STATISTICAL ANALYSIS PLAN (SAP)
BNT165-01

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 SAP APPROVAL

This Statistical Analysis Plan (SAP) has been prepared, reviewed, and approved in accordance with the ICON standard operating procedure (SOP). Documentation of this process is filed in the trial master file (TMF).

2 VERSION HISTORY

Table 1: SAP Version History Summary

SAP version	Version date	Change	Rationale
1.0	14 Feb 2023	N/A	Original Version
2.0	30 May 2023	- Section 3.1: Table 2 updated	Aligned to CTP V 4.0
		- Section 3.2: Table 3 updated	Aligned to CTP V 4.0
		- Section 8.5.2: Listing for delayed local reactions added.	Aligned to CTP V 4.0
		- Section 8.5.4: Analysis period for MAAEs modified	Aligned to CTP V 4.0
		- Section 8.5.4.1: Analysis of "any solicited reactogenicity event that continues longer than 7 d post-IMP administration or is an SAE" added to safety overview table	Clarification
		- Section 8.5.4.3: threshold of 5% deleted for analysis of non-serious AEs.	Given the small sample size per cohort, applying a threshold is not meaningful.
		- Section 8.5.5: Clarification that Urinalysis will be listed only.	Clarification
		- Section 8.5.8: Addition of listing of data collected during wellbeing calls.	Clarification
		- Section 10.4: Table 7 updated	Aligned to CTP V 4.0
3.0	08 May 2024	- Section 3.1: Removed the exploratory endpoint.	Immunogenicity endpoints analyses will not be in the CSR.
		- Section 8.1.2: Added instructions for handling the missing AE end dates.	Clarification
		- Section 8.4: Removed the phrase regarding the immunogenicity assessment.	Immunogenicity endpoints analyses will not be in the CSR.
		- Section 8.6.1: Removed the immunogenicity endpoints analysis. Removed the subsections 8.6.1.1 and 8.6.1.2.	Immunogenicity endpoints analyses will not be in the CSR.

3 INTRODUCTION

This is an exploratory Phase I, randomized, observer-blind, placebo-controlled dose escalation trial evaluating the safety, tolerability and immunogenicity of an investigational RNA-based vaccine for active immunization against malaria. The results might be included in a regulatory submission. This statistical analysis plan (SAP) describes the detailed procedures for the planned statistical analyses for protocol BNT165-01 to support the completion of the Clinical Trial Report (CTR). This SAP will also include the details of the presentation and analysis of any applicable interim analyses.

The statistical analyses will be conducted by ICON clinical research using SAS® software Version 9.4 or higher.

3.1 Objectives, estimands and endpoints

The estimands and endpoints corresponding to each primary and exploratory objective are described in Table 2.

This SAP provides details on the analysis of the primary endpoints.

The analysis of exploratory endpoints is out of scope of this SAP and will be described in a different document.

Table 2: Objective, estimands and endpoints

OBJECTIVES	ESTIMANDS	ENDPOINTS
Primary objectives		
To describe the safety and tolerability of BNT165b1 vaccination in healthy adults.	For each DL cohort: • Frequency of solicited local reactions at the injection site recorded up to 7 d after each dose. • Frequency of solicited systemic reactions recorded up to 7 d after each dose. • Proportion of subjects with at least one AE occurring up to 28 d after each dose. • Proportion of subjects with at least one MAAE occurring up to 28 d after each dose. • Proportion of subjects in each cohort with at least one SAE occurring up to 24 weeks after Dose 3.	• Solicited local reactions (pain, erythema/redness, induration/swelling) • Solicited systemic reactions (vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, and fever) • AEs • SAEs • MAAEs

OBJECTIVES	ESTIMANDS	ENDPOINTS
Exploratory objectives		
To describe the humoral immune responses induced by BNT165b1 vaccination at different DLs in healthy adults.	Not applicable	• Levels of antigen-specific serum and/or plasma antibodies (total IgG) measured using ELISA and/or similar assays CCI

CCI

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

3.2 Trial design

The trial design is as shown in below Table 3.

Table 3: Trial Design

Trial Design	The BNT165 multi-antigen vaccine clinical development will begin with this First-in-Human (FIH) clinical trial, a dose escalation multi-center trial designed to assess the safety, tolerability, and exploratory immunogenicity of the vaccine component. The vaccine component assessed in this trial will be BNT165b1, a Ribonucleic acid -lipid nanoparticle (RNA-LNP) encoding for part of *P. falciparum* circumsporozoite protein (*Pf*CSP). Subsequently, multiple other vaccine components will be assessed (either individually or combinations) as well. BNT165b1 will be evaluated at three dose levels (DLs) to select a safe and tolerable dose in a 3-dose schedule. A sponsor Internal Review Committee (IRC) will be used for the BNT165-01 clinical trial.
Trial population	This trial will enroll healthy volunteers aged 18 to 55 years with no history of previous or current malaria infection. Trial subjects must not have received any approved or investigational malaria vaccine or have participated in a previous malaria challenge trial. All subjects must meet the trial eligibility criteria listed in Section 5 of protocol.
Investigational medical product(s)	Name: BNT165b1 Type: Investigational Dose: • 3 µg BNT165b1 or isotonic NaCl solution (0.9%) • 10 µg or lower BNT165b1 or isotonic NaCl solution (0.9%) • 30 µg or lower BNT165b1 or isotonic NaCl solution (0.9%) Schedule: Three (one each on Days 1, 57, and 183) injections given at each dose level. Route of administration: Intramuscular injection in the deltoid muscle of the non-dominant arm. Other injection sites may be used if necessary. Allocation to IMP: Trial subjects will be randomized 4:1 to BNT165b1: placebo using an online randomization tool.
Treatment and trial duration	The planned trial duration for each trial subject is ~19 months (up to 4 weeks screening, ~26 weeks treatment phase, and ~52 weeks follow-up phase).

Planned number of patients	A total of 60 subjects are expected to enroll in the cohorts evaluating BNT165b1, such that there are 20 trial subjects for each of the cohorts as planned. Per cohort, trial subjects will be randomized 4:1, using an online randomization tool to receive either vaccine or placebo (i.e., of 20 subjects, 16 subjects and 4 subjects will receive the vaccine or placebo, respectively).
Randomization and blinding	Randomization: This is a 3-dose cohort observer-blind trial. Blinding: All randomized trial subjects will be blinded to their assigned trial treatments. The trial personnel dispensing and administering the vaccine will be unblinded, but all other trial personnel, including the principal investigator, and the subject, will be blinded. The investigator and any site personnel other than the unblinded dispenser/administrator must not be allowed to know the IMP assigned to any trial subject and must not be allowed to see the drug product containers. Because BNT165b1 and placebo differ in their physical appearance, the trial treatment will be provided in a manner that maintains the blinding, e.g., syringes will be masked or colored.
Other features	An IRC will 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.

Dose Escalation

Dose escalation decisions to progress to the next dose level (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 reactogenicity of the previous DL was considered acceptable by the IRC and no stopping/pausing rules were met.

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

3.3 Schema (graphical representation of the trial)

Figure 1: Trial schema

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

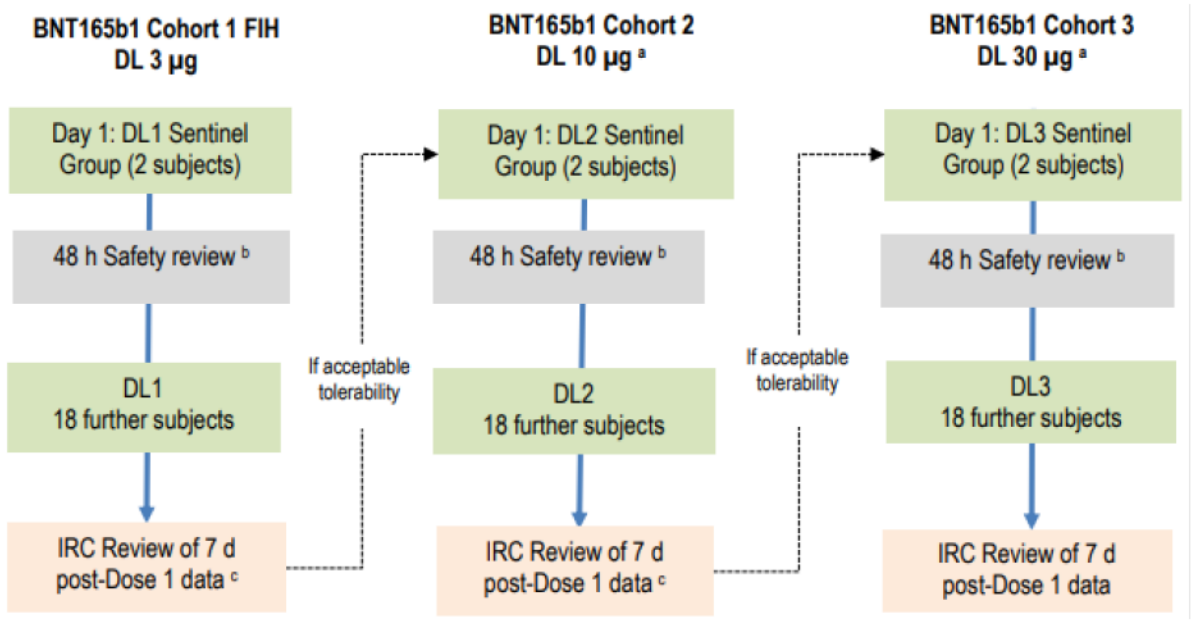

Figure 2: The staggered dosing process for the cohorts

a. In case of safety concerns the IRC can decide to reduce to an intermediate dose.
b. Further dosing of subjects will proceed if the investigator considers the vaccine reactogenicity is acceptable and no stopping/pausing rules are met.
c. Further opening of new cohorts will proceed if the IRC considers the vaccine reactogenicity is acceptable and no stopping/pausing rules are met.

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

3.4 Schedule of activities

See Section 10.4 Appendix 4 for the schedule of activities.

4 STATISTICAL HYPOTHESES

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

5 INTERIM ANALYSES AND ANALYSIS SEQUENCE

An interim analysis on adverse events, reactogenicity and immunogenicity data will be performed when data from the 28d follow-up visit post dose 2 are available for subjects in any cohort to inform further clinical development. Also, interim analyses at other timepoints may be prepared.

6 SAMPLE SIZE DETERMINATION

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

7 ANALYSIS SETS AND SUBGROUPS

Data for all subjects 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.

7.1 Analysis sets

Screened Set

All subjects who provided informed consent.

Randomized Set

All subjects who have been randomized to IMP.

Safety Set

All subjects who received at least one dose of the IMP.

Analyses of all safety endpoints will be performed using the safety set using the dose level the subject actually received.

Data for all subjects 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.

7.2 Protocol deviations

Protocol deviations are failures to adhere to the inclusion/exclusion criteria and protocol requirements and will be classified into key (important) protocol deviations (PDs) and non-key PDs.

All protocol deviations will be assessed and documented prior to releasing the database.

7.3 Subgroups

There are no planned subgroup analyses.

8 STATISTICAL ANALYSES

8.1 General considerations

In general, all summaries will be displayed by individual vaccine DL and combined placebo. A total group, combining all subjects on placebo and active vaccine, will be presented in addition for accounting (subject disposition), demographics and other baseline characteristics and protocol deviations as applicable unless otherwise specified.

No formal statistical comparisons between vaccine DL of BNT165b1 and placebo will be performed. Missing data, other than that described for partial or missing dates for AEs/concomitant medications/vaccinations (as described below) will not be imputed.

Continuous variables will be summarized using the following descriptive statistics: number of subjects with non-missing data (n), mean, SD, median, minimum (min) and maximum (max).

Categorical variables will be summarized by absolute and relative frequencies (n and %) of subjects in each category and the number of subjects 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, etc.) percentages will be based on the number of subjects in the analysis set (N). For reported visit data (e.g., lab etc.) percentages will be based on the number of subjects with non-missing values (n).

The rates of binary endpoints such as safety variables (systemic and local reactions) will be provided.

All data collected during the trial will be listed based on safety set unless otherwise specified. The trial day will be presented as appropriate. Listings will be sorted by dose level, site number, subject number, and date of assessment or date of onset (if applicable).

All trial data will be presented at the visit as assigned in the Case Report Form (CRF). No windowing of data for the purposes of assigning to a visit will occur. Unscheduled assessments will not be included in summaries/analysis but will be included in the listings.

8.1.1 General definitions

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

Generally, if there are multiple pre-baseline assessments available for a particular day, the assessment that is closest to the day (and time if collected) of the first dose of a trial treatment will be used as the baseline value.

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 °F will be converted to °C as follows:

$$°C = (°\text{F} - 32) * 5/9$$

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:

- If assessment/onset date < date of first IMP dose, then trial day = assessment date – date of first IMP dose
- If assessment/onset date >= date of first IMP dose, then trial day = assessment/onset date – date of first IMP dose + 1

That is, trial day 1 indicates the date of first IMP dose.

The day relative to dose 2 or dose 3 will be calculated as follows:

- If assessment/onset >= date of second IMP dose and < date of third IMP dose, then day relative to dose 2 = assessment/onset date – date of second IMP dose + 1
- If assessment/onset >= date of third IMP dose, then day relative to dose 3 = assessment/onset date – date of third IMP dose + 1

All trial data will be presented at the visit in the visit assigned in the Case Report Form (CRF)/visit assigned in external data. No windowing of data for the purposes of assigning to a visit will occur.

8.1.2 Handling missing data

For the purposes of assigning duration 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 unless it is the same month and year as the first dose of trial IMP. In this case, the onset date will be assumed to be the date of the first dose of trial IMP.
- If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the first dose of trial IMP. In this case, the event onset will be assumed to be the day and month of the first dose of IMP.
- A completely missing onset date will be assumed to be the date of the first dose of trial IMP.

End dates:

- If the day of the month is missing, the end day will be set to the last day of the month.
- If the end day and month are both missing, the day and month will be assumed to be December 31.
- A completely missing end date will be assumed to be the minimum of date of study discontinuation and date of data extract.
- If the imputed end date is less than the onset date, use the onset date as the imputed end date.

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

End dates:

- If end day is missing and month/year are non-missing, then day is assumed to be the last day of the month.
- If end day/month are missing and year is non-missing, then day and month are assumed to be the end of the year (31DECYYYY).

- If imputed end date is less than the start date, use the start date as the imputed end date.

Start dates:

- If the start date year is missing, the start date is set to one day prior to IMP start date.

- If the start date year is less than the year of the IMP first dose date, then:

  - If the month is missing, the start date is assumed to be mid-year point (01JULYYYY).
  - Else if the month is not missing, the start date is assumed to be mid-month point (15MONYYYY).

- If the start date year value is greater than the year of the IMP first dose date, then:

  - If the day and month is missing, the start date is assumed to be the year start point (01JANYYYY).
  - Else if the month is not missing, the start date is assumed to be the month start point (01MONYYYY).

- If the start date year value is equal to the year of the IMP first dose date:

  - If the month is missing or the month is equal to the month of the IMP first dose date, then the start date is assumed to be same day as the IMP first dose date.
  - Else if the month is less than the month of the IMP first dose date, the start date is assumed to the mid-month point (15MONYYYY).
  - Else if the month is greater than the month of the IMP first dose date, the start date is assumed to be the month start point (01MONYYYY).

If 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 should be set to the end date.

8.2 Subject disposition

The number of subjects who were screened and randomized and the number and percentage of subjects who were vaccinated (safety set), vaccinated with one, two and all the three doses will be summarized. In addition, the number and percentage of subjects who discontinued treatment along with a summary of the primary reason for treatment discontinuation as reported in the electronic case report form (eCRF) will be summarized.

The number and percentage of subjects who completed the trial and who discontinued the trial will be summarized.

The number and percentage of subjects that discontinued the trial before dose 2, after dose 2 but before dose 3 and after dose 3 together with the primary reason for discontinuation will be summarized.

The number and percentage of subjects in each analysis set will be summarized using the randomized set. In addition, for each analysis set, the number and percentage of subjects excluded from the analysis set will be presented, along with a summary of the reasons for exclusion.

Subject disposition and inclusion in analysis sets will be listed based on the screened set.

The number and percentage of subjects in the safety set with key PDs will also be presented.

8.3 Baseline characteristics

8.3.1 Demographics and baseline characteristics

The following demographic and baseline characteristics data will be summarized using the safety set:

- Age (years)
- Sex (male or female)
- Childbearing potential (yes or no)
- Race (Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, White, Not reported, Unknown, Other). Multiple race respondents will be summarized in a separate category (Multiple).
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported and Unknown)
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI (kg/m^2)) continuous and in categories (<18.5 kg/m^2, 18.5 to < 25.0 kg/m^2, 25.0 to < 30 kg/m^2, ≥ 30 kg/m^2)

Viral screen data (HIV 1 status, HIV 2 status, Hepatitis B status and Hepatitis C status (Positive or Negative)) and the COVID-19 tests data will be listed only.

8.3.2 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 the first dose of IMP.

If the medication started and stopped before the date of the first dose of trial IMP, the medication 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 (WHO Drug) drug codes of version B3 Sep 2022 or later. Resulting in Anatomical-Therapeutic-Chemical (ATC) codes indicating therapeutic classification.

The number and percentage of subjects who had prior medications/vaccinations and concomitant medications/vaccinations will be summarized by ATC classification level 4 and preferred name by vaccine dose levels of BNT165b1, combined placebo group and total for subjects in the safety set. The ATC codes and preferred names will be presented in alphabetical order.

Concomitant medications administered due to local and systemic reactions during time interval Day 1 to 7 days post each dose will be summarized. Bar chart with the number and percentage of subjects with any CM for local and systemic reactions will be presented.

Concomitant Procedures and Non-drug therapies will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) coding system version 25.1 or later. Concomitant Procedures and non-drug therapies will be listed only.

8.3.3 Medical history

Medical history data will be coded using MedDRA® version 25.1 or later. The number and percentage of subjects with each medical history and surgery will be summarized by System Organ Class (SOC) and Preferred Term (PT) by dose levels and total for subjects in the Safety Set. The summary will be sorted alphabetically by SOC and PT within SOC.

8.4 Efficacy analysis

There are no efficacy endpoints for this trial.

The primary objective is to describe the safety and tolerability of BNT165b1; the endpoints used for this are described in Section 8.5.2, Section 8.5.3 and Section 8.5.4 below.

8.5 Safety analyses

The primary endpoints of this trial include local reactions, systemic events, AEs, SAEs and MAAEs.

Other Safety data that will be summarized includes physical examinations, vital signs, height, body weight, electrocardiogram (ECGs) and clinical safety laboratory assessments (including Hematology and Clinical chemistry). All safety analyses will be based on the safety set and will be summarized by each dose level, combined placebo and visit if applicable.

8.5.1 Exposure to IMP

The number and percentage of subjects receiving trial doses will be tabulated by DL for the subjects in safety set.

For each dose, the following will be tabulated:

- Subjects receiving the dose,
- Subjects receiving the complete dose,
- Subjects receiving an incomplete dose,
- Reasons for receiving an incomplete dose,
- For dose 2 and 3 only: reason for not having received the dose.

8.5.2 Local reactions

The below subsections describe the analysis of solicited local reactions collected via the e-Diary and the analysis of acute local reactions as assessed by the investigator.

Delayed injection site reactions occurring between 7 days and 14 days after each dose will be solicited during a phone call that will occur 14 days after each dose. This data will be listed only.

8.5.2.1 Solicited local reactions

Local reactions assessed and reported in the e-diary are pain at the injection site, erythema/redness and induration/swelling from Day 1 through Day 7 after trial IMP dose, where Day 1 is the day of IMP injection. A subject is deemed to have had a local reaction if they report the reaction as “yes” on any day (Day 1 through Day 7).

Solicited local reactions will be categorized as mild, moderate, severe or potentially life-threatening) and graded from 1 to 4, as described in Table 4. The categories and grades are based on the FDA Guidance for Industry: “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials”[4].

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

Table 4: Local reaction grading scale

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

a. In addition to grading the measured local reaction at the greatest single diameter, the measurement will be recorded as a continuous variable.
b. Induration/swelling should be evaluated and graded using the actual measurement.
c. Investigator or medically qualified person confirmation is required.

For subjects recording at least one local reaction from Day 1 through Day 7 after IMP injection and for each specific local reaction mentioned in Table 4:

- The maximum severity grade is equal to the highest graded local reaction within the recording period. In case of a discrepancy between the subject and investigator assessment of severity, the confirmed assessment of the investigator will be used for analyses and a comment in the listings will be provided explaining the discrepancy.
- Duration will be calculated in days as the difference from the start of the reported event to the resolution of the event, inclusive. If an event resolves and occurs again within the reporting period of the eDiary, the duration will be calculated for each separate event and the maximum duration will be used for the analysis.
- Any missed assessment will be considered as “no reaction”. (e.g., if a subject has grade 1 headache on day 1 and 2, missing data on day 3 and 4 and grade 2 headache between day 5 and 7, this should be considered as 2 separate headache events, one of 2 days duration and one of 3 days duration. The maximum duration (3 days in this example) and the maximum severity (grade 2 in this example) would be used for the analysis.).
- For events that persist beyond Day 7, the duration of the reactogenicity event will be derived using the start and the end date of the AE (as recorded on the AE page).
- Onset day, defined as the first day of reporting any severity, will be derived for each recorded local reaction.

A reactogenicity overview summary will include the subjects with

- Any local reaction within 7 days of IMP injection
- Any local reaction that persisted beyond 7 days of IMP injection

Analyses in the overview summary will be provided for reactions of any grade and for reactions of grade ≥3. Analyses will be provided within 7 days of each IMP injections and overall regardless of the number of injections.

The number and percentage of subjects reporting local reactions (pain at the injection site, erythema/redness, induration/swelling) within 7 days after IMP dose will be summarized by maximum severity and cumulatively regardless of the severity. This summary will include categories “Any", “Grade 1”, “Grade 2”, “Grade 3” and “Grade 4”.

All local reaction summaries will be based on the safety set but excluding subjects without any e-diary data throughout the 7 days after vaccination.

In addition, local reactions will also be summarized by:

- Maximum duration (days) of each local reaction after each IMP injection and overall regardless of the number of injections
- Onset day of each local reaction after each IMP injection and overall regardless of the number of injections

For analyses overall across all injections, the subject will only be counted once for each local reaction reported.

Bar charts with the number of subjects for each local reaction throughout 7 days after each dose will be plotted. The bars will be divided into severity categories to highlight the proportions of subjects by maximum severity. In addition, listing of subjects in the safety set with reported local reactions, will be provided.

8.5.2.2 Acute local reactions

Investigators will assess acute local reactogenicity at the visits given in Section 10.4. Investigators will grade and record acute local reactions as described in Table 4. The number and percentage of subjects reporting acute local reactions (pain at the injection site, erythema/redness, induration/swelling) up to one hour after IMP dose will be summarized by severity and cumulatively regardless of the severity. This summary will include categories “Any", “Grade 1”, “Grade 2”, “Grade 3” and “Grade 4”. The number and percentage of subjects reporting local reactions (pain at the injection site, erythema/redness, induration/swelling) prior to administration of IMP dose will be summarized in a similar manner.

8.5.3 Systemic reactions

The systemic reactions assessed and recorded in the e-diary are vomiting, diarrhea, headache, fatigue/tiredness, Myalgia-muscle pain, Arthralgia-joint pain, chills and fever from Day 1 through Day 7 inclusive, where Day 1 is the day of each IMP injection. The derivations for systemic reactions will be handled similar to the way local reactions are handled for presence of event, severity level, duration, and onset day.

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

The highest oral temperature for each day will be recorded in the e-diary and the temperature from Day 1 through Day 7 will be graded as described in Table 5.

Solicited systemic reactions will be categorized as mild, moderate, severe or potentially life-threatening) and graded from 1 to 4 as described in Table 5. The categories and grades are based on the FDA Guidance for Industry: "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"[4]. Any systemic reaction of Grade 3 or higher will be confirmed by the investigator along with an assessment if it meets the definition of Grade 4.

Table 5: Systemic reaction grading scale

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

a. Investigator or medically qualified person confirmation is required.

Systemic reactions (vomiting, diarrhea, headache, fatigue/tiredness, myalgia-muscle pain, arthralgia-joint pain, chills and fever) reported within 7 days after IMP will be summarized in the same manner as local reactions (see Section 8.5.2) using the safety set but excluding subjects without any e-diary data throughout the 7 days after vaccination. Listing of subjects in the safety set, with reported systemic reactions, will be provided.

8.5.4 Adverse events

All AEs will be recorded from Visit 1 (Dose 1) until 28 days after each dose; only unsolicited AEs starting after the first IMP administration will be collected. SAEs will be collected from date of informed consent and throughout the whole trial (i.e., until Visit 14). Medically attended adverse events (MAAE) will be collected until 28 d after each dose.

Solicited AEs (i.e., reactogenicity events) are recorded in the trial subjects' e-diaries and should not be reported as AEs unless the solicited AE meets criteria for an SAE or continue past Day 7 of each IMP dose.

All AEs will be coded using the most recent version of MedDRA® coding system version 25.1 or later and graded for severity using FDA Guidance for Industry: "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"[4]. In case a subject has an AE with missing relationship status, the event will be assumed to be related. No imputation for missing grades will be performed.

If an AE is reported more than once by the same subject for a System Organ Class (SOC) / Preferred Term (PT) the associated AE will be counted once for the SOC / PT under the maximum severity.

All AE summary tables will be sorted alphabetically by SOC and PT within SOC.

8.5.4.1 Overall summary of adverse events

The number and percentage of subjects reporting the below events will be summarized for the subjects in safety set.

- Unsolicited AEs with onset from Day1 through Day 28 post IMP dose will be summarized for each dose (i.e., 1st dose, 2nd dose, 3rd dose) and regardless of the number of doses received. All events entered on the "Adverse Events" eCRF page with an onset date within the above-mentioned timeframe will be analysed. This includes solicited events that persisted beyond Day 7 after IMP administration or that qualified as an SAE. The following will be analysed:
    - Any unsolicited AEs
    - Related AEs
    - AE of grade >=3
    - Related AEs of grade >=3
    - Any solicited reactogenicity event that continues longer than 7 d post-IMP administration or is an SAE
- Unsolicited AEs leading to withdrawal of IMP
- Unsolicited AEs leading to study withdrawal
- SAEs, with onset from Day 1 through Visit 14. The following will be analysed:
    - Any SAEs
    - Related SAEs
    - SAEs of grade >=3
    - Related SAEs of grade >=3
- MAAE, with onset from Day1 through 28 days after each dose. The following will be analysed:
    - Any MAAEs
    - Related MAAEs

- MAAEs of grade >=3
- Related MAAEs of grade >=3

8.5.4.2 Adverse event summaries by SOC, PT and grade

The number and percentage of subjects reporting unsolicited AEs occurring up to 28 days post each dose and regardless of the number of doses will be summarized by PT nested within SOC and by grade. AEs with a missing grade will be presented in the summary table with a grade category of "Missing".

Similar analyses will be provided for:

- SAEs (from Day1 through Visit 14)
- SAEs related to IMP (from Day1 through Visit 14)
- AEs related to IMP (from Day 1 through 28 days post each dose and regardless of the number of doses)
- Solicited AEs that continue longer than 7 d post-dose or are a SAE (from Day 1 through 28 days post each dose and regardless of the number of doses)
- MAAEs (from Day 1 through 28 days after each dose)
- Non-serious AEs (from Day 1 through 28 days post each dose and regardless of the number of doses)
- AEs leading to study withdrawal (any such AEs reported during the study)
- AEs leading to IMP discontinuation (any such AEs reported during the study)

8.5.4.3 Adverse event summaries by SOC and PT

The number and percentage of subjects reporting the following events will be tabulated by SOC and PT, regardless of the grade:

- SAEs occurring from Day 1 through Visit 14
- Non-serious AEs occurring up to 28 days post each dose and regardless of the number of doses.

8.5.4.4 AE listings

All deaths, AEs, SAEs, MAAEs, AEs leading to withdrawal of IMP, AEs leading to study withdrawal and AEs leading to death will be presented. Solicited AEs will be flagged in all AE listings.

8.5.5 Laboratory assessments

Hematology, clinical chemistry, urinalysis, Follicle stimulating hormone (FSH) and pregnancy tests will be performed by a local laboratory.

For the purposes of summarizing and presentation in tables and listings, all laboratory values 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.

Absolute values of clinical laboratory variables at each protocol scheduled visit and its change from baseline will be summarized using descriptive summary statistics for each parameter listed in the protocol.

Categorical variables will be summarized using number and percentage.

Shift tables from baseline to each visit will be presented. Shifts will be done based upon grading from FDA guidance for industry 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical trials'.

Abnormal and clinically significant, abnormal and not clinically significant and normal laboratory values will be summarized for each parameter by visit.

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

The results of FSH, pregnancy test and Urinalysis (Dipstick and Microscopy tests) results will be listed only.

8.5.6 Vital signs

Vital sign parameters to be summarized include systolic and diastolic blood pressure, heart rate, respiratory rate and oral body temperature. Body temperature will be presented in Celsius (^{o}C).

Absolute values for vital sign parameters at each visit and change from baseline to each post-baseline visit will be summarized using descriptive summary statistics for each parameter. Note that vital signs will be collected both pre- and post-IMP administration.

Abnormal clinically significant, abnormal not clinically significant, and normal values of will be listed only.

8.5.7 12-Lead electrocardiogram (ECG)

Absolute values of heart rate collected at each time-point, and its change from baseline to each post-baseline time-point will be summarized using descriptive summary statistics for the subjects in safety set.

In addition, the investigators evaluation at each visit (Normal, Abnormal – not clinically significant and Abnormal – clinically significant) will be tabulated by visit.

8.5.8 Physical examination

A complete physical examination will be performed at screening Visit. At other visits, a symptom-directed examination will be performed.

The results from all physical examinations will be listed only. All data recorded during the wellbeing phone call will also be presented in a separate data listing.

8.6 Other analyses

8.6.1 Immunogenicity analysis

Immunogenicity endpoints have been defined as exploratory endpoints. These endpoints are out of scope of this SAP and may be described in a different document.

8.6.2 E-Diary transmission

E-diary transmission will be summarized for the subjects in the safety set. The summary will include the numbers and percentages of:

- subjects transmitting the e-diary for at least one day in the required reporting period
- subjects not transmitting the e-diary on any day of the required reporting period
- subjects transmitting the e-diary for every day of the required reporting period
- subjects transmitting the e-diary on all days of the required reporting period,

The above items will be tabulated and for each dose (i.e., dose 1, dose 2, dose 3) separately.

9 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline E3: Note for Guidance on Structure and Content of Clinical Trial Reports (CPMP/ICH/137/95), July 1996. Retrieved on 30 January 2018 from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96), March 1998. Retrieved on 21 April 2019 from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf
3. Belshe RB, Leone PA, Bernstein DI, et al. Efficacy results of a trial of a herpes simplex vaccine. N Engl J Med. 2012;366(1):34-43.
4. FDA Guidance 2007. US FDA Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

10 SUPPORTING DOCUMENTATION

10.1 Appendix 1: Changes to protocol-planned analyses

Not Applicable.

10.2 Appendix 2: List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CM	Concomitant Medication
CTR	Clinical Trial Report
CRF	Case report form
CRO	Contract Research Organization
D	day
DL	Dose Level
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
FIH	First-In-Human
FSH	Follicle stimulating hormone
IM	Intramuscular
IMP	Investigational medicinal product
IRC	Internal Review Committee
kg	kilogram
m^2	Meter square
MAAE	Medically attended adverse event
max	Maximum
MedDRA®	Medical Dictionary for Regulatory Activities
min	Minimum
N	Number of Subjects
n	Number of Observations
N/A	Not Applicable
PD	Protocol Deviation
PT	Preferred Term
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
SD	Standard Deviation
SI	International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedures
TMF	Trial Master File
WHO DD	World Health Organisation Drug Dictionary

10.3 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.

Dose level in the Table 6 will be used for the Tables/Figures/Listings display as appropriate:
The placebo data from all the dose levels of will be combined.

Table 6: Treatment Descriptors

Dose Level	Dose Level Label	Treatment Code
BNT165b1 3 (µg)	BNT165b1 - 3 µg	1
BNT165b1 10 (µg)	BNT165b1 - 10 µg	2
BNT165b1 30 (µg)	BNT165b1 - 30 µg	3
Placebo	Placebo	4
Total*	Total	NA

*Total of all dose levels including Placebo
NA=Not Applicable.

10.4 Appendix 4: Schedule of activities

10.4.1 Schedule of activities for three-dose vaccination schedule

Table 7 list of all the assessments to be performed in the trial.

Table 7: Schedule of activities for three-vaccination schedule

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

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

Activity	Visit (V) 0	V 1	V 2	V 3	V S 1 (Call) [p]	V 4 (Call)	V 5	V 6	V 7	V S 2 (Call) [p]	V 8	V 9	V 10	V S 3 (Call) [p]	V 11	V 12	V 13	V 14
Visit description	**Screening**	**Dose (D) 1 (Day 1)**	**1 d FU post-D 1**	**7 d FU post-D 1**	**(14 d post-D 1)**	**28 d FU post-D 1**	**D 2 (Day 57)**	**1 d FU post-D 2**	**7 d FU post-D 2**	**(14 d post-D 2)**	**28 d FU post-D 2**	**D 3 (Day 183)**	**7 d FU post-D 3**	**(14 d post-D 3)**	**28 d FU post-D 3**	**84 d FU post-D 3**	**168 d FU post-D 3**	**365 d FU post-D 3 or ET**
Visit window	**-30 to -1 d**	**N/A**	**±4 h**	**+2 d**	**+1 d**	**±2 d**	**±2 d**	**±4 h**	**+2 d**	**+1 d**	**±2 d**	**±7 d**	**+2 d**	**+1 d**	**±2 d**	**±10 d**	**±10 d**	**±10 d**
Blood draws for humoral response assessments [h]		X [f] 30 mL					X [f] 30 mL		X 30 mL		X 30 mL	X [f] 30 mL	X 30 mL		X 30 mL	X 30 mL	X 30 mL	X 30 mL
CCI																		
Blood draw for genetics		X [f] 4 mL																
CCI																		
Subject hotline availability	Start	=>	=>	=>		=>	=>	=>	=>		=>	=>	=>		=>	=>	=>	End
Issue, train and collect subject e-diaries		Issue, train [i]					Re-train [i]					Re-train [i]	Collect					
Subjects report reactogenicity (incl. oral body temperature) daily for 7 d after each IMP		Start after Dose 1	=>	End [n]			Start after Dose 2	=>	End [n]			Start after Dose 3	End [n]					

Activity	Visit (V) 0	V 1	V 2	V 3	V S 1 (Call) [p]	V 4 (Call)	V 5	V 6	V 7	V S 2 (Call) [p]	V 8	V 9	V 10	V S 3 (Call) [p]	V 11	V 12	V 13	V 14
Visit description	Screening	Dose (D) 1 (Day 1)	1 d FU post-D 1	7 d FU post-D 1	(14 d post-D 1)	28 d FU post-D 1	D 2 (Day 57)	1 d FU post-D 2	7 d FU post-D 2	(14 d post-D 2)	28 d FU post-D 2	D 3 (Day 183)	7 d FU post-D 3	(14 d post-D 3)	28 d FU post-D 3	84 d FU post-D 3	168 d FU post-D 3	365 d FU post-D 3 or ET
Visit window	-30 to -1 d	N/A	±4 h	+2 d	+1 d	±2 d	±2 d	±4 h	+2 d	+1 d	±2 d	±7 d	+2 d	+1 d	±2 d	±10 d	±10 d	±10 d
dose using an e-diary																		
Investigators review e-diary data daily		Start	=>	End			Start	=>	End			Start	End					
Record AEs, MAAEs, and SAEs [j]		X	X	X		X	X	X	X		X	X	X		X	X	X	X
Wellbeing phone call		X [k]			X [o]		X [k]			X [o]		X [k]		X [o]				
Investigator local reaction assessment		X [l]					X [l]					X [l]						
Cumulative blood volume (mL)	20	164	10	70		0	150	10	160		140	155	155		140	140	140	140

a Brief (symptom-orientated) physical examination.

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

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

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

e Clinical laboratory tests: (Chemistry) alkaline phosphatase, alanine transaminase, creatinine, c-reactive protein, albumin, amylase, aspartate transaminase, gamma glutamyl transpeptidase, total bilirubin, blood urea nitrogen, glucose, lipase, sodium, potassium, calcium, troponin, IgG, IgM and IgA; (Hematology) hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count. Only in women who are not VOCBP (to confirm postmenopausal status): follicle stimulating hormone at Visit 0. Only for VOCBP: serum β-HCG at Visit 0.

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

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

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

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

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

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

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

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

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

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

p Local reactogenicity calls after 14 d.

Notes:

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

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

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