STATISTICAL ANALYSIS PLAN (SAP)
BNT162-21

Version: 4.0 **Date:** 03 APR 2025

Sponsor: BioNTech SE

Protocol number:	BNT162-21
Protocol 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
Protocol version:	8.0
Protocol date:	16 SEP 2024
Investigational medicinal products:	BNT162b4, BNT162b2 Bivalent (WT/OMI BA.4/BA.5), BNT162b2 Monovalent (OMI XBB.1.5)
Trial Phase:	Phase I
Regulatory Identifiers:	BB-IND 28877 ClinicalTrials.gov ID: NCT05541861

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SAP VERSION HISTORY

SAP version	Version date	Change	Rationale
1.0	07 Feb 2023	N/A	N/A
2.0	24 May 2023	• Section 3.1 Objectives and endpoints updated • Section 3.2 Trial Design, Figure 1 and Table 2 updated to mention cohort "3a" and "3b". • Table 3 updated as well to mention changes related to Randomization • Section 3.3 Figure 2 updated to reflect changes of "Trial Schema" • Section 7.1 updated for "Immunogenicity Per Protocol Set" • Section 8.1 updated for General considerations • Section 8.5.1.3 modified for presentations of Adverse Event Overview summary output • Section 8.5.1.5 modified • Section 8.5.2.2 added • Section 8.5.2.6 modified to add Listing related to FSH • Section 8.6.2.1 modified for CCI Analysis • Section 8.7.2.1, 8.7.2.2 and 8.7.2.3 modified for analysis related Confirmed, Severe COVID-19 cases and Strain sequencing • Section 9 "Reference" not required for this SAP removed • Section 10.2 "Abbreviation section updated	Aligned to CTP V 4.0
3.0	17 Sep 2024	• Section 3.0: protocol version and date updated • Section 3.1 – 3.3: modified • Section 5: modified • Section 6: modified • Section 8.1: Added treatment groups and cohorts added • Section 8.2: count and reason of discontinuation for each dose • Section 8.5.1.3: Modified • Section 8.6 modified • Section 10.4.1: Updated the schedule of activities table	Aligned to CTP V 7.0, updates due to BNT review

SAP version	Version date	Change	Rationale
		• Updates: Introduction of Dose 2 safety set and clarification of EC presentations • Introduction of Cohort 5, • Typographical changes/ amendments and clarifications.	
		• Section 7.1: Immunogenicity Analysis Set was updated with “viral neutralization titer” replaced by “immunogenicity”.	Aligned with CTP version 8.0 (not yet approved).
		• Section 7.2: Added Major PDs that lead to sample exclusion from the per-protocol immunogenicity analyses will be identified and marked out. • Section 8.1.2: Rephrased “Clinical data summary for lab, vital sign, ECG, PE, the analysis visit post vaccination” to “Study data are reported according to Schedule of Activities Table 3 and 7 in CTP. The analysis visits of data” • Section 8.1.2: Added “Data reported at visit “Pre-Dose 1” on the same day of IMP Dose 1 administration will be taken as prior to IMP Dose 1.”.	Added details about data and analysis for clarification.
		• Section 8.2: Removed data listing for “failed inclusion and exclusion criteria”. • Section 8.2: Modified summary of analysis set based on Randomized/assigned set”. • Section 8.3.1: Added summary demographics based on Randomized/assigned set”. • Section 8.3.2: Removed bar chart for concomitant medication due to local reactions and systemic events. • Section 8.3.3: Added variable “time from the last infection to the first dose of IMP,” in the summary table. • Section 8.5.1.3: Refined the adverse events analysis detail. • Section 8.5.1.4: Removed summary analyses for urinalysis and abnormality shift tables for all hematology, chemistry, and urinalysis. • Section 8.5.2.1: Modified summary of IMP exposure to be based on Randomized/Assigned Set.	Updated analysis details for final safety analysis.

SAP version	Version date	Change	Rationale
		• Section 8.5.2.4: Removed summary tables for vital signs. • Updated Subjects to Participants throughout except for those carried over from CTP.	
4.0	03 Apr 2025	CCI [redacted] • Section 7.1: Changed that Immunogenicity Analysis Set will not be used for immunogenicity analyses. Only participants without breakthrough SARS-CoV-2 infections (without positive central or local NAAT) from pre-Dose 1 through the visit) will be analyzed for the respective visit. Added details on the exclusion criteria for Immunogenicity Per Protocol Set. • Section 7.2: Added details on the exclusion criteria for analysis sets based on protocol deviations. • Section 8.1.4: Added missing data imputation for medical history. • Section 8.3.1: Added "Dose 2 Safety Set" for the demographics and baseline characteristics summary table. CCI [redacted] • Section 8.3.2: Added "Immunogenicity Per Protocol Set" for the prior COVID-19 vaccination history summary table. • Section 8.3.3: Added "Immunogenicity Per Protocol Set" for the prior SARS-CoV-2 infection summary table. • Section 8.5.2.2: Added summary and listing for local laboratory results for oral swabs for NAAT-based SARS-CoV-2 testing for screening and surveillance.	• It is aligned with CTP v8.0. • Results based on Immunogenicity Per Protocol Set will serve the purpose of study objectives. • Updated details for immunogenicity analysis regarding strains, timepoints, treatment groups, and parameters. • Provided details for subgroup analysis. CCI [redacted]

SAP version	Version date	Change	Rationale
		• Moved Section 8.5.2.3 to Section 8.7.2.4 Serological testing for SARS-CoV-2 N-binding antibodies. The analysis details in this section were updated. • Section 8.6: Added Table 8 and 9 to specify strains and timepoints for immunogenicity analysis. • Section 8.6.1.1-8.6.1.3: Updated the secondary immunogenicity analysis for Cohorts 1-4 regarding strains, timepoints, and cohorts in the analysis. • Section 8.6.2.1-8.6.2.4: Updated the [redacted]	

1 INTRODUCTION

This is 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. This SAP describes the detailed procedures for the planned statistical analyses of the trial for protocol v8.0 dated 16 Sep 2024 to support the completion of the clinical study report (CSR). This SAP also includes the details of the presentation and analysis to support Internal Review Committee (IRC).

The statistical analyses will be conducted by ICON Clinical Research using SAS® software version 9.4 or higher.

Note that the RNA-based vaccine BNT162b2 Bivalent (WT/OMI BA.4/BA.5) is hereinafter referred to as “BNT162b2 Bivalent”.

1.1 Objectives, estimands and endpoints

The estimands and endpoints corresponding to each primary, secondary, and exploratory objective are described below.

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 dose level (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 participants 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. • Participants with at least one AE occurring up to 28 d after every IMP dose. • Participants 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 participants 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 of protocol)

OBJECTIVES	ESTIMAND*	ENDPOINTS
	For each DL cohort, the percentage of dosed participants 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
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.	For each DL cohort: • 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 participants 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]		

OBJECTIVES	ESTIMAND*	ENDPOINTS
CCI		

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

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.	<u>The frequency of dosed participants with:</u> • 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. • Participants with at least one AE occurring up to 28 d after each IMP dose. • Participants 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
	<u>The frequency of dosed participants with:</u> • 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 of the CTP)
	<u>The frequency of dosed participants with:</u> • New ECG abnormalities 7 d after each IMP dose.	• ECG abnormalities consistent with probable or possible myocarditis or

OBJECTIVES	ESTIMAND *	ENDPOINTS
		pericarditis as defined in the protocol
Exploratory objectives		
CCI		

Abbreviations: AE = adverse event; CCI COVID-19 = coronavirus disease 2019; d = day; ECG = electrocardiogram; 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.

1.2 Trial design

This is an exploratory Phase I, randomized, observer-blind, active-controlled, dose-escalation trial to evaluate four dose level 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 a flow diagram summary of the trial, see the schema in Section 1.3. For the planned assessments and visits, see the schedules of activities (SoAs) in Section 8.4.

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 participants will be permitted to be unblinded from Visit 5. Cohort 5 is single arm and open-label for Dose 1 and Dose 2. The trial will use a staggered dosing process schema with sentinel participants in Cohorts 1, 2, 3a and 4a as per Figure 1.
Cohort 5 trial participants will not be randomized and will be administered two doses of 30 µg BNT162b4 alone. For the dosing process schema for Cohort 5, see Figure 2.

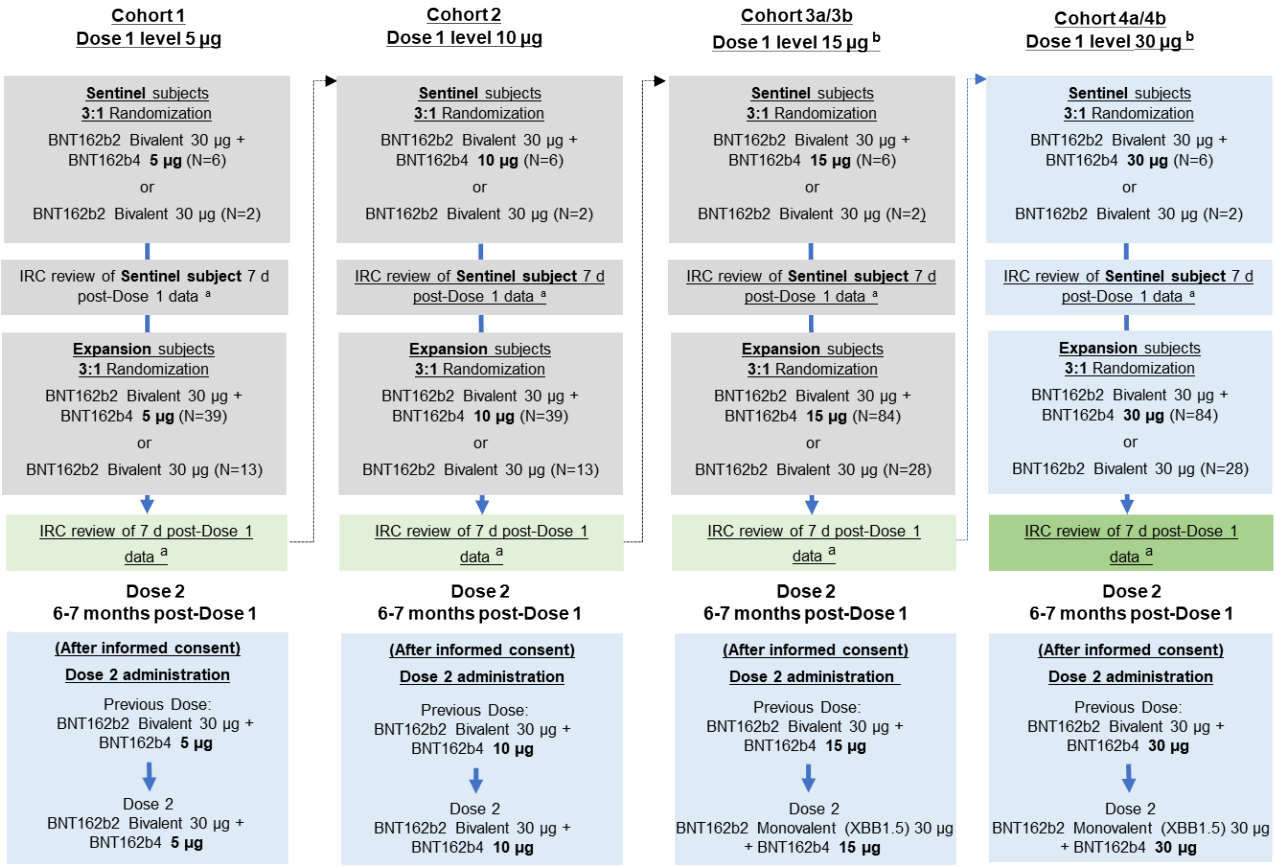


Figure 1: The staggered dosing process for Cohorts 1 to 4

a. Further dosing of participants 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 participants have been reviewed by the IRC and approval for progression is granted.

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

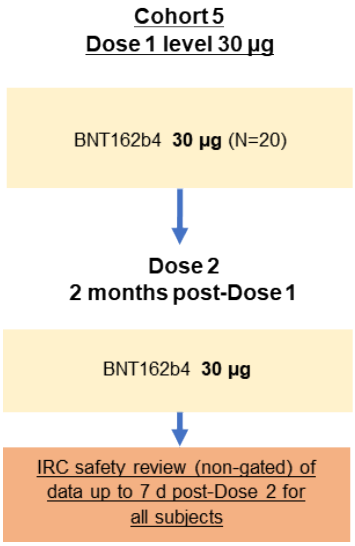


Figure 2: The dosing process for Cohort 5

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

For the trial populations (including the planned number of participants per cohort), dosing regimens, and blinding in Cohorts 1 to 5, please see Table 1.

Table 1: Number of trial participants per trial treatment (total number of participants enrolled = ~380)

Trial treatment – Dose 1 (Visit 1) [c]	Trial treatment – Dose 2 [d]	Number of trial participants	Randomization ratio to treatment groups
Cohort 1 – Sentinel participants aged 18-55 yrs	***Cohort 1 – Sentinel participants 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 participants aged 18-55 yrs	***Cohort 1 – Expansion participants 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

Trial treatment – Dose 1 (Visit 1) [c]	Trial treatment – Dose 2 [d]	Number of trial participants	Randomization ratio to treatment groups
Cohort 2 – Sentinel participants aged 18-55 yrs	***Cohort 2 – Sentinel participants 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 participants aged 18-55 yrs	***Cohort 2 – Expansion participants 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 participants aged 18-55 yrs	***Cohort 3a – Sentinel participants 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 participants aged 18-55 yrs	***Cohort 3a – Expansion participants 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	39 13	3:1
Cohort 3b – Participants aged >55 yrs [b]	***Cohort 3b – Participants 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 participants aged 18-55 yrs	***Cohort 4a – Sentinel participants 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

Trial treatment – Dose 1 (Visit 1) [c]	Trial treatment – Dose 2 [d]	Number of trial participants	Randomization ratio to treatment groups
Cohort 4a – Expansion participants aged 18-55 yrs	***Cohort 4a – Expansion participants 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 – Participants aged >55 yrs [b]	***Cohort 4b – Participants 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 – Participants aged 18-55 yrs	***Cohort 5 – Participants aged 18-55 yrs***		
• BNT162b4 30 µg	• BNT162b4 30 µg	20	Not applicable

a) If the participant 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 participants aged ≥65 yrs and ~40% of participants 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.

Dose Escalation

Dose escalation decisions to progress to the next dose level and dose level modifications (i.e., dropping the dose level to the previous acceptable dose level or to an 'in-between' dose level) will be confirmed by the IRC. Dose escalation will only continue if the safety and tolerability of the previous dose level 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 even discontinuation of trial treatment may be required. See Section 7.1 of the protocol for guidance on criteria for such cases.

For Dose 2 recipients, an IRC safety review will be performed for the first 8 participants 7 d post-Dose 2 in all dose level cohorts (see Table 2).

Table 2: 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 participants 7 d PD1 reviewed		First 8 participants 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 participants 7 d PD2	First 8 participants 7 d PD2	First 8 participants 7 d PD2		First 8 participants 7 d PD2		All Cohort 5 participant 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.

1.3 Schema (graphical representation of the trial)

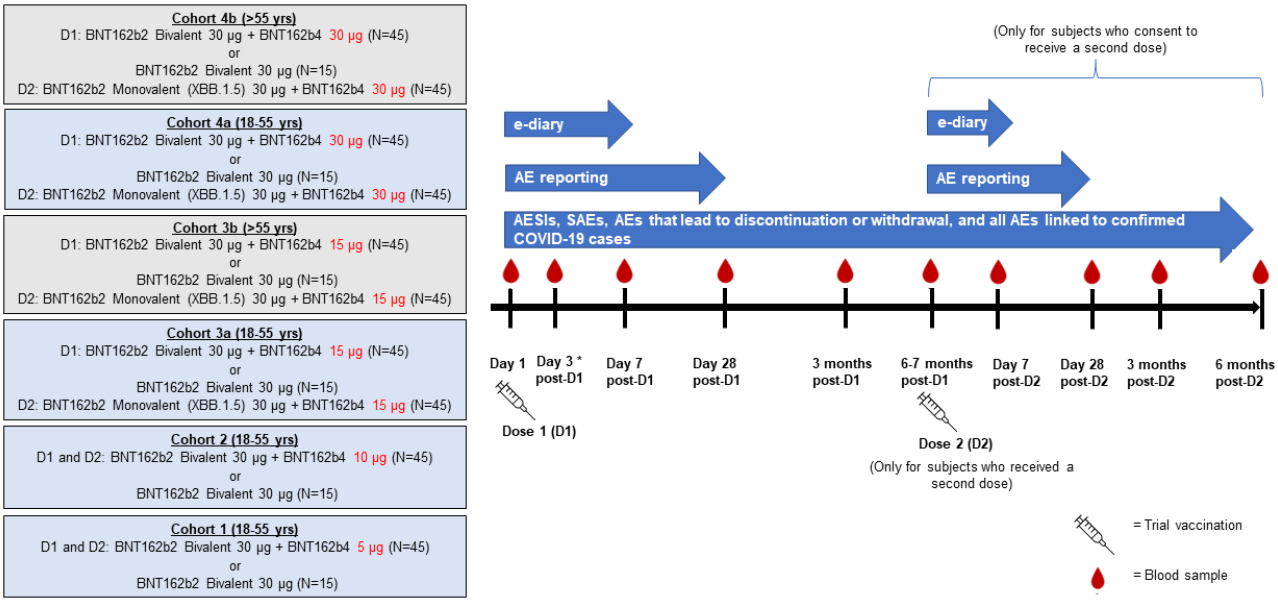


Figure 3: Schema for Cohorts 1 to 4

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

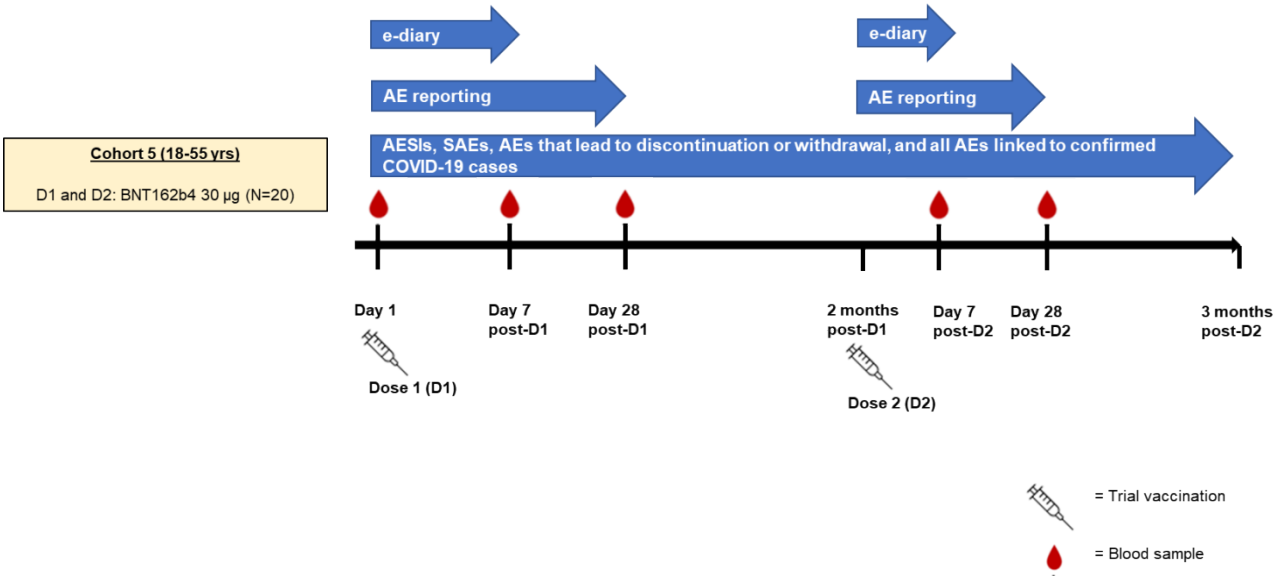


Figure 4: Schema for Cohort 5

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

1.4 Schedules of activities

See Section 8.4 of Appendix 4 for the schedules of activities.

2 STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested in this trial.

3 INTERIM ANALYSES AND ANALYSIS SEQUENCE

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.

Reports to support the IRC will also be produced as required by the review schedule in Table 2 Prior to each IRC review, a data cut-off date for the data to be provided will be established by the ICON Biostatistician, DMC Coordinator, and Data Management Group in consultation with the sponsor. In addition to data being cleaned on an ongoing basis, targeted data entry, data cleaning and reconciliation will be coordinated and performed by the ICON Data Management group based on the established cut-off date prior to analysis reporting. Unblinded IRC reports will be generated as required and shared with the IRC for decision making as per the IRC charter.

4 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 3 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 participants 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 3: 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
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 participants.

5 ANALYSIS SETS AND SUBGROUPS

Data for all participants will be assessed to determine if they meet the criteria for inclusion in each analysis set. All analysis sets will be assessed and documented prior to releasing the database for each cohort.

5.1 Analysis sets

Screened Set

All participants who provided informed consent.

Randomized/Assigned Set

All participants who were randomized/assigned with a participant number using the online randomization tool.

Safety Set

All participants who received at least one dose of IMP.

Analyses of all safety endpoints will be performed using the Safety Set, based on the treatment and dose the participants actually received. The analyses of data post-Dose 1 will be based on the Safety Set.

Dose 2 Safety Set

All participants who received two doses of IMP.

Analyses of safety endpoints will be performed using the Dose 2 Safety Set as appropriate, based on the dose the participants actually received. The analyses of data post-Dose 2 will be based on the Dose 2 Safety Set.

Immunogenicity Analysis Set

All participants who received the planned dose of the IMP on Day 1 and who have at least one valid immunogenicity assessment within an appropriate window of the target day.

Immunogenicity Per Protocol Set

All participants included in the Immunogenicity Analysis Set, that have no major protocol deviations (PDs) that can confound immunogenicity data. A participant will only be excluded from the Immunogenicity Per Protocol Set if the participant had an important protocol deviation that can confound all immunogenicity data as determined by the sponsor. If a participant has an important protocol deviation that can confound subsequent immunogenicity data as determined by the sponsor then the participant will remain in the Immunogenicity Per Protocol Set, and only samples before the event will be included in the analysis.

Participants who have positive central or local nucleic acid amplification-based test (NAAT) result at pre-Dose 1 will be excluded from Immunogenicity Per Protocol Set since active infection indicated by positive NAAT at pre-Dose 1 may impact immunogenicity assessments post dose even though this is not a protocol deviation.

For immunogenicity analyses, the sampling windows with grace periods specified in Table 4 will be used to define the valid samples for analysis sets. The samples drawn within the visit specific window with grace period will be valid for immunogenicity analysis in both the Immunogenicity Analysis Set and the Immunogenicity Per Protocol Set. Immunogenicity Per Protocol Set will be used for secondary and CCI endpoints in the BNT162-21 trial. Immunogenicity Analysis Set will not be used for immunogenicity analyses as the analyses based on Immunogenicity Per Protocol Set will serve the objectives of the study.

Only participants without breakthrough SARS-CoV-2 infections (without positive central or local NAAT results from pre-Dose 1 through the visit) will be analyzed for the respective visit.

Table 4: Immunogenicity sampling window

Visit relative to dose	Window per CTP	Additional grace period = No impact on immunogenicity Include in Immunogenicity Analysis Set and Immunogenicity Per Protocol Set	Impact on immunogenicity = Exclude from Immunogenicity Analysis Set and Immunogenicity Per Protocol Set, only for primary endpoints
Day 7 post-dose	8+2 8-10 days	N/A	All OOW
Day 28 post-dose	29±2 27-31 days	+/- 2 days OOW ≥25 to ≤33 days	≥+/- 3 and more days OOW <25 days or >33 days
Month 3 post-dose	90±7 83-97 days	+/- 7 days OOW ≥76 to ≤104days	≥+/- 8 and more days OOW <76 days or >104 days
Month 6 post-dose*	180±10 170-190 days	+/- 7 days OOW ≥163 to ≤197 days	≥+/- 8 and more days OOW <163 days or >197 days

Abbreviations: N/A = Not Applicable; OOW= Out of Window.

*Participants who received a pre-Dose 2 blood draw will be reported at this timepoint regardless of window as Month 6 post-Dose 1/Pre-Dose 2.

5.2 Protocol deviations

Protocol deviations are failures to adhere to the inclusion/exclusion criteria and protocol requirements. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect a participant's rights, safety, or well-being. Protocol deviations (PDs) will be classified into key PDs (important) and non-key PDs. Key PDs that lead to participant/sample exclusion from the immunogenicity analyses will be identified and provided for incorporation into the analysis datasets prior to database lock.

All PDs will be assessed and documented prior to releasing the database. Depending on the nature of the key PD, either the whole participant data might be excluded from the analysis sets (i.e., for key deviations on ICF), or only the data collected after the key PD

occurred might be excluded (e.g., for use of prohibited concomitant medications during the trial).

5.3 Subgroups

Subgroup analysis may be performed for certain CCI [redacted] endpoints based on N-binding antibody status at pre-Dose 1.

6 STATISTICAL ANALYSES

6.1 General considerations

In general, all the data summaries will be performed by the following treatment groups:

Age Strata	Cohorts	Treatment Group Description
≥18 years	3a, 3b	Dose 1: BNT162b2 (WT/OMI BA.4/5) 30µg + BNT162b4 15µg, Dose 2: BNT162b2 (OMI XBB.1.5) 30µg + BNT162b4 15µg (≥18y)
	4a, 4b	Dose 1: BNT162b2 (WT/OMI BA.4/5) 30µg + BNT162b4 30µg, Dose 2: BNT162b2 (OMI XBB.1.5) 30µg + BNT162b4 30µg (≥18y)
	1, 2, 3a, 3b, 4a, 4b	BNT162b2 (WT/OMI BA.4/5) one dose only (≥18y)
18-55 years	1	Dose 1 and Dose 2: BNT162b2 (WT/OMI BA.4/5) 30µg + BNT162b4 5µg (18-55y)
	2	Dose 1 and Dose 2: BNT162b2 (WT/OMI BA.4/5) 30µg + BNT162b4 10µg (18-55y)
	3a	Dose 1: BNT162b2 (WT/OMI BA.4/5) 30µg + BNT162b4 15µg, Dose 2: BNT162b2 (OMI XBB.1.5) 30µg + BNT162b4 15µg (18-55y)
	4a	Dose 1: BNT162b2 (WT/OMI BA.4/5) 30µg + BNT162b4 30µg, Dose 2: BNT162b2 (OMI XBB.1.5) 30µg + BNT162b4 30µg (18-55y)
	1, 2, 3a, 4a	BNT162b2 (WT/OMI +BA.4/5) 30µg one dose only (18-55y)
	5	Dose 1 and Dose 2: BNT162b4 30µg (18-55y)
>55 years	3b	Dose 1: BNT162b2 (WT/OMI BA.4/5) 30µg + BNT162b4 15µg, Dose 2: BNT162b2 (OMI XBB.1.5) 30µg + BNT162b4 15µg (>55y)
	4b	Dose 1: BNT162b2 (WT/OMI BA.4/5) 30µg + BNT162b4 30µg, Dose 2: BNT162b2 (OMI XBB.1.5) 30µg + BNT162b4 30µg (>55y)
	3b, 4b	BNT162b2 (WT/OMI BA.4/5) 30µg one dose only (>55y)
	1, 2, 3a, 3b, 4a, 4b, 5	All participants

"All participants" will be presented in disposition, baseline, and selected safety summary tables as specified.

No formal statistical comparisons between vaccine dose levels will be performed. Missing data, other than that described for AEs/Concomitant Medications/Vaccinations below will not be imputed.

6.1.1 General methods

In general, continuous variables will be summarized using the following descriptive statistics: number of participants (n), mean, standard deviation (SD), median, minimum (min) and maximum (max).

For the assay results geometric means (GMs) and geometric mean fold rises (GMFRs) will be calculated.

The GMs will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. 2-sided 95% confidence intervals (Cis) will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to the Student's t distribution, and then exponentiating the confidence limits.

GMFRs are defined as ratios of the results post-dose to the results before dose of IMP. GMFRs are limited to participants with non-missing values at both timepoints.

GMFRs will be calculated as the mean of the difference of logarithmically transformed assay results (later timepoint minus earlier timepoints) and exponentiating the mean. The associated 2-sided 95% CIs will be obtained by constructing CIs using the Student's t distribution for the mean difference on the logarithmic scale and exponentiating the confidence limits.

Categorical variables will be summarized by presenting absolute and relative frequencies (n and %) of participants in each category and the number of participants with missing data ('missing' category will be presented if there is one or more missing value).

For event-driven occurrence data (e.g., adverse event, concomitant medication.), the percentages will be calculated as the number of participants reporting each event over number of participants in the analysis set (N). Unless otherwise noted, also for reported visit data (e.g., clinical laboratory.) the percentages will be calculated on the participant-level, e.g. number of participants in the sentinel cohort only.

The rates of binary endpoints such as primary safety variables (local reactions and systemic events) and seroresponse will be provided by treatment group along with the corresponding 2-sided 95% exact CIs using the Clopper-Pearson method.

All critical data collected during the trial will be listed, the trial day to the first dose and /or the relative day to the last dose will be presented as appropriate. The data will be sorted by treatment group, participant number and date of assessment (if applicable).

Unless otherwise noted, unscheduled assessments will be listed only and not included in the by-visit summaries/analysis. Windowing of data for the purposes of assigning to a visit will occur as per Section 6.1.3.

6.1.2 General definitions

Baseline is defined as last available value prior to first dose of trial IMP. The same baseline definition will be used for the calculation of GMFR and seroresponse and for the clinical laboratory and 12-lead ECG shift from pre-Dose 1 to post-Dose 1 and post-Dose 2 visits unless otherwise specified.

Change from baseline: Unless otherwise specified, this will be calculated as follows:

> Change from baseline = post-baseline assessment value – baseline assessment value.

If either the baseline or post-baseline assessment value is missing, the change from baseline is set to missing as well.

Body mass index (BMI) will be calculated as follows:

$$\text{BMI}\left(\frac{\text{kg}}{\text{m}^2}\right) = \frac{\text{Weight (kg)}}{\text{Height(m)}^2}$$

Temperatures collected in degrees Fahrenheit will be converted to degrees Celsius using (°F – 32) × 5/9 and grading will be based on the unrounded conversions.

Duration will be calculated as follows:

- Duration = last observation date – first observation date + 1.

For conversion of days to months or years, the following rules will be applied:

- 1 month = 30.4375 days
- 1 year = 365.25 days

Trial day will be calculated as follows:

- Trial day:
  - If assessment date < treatment start date, then trial day = assessment date – date of Dose 1
  - If assessment date >= treatment start date, then trial day = assessment date – date of Dose 1+ 1

That is, trial day 1 indicates the date of treatment initiation.

6.1.3 Analysis visit

Study data are reported according to SoAs detailed in Table 3 and Table 7 in the CTP. The analysis visits of data will be based on the visits reported and validated in the electronic data capture (EDC) system.

If multiple valid non-missing observations exist in an analysis window for a specific visit, a single value will be chosen in the by-visit summary analyses based on the following rules:

For baseline,

- the last available records prior to the date and time of the first dose of IMP will be selected. Data reported at visit “Pre-Dose 1” on the same day of IMP Dose 1 administration will be taken as prior to IMP Dose 1.

For post-baseline visits,

- If the analysis values are numeric and the toxicity grades are available, the record with the highest toxicity grade will be selected.
- If the analysis values are numeric and the toxicity grades are identical or not available, the average (arithmetic mean) will be used.
- If the analysis values are categorical, the most conservative value will be selected (e.g., abnormal will be selected over normal).

6.1.4 Handling missing data

Missing data, other than that described for medical history, AE, and concomitant medication below, will not be imputed.

For partial missing date of prior positive SARS-CoV-2 infection result date,

- If the day of the month is missing, the onset day will be set to the first day of the month (01MMMYYYY).
- If the onset day and month are both missing, the day and month will be assumed to be 01 January (01JANYYYY).

For the purposes of assigning post-dose flag for AEs, partial or missing AE dates will be handled as follows:

- If the day of the month is missing, the onset day will be set to the first day of the month (01MMMYYYY), unless it is the same month and year as the first dose of trial treatment. In this case, in order to conservatively report the event as post-dose, the onset date will be assumed to be the same as Dose 1 date.
- If the onset day and month are both missing, the day and month will be assumed to be 01 January (01JANYYYY), unless the event occurred in the same year as the trial treatment. In this case, the event onset will be assumed to be the day and month of the first dose of treatment in order to conservatively report the event as post-dose.
- A completely missing onset date will be assumed to be the date of first dose of trial treatment. Such AEs will be considered post-dose.
- For AEs with onset date the same as Dose 1 or Dose 2 date, but with missing time of onset, such AE will be considered post-Dose 1 or post-Dose 2. If the time is not missing, onset time should be considered when assigning the post-dose flag.
- If an AE has a partial stop date that is in the same month/year as the first dose of trial treatment, then the AE will be reported as post-dose. If an AE has a missing start date, then the AE will be reported as post-dose.

For the purposes of assigning prior or concomitant flag for medications/vaccinations, partial or missing medication/vaccination dates will be handled as follows:

End dates (for events not ongoing):

- If end day is missing and month/year are non-missing, then day is the minimum of treatment end date and the last day of the month (e.g. 31MMMYYYY).
- If end day/month are missing and year is non-missing, then day is the minimum of treatment end date and the end of the year (e.g. 31DECYYYY).
- If imputed end date is before the start date, use the start date as the imputed end date.
- If end date is completely missing, then the event is assumed as concomitant.

Start dates:

- If the start date year is missing, the start date is set to one day prior to treatment start date.
- If the start date year is less than the treatment start date year, then:
  - If the month is missing, the start date is assumed to be mid-year point (e.g. 01JULYYYY).
  - If the month is not missing (day and year available), the start date is assumed to be mid-month point (e.g.15MONYYYY).
- If the start date year value is greater than the treatment start date year, then:
  - If the month is missing, the start date is assumed to be the year start point (e.g. 01JANYYYY).
  - If the month is not missing (day and year available), the start date is assumed to be the month start point (e.g. 01MONYYYY).
- If the start date year value is equal to the treatment start date year value, then:
  - If the month is missing or the month is equal to the treatment start date month, then the start date is assumed to be one day prior to the treatment start date.
  - If the month is less than the treatment start date month, the start date is assumed to the mid-month point (e.g. 15MONYYYY).
  - If the month is greater than the treatment start date month, the start date is assumed to be the month start point (e.g. 01MONYYYY).

If the complete end date is available, and the start date assumed from the steps above is greater than the end date, then the assumed start date will be set to the end date.

6.2 Participant disposition

For the Screened Set, the number and percentage of participants screened, randomized/assigned, who are vaccinated with each IMP dose, including the number of participants who are eligible for Dose 2 (Cohorts 1 to 4 only), the number of participants who received Dose 2 and non-vaccinated participants will be summarized. The number of participants that discontinued treatment together with the primary reason for treatment discontinuation as well as participants that discontinued the trial together with the primary reason for trial discontinuation will be summarized. Also, the participants who discontinued trial after Dose 1 and before Dose 2, and after Dose 2 will be summarized.

CCI

Participant-wise listings for disposition with randomization scheme, IMP doses received, trial completion status, and withdrawal reason will be presented.

The number and percentage of participants in each analysis set will be summarized with Randomized/Assigned Set. In addition, the number and percentage of participants excluded from each analysis set will be presented by treatment group along with the reasons for exclusion.

Participants excluded from analysis sets will also be listed.

The number and percentage of participants in the Safety Set with Key PDs will be summarized by PD category and sub-category. PDs will be presented in participant-wise listings as well.

6.3 Baseline characteristics

6.3.1 Demographics and baseline characteristics

Demographic and baseline characteristics data will be summarized on the Randomized /Assigned Set, Safety Set, Dose 2 Safety Set, and Immunogenicity Per Protocol Set.

Age at screening (years) will be summarized as continuous data. Sex (male or female), childbearing potential (yes or no; percentage is based on the number of female participants), race (Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, White, other, Multiple, Not reportable / Unknown) and Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reportable / Unknown), N-binding antibody status at screening (positive or negative), and N-binding status (positive, negative, or indeterminable) at pre-Dose 1, will be summarized as categorical data.

Height (cm), weight (kg), and BMI (kg/m^2) at screening will be summarized descriptively. BMI category Underweight (below 18.5), Normal weight (18.5 - < 25.0), Overweight (25.0 - < 30.0), and Obese (30.0 and above) will be summarized with frequency counts and percentages.

6.3.2 Prior and concomitant medication/vaccination/procedures/non-drug therapy

Prior and concomitant medications will be defined using medication start and stop dates recorded relative to first dose of IMP administration.

If the medication/procedure started and stopped before the date of the first dose of trial IMP, the medication/procedure will be assigned as being prior to trial IMP. Otherwise, the medication/procedure will be assigned as being concomitant with trial IMP.

Medications will be coded using the World Health Organization Drug Dictionary (WHODrug) drug codes of version B3 March 2022 or later resulting in Anatomical Therapeutic Chemical (ATC) codes indicating therapeutic classification.

The number and percentage of participants who had prior medications and concomitant medications/vaccinations will be summarized by ATC classification level 4 and preferred name by treatment group for participants in the Safety Set. The summary will be sorted by ATC alphabetically and, within each ATC, the preferred names will be sorted by descending frequency. If ATC level 4 is not available, the highest level available will be presented, e.g., level 3, 2 or 1.

Concomitant medications administered due to local reactions and systemic events after each IMP dose administration will also be summarized.

Concomitant procedures and non-drug therapies will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA®) coding system. Concomitant procedures and non-drug therapies will be listed only.

Prior COVID-19 vaccination history will also be presented. The number of prior COVID-19 vaccinations and time from the last vaccination to Dose 1 (days) will be summarized based on Safety Set and Immunogenicity Per Protocol Set, and listed.

6.3.3 Medical history and prior SARS-CoV-2 infection

Medical history and prior SARS-CoV-2 infection data will be coded using the most recent version of the MedDRA® coding system. The number and percentage of participants with each medical history and surgery will be summarized by System Organ Class (SOC) and Preferred Term (PT) by treatment group, for participants in the Safety Set. The summary will be sorted by SOC alphabetically and, within each PT, the PT will be sorted by descending frequency.

Prior SARS-CoV-2 infection data will be summarized including the type of test, time from the last infection to Dose 1 (days), and infection with SARS-CoV-2 Omicron variant confirmed (yes, no or unknown) with number and percentage of participants based on Safety Set and Immunogenicity Per Protocol Set.

A listing of medical history, prior SARS-CoV-2 infection and surgery data will be provided.

6.4 Efficacy analysis

Efficacy endpoints are not defined in the protocol and efficacy analysis will not be conducted.

6.5 Safety analysis

The primary endpoints are safety endpoints and are described in the below sections and in Section 1.1.

6.5.1 Primary endpoint safety analysis

6.5.1.1 Local reactions

The local reactions assessed and reported in the e-diary are pain, erythema/redness and induration/swelling within seven days after each trial IMP dose administration.

Solicited local and systemic events that are recorded in the participant e-diaries should not be reported as AEs unless they meet criteria for a serious adverse event (SAE) or start at Days 1 to 7 and continue past Day 7.

Solicited local reactions will be categorized as mild, moderate, severe, potentially life-threatening and graded from 1 to 4, during the analysis as described in Table 5.The categories and grades are based on the US Food and Drug Administration (FDA) Guidance for Industry: "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

Table 5: 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

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

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.

For participants recording at least one local reaction within seven days after each trial IMP dose administration, in the case of different value between participant reported and investigator confirmed results, investigator confirmed result will be included in the analysis:

- The maximum severity grade is equal to the highest graded local reaction within the recording period.
- Duration will be calculated in days as the difference from the start of the first reported event to the resolution of the last reported event, inclusive. The resolution date for events lasting longer than 7 days will be recorded in the participant's adverse event case report form. If the resolution date is partial or missing, the duration will be considered unknown.
- Onset day, defined as the first day of reporting any severity, will be derived for each recorded local reaction. If a participant report changes in severity of the local reaction, only the first day of reporting that specific local reaction will be counted.

The number and percentage of participants reporting local reactions up to seven days after each IMP dose administration will be summarized by maximum severity and cumulatively across severity levels. This summary will include categories "Any", "Grade 1", "Grade 2", "Grade 3", and "Grade 4". The associated 2-sided Clopper-Pearson 95% CIs will also be displayed.

The Safety Set and Dose 2 Safety Set will be used for post-Dose 1 and post-Dose 2 local reaction summaries respectively. Participants without any reactogenicity data up to seven days after each IMP dose administration will be excluded from the local reaction analysis. Missing values will not be imputed.

In addition, local reactions will also be summarized by:

- Duration (days) of each local reaction after each IMP dose.
- Onset day of each local reaction after each IMP dose.

Bar charts with the proportions of participants for each local reaction up to seven days after each IMP dose administration will be plotted. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity. In addition, a listing of participants in the Safety Set with reported local reactions will be provided.

6.5.1.2 Systemic events

The systemic events assessed and recorded in the e-diary are vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, and fever from within seven days after each IMP dose administration. The derivations for systemic events will be handled in a similar way to how local reactions are handled for presence of event, severity level, duration, and onset day (latency time).

Fever is defined as an oral body temperature ≥ 38.0°C (100.4°F). Temperatures collected in degrees Fahrenheit will be converted to degrees Celsius using (°F – 32) × 5/9 and grading will be based on the unrounded conversions.

The oral body temperature for each day will be recorded in the e-diary and temperature from Day 1 through Day 7 will be graded as described in Table 6.

Solicited systemic events will be categorized as mild, moderate, severe or potentially life-threatening) and graded from 1 to 4, during the analysis as described in Table 6.

Table 6: Systemic events 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".

Systemic events reported up to seven days post-Dose 1 and post-Dose 2 will be summarized in the same manner as local reactions (see Section 6.5.1.1 using the Safety Set and Dose 2 Safety Set. Participants without any reactogenicity data up to 7 days after each IMP dose administration will be excluded from the systemic events analysis. In addition, a listing of participants in the Safety Set with reported systemic events will be provided.

If data regarding local /systemic reactogenicity events were not entered into the e-diary tool as planned, and instead were recorded on the AE CRF page, SDTM data reconstruction will be implemented to align with the FDA guidance outlined in "Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review".

6.5.1.3 Adverse events

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

Summary tables will include AEs reported from each IMP administration up to 28 days after each IMP administration, SAEs and AESIs occurring from IMP Dose 1 up to 6 months after each IMP administration for participants in Cohorts 1 to 4 and SAEs occurring from IMP Dose 1 up to 3 months after last IMP administration for participants in Cohort 5. AEs leading to IMP discontinuation or trial withdrawal will be listed, and summarized when at least 10 events in all participants have been reported.

AEs/SAEs post-Dose 1 will be summarized by treatment group post-Dose 1 based on the Safety Set. AEs/SAEs post-Dose 2 will be summarized by treatment group post-Dose 2 based on Dose 2 Safety Set.

All AEs will be coded using the most recent version of the MedDRA® coding system and graded for severity using FDA guidance for "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". No imputation for missing grades will be performed.

If an AE is reported more than once for the same participant for a SOC / PT the AE will be counted once for this SOC / PT for the specified reporting period.

All AE (from post-dose) summary tables will be sorted alphabetically by SOC and PT within SOC, unless specified otherwise.

The Safety Set will be used for the summary of data reported during assessment period post-Dose 1 and prior to Dose 2 and Dose 2 Safety Set will be used for summary of data reported post-Dose 2.

Safety overview

The number and percentage of participants reporting at least one of the below events within the time frame specified above will be summarized by treatment group for the participants.

- Solicited local reactions and systemic events
  - Local reactions
    - Grade ≥3
  - Systemic events
    - Grade ≥3

- AE
- Related AE
- AE with Grade ≥3
- Related AE with Grade ≥3
- AE leading to treatment discontinuation
- AE leading to trial withdrawal
- SAE
- Related SAE
- AESI
- Related AESI
- AESI with Grade ≥3
- Death

The following safety data will be summarized by PT nested within SOC. The number and percentage of participants meeting the endpoint will be presented by treatment group:

- AEs from each IMP dose up to 28 days after each IMP dose
- Related AEs from each IMP dose up to 28 days after each IMP dose
- Related AEs with Grade ≥3 from each IMP dose up to 28 days after each IMP dose
- SAEs from each IMP dose through 6 months after each IMP dose for Cohorts 1 – 4. For Cohort 5, SAEs from IMP Dose 1 through 2 months after IMP Dose 1, from IMP Dose 2 through 3 months after IMP Dose 2 and from IMP Dose 1 through 3 months after last IMP dose.
- Non-serious AEs with percentage greater than 5% from each IMP dose up to 28 days post each IMP dose (data from two intervals combined)

Adverse Events (AEs) by grade

The number and percentage of participants with AEs from each IMP dose up to 28 days after each IMP dose will be summarized by worst grade by PT nested within SOC. Only the worst grade will be counted if an AE is reported more than once for the same participant for a SOC / PT. AEs with a missing grade will be presented in the summary table with a grade category of “Missing”.

Deaths

All deaths will be listed.

AE listings

All AEs, SAEs, AESIs and AEs leading to IMP discontinuation or trial withdrawal will be presented. AEs prior to IMP Dose 1 will be flagged in all AE listings.

6.5.1.4 Laboratory assessments

Laboratory assessments including hematology, clinical chemistry, and urinalysis will be tested by local laboratories. Summaries of hematology and clinical chemistry data will be presented by treatment group for the participants in the Safety Set and Dose 2 Safety Set as appropriate.

For the purposes of summarizing and presentation in tables and listings, all laboratory values of hematology and chemistry will be presented in System International (SI) units. If a laboratory value is reported using a nonnumeric qualifier, e.g., less than (<) a certain value, or greater than (>) a certain value, the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier. The data as collected will be presented in the listings.

Hematology and clinical chemistry parameters at each protocol scheduled visit and its change from baseline to each post-baseline protocol scheduled visit will be summarized using descriptive summary statistics by visit and treatment group.

Grading shift tables for hematology and chemistry laboratory assessments from baseline to 3 d (Cohort 1 to Cohort 4 sentinel group post-Dose 1 only) and 7 d post each dose visit will be provided for each laboratory parameter by treatment group, based on FDA guidance for "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

In addition, abnormal and normal laboratory values will be summarized for each parameter of hematology and clinical chemistry assessment by visit and treatment group.

All laboratory data including hematology, clinical chemistry, and urinalysis will be presented in the data listings and abnormal clinical laboratory values with toxicity grade will be flagged in the listing. Laboratory values that are below or above the normal reference ranges will be flagged.

6.5.1.5 ECG assessments

ECG variables to be summarized include heart rate, QRS, PR, QT and corrected QT (QTc) intervals. Absolute values collected at each timepoint, and its change from baseline to each post-baseline timepoint will be summarized using descriptive summary statistics by *treatment group for the participants in Safety Set and Dose 2 Safety Set as appropriate.*

The investigator's evaluation at each visit (Normal, Abnormal – not clinically significant and Abnormal – clinically significant) and any new ECGs changes which may support myocarditis/pericarditis following Brighton Collaboration definition ("paroxysmal or sustained atrial or ventricular arrhythmias", "atrioventricular (AV) block (grade 1-3) or bundle branch block", "diffuse ST-segment elevation or PR-segment inversion, compatible with pericarditis") results in categorical data. 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. The number and percentage of participants will be presented at baseline, 3 days (for sentinel groups only) and 7 days after each dose for following categories:

- Normal
- Abnormal
  - Not clinically significant
  - Clinically significant
- Abnormal
  - Paroxysmal or sustained atrial or ventricular arrhythmias
  - AV block (grade 1-3) or bundle branch block
  - Diffuse ST-segment elevation or PR-segment inversion, compatible with pericarditis

Shift tables from baseline to post- dose visits for “Normal”, “Abnormal – Not clinically significant” and “Abnormal – Clinically significant” categories will also be provided by treatment group.

All ECG data will be presented in the data listings and abnormal values will be flagged in the listing. Results that are below or above the normal reference ranges will be flagged.

6.5.2 Other safety analyses

6.5.2.1 Extent of exposure

The number and percentage of participants receiving IMP study dose will be tabulated by treatment group for each dose, for the participants in Randomized/Assigned Set.

A by-participant listing of treatment administration will be presented.

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

Oral swabs for NAAT-based SARS-CoV-2 testing for surveillance positive and negative test results based on central and local laboratory tests will be summarized respectively using descriptive statistics by treatment group. All central and local laboratory NAAT test results will listed as well.

6.5.2.3 Vital signs

All vital signs data will be presented in the data listings and abnormal values will be flagged in the listing. Results that are below or above the normal reference ranges will be flagged. Oral body temperature will be presented in Celsius (°C).

6.5.2.4 Physical examination

Physical examinations including body weight and height will be performed and clinically significant abnormalities will be summarized by treatment group, for the participants in Safety Set and Dose 2 Safety Set as appropriate.

The results from all physical examinations will be listed.

6.5.2.5 Viral screening

A listing of viral screening results will be provided.

6.5.2.6 Pregnancy testing and FSH

A listing of pregnancy testing and follicle stimulating hormone (FSH) test results will be provided for protocol specified timepoints.

6.5.2.7 E-diary

E-diary transmission after each IMP dose will be summarized by treatment group, for the participants in Safety Set and Dose 2 Safety Set. The summary will also include the numbers and percentages of vaccinated participants not transmitting the e-diary and transmitting the e-diary for any day in the required reporting period, by treatment group.

6.6 Immunogenicity analyses

The neutralizing antibody titers above the lower limit of quantitation (LLOQ) are considered accurate and their quantitated values will be reported. Neutralizing antibody titers below the LLOQ will be set to 0.5× LLOQ for all the analysis if not specified otherwise. Missing data will not be imputed.

Only participants without breakthrough SARS-CoV-2 infections (without positive central or local NAAT from pre-Dose 1 through the visit) will be analyzed for the respective visit.

The number of participants with blood samples drawn at each visit and their respective time windows as specified in Table 4 will be summarized for the Safety Set.

Table 7 and Table 8 below lists the neutralizing antibody titer assay results to be assessed for each variant strains at specific visit for Cohorts 1 to 5.

Table 7: Humoral immune response analysis against variants at selected timepoints for Cohorts 1 – 4 in the final study report

	Cohort 1 (≥18-55 yoa) N=45 BNT162b2 + 5ug BNT162b4 - once N=15 BNT162b2	Cohort 2 (≥18-55 yoa) N=45 BNT162b2 + 10ug BNT162b4 - twice N=15 BNT162b2	Cohort 3a (≥18-55 yoa) N=45 BNT162b2 + 15ug BNT162b4– 2nd dose XBB1.5 N=15 BNT162b2	Cohort 3b (>55 yoa) N=45 BNT162b2 + 15ug BNT162b4– 2nd dose XBB1.5 N=15 BNT162b2	Cohort 4a (≥18-55 yoa) N=45 BNT162b2 + 30ug BNT162b4– 2nd dose XBB1.5 N=15 BNT162b2	Cohort 4b (>55 yoa) N=45 BNT162b2 + 30ug BNT162b4– 2nd dose XBB1.5 N=15 BNT162b2
V1 – Baseline (Pre-Dose 1)	WT, BA.4/5	WT, BA.4/5	WT, BA.4/5	WT, BA.4/5	WT, BA.4/5	WT, BA.4/5
V4 – Day 28 post-Dose 1	WT, BA.4/5	WT, BA.4/5	WT, BA.4/5	WT, BA.4/5	WT, BA.4/5	WT, BA.4/5
V6 – Month 6 post-Dose 1; pre-Dose 2	WT, BA.4/5	WT, BA.4/5	WT, BA.4/5, and XBB.1.5	WT, BA.4/5, and XBB.1.5	WT, BA.4/5, and XBB.1.5	WT, BA.4/5, and XBB.1.5
V9 – Day 28 post-Dose 2	NA	WT, BA.4/5	WT, XBB.1.5	WT, XBB.1.5	WT, XBB.1.5	WT, XBB.1.5

WT: Ancestral strain. NA: Not applicable.

Table 8: Humoral immune response analysis against variants at selected timepoints for Cohort 5 in the final study report

	Cohort 5 (≥18-55 yoa) N=20 30ug BNT162b4
V1 – Baseline (Pre-Dose 1)	WT, BA.4/5, and XBB.1.5
V3 – Day 7 post-Dose 1	WT, BA.4/5, and XBB.1.5
V4 – Day 28 post-Dose 1	WT, BA.4/5, and XBB.1.5
V8 – Day 7 post-Dose 2	WT, BA.4/5, and XBB.1.5
V9 – Day 28 post-Dose 2	WT, BA.4/5, and XBB.1.5

6.6.1 Secondary endpoint immunogenicity analysis for Cohorts 1 to 4

6.6.1.1 GMTs of SARS-CoV-2 neutralizing titers for each strain at baseline and 28 days after IMP dose

The GMTs and associated 95% CIs of the following will be computed using the statistical methods specified in Section 6.1.1.

- SARS-CoV-2 ancestral strain neutralizing titers at baseline (pre-Dose 1) and 28 days after IMP Dose 1 in Cohorts 1 to 4 and 28 days after IMP Dose 2 in Cohort 2-4,
- SARS-CoV-2 Omicron BA.4/BA.5 neutralizing titers at baseline, 28 days after IMP Dose 1 in Cohorts 1 to 4 and 28 days after IMP Dose 2 in Cohort 2,
- SARS-CoV-2 Omicron XBB.1.5 neutralizing titers at IMP Dose 2, and 28 days after IMP Dose 2 in Cohorts 3 and 4.

The number of participants with valid assay results, GMTs and 95% CIs will be provided for each treatment group at each visit.

Bar charts with overlaid individual data points and line plots with mean and 95% CIs over time by treatment group for antibody titers will be presented.

6.6.1.2 GMFRs of SARS-CoV-2 neutralizing titers for each strain from baseline to 28 days after each IMP dose

The GMFRs and associated 95% CIs of the following will be computed using the statistical methods specified in Section 6.1.1.

- SARS-CoV-2 ancestral strain neutralizing titers from baseline (pre-Dose 1) to 28 days after IMP Dose 1, in Cohorts 1 to 4 and to 28 days after IMP Dose 2 in Cohort 2-4,
- SARS-CoV-2 Omicron BA.4/BA.5 neutralizing titers from baseline to 28 days after IMP Dose 1 in cohorts 1 to 4, baseline to 28 days after IMP Dose 2 in Cohort 2,
- SARS-CoV-2 Omicron XBB.1.5 neutralizing titers from IMP Dose 2 to 28 days after IMP Dose 2 in Cohorts 3 and 4.

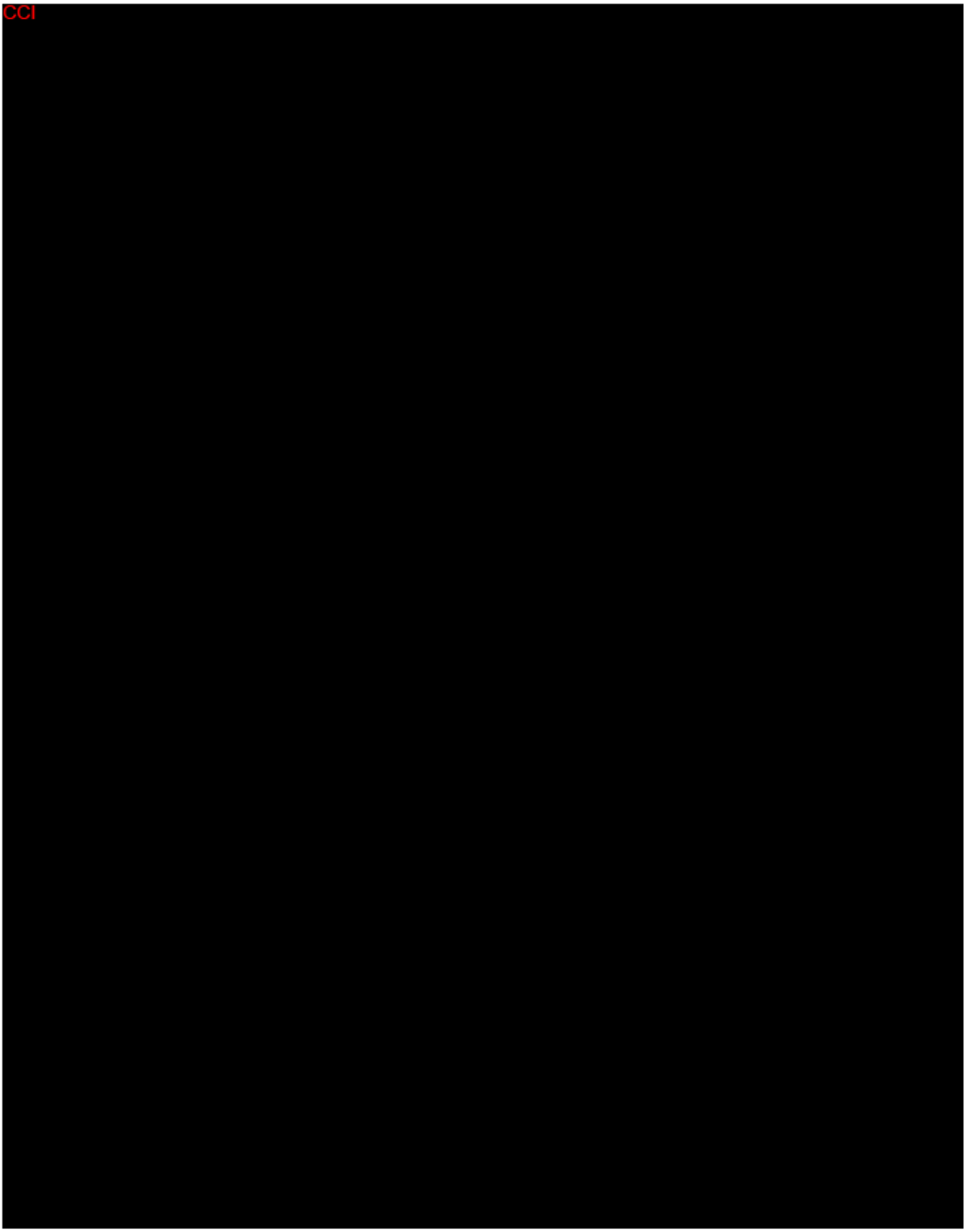
6.6.1.3 Seroresponse to SARS-CoV-2 strain at 28 days after each IMP dose

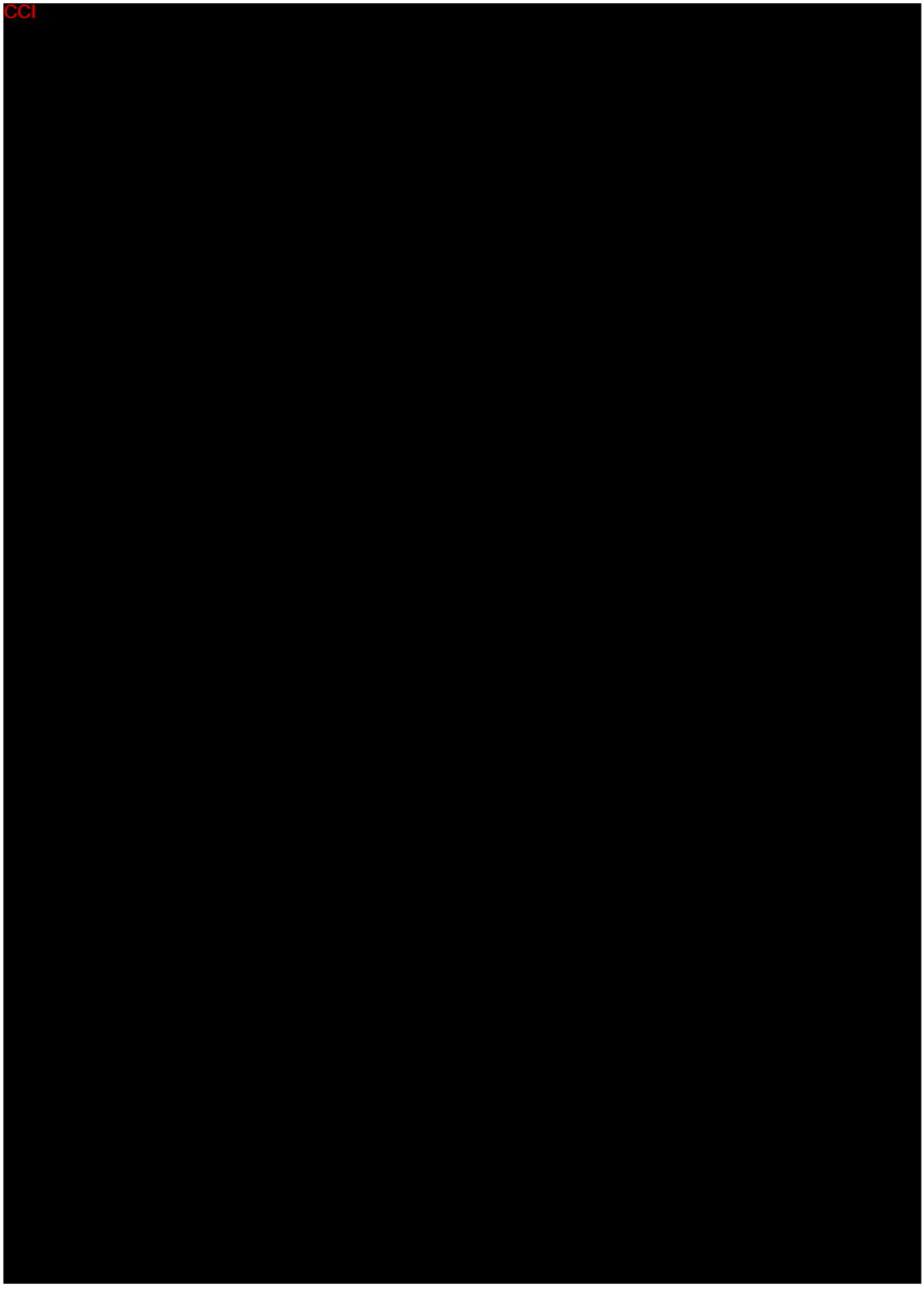
Seroresponse of neutralizing antibody titers is defined as achieving ≥4-fold rise from baseline (pre-Dose 1 unless specified otherwise). If the baseline measurement is below LLOQ, the post-dose measure of ≥4 LLOQ will be considered as seroresponse. Percentage of participants with seroresponse (achieving ≥4-fold rise from baseline) of neutralizing antibody titers will be calculated and the associated 2-sided 95% CIs will be obtained by constructing CIs using the Clopper-Pearson method.

The number and percentage of participants with seroresponse to SARS-CoV-2 ancestral strain, Omicron BA.4/BA.5 (BA.4/5) and Omicron XBB.1.5, including the associated 2-sided 95% CI will be presented by treatment group at 28 days post each IMP dose as applicable. Note that for SARS-CoV-2 Omicron XBB.1.5 strain the seroresponse will only be evaluated for 28 days post-Dose 2 from Dose 2 visit of Cohorts 3 and 4.

A participant listing of all assay data including within sampling window indicator will be presented.

CCI

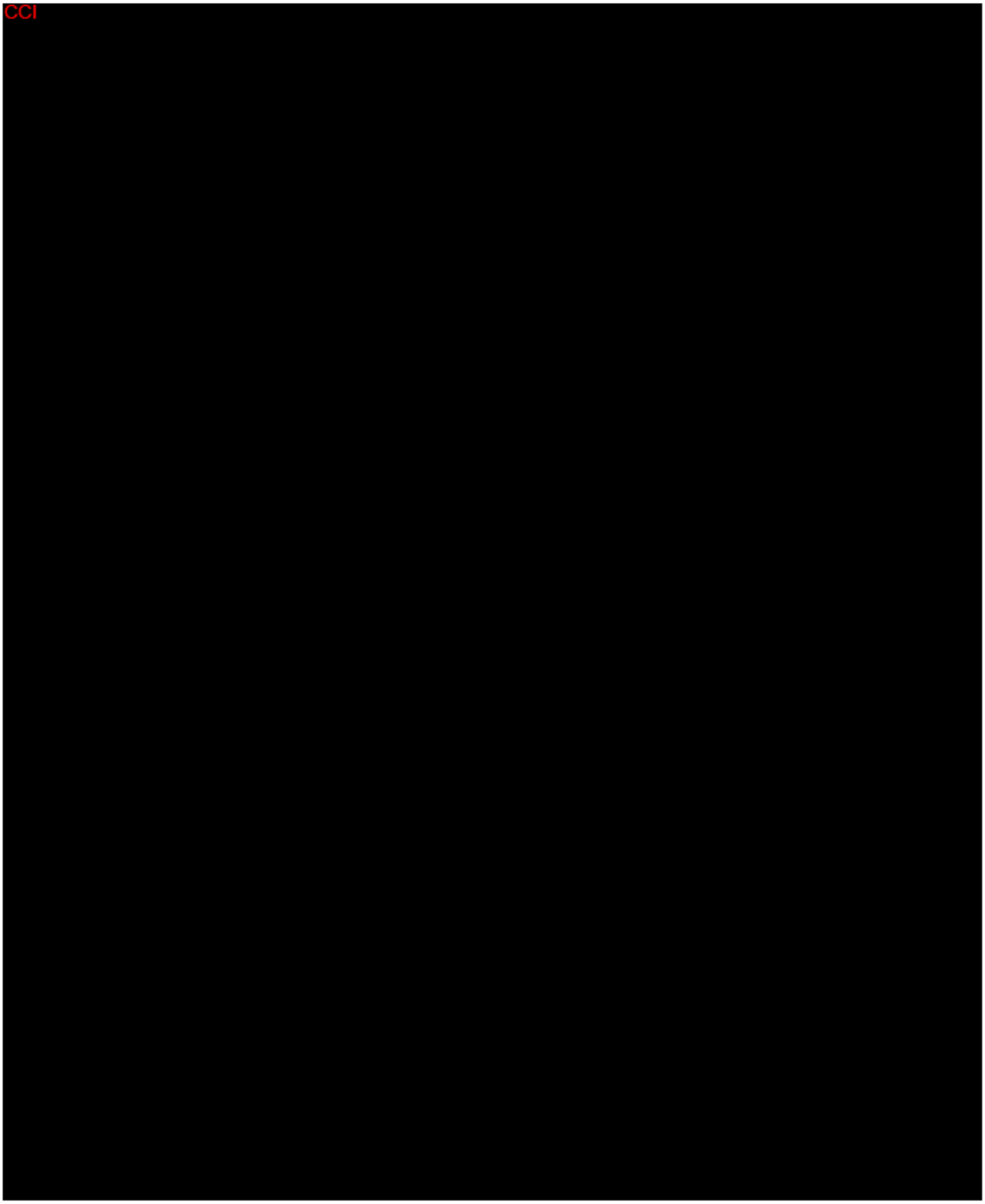



CCI

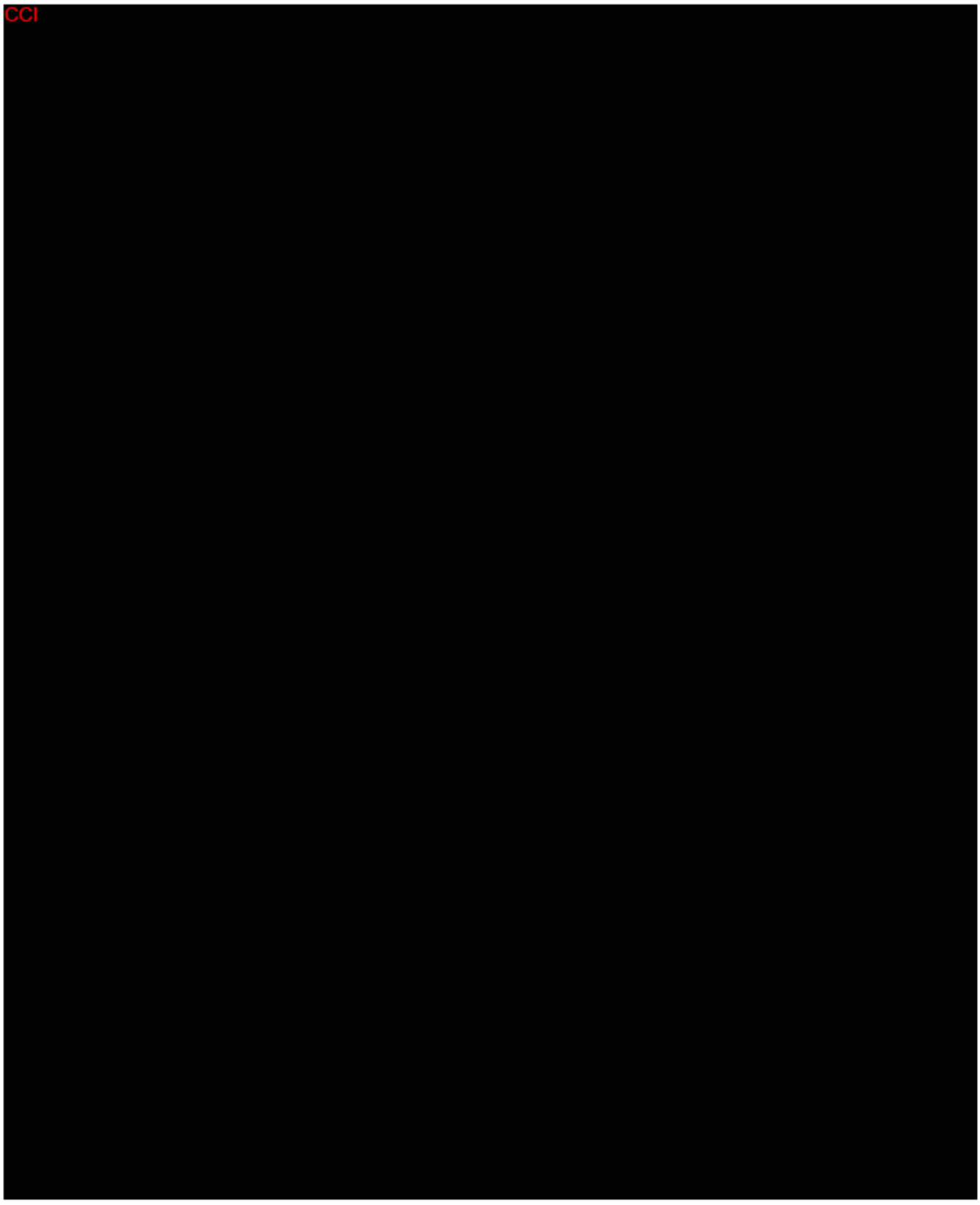

CCI

CCI

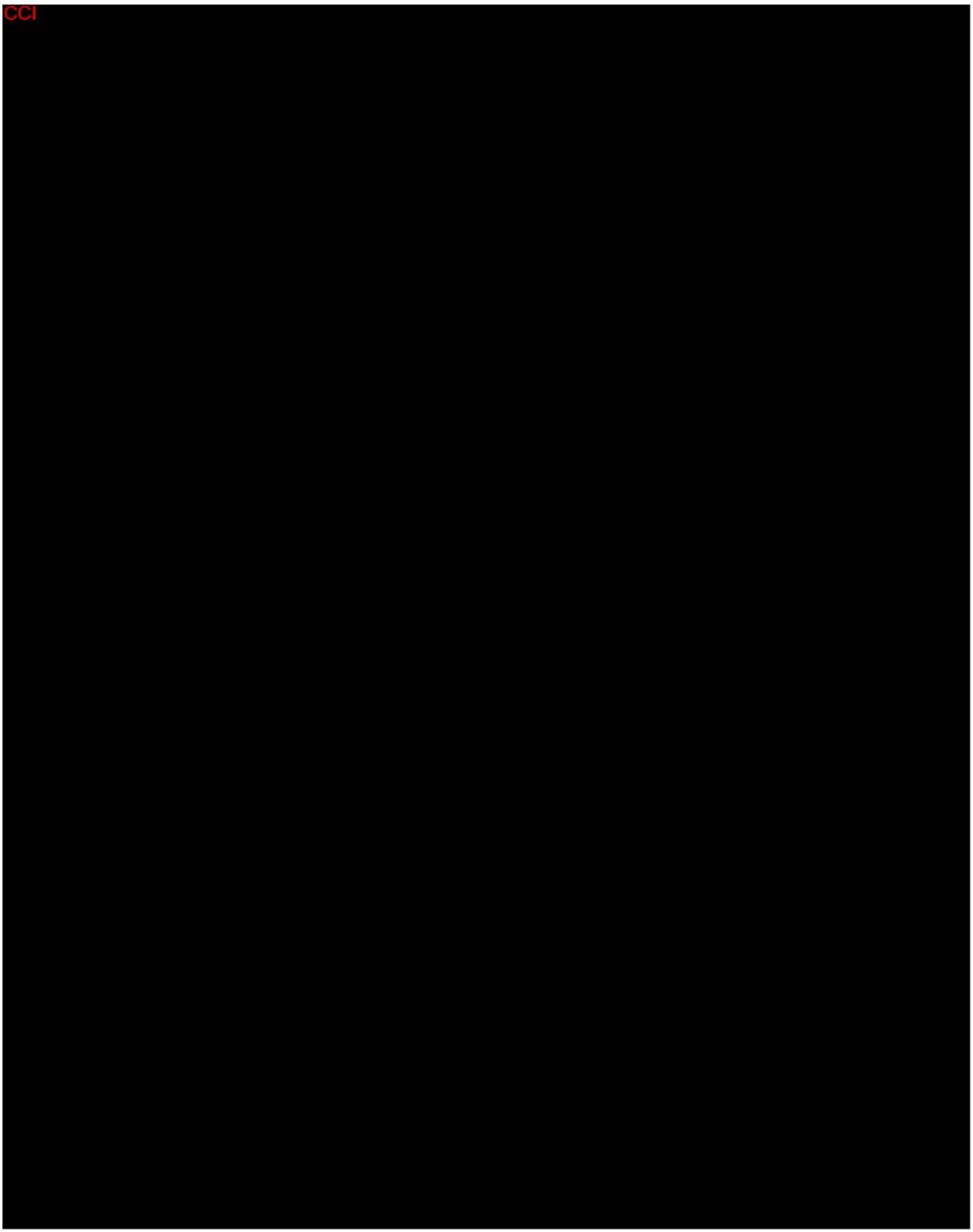
[redacted]


CCI

CCI



CCI




CCI

7 REFERENCES

1. FDA Guidance 2007. FDA Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.
2. Clopper, CJ and Pearson, ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-413, 1934.
3. Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review. Guidance for Industry. Technical Specifications Document. Version 2.1 December 2019.

8 SUPPORTING DOCUMENTATION

8.1 Appendix 1: Changes to protocol-planned analyses

No changes to the protocol-planned analyses have been made.

8.2 Appendix 2: List of abbreviations

AE	Adverse event
ATC	Anatomical therapeutic chemical
AESI	Adverse event of special interest
BMI	Body mass index
CCI [redacted]	
CI	Confidence interval
CCI [redacted]	
COVID-19	Coronavirus Disease 2019
d	day
DL	Dose level
ECG	Electrocardiogram
EDC	Electronic data capture (system)
CCI [redacted]	
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
h	Hour
CCI [redacted]	
IM	Intramuscular
IMP	Investigational medicinal product
IRC	Internal Review Committee
LLOQ	Lower limit of quantitation
M	Membrane protein of SARS-CoV-2
max	Maximum
MedDRA®	Medical Dictionary for Regulatory Activities
min	Minimum

N	Number of participants
N	Nucleocapsid protein of SARS-CoV-2
n	Number of observations
N/A	Not Applicable
NAAT	Nucleic acid amplification-based test
CCI [redacted]	
OMI	Omicron
CCI [redacted]	
PD	Protocol deviations
PT	Preferred term
S	Spike protein of SARS-CoV-2
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedures
CCI [redacted]	
WT	Wild type

8.3 Appendix 3: Reporting conventions

SAS version 9.4, or higher, will be used to produce all tables, listings, and figures.

For summary statistics, the mean and median will be displayed to one decimal place greater than the original value and the measure of variability (e.g., SD) will be displayed to two decimal places greater than the original value. Minimum and maximum will be reported to the same decimal places as the original value. Percentages (%) will be displayed with one decimal place and 95% CIs will be displayed with one decimal place greater than the original value.

Additional conventions will be detailed in the tables, listings and figure shell document for programming.

8.4 Appendix 4: Schedules of activities

Table 10 and Table 11 list all of the assessments to be performed in the trial.

Table 10: 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 q	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]	
Height & body weight	X														
Vital signs [c]	X	X [b]	X [b]	X	X	X			X [b]	X	X				
12-lead ECG	X	X		X	X					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**		
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 participants 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
Oral swabs for NAAT-based SARS-CoV-2 testing and sequencing for	X	X			X	X	X	X	X [t]	X	X	X	X	X	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**		
surveillance (central test site)															
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 participants 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 participants still have thermometer		Issue							Confirm						

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		
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
Issue, train, or collect subject e-diaries; remind participants [i]		Issue, train		Remind					Remind	Collect				Collect	
Participants 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 (SAEs only)		X	X	X	X [j]	X [j]	X	X	X	X [j]	X [j]	X	X
Record medication since last visit		X	X	X	X	X	X	X	X	X	X	X [k]	X [k]	X	X
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		
CCI															
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.
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 of protocol.
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 of protocol.
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 participants 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 participants 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 participants 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. For FU visits, only adverse event(s) of special interest, any SAEs, and all 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 participants, 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 of protocol. 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. If the initial N-binding antibody test is negative, this test needs to be repeated if performed >28 d prior to the planned vaccination.
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 participants 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 participants 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. The assessment/sampling at Visit 7 will only be performed if not done at Visit 6.
u. Not for Cohorts 4a and 4b.

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.

Table 11: Schedule of activities – Cohort 5

Activity	Visit 0 (V0)	V1	V1	V3	V4	V7	V8	V9	V10	Early term. Visit	Unscheduled [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				
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 participants to use contraception		X		X		X [n]	X				
Record pregnancies		Start	=>	=>	=>	=>	=>	=>	End	End	

Activity	Visit 0 (V0)	V1	V1	V3	V4	V7	V8	V9	V10	Early term. Visit	Unscheduled [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**		
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					
Issue thermometer/confirm participants 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 participants [i]		Issue, train				Remind	Collect			Collect	
Participants 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

Activity	Visit 0 (V0)	V1	V1	V3	V4	V7	V8	V9	V10	Early term. Visit	Unscheduled [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		
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
CCI											
CCI											
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 of protocol.
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 of protocol.
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 participants 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 participants 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 participants 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 participants, 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 of protocol. 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.