Title: A Phase 1/2, Randomized, Observer-Blind, Placebo-Controlled Trial to Evaluate the Safety and Immunogenicity of TAK-019 by Intramuscular Injection in Healthy Japanese Male and Female Adults Aged 20 Years and Older

NCT Number: NCT04712110

Statistical analysis plan Approve Date: 20-May-2021

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

Study Number: *TAK-019-1501*

Study Title: A phase 1/2, randomized, observer-blind, placebo-controlled trial to evaluate the safety and immunogenicity of TAK-019 by intramuscular injection in healthy Japanese male and female adults aged 20 years and older

Phase: 1/2

Version: *1. 0*

Date: *20 May 2021*

Prepared by:

[redacted]

[redacted]

Protocol Version: *Version 2.0 (Amendment 1)*

Protocol Date: *09Apr2021*

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
1.0		[Not Applicable]

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LIST OF IN-TEXT TABLES

ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ATC	Anatomical Therapeutic Class
bAb	binding antibody
BMI	body mass index
BLOQ	below the lower limit of quantification
CI	confidence interval
COVID-19	coronavirus disease 2019
eCRF	electronic case report form
eDiary	electronic diary
FAS	full analysis set
GMFR	geometric mean fold rise
GMT	geometric mean titer
IgG	Immunoglobulin G
IM	intramuscular
IMP	investigational medicinal product
LLOQ	lower limit of quantification
LOD	limit of detection
MAAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
PIMMC	Potential Immune-Mediated Medical Conditions
PPS	per-protocol analysis set
PT	Preferred Term (MedDRA)
rS	recombinant spike
S	Spike
SAE	serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus-2
SAP	statistical analysis plan
SCR	seroconversion rate
SD	standard deviation
SOC	System Organ Class
SRR	seroresponce rate
ULN	upper limit of normal
ULOQ	upper limit of quantification
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

The primary objective is to evaluate the safety and immunogenicity of 2 doses of TAK-019 by IM injection in healthy Japanese male and female adults aged ≥20 years, given 21 days apart.

Safety:

To assess the safety of TAK-019 in terms of:

- *Solicited local and systemic adverse events (AEs) for 7 days following each vaccination (day of vaccination + 6 subsequent days).*
- *Unsolicited AEs for 49 days following first vaccination (ie, 21 days following first vaccination [day of vaccination + 20 subsequent days] + 28 days following second vaccination [day of vaccination + 27 subsequent days]).*
- *Serious adverse events (SAEs), adverse event of special interest (AESI), medically-attended adverse events (MAAEs), AEs leading to trial withdrawal or discontinuation of vaccination and Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) infection until Day 50.*

Immunogenicity:

To assess the immunogenicity of TAK-019 in terms of:

- *Serum Immunoglobulin G (IgG) antibody levels to SARS-CoV-2 protein on Day 36.*

1.1.2 Secondary Objective(s)

Safety:

To assess the safety of TAK-019 in terms of:

- *SAEs, AESI, MAAEs, AEs leading to trial withdrawal or discontinuation of vaccination and SARS-CoV-2 infection throughout the trial.*

Immunogenicity:

To assess the immunogenicity of TAK-019 in terms of:

- *Serum IgG antibody levels to SARS-CoV-2 recombinant spike (rS) protein on Day 22, Day 50, Day 202, and Day 387.*
- *Serum neutralizing antibody titers to wild-type virus on Day 22, Day 36, Day 50, Day 202, and Day 387.*

[redacted]

[redacted]

1.2 Endpoints

1.2.1 Primary Endpoint(s)

Safety:

- *Percentage of subjects with reported solicited local AEs: injection site pain, tenderness, erythema/redness, induration, and swelling for 7 days following each vaccination (day of vaccination + 6 subsequent days).*
- *Percentage of subjects with solicited systemic AEs: fever, fatigue, malaise, myalgia, arthralgia, nausea/vomiting, and headache for 7 days following each vaccination (day of vaccination + 6 subsequent days).*
- *Percentage of subjects with unsolicited AEs for 49 days following first vaccination (ie, 21 days following first vaccination [day of vaccination + 20 subsequent days] + 28 days following second vaccination [day of vaccination + 27 subsequent days]).*
- *Percentage of subjects with SAE until Day 50.*
- *Percentage of subjects with AESI until Day 50.*
- *Percentage of subjects with MAAEs until Day 50.*
- *Percentage of subjects with any AE leading to discontinuation of vaccination.*
- *Percentage of subjects with any AE leading to subject's withdrawal from the trial until Day 50.*
- *Percentage of subjects with SARS-CoV-2 infection until Day 50.*

Immunogenicity:

- *Geometric mean titers (GMT), geometric mean fold rise (GMFR), seroconversion rate (SCR; defined at proportion of subjects with ≥4-fold rises in titer if seronegative at baseline OR proportion of subjects with ≥2-fold rises in titer if seropositive at baseline), and seroresponce rate (SRR; defined at proportion of subjects with ≥95 percentile in titer at baseline (Day 1) for all subjects) of serum IgG antibody levels to SARS-CoV-2 rS protein on Day 36.*

1.2.2 Secondary Endpoint(s)

Safety:

- *Percentage of subjects with SAE throughout the trial.*
- *Percentage of subjects with AESI throughout the trial.*
- *Percentage of subjects with MAAEs throughout the trial.*

- *Percentage of subjects with any AE leading to subject's withdrawal from the trial from the day of vaccination throughout the trial.*
- *Percentage of subjects with SARS-CoV-2 infection throughout the trial.*

Immunogenicity:

- *GMT, GMFR, SCR, and SRR of serum IgG antibody levels to SARS-CoV-2 rS protein on Day 22, Day 50, Day 202, and Day 387.*
- *GMT, GMFR, SCR, and SRR of serum neutralizing antibody titers to wild-type virus on Day 22, Day 36, Day 50, Day 202, and Day 387.*

[redacted]

2.0 STUDY DESIGN

This is a phase 1/2 randomized, observer-blind, placebo-controlled trial to evaluate the safety and immunogenicity of 2 doses of TAK-019 by IM injection 21 days apart in healthy Japanese male and female adults.

The trial is planned to enroll 200 subjects (150 subjects in the TAK-019 arm and 50 subjects in the placebo arm). Of them, 140 subjects will be stratified by age as ≥20 years to <65 years (100 subjects in the TAK-019 arm and 40 subjects in the placebo arm), and 60 subjects will be stratified by age of ≥65 years (50 subjects in the TAK-019 arm and 10 subjects in the placebo arm).

Once all screening assessments following informed consent are completed and eligibility is confirmed, the subject will receive the first dose of TAK-019 or saline placebo, by IM injection. And the subject will receive the second dose of TAK-019 or saline placebo after 21 days of the first vaccination (Day 22). All subjects will be followed up for safety and immunogenicity for 12 months after the last trial vaccination.

Each subject will be provided with an electronic diary (eDiary). Oral body temperature and solicited local and systemic adverse events (AEs) will be recorded in the eDiary by the subjects for 7 days after each vaccination (including the day of vaccination). All subjects will be followed for unsolicited AEs for 49 days following first vaccination (ie, 21 days following first vaccination [day of vaccination + 20 subsequent days]) + 28 days following second vaccination [day of vaccination + 27 subsequent days]).

All subjects will be followed for SAEs, AESI, MAAEs, and AEs leading to trial withdrawal during their entire participation in the trial. All subjects will also be tested for SARS-CoV-2 infection at

prespecified visits (Day 1, Day 22, and Day 50) and in case of clinical symptoms suspected for COVID-19 throughout the trial.

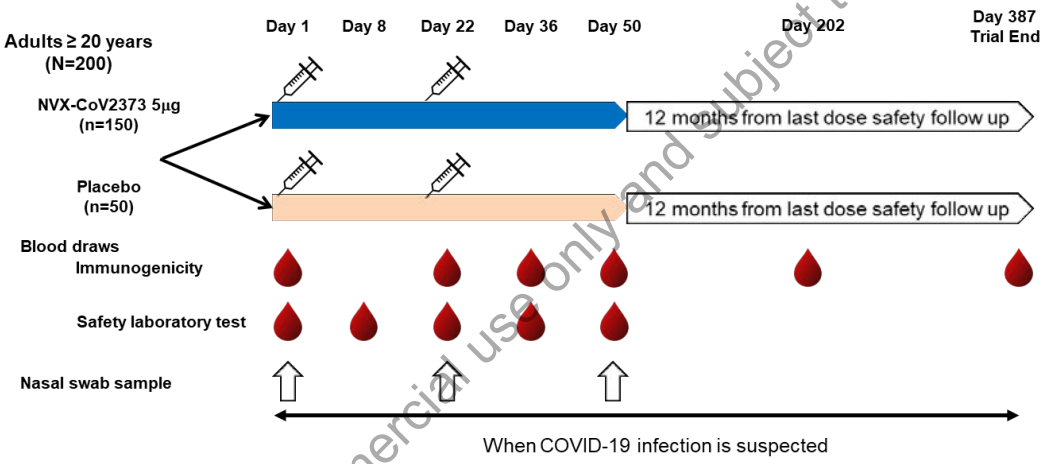
The primary analysis will be performed for safety and immunogenicity after all subjects have completed the Day 50 (the trial visit after 28 days from the date of the second vaccination) visit.

After the database lock of the primary analysis (ie, Day 50 data), the trial will be unblinded and changed to an Open-Label study. The subjects will be informed about the vaccination assignment (TAK-019 or Placebo) and reconsent about study continuation will be obtained from subjects.

A schematic of the trial design is included as Figure 2.a.

Schedule of events can be found in protocol Section 2.1.

Figure 2.a Schematic of Trial Design



Abbreviations: COVID-19=coronavirus disease 2019, N/n=number of subjects.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not Applicable.

3.2 Statistical Decision Rules

Not Applicable.

3.3 Multiplicity Adjustment

Given the exploratory nature of this study, no adjustment for multiple comparisons and multiplicity will be performed. That is, only nominal p-values will be provided if applicable..

No statistical testing will be performed for the safety endpoints.

4.0 SAMPLE-SIZE DETERMINATION

The objective of this trial is to evaluate the safety and immunogenicity of TAK-019 in the Japanese population. This trial is designed to be descriptive, and therefore the sample size was not determined based on formal statistical power calculations. The sample size for the trial is based on clinical and practical consideration and is considered sufficient to evaluate the objective of the trial. With 150 subjects in the TAK-019 group, the probability to observe at least one AE of 2% event rate is 95%. Considering the risk of disease burden of COVID-19, the number of placebo group in this trial was set as minimum as possible especially in the subjects ≥65 years old.

5.0 ANALYSIS SETS

The Full Analysis Set (FAS), Per-protocol Set (PPS) and Safety Analysis Set are defined for this trial. The FAS is defined as all randomized subjects who receive at least 1 dose of the treatment. Immunogenicity analyses will be conducted using the PPS defined to include subjects in the FAS and who have evaluable immunogenicity data and do not have significant protocol deviations which influence the immunogenicity assessment. Safety analyses will be conducted using the Safety Analysis Set defined as all subjects who receive at least 1 dose of the treatment.

Subject evaluability criteria for each analysis set will be fixed before unblinding of IMP assignment.

5.1 All Screened Subjects Analysis Set

The All Screened Subjects Analysis Set will consist of all subjects who provide informed consent for this study, to be used for reporting disposition and screening failures.

5.2 Safety Analysis Set

The Safety Analysis Set will consist of all subjects who receive at least 1 dose. Subjects will be analyzed according to the vaccine actually received. If 1st treatment is different from 2nd treatment due to error, subjects who receive at least one Active treatment is treated as "TAK-019".

5.3 Full Analysis Set

FAS will consist of all randomized subjects who receive at least 1 dose of the treatment. Subjects will be analyzed according to the study vaccine that the subject was randomized to receive and not according to what was actually received.

5.4 Per-Protocol Analysis Set

PPS will consist of all subjects who include in the FAS and who have evaluable immunogenicity data and do not have below significant protocol deviations which influence the immunogenicity assessment. Subjects with other protocol deviations might be excluded as necessary. Subjects will be analyzed according to the study vaccine that the subject was randomized to receive and not according to what was actually received.

- Missed dose of any planned injections.
- Usage of prohibited medications specified in the protocol (section 7.3).
- Confirmation of SARS-CoV-2 infection before the 1st injection.
- Out of allowance of blood sampling for immunogenicity on Day 36.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Baseline values are defined as the last observed value before the first dose of study intervention.

Where applicable, variables will be summarized descriptively by study visit. For the categorical variables, the counts and proportions of each possible value will be tabulated by treatment group. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. Study day will be calculated relative to the first study intervention date as:

- If assessment date is on or after the first study intervention date, then

Study Day = Assessment Date − First Study Intervention Date + 1

- Otherwise, Study Day = Assessment Date − First Study Intervention Date

In addition, day relative to vaccination will be derived for each vaccination dose. For example, day relative to the first dose will be equal to the Study Day. Day relative to the second dose will start with a value of 1 on the day of the second dose.

In the situation where the event date is partial or missing, Study Day and any corresponding durations will appear partial or missing in the listings.

For GMT, GMFR, SCR and SRR calculations, antibody values reported as below LLOQ will be replaced by 0.5 × LLOQ as applicable. Values that are greater than the upper limit of quantification (ULOQ) will be replaced by the ULOQ as applicable but will be listed as reported in the raw data. Values of blood sampling for immunogenicity after confirmation of SARS-CoV-2 infection will be excluded. Missing results will not be imputed. No other imputations will be performed.

A windowing convention will be used to determine the analysis value for a given study visit for immunogenicity analyses (Refer to Section 9.2.4).

Change from baseline will be calculated as:

- Change from baseline = Test value at post-baseline visit – Baseline value

6.1.1 Handling of Treatment Misallocations

All analyses using FAS and PPS will be performed as randomized, the other analysis will be performed as actually received, unless otherwise specified.

6.2 Disposition of Subjects

Number of subjects screened will be presented for the All Screened Subjects Analysis Set. Number and percentages of subjects with screen failure and reason for screen failure will also be presented based on the All Screened Subjects Analysis Set. A listing will present subjects not meeting all eligibility criteria with the details of criteria not met.

Number of subjects randomized will be presented overall and by randomized group for the All Screened Subjects Analysis Set. Number of subjects randomized but not vaccinated will also be presented overall and by randomized group for the All Screened Subjects Analysis Set.

Number and percentages of subjects vaccinated will be presented overall and by treatment group for the Safety Analysis Set. Number and percentages of subjects who completed full course of study intervention, who discontinued early from study intervention (including reason for withdrawal), and who completed/discontinued early from the study (including reason for withdrawal) will be provided based on the Safety Analysis Set.

Similar summaries will be provided for each dose:

- Number and percentages of subjects vaccinated for first dose, ongoing in study after first dose, and discontinued early from the study (including reason for withdrawal) before second dose will be presented based on the Safety Analysis Set.
- Number and percentages of subjects vaccinated for second dose, ongoing in study (for primary analysis only) after second dose and discontinued early from the study (including reason for withdrawal) before 21 days post second dose and who discontinued early from the study (including reason for withdrawal) after 28 days (including 28 days) post second dose will be presented based on the Safety Analysis Set.

The analysis of number of ongoing subjects after first or second dose will only be presented for primary analysis and will not be included in the final analysis.

Number of subjects included and excluded from each analysis set (including reason for exclusion) will be summarized overall and by treatment group based on the All Screened Subjects Analysis Set. A listing showing inclusion and exclusion of each subject from each analysis set, including reason for exclusion, will be provided.

Number and percentage of subjects with important protocol deviations, as identified by the study team in a blinded manner as being major or critical, will be provided overall and by treatment

group based on the Safety Analysis Set for each category specified in the Protocol Deviations Management Plan.

A listing of protocol deviations identified by the study team (important or not) will be provided.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Demographic data and other baseline characteristics will be presented for the Safety Analysis Set and PPS.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) – at the date of signed informed consent.
- Age group (years): 20 ≤ <65 and ≥65.
- Age group (years): 20 ≤ <65, 65 ≤ <75, 75 ≤ <85, ≥85.
- Sex.
- Race.
- Weight (kg).
- Height (cm).
- Body mass index (BMI) (kg/m^2).

Continuous demographic and other baseline characteristics will be summarised using descriptive statistics overall and by treatment group. Categorical demographic and other baseline characteristics using number and percentages of patients in each category overall and by treatment group. No statistical testing will be carried out for demographic or other baseline characteristics.

6.3.2 Medical History and Concurrent Medical Conditions

- Medical history is defined as any medical conditions/diseases that started and stopped prior to signing of informed consent.
- Concurrent medical conditions are defined as any medical conditions that started prior to signing of informed consent AND were ongoing at the time of signing of informed consent or ended on the day of signing of informed consent.

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0 or later, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) based on the Safety Analysis Set. A subject having more than one medical condition within the same SOC/PT will be counted only once for that SOC or PT.

All medical history and concurrent medical conditions will be listed.

6.4 Medication History and Concomitant Medications

- Prior medications are defined as any medication that started and stopped prior to the first dose of study intervention.
- Concomitant medications are defined as:
  - Any medication that started before the first dose of study intervention AND was ongoing at the time of the first dose of study intervention or ended on the date of first dose of study intervention;
  - Any medication that started on or after the day of first dose of study intervention.

Partially or completely missing medication start and stop dates will be handled as described in section 9.2.1.1.

All medications will be coded using the World Health Organization (WHO) Drug Global dictionary, version B3 March 2020 or later.

Prior and concomitant medications will be summarized by Anatomical Therapeutic Class (ATC) level 2 and preferred drug name based on the Safety Analysis Set. A subject having more than one medication within the same ATC Level 2 or preferred drug name will be counted only once for that ATC Level 2 or preferred drug name.

All prior, concomitant medications and concomitant procedures will be listed.

6.5 Efficacy Analysis (Immunogenicity Analysis)

Unless otherwise specified, all summaries and figures for immunogenicity will be presented by treatment group, using the PPS and FAS.

6.5.1 Primary Endpoint(s) Analysis

Geometric mean titers (GMT), geometric mean fold rise (GMFR), seroconversion rate (SCR; defined at proportion of subjects with ≥4-fold rises in titer if seronegative at baseline OR proportion of subjects with ≥2-fold rises in titer if seropositive at baseline), and seroresponce rate (SRR; defined at proportion of subjects with ≥95 percentile in titer at baseline (Day 1) for all subjects) of serum IgG antibody levels to SARS-CoV-2 rS protein on Day 36.

6.5.1.1 Derivation of Endpoint(s)

Analyses will be conducted using the PPS and FAS.

SCR and SRR of each endpoint at Day 36 will be calculated along with its 95% confidence interval (CI) in each treatment group.

For antibody titer values and the changes from baseline, GMT, GMFR, summary statistics, and 95% CIs of each endpoint at Day 36 will be calculated in each treatment group.

6.5.1.2 Main Analytical Approach

6.5.1.2.1 Seroconversion Rate and Seroresponse Rate

Seroconversion is a binary outcome where a success is when subjects with ≥4-fold rises in titer if seronegative at baseline OR subjects with ≥2-fold rises in titer if seropositive at baseline.

Seroresponse is a binary outcome where a success is when subjects with ≥95 percentile in titer at baseline (Day 1) for all subjects across treatment groups in the corresponding analysis set.

The number and proportion of subjects who have a seroconversion and seroresponse at Day 36 will be summarized for each endpoint and treatment group. The summary will also include the 95% CI of the proportion of subjects achieving seroconversion and seroresponse at Day 36, calculated based on the Clopper-Pearson method. For seroconversion, the number and percentage of subjects with fold-rise ≥2, and fold- rise ≥4 from baseline will be summarized with 95% CI calculated based on the Clopper-Pearson method in the same way.

6.5.1.2.2 GMTs and GMFRs

GMT and GMFR will be calculated and will be summarized at Day 36.

Descriptive statistics for GMT and GMFR will include number of subjects, geometric mean, 95% CI, minimum and maximum and will be presented for each treatment group.

The GMT will be calculated as the anti-logarithm of Σ (common log transformed titer/n), ie, as the anti-logarithm transformation of the mean of the log-transformed titer, where n is the number of participants with titer information.

The 95% CI will be calculated as the anti-logarithm transformation of the upper and lower limits for a two-sided CI for the mean of the log-transformed titers.

The fold rise is calculated as the ratio of the post-vaccination titer level to the pre-vaccination titer level. GMFR will be calculated as anti-logarithm of Σ (common log transformed (post-vaccination titer/ pre-vaccination titer)/n). The 95% CIs for GMFR will be calculated similarly to those for GMT.

6.5.2 Secondary Endpoint(s) Analysis

- *GMT, GMFR, SCR, and SRR of serum IgG antibody levels to SARS-CoV-2 rS protein on Day 22, Day 50, Day 202, and Day 387.*
- *GMT, GMFR, SCR, and SRR of serum neutralizing antibody titers to wild-type virus on Day 22, Day 36, Day 50, Day 202, and Day 387.*

6.5.2.1 Derivation of Endpoint(s)

Analyses will be conducted using the PPS and FAS.

SCR and SRR of each endpoint at each time point will be calculated along with its 95% CI in each treatment group.

For antibody titer values and the changes from baseline, GMT, GMFR, summary statistics and 95% CIs of each endpoint at each time point will be calculated in each treatment group.

6.5.2.2 Main Analytical Approach

6.5.2.2.1 Seroconversion Rate and Seroresponse Rate

Seroconversion and seroresponse of serum IgG antibody levels to SARS-CoV-2 rS protein is defined in Section 6.5.1.2.1.

SCR and SRR of each endpoint at each time point will be performed the same analysis of the primary endpoint analysis, as Section 6.5.1.2.1.

6.5.2.2.2 GMTs and GMFRs

GMTs and GMFRs of each endpoint at each time point will be performed the same analysis of the primary endpoint analysis, as Section 6.5.1.2.2.

[redacted]

6.5.4 Subgroup Analyses

Perform subgroup analyses on the items described in Section 6.5.1and Section 6.5.2. Subgroup analyses will be conducted using the PPS.

The subgroup is:

- Age group (years): 20 ≤ <65 and ≥65.
- Sex: Male, Female.

6.6 Safety Analysis

All safety summaries will be presented by treatment group based on the Safety Analysis Set. There will be no statistical comparisons between the treatment groups for safety data.

The primary safety endpoints are:

- *Percentage of subjects with reported solicited local AEs: injection site pain, tenderness, erythema/redness, induration, and swelling for 7 days following each vaccination (day of vaccination + 6 subsequent days).*
- *Percentage of subjects with solicited systemic AEs: fever, fatigue, malaise, myalgia, arthralgia, nausea/vomiting, and headache for 7 days following each vaccination (day of vaccination + 6 subsequent days).*

- *Percentage of subjects with unsolicited AEs for 49 days following first vaccination (ie, 21 days following first vaccination [day of vaccination + 20 subsequent days] + 28 days following second vaccination [day of vaccination + 27 subsequent days]).*
- *Percentage of subjects with SAE until Day 50.*
- *Percentage of subjects with AESI until Day 50.*
- *Percentage of subjects with MAAEs until Day 50.*
- *Percentage of subjects with any AE leading to discontinuation of vaccination.*
- *Percentage of subjects with any AE leading to subject's withdrawal from the trial until Day 50.*
- *Percentage of subjects with SARS-CoV-2 infection until Day 50.*

The secondary safety endpoints are:

- *Percentage of subjects with SAE throughout the trial.*
- *Percentage of subjects with AESI throughout the trial.*
- *Percentage of subjects with MAAEs throughout the trial.*
- *Percentage of subjects with any AE leading to subject's withdrawal from the trial from the day of vaccination throughout the trial.*
- *Percentage of subjects with SARS-CoV-2 infection throughout the trial.*

6.6.1 Adverse Events

Unsolicited adverse events will be coded using the MedDRA dictionary, version 23.0 or later.

Only AEs that started or worsened in severity on or after the first dose of study intervention will be presented in the summary. A listing of all AEs including those prior to the first vaccination will be provided.

6.6.1.1 All Adverse Events

An overall summary of number and percentages of subjects within each of the categories described in the sub-sections below will be provided based on the Safety Analysis Set. Should a subject experience multiple events within a category, the subject will be counted only once for that category.

6.6.1.1.1 Severity Grading for AEs

Severity is classed as mild/ moderate/ severe as defined in the protocol Section 10.1.2. AEs with a missing severity will be classified as severe. AEs will be collected on AE page of eCRF. Should a subject experience multiple events within a SOC or PT, only the subject's worst grade will be counted for that SOC or PT.

6.6.1.1.2 AEs Related to Study Intervention

AEs related to study intervention, as indicated by the Investigator as "Causality" in eCRF, will be provided. AEs with a missing "Causality" will be classified as related.

Should a subject experience multiple events within a SOC or PT, only the subject's worst relationship will be counted for that SOC or PT.

6.6.2 Primary Safety Endpoints

6.6.2.1 Occurrence of Solicited AEs for 7 Days Following Each Vaccination

Subjects will record solicited local and systemic AEs (Table 6.a), and oral body temperature, for 7 days following each vaccination (day of vaccination + 6 subsequent days) in the eDiary.

Severity grading of solicited AEs will occur automatically based on subject's entry into the eDiary according to the grading scales presented in Table 6.a modified from the Food and Drug Administration guidance (Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials)[1].

If a solicited local or systemic AE continues beyond 7 days after dosing, the subject will capture the AE in the eDiary until resolution. The solicited AEs recorded in eDiaries beyond Day 7 should be reviewed by the Investigator either via phone call or at the following trial visit.

Table 6.a Solicited Local (Injection Site) Reactions and Systemic AEs

Local Reaction to Injectable Product				
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4)**
Injection site pain	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/ redness [a]	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration [a]	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis
Swelling [a]	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis
Systemic (General)				
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4)**
Fever [b]	38.0°C – 38.4°C	38.5°C – 38.9°C	39.0°C – 40.0°C	>40.0°C
Fatigue	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room visit or hospitalization
Malaise	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room visit or hospitalization
Arthralgia	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room visit or hospitalization
Nausea/ vomiting	No interference with activity or 1–2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, or requires outpatient intravenous hydration	Emergency room visit or hospitalization for hypotensive shock
Headache	No interference with activity	Repeated use of OTC pain reliever >24 hours or some interference with activity	Any use of prescription pain reliever or prevents daily activity	Emergency room visit or hospitalization

Abbreviations: AE: adverse event; OTC: over-the-counter.

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[b] Oral temperature; no recent hot or cold beverages.

They will not be assessed for relationship to study intervention because solicited AEs are expected to occur after vaccination.

Solicited AEs up to 7 days following each vaccination uses data collected by eDiary, on the other hands solicited AEs after 7 days following each vaccination uses data collected by eCRF.

Solicited AEs will be summarized for each day post vaccination and the total duration (day of vaccination + 6 subsequent days). For each interval, the count and percentages of subjects will be determined for each of the following categories: subjects evaluated, subjects without any events, subjects with any events, mild events, moderate events, severe events, and potentially life-threatening events. Subjects should not be double counted; therefore, the event of greatest severity will be used for subjects with more than 1 episode of the same event. Similar count and percentages of subjects will be presented for solicited local AEs and solicited systemic AEs.

Also Solicited AEs persisting beyond 7 days after vaccination will be summarized by severity for each vaccination. Subjects should not be double counted; therefore, the event of greatest severity will be used for subjects with more than 1 episode of the same event.

Quantitative and categorical summary of the day of first onset of each event and the number of days subjects reported experiencing each event will be presented. The number of days a subject reported experiencing an event is calculated as the total of all days the subject reported the event, regardless of whether the symptom was reported on consecutive days (eg, a headache reported on Day 1, Day 3, and Day 4 would be included with a duration of 3 days).

A listing of all solicited AEs will be provided.

6.6.2.2 Occurrence of Unsolicited AEs for 49 Days Following First Vaccination

All AEs are considered to be unsolicited AEs unless categorized as solicited AEs recorded in an eDiary. All unsolicited AEs will be recorded from the start of first dose for 49 days (ie, 21 days following first vaccination [day of vaccination + 20 subsequent days] + 28 days following second vaccination [day of vaccination + 27 subsequent days]).

Number and percentages of subjects with at least one unsolicited AE will be presented by SOC and PT. Should a subject experience multiple events within a SOC or PT, the subject will be counted only once for that SOC or PT.

Number and percentage of subjects with at least one unsolicited AE will be presented by PT. Should a subject experience multiple events within a PT, the subject will be counted only once for that PT.

Number and percentage of subjects with at least one unsolicited AE will be broken down further by 21 (following first vaccination) and 28 (following second vaccination) days interval post each dose (based on the start date of the event), maximum severity (refer to Section 6.6.1.1.1), relationship to study intervention (refer to Section 6.6.1.1.2).

A summary of AEs started on and after first dose of study intervention will be presented by SOC and PT throughout the trial.

A listing of all unsolicited AEs will be provided.

6.6.2.3 Occurrence of Serious AEs Until Day 50

Serious adverse events are those events recorded as "Serious" on the AE page of the eCRF. Only SAEs that started or worsened in severity on or after the first dose of study intervention will be presented in the summary.

Should a subject experience multiple events within a SOC or PT, the subject will be counted only once for that SOC or PT. Number and percentage of subjects with at least one SAE will be broken down further by 21 and 28 days interval post each dose (based on the start date of the event).

A listing of all SAEs including those prior to the first vaccination will be provided.

6.6.2.4 Occurrence of Adverse Event of Special Interest Until Day 50

AESIs are defined as AEs that will be specifically highlighted to the Investigator.

AESIs for the study include the Potential Immune Mediated Medical Conditions (PIMMC) listed below and AEs specific to COVID-19. The Investigators have to be especially vigilant to AESIs. Any AEs considered AESIs will be recorded on the AE page of the eCRF.

PIMMC is included as Table 6.b, and AEs specific to COVID-19 is included as Table 6.c.

Table 6.b Potential Immune-Mediated Medical Conditions (PIMMC)

Categories	Diagnoses (as MedDRA Preferred Terms)
Neuroinflammatory Disorders	Acute disseminated encephalomyelitis (including site specific variants: eg, non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis), cranial nerve disorders including paralysis/paresis (eg, Bell's palsy), generalized convulsion, Guillain-Barre syndrome (including Miller Fischer and other variants), immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and polyneuropathies associated with monoclonal gammopathy), myasthenia gravis, multiple sclerosis, narcolepsy, optic neuritis, transverse myelitis, and uveitis.
Musculoskeletal and Connective Tissue Disorders:	Antisynthetase syndrome, dermatomyositis, juvenile chronic arthritis (including Still's disease), mixed connective tissue disorder, polymyalgia rheumatic, polymyositis, psoriatic arthropathy, relapsing polychondritis, rheumatoid arthritis, scleroderma (including diffuse systemic form and CREST syndrome), spondyloarthritis (including ankylosing spondylitis, reactive arthritis [Reiter's Syndrome], and undifferentiated spondyloarthritis), systemic lupus erythematosus, systemic sclerosis, and Sjogren's syndrome.
Vasculitides	Large vessels vasculitis (including giant cell arteritis such as Takayasu's arteritis and temporal arteritis), medium sized and/or small vessels vasculitis (including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome [allergic granulomatous angiitis], Buerger's disease [thromboangiitis obliterans], necrotizing vasculitis and ANCA-positive vasculitis [type unspecified], Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis).

Table 6.b Potential Immune-Mediated Medical Conditions (PIMMC)

Categories	Diagnoses (as MedDRA Preferred Terms)
Gastrointestinal Disorders	Crohn's disease, celiac disease, ulcerative colitis, and ulcerative proctitis.
Hepatic Disorders	Autoimmune hepatitis, autoimmune cholangitis, primary sclerosing cholangitis, and primary biliary cirrhosis.
Renal Disorders	Autoimmune glomerulonephritis (including IgA neuropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis).
Cardiac Disorders	Autoimmune myocarditis/cardiomyopathy.
Skin Disorder	Alopecia areata, psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases (including pemphigus, pemphigoid, and dermatitis herpetiformis), cutaneous lupus erythematosus, morphoea, lichen planus, Stevens-Johnson syndrome, and Sweet's syndrome.
Hematologic Disorders	Autoimmune hemolytic anemia, autoimmune thrombocytopenia, antiphospholipid syndrome, and thrombocytopenia.
Metabolic Disorders	Autoimmune thyroiditis, Grave's or Basedow's disease, Hashimoto's thyroiditis[a], diabetes mellitus type I, and Addison's disease.
Other Disorders	Goodpasture syndrome, idiopathic pulmonary fibrosis, pernicious anemia, and sarcoidosis.

Abbreviations: ANCA: anti-neutrophil cytoplasmic antibody; CREST: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; IgA: immunoglobulin A; MedDRA: Medical Dictionary for Regulatory Activities.

[a] For Hashimoto thyroiditis: new onset only.

Table 6.c Adverse Events Specific to COVID-19[a]

Categories	Diagnoses (as MedDRA System Organ Class/Preferred Term)
Respiratory/Infectious Disorders	ARDS, pneumonitis, and septic shock-like syndrome
Cardiac Disorders	Acute cardiac injury, and arrhythmia
Coagulopathy	Deep vein thrombosis, myocardial infarction, and stroke
Renal Disorder	Acute kidney injury
Hematologic Disorders	Thrombocytopenia, and septic shock-like syndrome.
Inflammatory Disorders	Cytokine Release Syndrome related to COVID-19 infection[b] and multisystem inflammatory syndrome in children.
Neurologic Disorder	Generalized convulsions.

Abbreviations: ARDS: acute respiratory distress syndrome; CEPI: Coalition for Epidemic Preparedness Innovations; COVID-19: coronavirus disease 2019; DAIDS: Division of AIDS; MedDRA: Medical Dictionary for Regulatory Activities.

[a] COVID-19 manifestations associated with more severe presentation and decompensation with consideration of enhanced disease potential. The current listing is based on CEPI/Brighton Collaborations Consensus Meeting (12/13 March 2020) and expected to evolve as evidence accumulates.

[b] Cytokines release syndrome related to COVID-19 infection is a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath [2].

A summary of AESIs by Categories and PT will be presented. Should a subject experience multiple events within a Categories or PT during an interval, the subject will be counted only once for that Categories or PT during that particular interval. The summary of AESIs will be broken down further by 21 and 28 days interval post each dose (based on the start date of the event).

A summary of related AESIs by Categories and PT will be presented.

A listing of all AESIs will be provided.

6.6.2.5 Occurrence of Medically-Attended Adverse Events Until Day 50

MAAEs are defined as AEs leading to an unscheduled visit to or by a healthcare professional including visits to an emergency department, but not fulfilling seriousness criteria.

A summary of MAAEs by SOC and PT will be presented. Should a subject experience multiple events within a SOC or PT during an interval, the subject will be counted only once for that SOC or PT during that particular interval. The summary of MAAEs will be broken down further by 21 and 28 days interval post each dose (based on the start date of the event).

A listing of all MAAEs will be provided.

6.6.2.6 AEs Leading to Discontinuation of Vaccination

AEs leading to discontinuation of vaccination are recorded as "Drug Withdrawn" for the question "Action Taken with Study Treatment" on the AE pages of the eCRF. A summary of AEs leading to discontinuation of vaccination by SOC and PT will be presented. The summary

of AEs leading to discontinuation of vaccination will be broken down further by 21 and 28 days interval post each dose (based on the start date of the event).

A listing of all AEs leading to discontinuation of vaccination will be provided.

6.6.2.7 AEs Leading to Subject's Withdrawal From the Trial Until Day 50

AEs leading to subject's withdrawal from the trial are recorded as "Yes" for the question "AE Caused Study Discontinuation?" on the AE pages of the eCRF. A summary of AEs leading to withdrawal from the trial by SOC and PT will be presented. The summary of AEs leading to subject's withdrawal from the trial will be broken down further by 21 and 28 days interval post each dose (based on the start date of the event).

A listing of all AEs leading to subject's withdrawal from the trial will be provided.

6.6.2.8 SARS-CoV-2 Infection Until Day 50.

The incidence of the first SARS-CoV-2 infection will be summarized by treatment group based on the Safety Analysis Set.

A subject who is found to be positive to COVID-19 based on the PCR or other testing of SARS-CoV-2 infection is considered as having SARS-CoV-2 infection.

A listing of the PCR or other testing of SARS-CoV-2 infection will be provided.

6.6.3 Secondary safety endpoints

6.6.3.1 Occurrence of Serious AEs Throughout the Trial

A summary of SAEs started on and after first dose of study intervention will be presented by SOC and PT throughout the trial. Should a subject experience multiple events within a SOC or PT, the subject will be counted only once for that SOC or PT.

A listing of all SAEs (including SAE started prior to the start of first dose of study intervention) will be provided.

This analysis will be conducted only at the Final analysis.

6.6.3.2 Occurrence of AESI Throughout the Trial

A summary of AESIs by SOC and PT throughout the trial will be presented. Should a subject experience multiple events within a SOC or PT, the subject will be counted only once for that SOC or PT.

A listing of all AESIs will be provided.

This analysis will be conducted only at the Final analysis.

6.6.3.3 Occurrence of MAAEs Throughout the Trial

A summary of MAAEs by SOC and PT throughout the trial will be presented. Should a subject experience multiple events within a SOC or PT, the subject will be counted only once for that SOC or PT.

A listing of all MAAEs will be provided.

This analysis will be conducted only at the Final analysis.

6.6.3.4 AEs Leading to Subject's Withdrawal From the Trial From the Day of Vaccination Throughout the Trial

AEs leading to subject's withdrawal from the trial are recorded as "Yes" for the question "AE Caused Study Discontinuation?" on the AE pages of the eCRF. A summary of AEs leading to withdrawal from the trial by SOC and PT will be presented.

A listing of all AEs leading to subject's withdrawal from the trial will be provided.

This analysis will be conducted only at the Final analysis.

6.6.3.5 SARS-CoV-2 Infection Throughout the Trial

The incidence of the first SARS-CoV-2 infection will be performed the same analysis of the primary safety analysis, as Section 6.6.2.8.

A subject who is found to be positive to COVID-19 based on the PCR or other testing of SARS-CoV-2 infection is considered as having SARS-CoV-2 infection.

A listing of the PCR or other testing of SARS-CoV-2 infection will be provided.

6.6.4 Other Adverse Event Safety Endpoint

6.6.4.1 Adverse Events with an Outcome of Death throughout the trial

AEs with an outcome of death are those events which are recorded as "Fatal" on the AE page of the eCRF.

A listing of all AEs with an outcome of death will be provided.

6.6.4.2 Unsolicited Adverse Events of Hypersensitivity

A summary of hypersensitivity AEs (refer to APPENDIX 9.2.6 for the list of SMQs) by PT throughout the trial will be presented. Should a subject experience multiple events within a PT, the subject will be counted only once for that PT.

A listing of all hypersensitivity AEs will be provided.

6.6.4.3 Related Unsolicited Adverse Events of Hypersensitivity

A summary of related hypersensitivity AEs by PT throughout the trial will be presented. Should a subject experience multiple events within a PT, the subject will be counted only once for that PT.

A listing of all related hypersensitivity AEs will be provided.

6.6.5 Other Safety Analysis

6.6.5.1 Laboratory Evaluations

Clinical chemistry and hematology will be performed as per the schedule of events (refer to protocol Section 2.1). Table 6.d lists the clinical safety laboratory tests that will be performed.

Table 6.d Lists the Clinical Safety Laboratory Tests

Hematology	Blood Chemistry
Hemoglobin,	Alanine aminotransferase (ALT)
Hematocrit	Aspartate aminotransferase (AST)
Platelet count	Alkaline phosphatase (ALP)
Complete white blood cell count	Total bilirubin
Prothrombin time	Urea (blood urea nitrogen)
Partial thromboplastin time	Creatinine
	Lipase

Quantitative laboratory parameters reported as "<X", ie, below the lower limit of quantification (BLOQ) or ">X", ie, above the upper limit of quantification (ULOQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, ie, as "<X" or ">X" in the listings.

The following summaries will be provided based on the Safety Analysis Set for each of blood chemistry and hematology laboratory parameter:

- Observed and change from baseline in Standard International (SI) units by visit;
- Categorical value according to FDA grading guidance (FDA 2007) toxicity grades (for quantitative parameters with available FDA toxicity grades; refer to APPENDIX 9.2.5) by visit;
- A listing of subjects with at least one observed value in alanine aminotransferase (ALT) value ≥3 x upper limit of normal (ULN) or aspartate aminotransferase (AST) value ≥3 x ULN together with total bilirubin value ≥2 x ULN will be provided.

Serology, pregnancy, and urine drug screen data will not be summarized

All laboratory data excluding urine drug screen data will be listed.

6.6.5.1.1 Laboratory Toxicity Grades

Quantitative laboratory parameters with available FDA toxicity grades will be categorized as follows where higher grades representing a more severe toxicity (refer to APPENDIX 9.2.5 for each parameter toxicity grade criteria). FDA grading will be categorized for laboratory parameters listed in Table 6.d:

- Grade 1 (ie, mild);
- Grade 2 (ie, moderate);
- Grade 3 (ie, severe);
- Grade 4 (ie, potentially life-threatening)

Although not defined in the FDA toxicity grading system, non-missing laboratory parameter results not meeting any of the 4 grades defined in the FDA toxicity grading system will be categorized as 'No Toxicity'.

6.6.5.2 Vital Sign Measurements

The following vital sign parameters will be collected for this study as per the schedule of events (refer to protocol Section 2.1):

- Systolic blood pressure (SBP) (mmHg).
- Diastolic blood pressure (DBP) (mmHg).
- Pulse rate (beats per minute [bpm]).
- Body temperature (°C).
- Respiratory rate (beats per minute [bpm]).

The following summaries will be provided based on the Safety Analysis Set for all scheduled visits.

- Observed and change from baseline by visit;
- Categorical value according to FDA grading guidance (FDA 2007) toxicity grades (for quantitative parameters with available FDA toxicity grades; refer to APPENDIX 9.2.5) by visit.

A listing of all vital sign data will also be provided.

6.6.5.2.1 Vital Sign Toxicity Grades

Vital sign toxicity grades will be performed the same analysis of laboratory toxicity grades, as Section 6.6.5.1.1. But Grade 4 is considered only for Fever due to the limited data collection.

6.6.6 Extent of Exposure and Compliance

6.6.6.1 Exposure to Study Intervention

Due to the simplicity of dosing for this study, exposure is summarized in the Disposition table. No other summary will be reported. A listing will provide exposure information for all subjects in the Safety Analysis Set.

Report of overdose and medication error, if any, will be listed for the Safety Analysis Set.

6.6.6.2 Compliance with Study Intervention

Compliance will not be calculated since subjects are vaccinated within at most twice.

6.6.7 Subgroup Analyses

Perform subgroup analyses on the items described in Section 6.6.2.

The subgroup is:

- Age group (years): 20 ≤ <65 and ≥65
- Sex: Male, Female

6.7 Interim Analyses

An interim analysis is not planned in the trial.

The primary analysis will be performed for safety and immunogenicity after all subjects have completed the Day 50 visit. After the primary analysis, the trial will be unblinded only for the Sponsor personnel. After the database lock of the primary analysis (ie, Day 50 data), the trial will be unblinded and changed to an Open-Label study.

7.0 REFERENCES

1. Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007 [cited 10 Apr 2020] [10 screens]. Available from: https://www.fda.gov/media/73679/download/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf
2. Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events. July 2017 [cited 01 Apr 2020]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not Applicable.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Not Applicable.

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

9.2.1.1 Partial Date Conventions

Start Date	Stop Date	Action
Known or before	Known or ongoing	If medication stop date < study intervention start date, assign as prior; If medication start date < study intervention start date and (medication stop date ≥ study intervention start date or medication is ongoing at study intervention start date), assign as concomitant; If study intervention start date ≤ medication start date, assign as concomitant.
	Partial	If known components of medication stop date show that medication stopped before study intervention start date, assign as prior; If medication start date < study intervention start date and (known components of medication stop date show that medication stopped on or after study intervention start date), assign as concomitant; If study intervention start date ≤ medication start date, assign as concomitant.
	Missing, not ongoing	If medication stop date is missing, then it can never be assigned as prior only; If medication start date < study intervention start date, assign as concomitant; If study intervention start date ≤ medication start date, assign as concomitant.
Partial	Known or ongoing	If medication stop date <study intervention start date, assign as prior; If (known components of medication start date show that medication started before study intervention start date) and (medication stop date ≥ study intervention start date or medication is ongoing at study intervention start date), assign as concomitant; If known components of medication start date show that medication started on or after study intervention start date, assign as concomitant.

Start Date	Stop Date	Action
	Partial	If known components of medication stop date show that medication stopped before study intervention start date, assign as prior; If (known components of medication start date show that medication started before study intervention start date) and (known components of medication stop date show that medication stopped on or after study intervention start date), assign as concomitant; If known components of medication start date show that medication started on or after study intervention start date, assign as concomitant.
	Missing, not ongoing	Cannot be assigned as prior only; If known components of medication start date show that medication started before study intervention start date, assign as concomitant; If known components of medication start date show that medication started on or after study intervention start date, assign as concomitant.
Missing	Known or ongoing	If medication stop date < study intervention start date, assign as prior; If medication stop date >= study intervention start date or medication is ongoing at study intervention start date, assign as concomitant.
	Partial	If known components of medication stop date show that medication stopped before study intervention start date, assign as prior; If known components of medication stop date show that medication stopped on or after study intervention start date, assign as concomitant.
	Missing, not ongoing	Assign as concomitant.

9.2.2 Definition of Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the first dose of study intervention (including unscheduled assessments). In the case where the last non-missing measurement and the date and time of the first dose of study intervention coincide, that measurement will be considered pre-baseline, but AEs and medications commencing on the date of the first dose of study intervention will be considered post-baseline.

9.2.3 Unscheduled Visits, and Early Termination Data

For by-visit summaries, data recorded at the nominal visit will be presented. That is, unscheduled, and early termination measurements will not be included in by-visit summaries but might contribute to the baseline timepoint and/or maximum value, where required (eg, shift table). An exception to this rule applies to immunogenicity analysis as stated in Section 9.2.4.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

9.2.4 Definition of Visit Windows

A windowing convention will be used to determine the analysis value for a given study visit for immunogenicity data analyses. The date will be used eCRF data.

The window conventions are:

Table 9.a Analysis Windows for Immunogenicity by Visit

Dosing Period	Visit	Day Relative to Dose within the Dosing Period [b]	Visit Window (Study Day) Relative to the Dosing Period
Period 1 (Relative to Dose 1)	Baseline [a]	≤1	≤1
	Day 22	22	15 - 29
Period 2 (Relative to Dose 2)	Day 36	15	8 - 21
	Day 50	29	22 - 150
	Day 202	181	151 - 335
	Day 387	366	336 - 396

(a) Where time is available, the time of the collection must be prior to the first dose of study intervention. Day 1 observations taken after the first dose are considered post-baseline values.

(b) For each dosing period, the administration of the study intervention is designated as Study Day 1. For analyses within a period, the study day value is incremented by 1 for each date following the vaccine administration.

One or more results for a particular immunogenicity variable may be obtained in the same visit window. In such an event, the result with the date closest to the expected visit date will be used in the analysis. In the event that two observations are equidistant from the expected visit date, the later observation will be used in the analysis.

Beside the immunogenicity analyses, no visit windowing will be performed for analysis of other variables in this study.

9.2.5 Tables for Laboratory and Vital Sign Abnormalities

The laboratory and vital sign values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate. For Vital Sign grading, Grade 4 is considered only for Fever due to the limited data collection.

Vital Signs *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***"ULN" is the upper limit of the normal range.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

9.2.6 Tables for Unsolicited Adverse Events of Hypersensitivity

Hypersensitivity are defined by the narrow terms pertaining to hypersensitivity SMQs.

9.3 Programming Conventions for Output

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-dd hh:mm:ss.

Spelling Format

English US.

Paper size, Orientation, and Margins

The size of paper will be A4 and the page orientation will be landscape. Margins will provide at least 1 inch (2.54 centimeters) of white space all around the page.

Fonts

The font type 'Courier New' will be used, with a font size of 8. The font color will be black with no bolding, underlining, italics or subscripting.

Presentation of Treatment Groups

For outputs, treatment groups will be represented as follows and in the given order:

Treatment Group	Tables and Graphs	Listings
Placebo	1	1
TAK-019	2	2
Randomized, Not Vaccinated	N/A	3
Screen Failure	N/A	4

Presentation of Nominal visits

For outputs, analysis visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Scrn
Baseline	Base
Day 1	D1
Day 8	D8
Day 22	D22
Day 36	D36
Day 50	D50
Day 202	D202
Day 387	D387

Descriptive Statistics

If the original data has N decimal places, then the summary statistics will have the following decimal places:

- Minimum, maximum and lower and upper bounds of two-sided 95% CI for percentages: N;
- Mean (including GMT and GMFR), median, lower and upper bounds of two-sided 95% CI for GMT/GMFR: N + 1;
- SD: N + 2.

Percentages

Percentages will be reported to one decimal place. Rounding will be applied, except for percentages <0.1 but >0.0 which will be presented as '<0.1', percentages <100.0 but >99.9 which will be presented as '>99.9' and the percentage equals exactly 100 where it shall be displayed as an integer (100).

Where counts are zero, no percentages will appear in the output.

P-values

p-values will be reported to three decimal places. Rounding will be applied, except for the p-values <0.001 which will be presented as '<0.001' and p-values <1.000 but >0.999 which will be presented as '>0.999'.

Listings

All listings will be ordered by the following (unless otherwise indicated in the output template):

- Randomized treatment group (or treatment received if it's a safety output);
- Subject ID;
- Parameter, when applicable;
- Date/Time, when applicable.
- Timepoint, when applicable.

9.4 Analysis Software

All analyses will be conducted using SAS version 9.4 or higher.