduction – Cohort 5

13.2.1 Background

See Section 2 for an introduction including trial background.

13.2.2 Rationale

Cohort 5 will investigate the safety, reactogenicity, and immunogenicity of two doses of 30 µg BNT162b4 alone in healthy subjects aged 18 to 55 yrs. See Section 2.2 for the trial rationale.

13.2.3 Benefit/risk assessment

No additional risks are anticipated for Cohort 5 beyond those described in Section 2.3. The benefit-risk balance is assessed as positive for BNT162b4 administered as monotherapy.

13.3 Trial design – Cohort 5

13.3.1 Planned number of trial subjects

See Table 2 for the planned number of trial subjects.

13.3.2 Trial duration

The planned trial duration for each trial subject in Cohort 5 who receives two doses of IMP is up to ~6 months (up to ~1 month [28 d] screening and ~3 months follow-up after Dose 2 of IMP).

13.4 Trial assessments and procedures – Cohort 5

For assessments and procedures, see Section 8.

13.5 Schedule of activities – Cohort 5

The SoAs provide an overview of the trial visits and procedures. The investigator may conduct 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.

If, for any reason, subjects are permanently discontinued from the trial before completing all scheduled visits, if possible trial subjects should complete all assessments planned for the Early Termination Visit.

Table 7: Schedule of activities – Cohort 5

Activity	Visit 0 (V0)	V1	V1	V3	V4	V7	V8	V9	V10	Early term. Visit	Unsche-duled [l]
Visit description	Screening at ≤28 d pre-V1	Pre-dose	Dose 1 (D1)	7 d post-D1	28 d post-D1	Dose 2 (2 m post-D1)	7 d post-D2	28 d post-D2	3 m FU post-D2		Potential COVID-19 Illness Visit
Days relative to Dose 1	N/A	1	1	8	29					N/A	N/A
Permitted visit window				+2 d	±3 d	±7 d post-V3	+2 d from 7 d post-D2	±3 d from 28 d post-D2	±7 d from 3 m post-D2		
Obtain informed consent	X										
Inclusion / exclusion criteria	X	X (review)									
Medical history incl. prior medication and COVID-19 vaccinations / SARS-CoV-2 infections	X	X (update)									
Physical examination	X	X [a]		X [a]	X [a]	X [a, n]	X [a]	X [a]	X [a]	X [a]	X [a]
Height & body weight	X										
Vital signs [c]	X	X [b]	X [b]	X	X	X [b]	X	X			
12-lead ECG	X	X		X			X				

Activity	Visit 0 (V0)	V1	V1	V3	V4	V7	V8	V9	V10	Early term. Visit	Unsche-duled [l]
Visit description	Screening at ≤28 d pre-V1	Pre-dose	Dose 1 (D1)	7 d post-D1	28 d post-D1	Dose 2 (2 m post-D1)	7 d post-D2	28 d post-D2	3 m FU post-D2		Potential COVID-19 Illness Visit
Days relative to Dose 1	N/A	1	1	8	29					N/A	N/A
Permitted visit window				+2 d	±3 d	±7 d post-V3	+2 d from 7 d post-D2	±3 d from 28 d post-D2	±7 d from 3 m post-D2		
Urine sample for clinical laboratory [d]	X	X		X			X				
Blood draw for clinical laboratory [f]	X 15 mL	X 15 mL		X 15 mL			X 15 mL				
Blood draw for viral screen [e]	X 5 mL										
Pregnancy test for VOCBP [g]	X	X			X	X [n]		X	X	X	
Counsel / remind subjects to use contraception		X		X		X [n]	X				
Record pregnancies		Start	=>	=>	=>	=>	=>	=>	End	End	
N-binding antibody test to detect prior SARS-CoV-2 infection	X [m] 5 mL										
Rapid antigen test for SARS-CoV-2 infection		X [m]									X
Oral swabs for NAAT-based SARS-CoV-2 testing and sequencing for surveillance (central test site)	X	X		X	X	X	X	X		X	X
IMP administration			X			X					
Investigator assessment of reactogenicity for up to 1 h after IMP administration			X			X					

Activity	Visit 0 (V0)	V1	V1	V3	V4	V7	V8	V9	V10	Early term. Visit	Unsche-duled [l]
Visit description	Screening at ≤28 d pre-V1	Pre-dose	Dose 1 (D1)	7 d post-D1	28 d post-D1	Dose 2 (2 m post-D1)	7 d post-D2	28 d post-D2	3 m FU post-D2		Potential COVID-19 Illness Visit
Days relative to Dose 1	N/A	1	1	8	29					N/A	N/A
Permitted visit window				+2 d	±3 d	±7 d post-V3	+2 d from 7 d post-D2	±3 d from 28 d post-D2	±7 d from 3 m post-D2		
Issue thermometer/confirm subjects still have thermometer		Issue				Confirm					
Blood draws for humoral response assessments [h]		X 20 mL		X 20 mL	X 20 mL		X 20 mL	X 20 mL			
Issue, train, or collect subject e-diaries; remind subjects [i]		Issue, train				Remind	Collect			Collect	
Subjects report reactogenicity (incl. oral body temperature) daily for 7 d after each IMP dose using an e-diary [i]			Start after Dose 1	End		Start after Dose 2	End			End	
Investigators review e-diary data daily			Start	End		Start	End			End	X
Record AEs since last visit		X		X	X	X	X	X		X	X
Record SAEs and specific AEs types since last visit [j]		X		X	X	X	X	X	X	X	X
Record medical occurrences since just before Dose 1		X									
Record medication since last visit		X		X	X	X	X	X	X [k]	X	X
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CCI											

Activity	Visit 0 (V0)	V1	V1	V3	V4	V7	V8	V9	V10	Early term. Visit	Unsche-duled [l]
Visit description	Screening at ≤28 d pre-V1	Pre-dose	Dose 1 (D1)	7 d post-D1	28 d post-D1	Dose 2 (2 m post-D1)	7 d post-D2	28 d post-D2	3 m FU post-D2		Potential COVID-19 Illness Visit
Days relative to Dose 1	N/A	1	1	8	29					N/A	N/A
Permitted visit window				+2 d	±3 d	±7 d post-V3	+2 d from 7 d post-D2	±3 d from 28 d post-D2	±7 d from 3 m post-D2		
Maximum total blood volume (mL) drawn per visit	25	175	0	170	155	0	170	155	0		135

a. Brief (symptom-directed) physical examination as indicated.
b. At 1 h (±15 minutes) before and after dosing.
c. Vital signs: systolic/diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature.
d. Dipstick urine analysis: For details of all assessed urine clinical laboratory parameters, see Section 10.3.
e. Viral screen: screen for human immunodeficiency virus (HIV)-1 and HIV-2, Hepatitis B, and Hepatitis C.
f. Clinical laboratory tests: Chemistry and hematology. Only in women who are not VOCBP (to confirm postmenopausal status): follicle stimulating hormone at Visit 0. Only for VOCBP: serum β-HCG at Visit 0. For details of all assessed blood clinical laboratory parameters, see Section 10.3.
g. In VOCBP: The serum β-HCG pregnancy test at Visit 0 will be performed using the sample collected for clinical laboratory tests. Before each dosing, urine pregnancy tests will be performed using a commercial kit at the site and the trial subjects will be counseled about the need for consistent and correct use of a highly effective method of contraception.
h. Leftover blood after completion of the assessments may be used for additional biomarker analyses and/or development of analytical methods.
i. Trial site personnel will remind the subjects to record the oral body temperature and the worst grade for each symptom in the e-diary at approximately the same time every evening on the day of IMP administration and then every day in the evening for a total of seven consecutive days. Ask/remind the subject to contact the site if they experience any severe or potentially life-threatening reactogenicity events. Trial site personnel will remind the subjects to record the use of antipyretic/analgesic medication to treat symptoms associated with IMP administration for 7 d after each IMP dose using the e-diary.
j. Only SAEs, adverse event(s) of special interest, AEs that lead to discontinuation or withdrawal, and AEs linked to confirmed COVID-19 cases will be recorded. SAEs must be recorded upon awareness.
k. For FU visit, only any prohibited medication (including SARS-CoV-2 non-trial vaccinations) will be recorded.
l. Optimally within 3 d after potential COVID-19 illness onset. All known NAAT-based SARS-CoV-2 positive subjects, from randomization until end of trial, will be asked for an additional unscheduled visit to define the COVID-19 illness as per Section 8.2.8. The COVID-19 illness visit will define the illness as either confirmed COVID-19, unconfirmed COVID-19, or confirmed severe COVID-19.
m. The results must be available prior to administration of trial treatment at Visit 1.
n. To be completed before administration of Dose 2.

Notes

The total blood volume drawn over any 8-week period in any cohort will always be less than 550 mL. Additional blood samples may be taken, e.g., for safety assessments after AEs or SAEs. Assuming there are no unplanned visits, the total volume of blood drawn from each subject during trial participation will be up to ~850 mL.

Abbreviations: AE = adverse event; CCI COVID-19 = coronavirus disease 2019; d = day(s); D = dose; Early term. = early termination (visit); ECG = electrocardiogram; FU = follow-up (visit); h = hour(s); β-HCG = beta human chorionic gonadotropin; CCI IMP = investigational medicinal product; m = month(s); NAAT = nucleic acid amplification-based test; N/A = not applicable; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VOCBP = volunteers of childbearing potential.

13.6 Objectives and endpoints – Cohort 5

OBJECTIVES	ESTIMAND *	ENDPOINTS
Primary objectives		
To describe the safety and tolerability of two doses of 30 µg BNT162b4 alone in healthy adults aged 18 to 55 years, with and without evidence of prior SARS-CoV-2 infection, who received at least three prior doses of an authorized RNA-based COVID-19 vaccine.	The frequency of dosed subjects with: • Solicited local reactions at the injection site recorded up to 7 d after each IMP dose. • Solicited systemic events recorded up to 7 d after each IMP dose. • Subjects with at least one AE occurring up to 28 d after each IMP dose. • Subjects with at least one SAE occurring up to 3 months after last dose.	• Solicited local reactions (pain, erythema / redness, induration / swelling) • Solicited systemic events (vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills and fever) • AEs • SAEs
	The frequency of dosed subjects with: • Abnormal hematology or chemistry laboratory values 7 d after each IMP dose. • Grading shifts in hematology or chemistry laboratory assessments between baseline and 7 d after each IMP dose.	• Hematology and chemistry laboratory parameters (see Section 10.3)
	The frequency of dosed subjects with: • New ECG abnormalities 7 d after each IMP dose.	• ECG abnormalities consistent with probable or possible myocarditis or pericarditis as defined in the protocol
Exploratory objectives		
CCI [redacted]		

OBJECTIVES	ESTIMAND *	ENDPOINTS
CCI		

Abbreviations: AE = adverse event; CCI COVID-19 = coronavirus disease 2019; d = day; ECG = electrocardiogram; CCI GMT = geometric mean titer; CCI IMP = investigational medicinal product; CCI SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; CCI

* All assessments as described in the estimands will be conducted within the schedule of visits window.

13.7 Trial population – Cohort 5

13.7.1 Inclusion criteria – Cohort 5

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

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

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

3 Are aged 18 to 55 yrs, have a body mass index over 18.5 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0.

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

Note: Healthy volunteers with pre-existing stable disease (e.g., obesity), defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 84 d before Visit 0, can be included.

5 Agree not to enroll in another trial with an IMP starting from Visit 0 and until 90 d after receiving the last IMP dose.

6 Agree not to be vaccinated with:

- Non-trial vaccines (except COVID-19 vaccines, as per next sub-bullet) starting 28 d prior to Dose 1 and until 28 d after receiving the last IMP dose. Seasonal influenza vaccine is allowed; however, it should be given at least 14 d before or after any administration of IMP.
- Non-trial COVID-19 vaccines starting at least 90 d prior to the Visit 1 and until 28 d post-Dose 2.

7 Have been vaccinated with at least three doses of an RNA-based COVID-19 vaccine authorized in the US before Visit 0. The last COVID-19 RNA vaccine dose must have been administered at least 90 d before Visit 1.

Note: Documented confirmation of prior COVID-19 vaccine receipt must be obtained prior to Visit 1.

Virology

8 Have negative human immunodeficiency virus (HIV)-1 and HIV-2 test results at Visit 0.

9 Have negative Hepatitis B surface antigen (HBsAg) test results at Visit 0.

10 Have negative anti-Hepatitis C virus (HCV) antibodies, or negative HCV polymerase chain reaction (PCR) test results if the anti-HCV is positive at Visit 0.

Reproductive status and contraception

11 Volunteers of childbearing potential (VOCBP) that have a negative serum β-HCG pregnancy test result at Visit 0 and negative urine pregnancy test results prior to receiving Dose 1 and a negative urine pregnancy test result prior to receiving Dose 2. Volunteers born female that are postmenopausal or permanently sterilized (verified by medical records) will not be considered VOCBP (for definitions of postmenopausal or permanently sterilized, see Section 10.5).

12 VOCBP who agree to practice a highly effective form of contraception (for guidance on contraception, see Section 10.5) and to require their male sexual partners to use condoms with a spermicidal agent, starting at Visit 0 and continuously until 28 d after receiving the last IMP dose.

13 VOCBP who agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during trial, starting at Visit 0 and continuously until 28 d after receiving the last IMP dose.

14 Men who are sexually active with partners of childbearing potential and who have not had a verified vasectomy (documented in medical records) that agree to use condoms with a spermicidal agent and to practice a highly effective form of contraception with their sexual partners born female (for guidance on contraception, see Section 10.5) starting at Visit 0 and continuously until 28 d after receiving the last IMP dose.

15 Men who are willing to refrain from sperm donation, starting at Visit 0 and continuously until 28 d after receiving the last IMP dose.

13.7.2 Exclusion criteria – Cohort 5

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

1 Breastfeeding or intending to become pregnant starting with Visit 0 until 28 d after receiving the last dose of trial IMP or intending to father children starting with Visit 0 until 28 d after receiving the last trial IMP dose.

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

3 Current or history of the following medical conditions:

a) Uncontrolled or moderate or severe respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease); symptoms of asthma severity as defined in the most recent US National Heart, Lung, and Blood Institute asthma management guidelines - e.g., exclude a volunteer who:

- Uses a short-acting rescue inhaler (typically a beta 2 agonist) daily, or
- Uses high dose inhaled corticosteroids (per National Heart, Lung, and Blood Institute asthma management guidelines [Tables 4–8b]), or
- In the past year has either of the following:
  - Greater than one exacerbation of symptoms treated with oral/parenteral corticosteroids;
  - Needed emergency care, urgent care, hospitalization, or intubation for asthma.

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

c) Hypertension:

- If a person has been found to have elevated blood pressure or hypertension during screening or previously, exclude for “blood pressure that is not well controlled”. Well controlled blood pressure is defined as consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic, with or without medication, with only isolated, brief instances of higher readings, which must be ≤150 mm Hg systolic and ≤90 mm Hg diastolic at Visit 0.

- If a person does not have a history of elevated blood pressure or hypertension previously or during screening, also exclude for systolic blood pressure ≥150 mm Hg at Visit 0 or diastolic blood pressure ≥100 mm Hg at Visit 0.

Subjects who have new onset of worsening hypertension since enrollment that, in the opinion of the investigator, would constitute an increased risk to the subject's participation in Dose 2 will not receive Dose 2.

d) Any current or history of cardiovascular diseases such as myocarditis, pericarditis, myocardial infarction, symptomatic congestive heart failure, cardiomyopathy or clinically significant arrhythmias.

Subjects who have new onset of cardiovascular disease since enrollment that, in the opinion of the investigator, would constitute an increased risk to the subject's participation in Dose 2 will not receive Dose 2.

e) A diagnosed bleeding disorder (e.g., factor deficiency, coagulopathy, or platelet disorder requiring special precautions).

Subjects who have new onset of a bleeding disorder since enrollment that, in the opinion of the investigator, would constitute an increased risk to the subject's participation in Dose 2 will not receive Dose 2.

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

g) Screening 12-lead ECG that is consistent with probable or possible myocarditis or pericarditis or demonstrates clinically relevant abnormalities that may affect subject safety or interpretation of the trial results.

Only symptomatic subjects or whose clinical picture, in the opinion of the investigator, warrant ECG will have a repeat 12-lead ECG.

Note for exclusion criteria 3g: ECG changes including but not limited to: paroxysmal or sustained atrial or ventricular arrhythmias, atrioventricular (AV) block (grade 2-3) or bundle branch block, diffuse ST-segment elevation or PR-segment inversion, QTcF interval (QT interval corrected by the Fridericia formula) >450 ms in men and >460 ms in women, changes supporting myocardial infarction and/or myocardial ischemia.

Subjects who have a repeat ECG prior to Dose 2 and have a change or new onset that in the opinion of the investigator should not receive Dose 2, will not receive Dose 2.

4 Current or history of major psychiatric illness, including but not limited to bipolar disorder, major depressive disorder, schizophrenia, autism, and attention deficit-

hyperactivity disorder that could interfere with participation and follow-up as required by the trial protocol.

5 Current or history of the following diseases associated with immune dysregulation:

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

Prior/concomitant therapy

6 Received any non-trial IMP within 28 d before Dose 1 and Dose 2 (except seasonal influenza vaccine, which should be given at least 14 d before or after any administration of IMP).

7 Received or planned treatment throughout the entire trial with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 d at a dose of ≥20 mg/d of prednisone or equivalent), e.g., for cancer or an autoimmune disease, or planned receipt throughout this trial. Inhaled/nebulized (except high doses as per exclusion criteria 3a), intraarticular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

8 Blood/plasma products and/or immunoglobulin containing therapy (including monoclonal antibodies) received within 120 d before dosing or administration is planned starting at Visit 0 or prior to Dose 2 until 90 d after the last IMP administration in this trial.

9 Received allergy treatment with antigen injections within 28 d before dosing or where allergy treatment with antigen injections are scheduled within 14 d after any visit with IMP administration in this trial.

10 Subjects with a history of SARS-CoV-2 infection (symptomatic or asymptomatic) <60 d prior to Visit 1.

11 Have received any non-RNA or unauthorized COVID-19 vaccine, aside from Dose 1 of the current trial.

Additional exclusions

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

13 Are vulnerable individuals as per ICH E6 definition, i.e., are individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of

a retaliatory response from senior members of a hierarchy in case of refusal to participate.

14 Any screening hematology and/or blood chemistry laboratory value that meets the definition of a Grade ≥1 abnormality at Visit 0, or an abnormal C-reactive protein (identified by any method) or troponin I value.

Note: Volunteers with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: “stable” Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains ≤ Grade 1 upon repeat testing on a second sample from the same volunteer).

Gilberts disease, in and of itself, is not considered exclusionary.

Only symptomatic subjects or whose clinical picture, in the opinion of the investigator, warrant laboratory investigation will have a repeat lab(s).

15 History of alcohol abuse or drug addiction within 1 yr before Visit 0, or a history (within the past 5 yrs) of substance abuse or known medical, psychological, or social conditions which, in the opinion of the investigator, could compromise their wellbeing if they participate as subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.

13.8 Trial treatments – Cohort 5

For trial treatments, see Section 6.1.

13.9 Statistical considerations – Cohort 5

For statistical considerations, see Section 9.