STATISTICAL ANALYSIS PLAN (SAP)
BNT165-02

SAP Version Number:	3.0	**SAP Version Date:**	28 Jan 2025
Sponsor Name:	BioNTech SE		

Protocol Number:	BNT165-02
Protocol Title:	A randomized, dose-escalation Phase I/IIa trial with controlled human malaria infection to evaluate safety, tolerability, immunogenicity and efficacy of an investigational RNA-based vaccine for prevention of *P. falciparum* malaria in healthy malaria naïve adults
Protocol Version:	7.0
Protocol Date:	15 AUG 2024
Compound Name:	BNT165e; a combination of BNT165c and BNT165d (composed of BNT165d1 and BNT165d2)
Study Phase:	Phase I/IIa
Regulatory Agency Identifier(s):	National Clinical Trial (NCT) number: 06069544; Investigational New Drug application (IND) number: 29905
Registry Identifier(s):	ClinicalTrials.gov NCT06069544

SAP VERSION HISTORY

SAP version	Version date	Change	Rationale
1.0	03 JAN 2024	Not applicable	Original version
2.0	04 JUL 2024	Section 3.2 (Trial design) updated	To match CTP v5
		Section 6 (Sample size determination) updated	To match CTP v5
		Section 8.5.1 (Extent of exposure) updated	To match the CRF
		Sections 8.5.2.1 (Solicited local reactions) and 8.5.3 (Systemic reactions): details added to clarify that the investigator can provide an assessment for any events and days, including on those dose where the subject has missed to fill in the e-diary.	For clarification purpose
		Section 8.6.2 (e-diary transmission) updated	For clarification purpose
		Section 10.4 (Schedule of activities) updated	To match CTP v5
3.0	28 JAN 2025	Section 1 “SAP Approval” deleted. Section numbering removed for SAP version history. For the below mentioned changes, the actual Section number is referenced.	To match current SAP template
		Section 1.2 (Trial design) updated, to add Cohort 10	To match CTP v6 and v7
		Section 4 (Sample size determination) updated	To match CTP v6
		Section 6.1.2 (Windowing, unscheduled visits and repeat test results): time windows added for dosing visits.	For clarification purpose
		Sections 6.5.2 and 6.5.3: wording on e-Diary reporting period updated	For clarification purpose
		Section 6.6.1.1.2 (Antibody magnitude fold rise): details added on how to derive fold rise when the baseline or post-baseline measurement is < LLOQ. Information added on how to set GMFR at baseline for line plots.	For clarification purpose
		Section 8.3 (Appendix 3: Reporting conventions): Cohort 10 added	To match CTP v6

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1 INTRODUCTION

This is an exploratory Phase I/IIa, 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. This part of the trial is also referred to as Part A. CCI

The results of this study might be included in a regulatory submission. This statistical analysis plan (SAP) describes the detailed procedures for the planned statistical analyses for protocol BNT165-02 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.

1.1 Objectives and endpoints

The objectives and endpoints corresponding to each primary, secondary and exploratory objective are described in Table 1.

This SAP provides details on the analysis of the primary and secondary endpoints. The analysis of the exploratory endpoints is out of scope of this SAP and will be described in a different document.

Table 1: Objectives and endpoints

OBJECTIVES	ENDPOINTS	OUTCOME MEASURES
Primary objective (Part A)		
To describe the safety and tolerability of BNT165e and its components in healthy adults.	• Solicited local reactions (pain, erythema/redness, induration/swelling). • Solicited systemic reactions (vomiting, diarrhea, headache, fatigue, muscle/joint pain, and fever). • AEs • SAEs • MAAEs	For each cohort in subjects receiving at least one dose of trial intervention: • 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. • Frequency of subjects with at least one AE occurring until 28 d after each dose. • Frequency of subjects with at least one MAAE occurring until 24 weeks after Dose 3. • Frequency of subjects in each cohort with at least one SAE occurring until 24 weeks after Dose 3.

OBJECTIVES	ENDPOINTS	OUTCOME MEASURES
Secondary objective (Part A)		
To evaluate the CSP-specific humoral immune response of BNT165e and its components.	Anti-CSP IgG levels at specified timepoints in the SoA (Section 8.4).	For each cohort: • Descriptive statistics on antibody levels at assessed timepoints.
Exploratory objective (Part A)		
To evaluate the cell mediated immune response.	CD4 and CD8 T-cell responses at baseline and specified timepoints post-immunization (Section 8.4).	• Frequency of antigen-specific T cells at assessed timepoints.

Abbreviations: AE = adverse event; CD = clusters of differentiation; CSP = circumsporozoite protein; d = day(s); IgG = immunoglobulin G; MAAE = medically attended adverse event; SAE = serious adverse event; SoA = schedule of activity.

1.2 Trial design

The trial design is as shown in below Table 2.

Table 2: Trial design

Trial design	Within this trial we will evaluate the safety, tolerability, and immunogenicity (Part A) of a multi-component vaccine BNT165e, consisting of three mRNA components encoding the *Plasmodium falciparum* circumsporozoite protein (*Pf*CSP) and immunogenic segments of liver-stage expressed proteins. In Part A, the combination of the three components will be evaluated in different dose combinations in a 3-dose schedule to select a safe, tolerable, and immunogenic dose combination, and to assess the impact of third dose on immunogenicity. This part of the trial will be observer-blind.
Trial population	This trial will recruit healthy, malaria-naïve adult volunteers based on medical history, screening laboratory values, and other inclusion/exclusion criteria. Inclusion and exclusion criteria for Part A are described in Sections 5.1 and 5.2 of the clinical trial protocol (CTP), respectively.
Investigational medical product(s)	BNT165e, consisting of the following components: • BNT165c • BNT165d (a 1:1 mixture of BNT165d1 and BNT165d2). Isotonic NaCl solution (0.9%) will be used as placebo in Part A. **Type:** Investigational **Schedule:** Part A: Three (one each on Days 1, 57, and 183 for Cohorts 1 to 9, one each on Days 1, 29 and 57 for Cohort 10) injections given within each cohort. **Route of administration:** Intramuscular injection in the deltoid muscle of the non-dominant arm. Other injection sites may be used if necessary. **Dose levels:** Part A: Refer to Table 3. **Allocation to investigational medicinal product (IMP):** Part A: Trial subjects will be randomized 5:1 to active:placebo using an online randomization tool.

Treatment and trial duration	The planned trial duration for subjects in Cohort 1 to 9 is up to 6 weeks screening, 26 weeks vaccination phase, and 52 weeks follow-up phase, amounting to a maximum of 84 weeks. The planned trial duration for subjects in Cohort 10 is up to 6 weeks screening, 8 weeks vaccination phase, and 52 weeks follow-up phase, amounting to a maximum of 66 weeks. Trial duration may exceed the listed maximum time in the event of a trial pause.
Planned number of subjects	In Part A, up to 138 healthy subjects divided into ten cohorts with different dose combinations will be randomized 5:1 active:placebo. Table 3 denotes the dose combinations being tested in the different cohorts and the planned number of subjects to be included. Number of subjects may be increased up to 177 in the event of subject replacement or re-enrollment.
Randomization and blinding	Randomization: In Part A, subjects will be randomized in a 5:1 ratio to either active IMP or placebo. Blinding: Part A: 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 BNT165e 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 by applying a colored occluding label. To facilitate rapid review of data in real time, sponsor staff will be unblinded to trial intervention allocation. However, sponsor staff who routinely have contact with blinded site personnel, and who are not involved in ensuring that protocol requirements for trial treatment preparation, handling, allocation, and administration are fulfilled at the site, will also remain blinded. Further details will be specified in a Blind Management Plan.
Other features	An internal review committee (IRC) will provide medical oversight of trial subject safety, reactogenicity, and immunogenicity 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. The Independent Data Monitoring Committee (IDMC) will be responsible for ongoing monitoring of the safety of subjects in this trial, according to the charter. This may include but is not limited to a quarterly review of cumulative safety data of all clinical trial subjects. Suspected unexpected serious adverse reactions (SUSARs) and possible cases of myocarditis, pericarditis or myopericarditis will trigger an ad hoc review by the IDMC. Possible cases of myocarditis, pericarditis, or myopericarditis will be independently assessed by the IDMC using the Brighton Collaboration Case Definition.

Table 3 denotes the dose combinations being tested in the different cohorts and the planned number of subjects to be included.

Table 3: Dose combinations (Part A)

Cohort	Dose level (µg) BNT165c	Dose level (µg) BNT165d [a]	Sample size (active:placebo) [b]
1	10	0	10:2
2	30	0	10:2
3	70	0	10:2
4	0	30	10:2
5	30	10	10:2
6	10	30	10:2
7	30	30	15:3
8	70	30	15:3
9	100	0	10:2
10	30	10	10:2

a BNT165d will be a 1:1 ratio of BNT165d1 and BNT165d2.

b Subject numbers may increase to replace subjects that are either discontinued from further vaccination or discontinued from the trial.

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 the protocol for guidance on criteria for such cases.

Schema (graphical representation of the trial)

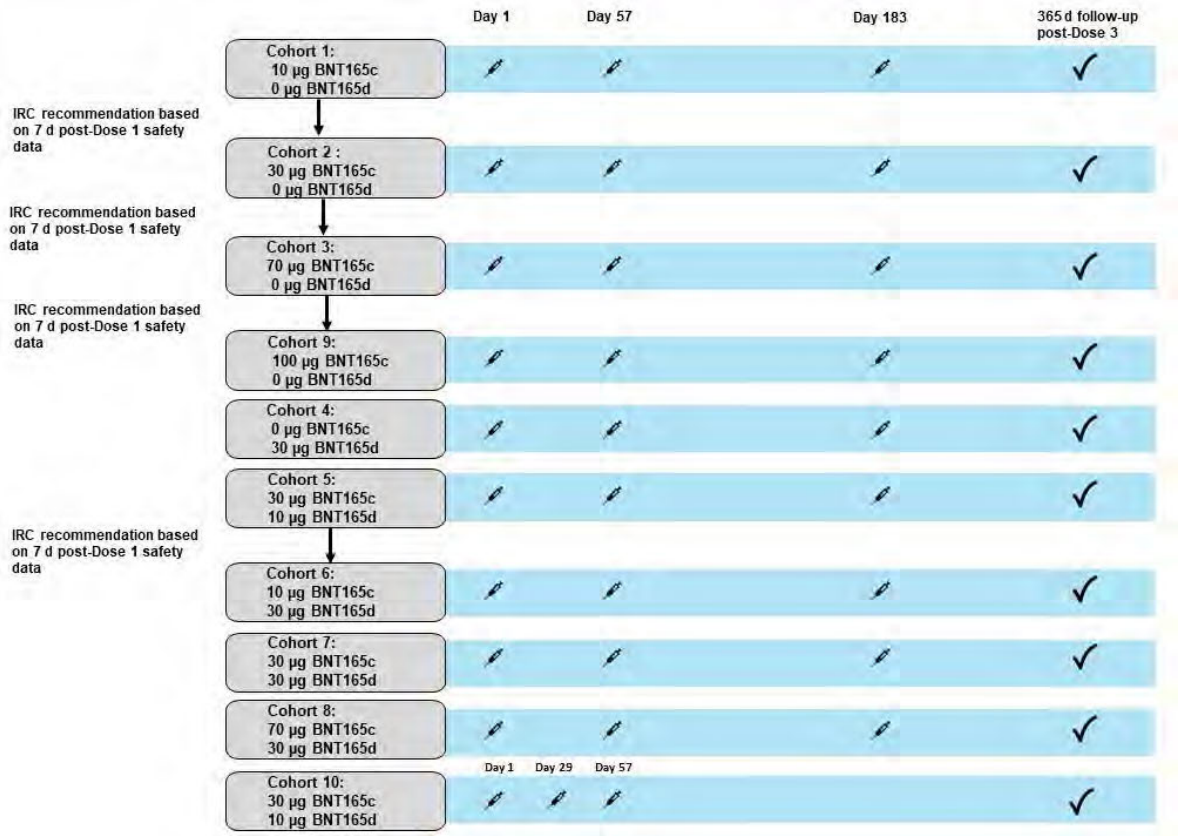

Figure 1: Trial schema

Notes: Syringes indicate vaccination. Blood vials indicate blood draws.
Abbreviations: d = day(s); IRC = Internal Review Committee.

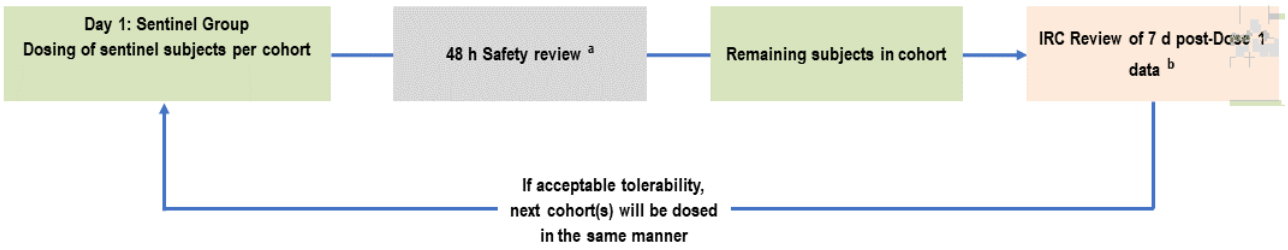

Figure 2: The staggered dosing process for the cohorts

a Further dosing of subjects will proceed if the investigator considers the vaccine reactogenicity is acceptable (only Grade 2 or lower events or after consultation with medical monitor) and no stopping/pausing rules are met.

b Further opening of new cohorts will proceed if the IRC considers the reactogenicity and safety profile of the vaccine to be acceptable and no stopping/pausing rules are met.

Abbreviations: d = day(s); h = hour(s); IRC = Internal Review Committee.

1.3 Schedule of activities

See Section 8.4 Appendix 4 for the schedule of activities.

2 STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested in this trial.

3 INTERIM ANALYSES AND ANALYSIS SEQUENCE

An interim analysis on all available safety and immunogenicity data will be performed when subjects in all cohorts of Part A have completed 28 days (d) of follow-up after second injection. Also, interim analyses at other time points may be prepared to inform further clinical development. The details on how the blinding will be maintained for functions that are not unblinded is described in a blind management plan.

The final analysis of Part A will be performed when the last trial subject enrolled in Part A completes the trial or is discontinued from the trial.

4 SAMPLE SIZE DETERMINATION

In Part A, the sample size for each cohort is mainly driven by a dose-escalation trial in a limited number of subjects designed for early detection of potential safety and reactogenicity events, and is considered adequate to support the trial objectives, while minimizing the number of trial subjects exposed to a new IMP. The sample size of 10 subjects in Cohorts 1 to 6, 9 and 10 and of 15 in Cohorts 7 and 8 receiving the vaccine allow the detection of the most frequent AEs with high probability. With 10 subjects, the probability of detecting at least 1 AE is 65% if the underlying AE rate is 10%. With 15 subjects, the probability of detecting at least 1 AE is 79% if the underlying AE rate is 10%. Table 4 summarizes the probability of detecting at least one subject with an AE for AE rates of 10% and 15%, depending on the number of subjects.

Table 4: Probability of detecting at least one AE, depending on the sample size and event rate

Number of subjects	AE rate	Probability of detecting at least one subject with an AE
10	10%	65%
10	15%	80%
15	10%	79%
15	15%	91%

Abbreviation: AE = adverse event.

5 ANALYSIS SETS AND SUBGROUPS

5.1 Analysis sets

The following analyses sets are defined:

Screened Set: All subjects who provided informed consent.

Enrolled Set: All subjects who have been randomized to IMP (for Part A).

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

Immunogenicity Set: All subjects who received at least one dose of IMP and who have at least one valid assessment of anti-circumsporozoite protein (CSP) immunoglobulin G (IgG) concentrations post-baseline and that have no important protocol deviations that could confound the immunogenicity data. The sampling time-windows specified in Table 5 and Table 6 will be used to define the valid samples for the analysis set.

Analyses of all safety endpoints will be performed using the safety set and 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.

5.2 Protocol deviations

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

All PDs will be assessed and documented prior to releasing the database. Depending on the nature of the key PD, either the whole subject data might be excluded from the analysis sets (i.e., for key deviations on ICF), or only the data collected during a specific timeframe might be excluded (e.g., for use of prohibited concomitant medications during the trial).

5.3 Subgroups

There are no planned subgroup analyses.

6 STATISTICAL ANALYSES

6.1 General considerations

In Part A, analyses will be performed by cohort for subjects receiving active IMP. Subjects recruited in cohorts 1 to 9 and who received placebo will be analyzed in a pooled manner. Due to the different dosing regimen used in Cohort 10 (0-1-2 month schedule for Cohort 10 instead of 0-2-6 month schedule for Cohorts 1-9) the placebo subjects recruited in Cohort 10 will be analysed separately.

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, protocol deviations and prior medications as applicable unless otherwise specified.

No formal statistical comparisons between the dose combinations of BNT165c/BNT165d and placebo will be performed. Missing data, other than that described for partial or missing dates for AEs/concomitant medications/vaccinations (as described Section 6.1.2) will not be imputed.

Continuous variables will be summarized using the following descriptive statistics: number of subjects with non-missing data (n), mean or geometric 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 event-driven occurrence endpoints after a specific dose (e.g., adverse events post-Dose 2) percentages will be based on the number of subjects who received the specific dose. 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. For binary endpoints after a specific dose (e.g., systemic reactions post-Dose 2) percentages will be based on the number of subjects who received the specific dose and where the e-diary has been entered on at least one day.

All data collected during the trial will be listed based on the enrolled 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 data collected in EDC, via e-diary or via central laboratory 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 for this data. Unscheduled assessments will not be included in summaries/analysis but will be included in the listings. For the analysis of immunogenicity data, time-windows have been defined in Section 6.1.2.

6.1.1 General definitions

Baseline: For subjects receiving IMP, 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

6.1.2 Windowing, unscheduled visits and repeat test results

Immunogenicity data will be assigned to visits for the analysis using the time-windows described in Table 5 for Cohorts 1 to 9 and in Table 6 for Cohorts 10. These time-windows include the protocol-defined visit window plus an additional grace-period, which is considered appropriate for the scope of the immunogenicity analysis.

Table 5: Assigned visits and time-windows for the analysis of immunogenicity data of Cohorts 1 to 9

Visit	Visit description	Planned day	Time-window start day	Time-window end day
Visit 1	pre-Dose 1	1	Sample has to be taken on same day as Dose 1, and before IMP administration	
Visit 7	pre-Dose 2	Dose 2 Day 57	For subjects receiving Dose 2: Sample must be taken on the same day as Dose 2 AND not earlier than Dose 1 + 52 For subjects who discontinued IMP before Dose 2: Dose 1 + 52	For subjects receiving Dose 2: Sample must be taken on the same day as Dose 2 AND no later than Dose 1 + 63 For subjects who discontinued IMP before Dose 2: Dose 1 + 63
Visit 10	7 days post-Dose 2	Dose 2 + 7	Dose 2 + 6	Dose 2 + 10
Visit 12	28 days post-Dose 2	Dose 2 + 28	Dose 2 + 24	Dose 2 + 33
Visit 13	pre-Dose 3	Dose 3 Day 183	For subjects receiving Dose 3: Sample must be taken on the same day as Dose 3 AND not earlier than Dose 2 + 112 For subjects who discontinued IMP before Dose 3: Dose 2 + 112	For subjects receiving Dose 3: Sample must be taken on the same day as Dose 3 AND no later than Dose 2 + 156 For subjects who discontinued IMP before Dose 3: Dose 2 + 156
Visit 16	7 days post-Dose 3	Dose 3 + 7	Dose 3 + 6	Dose 3 + 10
Visit 18	28 days post-Dose 3	Dose 3 + 28	Dose 3 + 24	Dose 3 + 33
Visit 19	84 days post-Dose 3	Dose 3 + 84	Dose 3 + 70	Dose 3 + 98
Visit 20	168 days post-Dose 3	Dose 3 + 168	Dose 3 + 140	Dose 3 + 196
Visit 21	365 days post-Dose 3	Dose 3 + 365	Dose 3 + 337	Dose 3 + 393

Abbreviations: IMP = investigational medicinal product; NA = not applicable.

Table 6: Assigned visits and time-windows for the analysis of immunogenicity data of Cohort 10

Visit	Visit description	Planned day	Time-window start day	Time-window end day
Visit 1	pre-Dose 1	1	Sample has to be taken on same day as Dose 1, and before IMP administration	
Visit 6	pre-Dose 2	Dose 2 Day 29	For subjects receiving Dose 2: Sample must be taken on the same day as Dose 2 AND not earlier than Dose 1 + 24 For subjects who discontinued IMP before Dose 2: Dose 1 + 24	For subjects receiving Dose 2: Sample must be taken on the same day as Dose 2 AND no later than Dose 1 + 35 For subjects who discontinued IMP before Dose 2: Dose 1 + 35
Visit 9	7 days post-Dose 2	Dose 2 + 7	Dose 2 + 6	Dose 2 + 10
Visit 11	pre-Dose 3	Dose 3 Day 57	For subjects receiving Dose 3: Sample must be taken on the same day as Dose 3 AND not earlier than Dose 2 + 24 For subjects who discontinued IMP before Dose 3: Dose 2 + 24	For subjects receiving Dose 3: Sample must be taken on the same day as Dose 3 AND no later than Dose 2 + 35 For subjects who discontinued IMP before Dose 3: Dose 2 + 35
Visit 14	7 days post-Dose 3	Dose 3 + 7	Dose 3 + 6	Dose 3 + 10
Visit 16	28 days post-Dose 3	Dose 3 + 28	Dose 3 + 24	Dose 3 + 33
Visit 17	84 days post-Dose 3	Dose 3 + 84	Dose 3 + 70	Dose 3 + 98
Visit 18	168 days post-Dose 3	Dose 3 + 168	Dose 3 + 140	Dose 3 + 196
Visit 19	365 days post-Dose 3	Dose 3 + 365	Dose 3 + 337	Dose 3 + 393

Abbreviations: IMP = investigational medicinal product; NA = not applicable.

Samples that do not fall into any time-window will not be used in the statistical analysis, but will be included in listings. If more than one sample falls into the same time-window, a single value will be chosen in the by-visit summary analyses based on the following rules:

- for baseline and any pre-dose visits (i.e., visits on which IMP is administered), the last available record prior to the date and time of IMP administration will be selected.
- For post-dose visits, the sample that was drawn closest to the planned visit day will be selected.

6.1.3 Handling of missing data

For the purposes of assigning duration for AEs, partial or missing AE dates will be handled as follows:

Onset dates:

- 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:

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).
  - 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 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 should be set to the end date.

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.

6.2 Subject disposition

The number of subjects who were screened and enrolled 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.

For Part A, the number and percentage of subjects who 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 enrolled 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 enrolled set with key PDs will also be presented.

6.3 Baseline characteristics

6.3.1 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 surface antigen status and Hepatitis C status [Positive or Negative]) will be listed only.

6.3.2 Prior and concomitant medication/vaccination, procedures and non-drug therapies

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 most recent version of the World Health Organization Drug Dictionary (WHO Drug) dictionary.

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 for subjects in the safety set. The ATC codes and preferred names will be presented in alphabetical order.

Concomitant medications administered due to local or systemic reactions during time interval Day 1 to 7 days post each dose will be summarized using the safety set.

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.

6.3.3 Medical history

Medical history data will be coded using the most recent version of MedDRA. The number and percentage of subjects with each medical history and surgery will be summarized by System Organ Class (SOC) and Preferred Term (PT) in the Safety Set. The summary will be sorted alphabetically by SOC and PT within SOC.

6.4 Efficacy analyses

In Part A, no efficacy endpoints are defined. The primary safety endpoints are described in Section 6.5.2, Section 6.5.3 and Section 6.5.4.

6.5 Safety analyses

The primary safety endpoints include local reactions, systemic reactions, AEs, SAEs and MAAEs.

Other safety data that will be summarized include 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.

6.5.1 Extent of exposure

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

- For each dose, the following will be tabulated:
  - Subjects receiving the dose,
  - Subjects with any deviation to the planned dose
- For Dose 2 and 3 only: reason for not having received the dose.

6.5.2 Local reactions

The below subsections describe the analyses 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.

6.5.2.1 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 and Day 7 is the 6th day after 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 7. 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" (US FDA 2007).

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. The investigator also has the possibility to provide a grading for any reactions, regardless of which grade was entered by the subject, for cases where the subject entered a wrong grade or diameter assessment by mistake or completely missed the diary entry on a specific day.

Table 7: Local reaction grading scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4) [a]
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	2.5 cm to 5.0 cm	>5.0 cm to 10.0 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration / swelling	2.5 cm to 5.0 cm	>5.0 cm to 10.0 cm	>10 cm	Necrosis

a Investigator or medically qualified person confirmation is required.
Source: Modified from the US FDA guidance (US FDA 2007).

For subjects recording at least one local reaction during the reporting period after each IMP injection and for each specific local reaction mentioned in Table 7:

- 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, or if the subject assessment is missing but an investigator assessment is available, the 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 e-diary, 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", unless an investigator assessment is available for the days that were missed by the subject (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 with a 2-day duration and one with a 3-day 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). Please refer to Section 6.1.3 for the imputation of missing AE end dates.

- 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.

Analyses in the overview summary will be provided for reactions of any grade and for reactions of Grade ≥3. Analyses will be provided for each IMP injection and overall regardless of the injection number.

The number and percentage of subjects reporting local reactions (pain at the injection site, erythema/redness, induration/swelling) after each 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 or investigator assessment throughout the e-diary reporting period.

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 percentage of subjects having at least one local reaction will be plotted for each local reaction and each dose. 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.

6.5.2.2 Acute local reactions

Investigators will assess acute local reactogenicity at the visits given in Section 8.4. Investigators will grade and record acute local reactions as described in Table 7. This data will be listed.

6.5.3 Systemic reactions

The systemic reactions assessed and recorded in the e-diary are fever, vomiting, diarrhea, headache, fatigue/tiredness, muscle/joint pain from Day 1 through Day 7 inclusive, where Day 1 is the day of each IMP injection and Day 7 is the 6th day after 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.

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 8.

Solicited systemic reactions will be categorized as mild, moderate, severe or potentially life-threatening) and graded from 1 to 4 as described in Table 8. 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" (US FDA 2007). 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. The investigator also has the possibility to provide a grading for any reactions, regardless of which grade was entered by the subject, for cases where the subject entered a wrong grade or diameter assessment by mistake or completely missed the diary entry on a specific day.

Table 8: Systemic reaction grading scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4) [a]
Fever (oral temperature of ≥38.0°C / ≥100.4°F)	38.0°C - 38.4°C 100.4°F - 101.1°F	38.5°C - 38.9°C 101.2°F - 102.0°F	39.0°C - 40.0°C 102.1°F - 104.0°F	>40.0°C >104.0°F
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
Muscle / joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle / joint pain

a Investigator or medically qualified person confirmation is required.
Source: Modified from the US FDA guidance (US FDA 2007).

Systemic reactions reported after each IMP administration will be summarized in the same manner as local reactions (see Section 6.5.2.1) using the safety set but excluding subjects without any e-diary data or investigator assessment throughout the e-diary reporting period. A listing of subjects in the safety set, with reported systemic reactions, will be provided.

6.5.4 Adverse events

In Part A, AEs will be recorded continuously from Visit 1 (Dose 1) until 28 days after Dose 3, or until 28 days after last dose, if IMP is prematurely discontinued. SAEs will be collected from date of informed consent and throughout the whole trial. MAAEs will be collected from Visit 1 (Dose 1) and throughout the whole trial.

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 continues past Day 7 of any IMP dose.

All AEs will be coded using the most recent version of MedDRA® coding system and graded for severity using FDA Guidance for Industry: "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (US FDA 2007). 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 SOC / PT, the associated AE will be counted once for the SOC / PT under the maximum severity.

All AE summary tables will be sorted in descending order of frequency among all subjects included in the analysis, by SOC and PT within SOC.

6.5.4.1 Overall summary of adverse events

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

- AEs with onset from Day 1 through Day 28 post IMP dose will be summarized for each dose (i.e., 1st dose, 2nd dose, 3rd dose) and overall, 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 analyzed. This includes solicited events that persisted beyond Day 7 after IMP administration or that qualified as an SAE. The following will be analyzed:
  - Any 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 or local reactions with an onset between Day 8 and Day 14 (included) after IMP administration. These events will also be analyzed separately for:
    - Any solicited reactogenicity event that continues longer than 7 d post-IMP administration
    - Any solicited reactogenicity event that is a SAE
    - Any local reaction with an onset between Day 8 and Day 14 (inclusive) after IMP administration
- AEs leading to withdrawal of IMP
- AEs leading to study withdrawal
- SAEs from Dose 1 to 24 weeks post-Dose 3 (to 24 weeks after last dose for subjects who did no receive all 3 doses) in Part A. The following will be analyzed:
  - Any SAEs

  - Related SAEs
  - SAEs of Grade ≥3
  - Related SAEs of Grade ≥3
- MAAEs from Dose 1 to 24 weeks post-Dose 3 (to 24 weeks after last dose for subjects who did no receive all 3 doses) in Part A. The following will be analyzed:
  - Any MAAEs
  - Related MAAEs
  - MAAEs of Grade ≥3

6.5.4.2 Adverse event summaries by SOC and PT

The number and percentage of subjects reporting unsolicited AEs will be summarized by PT nested within SOC.

Similar analyses will be provided for related AEs, SAEs and other types of AEs.

For analyses by grade, AEs with a missing grade will be presented in the summary table with a grade category of “Missing”.

Table 9 provides an overview of all planned AE analyses including the analysis populations and analysis periods used depending on the trial part:

Table 9: Overview of AE analyses and corresponding analysis periods in Part A

AE analysis	Population	Analysis period
any AEs any AEs by grade related AEs related AEs ≥ Grade 3	Safety Set	From Day 1 through Day 28 post each IMP dose and overall, regardless of dose.
SAEs related SAEs MAAEs MAAEs ≥ Grade 3 related MAAEs	Safety Set	From Day 1 to 24 weeks post-Dose 3. For subjects who prematurely discontinued IMP: from Day 1 to 24 weeks post last IMP dose.
Any solicited local and systemic reaction that continues longer than 7 d post-vaccination or is an SAE or local reactions with an onset between Day 8 and Day 14 (included) after IMP administration	Safety Set	From Day 1 through Day 28 post each IMP dose and overall, regardless of dose.
AEs leading to IMP discontinuation	Safety Set	From Day 1 through Visit 13 for Cohorts 1 to 9 and through Visit 11 for Cohort 10.
AEs leading to study withdrawal	Safety Set	From Day 1 throughout the whole trial. (SAEs and MAAEs are collected throughout the trial, AEs are collected until 28 days after last IMP dose.)

Abbreviations: AE = adverse event; IMP = investigational medicinal product; MAAE = medically attended adverse event; SAE = serious adverse event.

6.5.4.3 AE listings

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

6.5.5 Laboratory assessments

Hematology, clinical chemistry, follicle stimulating hormone (FSH) and pregnancy tests will be performed by a central laboratory.

For the purposes of summarizing and presenting in tables and listings, all laboratory values will be presented in Système 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 hematology and clinical chemistry 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 for hematology, clinical chemistry. 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” (US FDA 2007). In addition, Grade 3 and Grade 4 events will be tabulated for each parameter by visit.

Laboratory values outside of the reference range (i.e., abnormal values), which are abnormal and clinically significant, and normal laboratory values will be tabulated for each parameter by visit.

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

The results of FSH and pregnancy tests will be listed only.

6.5.6 Vital signs

Vital sign parameters include systolic and diastolic blood pressure, heart rate, respiratory rate and oral body temperature. Body temperature will be presented in Celsius (˚C). Vital signs will be presented in listings only.

6.5.7 12-lead electrocardiogram (ECG)

In Part A, ECGs will be assessed and interpreted by the investigator. The investigators evaluation at each visit (Normal, Abnormal – not clinically significant and Abnormal – clinically significant) will be tabulated by visit based on the safety set. All available ECG data will also be provided in a listing.

6.5.8 Physical examination and wellbeing phone calls

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.

6.6 Other analyses

6.6.1 Immunogenicity analysis

Immunogenicity data will be assigned to visits for the analysis using the time-windows described in Table 5 and Table 6.

Anti-CSP IgG (NANP) concentrations at specified timepoints have been defined as a secondary endpoint. This endpoint is described in Section 6.6.1.1.

6.6.1.1 Anti-CSP IgG (NANP) concentrations at specified timepoints

Samples for the assessment of anti-CSP IgG concentrations will be collected at the visits described in the SoA.

Antigen-specific serum antibody concentrations will be measured using a multiplex electrochemiluminescence (ECL) assay. Data will be reported in Arbitrary units per mL

(AU/mL). Missing data will not be imputed. Samples will be analyzed in duplicate, and the geometric mean of both results will be used for the statistical analysis.

For the secondary endpoint analyses, anti-CSP IgG antibody responses will be analyzed for the major (NANP) repeats (= responses to ECL peptide 29C) as anti-CSP (NANP) IgG.

Values below the LLOQ will be set to 0.5 × LLOQ for the calculation of summary statistics on the concentrations and to LLOQ for the derivation of fold rise and seroresponse. Assay results above ULOQ will be set to ULOQ.

6.6.1.1.1 Antibody magnitude

For all humoral immunogenicity results the geometric means will be computed along with associated 95% CI at each timepoint indicated in Table 5 and Table 6.

The geometric mean of the anti-CSP IgG (NANP) concentrations will be calculated as the mean of the assay results after taking the natural log scale transformation and then exponentiating the mean to express results on the original scale.

Similarly, two-sided 95% CIs will be obtained by taking the natural log transformation of assay results, calculating the 95% CI with reference to Student's t-distribution, and then exponentiating the confidence limits. The number of subjects with valid and determinate assay results for each antibody at specified timepoints (Table 5 and Table 6) will also be presented.

Analyses will be performed using the Immunogenicity Set. The analysis of the geometric means and 95% CIs will be the primary analysis of the secondary endpoint. Median, Q1, Q3, Min and Max of the anti-CSP IgG (NANP) concentrations will be presented in addition.

Figures will be provided to show:

- For a given cohort and placebo, boxplots of anti-CSP IgG (NANP) concentrations for all sampling timepoints
- Line plots of geometric means and 95% CIs of anti-CSP IgG (NANP) concentrations over time and by cohort (and placebo)

6.6.1.1.2 Antibody magnitude fold rise

The fold rise of the antibody response will be calculated for all post-baseline timepoints as post-dose value divided by baseline value. If the baseline measurement is below LLOQ, fold rise will be calculated as post-dose value divided by LLOQ. Similarly, if the post-dose measurement is below LLOQ, fold rise will be calculated as LLOQ divided by the baseline measurement. The baseline value will be the antibody concentration (AU/mL) at V1 prior to the first injection of IMP.

The fold rise in antibody concentrations (anti-CSP IgG (NANP)) will be summarized using descriptive statistics (Median, Q1, Q3, Min and Max) for all time points indicated in Table 5 and Table 6.

Additionally, the geometric mean fold rise (GMFR) with 95% CI will be presented.

Box plots will be provided for all sampling timepoints. Line plots of geometric mean fold rise and 95% CIs of baseline and all post-baseline timepoints will be provided, with the GMFR at baseline being equal to 1 for all cohorts and placebo.

Anti-CSP IgG (NANP) concentrations and fold rise will be listed.

6.6.1.1.3 Seroresponse

Seroresponse of the antibody concentrations is defined as achieving ≥4-fold rise from baseline (pre-Dose 1). If the baseline measurement is below LLOQ, a post-vaccination measure of ≥4 × LLOQ will be considered as seroresponse.

The number and percentage of subjects with seroresponse in anti-CSP IgG (NANP) antibody concentrations will be presented for all time points indicated in Table 5 and Table 6. Seroresponse will also be listed.

6.6.1.2 Additional serology analyses

In addition to the secondary endpoint described above, the multiplex ECL assay will be used to measure serum IgG concentrations to five additional antigens. Data will be reported in Arbitrary units per ml (AU/mL). Values below the LLOQ will be set to 0.5 × LLOQ for the calculation of summary statistics on the concentrations and to LLOQ for the derivation of fold rise and seroresponse. Assay results above ULOQ will be set to ULOQ. Missing data will not be imputed.

For these additional serology analyses, anti-CSP IgG antibody responses will be presented as:

a. anti-CSP IgG (junctional region, JunctR) (= responses to ECL peptide 21C)
b. anti-CSP IgG (minor repeats, MinorR) (= responses to ECL peptide 22C)
c. anti-CSP IgG (NVDP $NANP_2$) (= responses to ECL peptide 27C)
d. anti-CSP IgG (C-term) (= responses to ECL peptide Pf16)
e. anti-CSP IgG (N-term) (= responses to ECL peptide 17C*)

These additional serology analyses will not be added to the CSR but will be summarized in a separate document.

The same analysis described for anti-CSP IgG (NANP) in Section 6.6.1.1 will be performed.

6.6.1.3 Exploratory analyses

Further immunogenicity endpoints have been defined as exploratory endpoints. These endpoints are out of scope for this SAP and will be described in a separate biomarker SAP developed by BioNTech.

6.6.2 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,

- for each individual day of the required reporting period, subjects transmitting the e-diary.

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

For each subject and for each dose, overall diary compliance is defined as:

$$Overall\ diary\ compliance\ per\ dose\ (\%) = \left(\frac{number\ of\ diary\ days\ completed}{7}\right) \cdot 100$$

Overall diary compliance will be analyzed for each dose using descriptive statistics.

7 REFERENCES

FDA Guidance 2007. US FDA Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Issued September 2007

Brighton Collaboration Case Definition: Tejtel SKS, Munoz FM, Ammouri IA, et al. Myocarditis and pericarditis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2022;40(10):1499-1511. https://doi.org/10.1016/j.vaccine.2021.11.074

8 SUPPORTING DOCUMENTATION

8.1 Appendix 1: Changes to protocol-planned analyses

Clarifications to the protocol-planned analyses:

In the CTP, the outcome measures for the primary endpoint on solicited events reads as follows:

- 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.

The statistical analysis of solicited local and systemic reactions will be based on the number and frequency of subjects with solicited local reactions at the injection site/solicited systemic reactions recorded up to 7 d after each dose and not on the number and frequency of events.

8.2 Appendix 2: List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CHMI	Controlled Human Malaria Infection
CI	Confidence Interval
CM	Concomitant Medication
CSP	Circumsporozoite Protein
CTR	Clinical Trial Report
CRF	Case report form
CRO	Contract Research Organization
d	days
DL	Dose Level
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
FIH	First-In-Human
FSH	Follicle Stimulating Hormone
GMFR	Geometric Mean Fold Rise
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IM	Intramuscular
IMP	Investigational Medicinal Product
IRC	Internal Review Committee
Kg	Kilogram
m^2	square meter
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
SD	Standard Deviation

SI	International System of Units
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedures
TMF	Trial Master File
µg	Microgram
WHO DD	World Health Organisation Drug Dictionary

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, median and quartiles 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 Table 10 will be used for the Tables/Figures/Listings display as appropriate in Part A. The placebo data from all the dose levels will be combined.

Table 10: Treatment descriptors in Part A

Dose level	Dose level label	Treatment code
BNT165c 10	BNT165c 10 µg	1
BNT165c 30	BNT165c 30 µg	2
BNT165c 70	BNT165c 70 µg	3
BNT165c 100	BNT165c 100 µg	9
BNT165d 30	BNT165d 30 µg	4
BNT165c 30 + BNT165d 10	BNT165c 30 µg + BNT165d 10 µg	5
BNT165c 10 + BNT165d 30	BNT165c 10 µg + BNT165d 30 µg	6
BNT165c 30 + BNT165d 30	BNT165c 30 µg + BNT165d 30 µg	7
BNT165c 70 + BNT165d 30	BNT165c 70 µg + BNT165d 30 µg	8
BNT165c 30 + BNT165d 10 0-1-2	BNT165c 30 µg + BNT165d 10 µg 0-1-2	10
Placebo	Placebo	11
Placebo 0-1-2	Placebo 0-1-2	12
Total*	Total	NA

*Total of all dose levels and all dose regimens including Placebo.
Abbreviation: NA = not applicable.

8.4 Appendix 4: Schedule of activities

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

Table 11: Schedule of activities for Cohorts 1 to 9 (Part A)

Activity	Visit (V) 0	V 1	V 2 (Call)	V 3 (Call)	V 4	V 5 (Call)	V 6 (Call)	V 7	V 8 (Call)	V 9 (Call)	V 10	V 11 (Call)	V 12	V 13	V 14 (Call)	V 15 (Call)	V 16	V 17 (Call)	V 18	V 19	V 20	V 21 [n]
Visit description	**Scr**	**Dose (D) 1 Day 1**	**24 h post-D 1**	**48 h post-D 1**	**7 d post-D 1**	**14 d post-D 1**	**28 d post-D 1**	**D 2 Day 57**	**24 h post-D 2**	**48 h post-D 2**	**7 d post-D 2**	**14 d post-D 2**	**28 d post-D 2**	**D 3 Day 183**	**24 h post-D 3**	**48 h post-D 3**	**7 d post-D 3**	**14 d post-D 3**	**28 d post-D 3**	**84 d post-D 3**	**168 d post-D 3**	**365 d post-D 3 or ET**
Visit window	**up to 42 d before V 1**	**NA**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**±4 d**	**±2 d**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**±4 d**	**±7 d [m]**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**±4 d**	**±14 d**	**±14 d**	**±14 d**
Informed consent	X																					
Inclusion / exclusion criteria	X	X review																				
Medical history	X	X update																				
Physical exam.	X	X [a]			X [a]			X [a]			X [a]			X [a]			X [a]					
Height & body weight	X																					
Vital signs	X	X [b]			X			X [b]			X			X [b]			X					

Activity	**Visit (V) 0**	**V 1**	**V 2 (Call)**	**V 3 (Call)**	**V 4**	**V 5 (Call)**	**V 6 (Call)**	**V 7**	**V 8 (Call)**	**V 9 (Call)**	**V 10**	**V 11 (Call)**	**V 12**	**V 13**	**V 14 (Call)**	**V 15 (Call)**	**V 16**	**V 17 (Call)**	**V 18**	**V 19**	**V 20**	**V 21 [n]**
Visit description	**Scr**	**Dose (D) 1 Day 1**	**24 h post-D 1**	**48 h post-D 1**	**7 d post-D 1**	**14 d post-D 1**	**28 d post-D 1**	**D 2 Day 57**	**24 h post-D 2**	**48 h post-D 2**	**7 d post-D 2**	**14 d post-D 2**	**28 d post-D 2**	**D 3 Day 183**	**24 h post-D 3**	**48 h post-D 3**	**7 d post-D 3**	**14 d post-D 3**	**28 d post-D 3**	**84 d post-D 3**	**168 d post-D 3**	**365 d post-D 3 or ET**
Visit window	**up to 42 d before V 1**	**NA**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**±4 d**	**±2 d**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**±4 d**	**±7 d [m]**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**±4 d**	**±14 d**	**±14 d**	**±14 d**
12-lead ECG k	X	X			X			X			X			X			X					
Blood draw for viral screen c	13 mL																					
Blood for clinical lab. d	6 mL	4.5 mL [e]			4.5 mL			4.5 mL [e]			4.5 mL			4.5 mL [e]			4.5 mL					
Pregnancy test for VOCBP f	X	X						X						X								
Randomization to IMP or placebo		X																				
IMP or placebo injection		X						X						X								
Record pregnancies		X	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	End

Activity	Visit (V) 0	V 1	V 2 (Call)	V 3 (Call)	V 4	V 5 (Call)	V 6 (Call)	V 7	V 8 (Call)	V 9 (Call)	V 10	V 11 (Call)	V 12	V 13	V 14 (Call)	V 15 (Call)	V 16	V 17 (Call)	V 18	V 19	V 20	V 21 [n]
Visit description	**Scr**	**Dose (D) 1 Day 1**	**24 h post-D 1**	**48 h post-D 1**	**7 d post-D 1**	**14 d post-D 1**	**28 d post-D 1**	**D 2 Day 57**	**24 h post-D 2**	**48 h post-D 2**	**7 d post-D 2**	**14 d post-D 2**	**28 d post-D 2**	**D 3 Day 183**	**24 h post-D 3**	**48 h post-D 3**	**7 d post-D 3**	**14 d post-D 3**	**28 d post-D 3**	**84 d post-D 3**	**168 d post-D 3**	**365 d post-D 3 or ET**
Visit window	**up to 42 d before V 1**	**NA**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**±4 d**	**±2 d**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**±4 d**	**±7 d [m]**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**±4 d**	**±14 d**	**±14 d**	**±14 d**
Counsel / remind subjects to use contraception	X	X			X			X			X		X	X			X		X	X		
Prior medications and vaccinations	X	X update																				
Record concomitant medications and vaccinations since last visit		X			X			X			X		X	X			X		X	X	X	X
Blood for humoral response assessments		30 mL [e]						30 mL [e]			30 mL		30 mL	30 mL [e]			30 mL		30 mL	30 mL	30 mL	30 mL

Activity	**Visit (V) 0**	**V 1**	**V 2 (Call)**	**V 3 (Call)**	**V 4**	**V 5 (Call)**	**V 6 (Call)**	**V 7**	**V 8 (Call)**	**V 9 (Call)**	**V 10**	**V 11 (Call)**	**V 12**	**V 13**	**V 14 (Call)**	**V 15 (Call)**	**V 16**	**V 17 (Call)**	**V 18**	**V 19**	**V 20**	**V 21 [n]**
Visit description	**Scr**	**Dose (D) 1 Day 1**	**24 h post-D 1**	**48 h post-D 1**	**7 d post-D 1**	**14 d post-D 1**	**28 d post-D 1**	**D 2 Day 57**	**24 h post-D 2**	**48 h post-D 2**	**7 d post-D 2**	**14 d post-D 2**	**28 d post-D 2**	**D 3 Day 183**	**24 h post-D 3**	**48 h post-D 3**	**7 d post-D 3**	**14 d post-D 3**	**28 d post-D 3**	**84 d post-D 3**	**168 d post-D 3**	**365 d post-D 3 or ET**
Visit window	**up to 42 d before V 1**	**NA**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**±4 d**	**±2 d**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**±4 d**	**±7 d [m]**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**±4 d**	**±14 d**	**±14 d**	**±14 d**
Blood for CMI assessment		100 mL [e]						70 mL [e]			100 mL		70 mL	70 mL [e]			100 mL		70 mL	70 mL	70 mL	70 mL [e]
Blood for HLA typing		4 mL [e]																				
Subject hotline availability	Start	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	End
Issue, train and collect subject e-diaries		Issue, train						Re-train						Re-train			Collect					
Subjects report reactogenicity daily for 7 d using an e-diary		Start	=>	=>	End			Start	=>	=>	End			Start	=>	=>	End					

Activity	**Visit (V) 0**	**V 1**	**V 2 (Call)**	**V 3 (Call)**	**V 4**	**V 5 (Call)**	**V 6 (Call)**	**V 7**	**V 8 (Call)**	**V 9 (Call)**	**V 10**	**V 11 (Call)**	**V 12**	**V 13**	**V 14 (Call)**	**V 15 (Call)**	**V 16**	**V 17 (Call)**	**V 18**	**V 19**	**V 20**	**V 21 [n]**
Visit description	**Scr**	**Dose (D) 1 Day 1**	**24 h post-D 1**	**48 h post-D 1**	**7 d post-D 1**	**14 d post-D 1**	**28 d post-D 1**	**D 2 Day 57**	**24 h post-D 2**	**48 h post-D 2**	**7 d post-D 2**	**14 d post-D 2**	**28 d post-D 2**	**D 3 Day 183**	**24 h post-D 3**	**48 h post-D 3**	**7 d post-D 3**	**14 d post-D 3**	**28 d post-D 3**	**84 d post-D 3**	**168 d post-D 3**	**365 d post-D 3 or ET**
Visit window	**up to 42 d before V 1**	**NA**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**±4 d**	**±2 d**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**±4 d**	**±7 d [m]**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**±4 d**	**±14 d**	**±14 d**	**±14 d**
Investigators review e-diary data daily		Start	=>	=>	End			Start	=>	=>	End			Start	=>	=>	End					
Record AEs, MAAEs, and SAEs	X [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [l]	X [l]	X [l]
Subject phone call		X [h]	X	X		X [j]	X	X [h]	X	X		X [j]		X [h]	X	X		X [j]				
Investigator local reaction assessment		X [i]						X [i]						X [i]								
Blood volume at visit (mL)	**19**	**138.5**			**4.5**			**104.5**			**134.5**		**100**	**104.5**			**134.5**		**100**	**100**	**100**	**100**

a Brief (symptom-targeted) physical examination, if clinically indicated. If subject has no symptoms and a physical examination is not clinically indicated, it is not required. Further details are provided in Section 8.3.1 of the protocol.

b On dosing days to be taken within 1 h pre-dose and at 1 h (±15 minutes) post-dose. Further details are provided in Section 8.3.2 of the protocol.

c Viral screening details are provided in Section 8.3.5 of the protocol.

d Clinical laboratory tests details are provided in Section 8.3.4 of the protocol.

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

f 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.

g Only SAEs.

h Trial subjects will be contacted by phone for calls at 5±2 h after each IMP dose.

i Local reactogenicity assessed by the investigator pre-dose and up to 1 h after dosing. Further details are provided in Section 8.3.6.1 of the protocol.

j Trial subjects will be contacted by phone at 14 (+1) d after each IMP dose and will specifically be asked about potential delayed local injection site reactions starting after 7 d and through 14 d post-IMP administration. Further details are provided in Section 8.3.10 of the protocol.

k ECG will be performed pre-dose on the dosing days. Further details are provided in Section 8.3.3 of the protocol.

l Only SAEs and MAAEs.

m In the setting of a temporary trial pause, the visit window for subjects for V 13 (Dose 3) in Cohorts 1-9 can be extended for an additional 23 d (dosing window -7 d/+30 d).

n Subjects that are discontinued from the trial or trial treatment after any dose should receive a phone call to collect any MAAEs and SAEs at 6 months and 12 months post last dose received. The visit window for these phone calls is ±14 d.

Notes:

If a subject is early terminated from treatment or from the trial, they should undergo regularly scheduled activities through 28 d post last received IMP dose, per SoA (Section 1.3 of the protocol) except for cases of pregnancy and other instances where further blood draws may be medically contraindicated in the opinion of the site investigator.

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 78 weeks will be up to ~1,140 mL.

As long as the volume of blood drawn over any 8-week period is not increased, and as long as the maximum blood volume drawn per day does not exceed the cumulative blood volume specified for that visit in the SoA, the volume of individual blood draws may be adapted if required, e.g., due to unforeseen shortage of specific tubes.

Abbreviations: AE = adverse event; CMI = cell mediated immune response; D = dose; d = day(s); ECG = electrocardiogram; ET = early termination; h = hour(s); β-HCG = beta human chorionic gonadotropin; HLA = human leukocyte antigens; IMP = investigation medicinal product; MAAE = medically attended adverse event; NA = not applicable; SAE = serious adverse event; Scr = screening; SoA = schedule of activities; V = visit; VOCBP = volunteers of childbearing potential.

Table 12: Schedule of activities for Cohort 10 (Part A)

Activity	Visit (V) 0	V 1	V 2 (Call)	V 3 (Call)	V 4	V 5 (Call)	V 6	V 7 (Call)	V 8 (Call)	V 9	V 10 (Call)	V 11	V 12 (Call)	V 13 (Call)	V 14	V 15 (Call)	V 16	V 17	V 18	V 19 m
Visit description	**Scr**	**Dose (D) 1 Day 1**	**24 h post-D 1**	**48 h post-D 1**	**7 d post-D 1**	**14 d post-D 1**	**D 2 (28 d post-D 1) Day 29**	**24 h post-D 2**	**48 h post-D 2**	**7 d post-D 2**	**14 d post-D 2**	**D 3 (28 d post-D 2) Day 57**	**24 h post-D 3**	**48 h post-D 3**	**7 d post-D 3**	**14 d post-D 3**	**28 d post-D 3**	**84 d post-D 3**	**168 d post-D 3**	**365 d post-D 3 or ET**
Visit window	**up to 42 d before V 1**	**NA**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**+4 d**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**+4 d**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**+4 d**	**±14 d**	**±14 d**	**±14 d**
Informed consent	X																			
Inclusion / exclusion criteria	X	X review																		
Medical history	X	X update																		
Physical exam.	X	X [a]			X [a]		X [a]			X [a]		X [a]			X [a]					
Height & body weight	X																			
Vital signs	X	X [b]			X		X [b]			X		X [b]			X					
12-lead ECG [k]	X	X			X		X			X		X			X					
Blood draw for viral screen [c]	13 mL																			

Activity	**Visit (V) 0**	**V 1**	**V 2 (Call)**	**V 3 (Call)**	**V 4**	**V 5 (Call)**	**V 6**	**V 7 (Call)**	**V 8 (Call)**	**V 9**	**V 10 (Call)**	**V 11**	**V 12 (Call)**	**V 13 (Call)**	**V 14**	**V 15 (Call)**	**V 16**	**V 17**	**V 18**	**V 19 m**
Visit description	**Scr**	**Dose (D) 1 Day 1**	**24 h post-D 1**	**48 h post-D 1**	**7 d post-D 1**	**14 d post-D 1**	**D 2 (28 d post-D 1) Day 29**	**24 h post-D 2**	**48 h post-D 2**	**7 d post-D 2**	**14 d post-D 2**	**D 3 (28 d post-D 2) Day 57**	**24 h post-D 3**	**48 h post-D 3**	**7 d post-D 3**	**14 d post-D 3**	**28 d post-D 3**	**84 d post-D 3**	**168 d post-D 3**	**365 d post-D 3 or ET**
Visit window	**up to 42 d before V 1**	**NA**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**+4 d**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**+4 d**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**+4 d**	**±14 d**	**±14 d**	**±14 d**
Blood for clinical lab. [d]	6 mL	4.5 mL [e]			4.5 mL		4.5 mL [e]			4.5 mL		4.5 mL [e]			4.5 mL					
Pregnancy test for VOCBP [f]	X	X					X					X								
Randomization to IMP or placebo		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		

Activity	**Visit (V) 0**	**V 1**	**V 2 (Call)**	**V 3 (Call)**	**V 4**	**V 5 (Call)**	**V 6**	**V 7 (Call)**	**V 8 (Call)**	**V 9**	**V 10 (Call)**	**V 11**	**V 12 (Call)**	**V 13 (Call)**	**V 14**	**V 15 (Call)**	**V 16**	**V 17**	**V 18**	**V 19 m**
Visit description	**Scr**	**Dose (D) 1 Day 1**	**24 h post-D 1**	**48 h post-D 1**	**7 d post-D 1**	**14 d post-D 1**	**D 2 (28 d post-D 1) Day 29**	**24 h post-D 2**	**48 h post-D 2**	**7 d post-D 2**	**14 d post-D 2**	**D 3 (28 d post-D 2) Day 57**	**24 h post-D 3**	**48 h post-D 3**	**7 d post-D 3**	**14 d post-D 3**	**28 d post-D 3**	**84 d post-D 3**	**168 d post-D 3**	**365 d post-D 3 or ET**
Visit window	**up to 42 d before V 1**	**NA**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**+4 d**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**+4 d**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**+4 d**	**±14 d**	**±14 d**	**±14 d**
Prior medications and vaccinations	X	X update																		
Record concomitant medications and vaccinations since last visit		X			X		X			X		X			X		X	X	X	X
Blood for humoral response assessments		30 mL [e]					30 mL [e]			30 mL		30 mL [e]			30 mL		30 mL	30 mL	30 mL	30 mL
Blood for CMI assessment		100 mL [e]					60 mL [e]			100 mL		60 mL [e]			100 mL		60 mL	70 mL	70 mL	70 mL
Blood for HLA typing		4 mL [e]																		

Activity	**Visit (V) 0**	**V 1**	**V 2 (Call)**	**V 3 (Call)**	**V 4**	**V 5 (Call)**	**V 6**	**V 7 (Call)**	**V 8 (Call)**	**V 9**	**V 10 (Call)**	**V 11**	**V 12 (Call)**	**V 13 (Call)**	**V 14**	**V 15 (Call)**	**V 16**	**V 17**	**V 18**	**V 19 m**
Visit description	**Scr**	**Dose (D) 1 Day 1**	**24 h post-D 1**	**48 h post-D 1**	**7 d post-D 1**	**14 d post-D 1**	**D 2 (28 d post-D 1) Day 29**	**24 h post-D 2**	**48 h post-D 2**	**7 d post-D 2**	**14 d post-D 2**	**D 3 (28 d post-D 2) Day 57**	**24 h post-D 3**	**48 h post-D 3**	**7 d post-D 3**	**14 d post-D 3**	**28 d post-D 3**	**84 d post-D 3**	**168 d post-D 3**	**365 d post-D 3 or ET**
Visit window	**up to 42 d before V 1**	**NA**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**+4 d**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**+4 d**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**+4 d**	**±14 d**	**±14 d**	**±14 d**
Subject hotline availability	Start	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	End
Issue, train and collect subject e-diaries		Issue, train					Re-train					Re-train			Collect					
Subjects report reactogenicity daily for 7 d using an e-diary		Start	=>	=>	End		Start	=>	=>	End		Start	=>	=>	End					
Investigators review e-diary data daily		Start	=>	=>	End		Start	=>	=>	End		Start	=>	=>	End					
Record AEs, MAAEs, and SAEs	X [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [l]	X [l]	X [l]
Subject phone call		X [h]	X	X		X [j]	X [h]	X	X		X [j]	X [h]	X	X		X [j]				

Activity	Visit (V) 0	V 1	V 2 (Call)	V 3 (Call)	V 4	V 5 (Call)	V 6	V 7 (Call)	V 8 (Call)	V 9	V 10 (Call)	V 11	V 12 (Call)	V 13 (Call)	V 14	V 15 (Call)	V 16	V 17	V 18	V 19 m
Visit description	**Scr**	**Dose (D) 1 Day 1**	**24 h post-D 1**	**48 h post-D 1**	**7 d post-D 1**	**14 d post-D 1**	**D 2 (28 d post-D 1) Day 29**	**24 h post-D 2**	**48 h post-D 2**	**7 d post-D 2**	**14 d post-D 2**	**D 3 (28 d post-D 2) Day 57**	**24 h post-D 3**	**48 h post-D 3**	**7 d post-D 3**	**14 d post-D 3**	**28 d post-D 3**	**84 d post-D 3**	**168 d post-D 3**	**365 d post-D 3 or ET**
Visit window	**up to 42 d before V 1**	**NA**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**+4 d**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**+4 d**	**±4 h**	**±6 h**	**+1 d**	**+3 d**	**+4 d**	**±14 d**	**±14 d**	**±14 d**
Investigator local reaction assessment		X [i]					X [i]					X [i]								
Blood volume at visit (mL)	**19**	**138.5**			**4.5**		**94.5**			**134.5**		**94.5**			**134.5**		**90**	**100**	**100**	**100**

a Brief (symptom-targeted) physical examination, if clinically indicated. If subject has no symptoms and a physical examination is not clinically indicated, it is not required. Further details are provided in Section 8.3.1 of the protocol.

b On dosing days to be taken within 1 h pre-dose and at 1 h (±15 minutes) post-dose. Further details are provided in Section 8.3.2 of the protocol.

c Viral screening details are provided in Section 8.3.5 of the protocol.

d Clinical laboratory tests details are provided in Section 8.3.4 of the protocol.

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

f 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.

g Only SAEs.

h Trial subjects will be contacted by phone for calls at 5±2 h after each IMP dose.

i Local reactogenicity assessed by the investigator pre-dose and up to 1 h after dosing. Further details are provided in Section 8.3.6.1 of the protocol.

j Trial subjects will be contacted by phone at 14 (+1) d after each IMP dose and will specifically be asked about potential delayed local injection site reactions starting after 7 d and through 14 d post-IMP administration. Further details are provided in Section 8.3.10 of the protocol.

k ECG will be performed pre-dose on the dosing days. Further details are provided in Section 8.3.3 of the protocol.

l Only SAEs and MAAEs.

m Subjects that are discontinued from the trial or trial treatment after any dose should receive a phone call to collect any MAAEs and SAEs at 6 months and 12 months post last dose received. The visit window for these phone calls is ±14 d.

Notes:

If a subject is early terminated from treatment or from the trial, they should undergo regularly scheduled activities through 28 d post last received IMP dose, per SoA (Section 1.3 of the protocol) except for cases of pregnancy and other instances where further blood draws may be medically contraindicated in the opinion of the site investigator.

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 66 weeks will be up to ~1,010 mL.

As long as the volume of blood drawn over any 8-week period is not increased, and as long as the maximum blood volume drawn per day does not exceed the cumulative blood volume specified for that visit in the SoA, the volume of individual blood draws may be adapted if required, e.g., due to unforeseen shortage of specific tubes.

Abbreviations: AE = adverse event; CMI = cell mediated immune response; D = dose; d = day(s); ECG = electrocardiogram; ET = early termination; h = hour(s); β-HCG = beta human chorionic gonadotropin; HLA = human leukocyte antigens; IMP = investigation medicinal product; MAAE = medically attended adverse event; NA = not applicable; SAE = serious adverse event; Scr = screening; SoA = schedule of activities; V = visit; VOCBP = volunteers of childbearing potential.