Title: A Phase 1/2, Randomized, Observer-Blind, Placebo-Controlled Trial to Evaluate the Safety and Immunogenicity of TAK-919 by Intramuscular Injection in Healthy Japanese Male and Female Adults Aged 20 Years and Older

NCT Number: NCT04677660

Statistical analysis plan Approve Date: 19-Mar-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-919-1501*

Study Title: A Phase 1/2, Randomized, Observer-Blind, Placebo-Controlled Trial to Evaluate the Safety and Immunogenicity of TAK-919 by Intramuscular Injection in Healthy Japanese Male and Female Adults Aged 20 Years and Older

Phase: *1/2*

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Prepared by:

[redacted]

[redacted]

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REVISION HISTORY

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

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ABBREVIATIONS

AE	adverse event
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
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
nAb	neutralizing antibody
PPS	per-protocol analysis set
PT	Preferred Term (MedDRA)
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
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

To evaluate the safety and immunogenicity of 2 doses of TAK-919 by intramuscular (IM) injection in healthy Japanese male and female adults aged ≥ 20 years, given 28 days apart.

Safety:

To assess the safety of TAK-919 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 28 days following each vaccination (day of vaccination +27 subsequent days).*
- *Serious adverse events (SAEs), 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 57.*

Immunogenicity:

To assess the immunogenicity of TAK-919 in terms of:

- *Serum binding antibody (bAb) levels against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 spike (S) protein on Day 57.*

1.1.2 Secondary Objective(s)

Safety:

To assess the safety of TAK-919 in terms of:

- *SAEs, 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-919 in terms of:

- *Serum bAb levels against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 S protein on Day 29, Day 43, Day 209, and Day 394.*
- *Serum neutralizing antibody (nAb) titers against SARS-CoV-2 as measured by assay specific to wild-type virus on Day 29, Day 43, Day 57, Day 209, and Day 394.*

1.1.3 Exploratory Objectives

Immunogenicity:

To assess the immunogenicity of TAK-919 in terms of:

- *Serum nAb levels against SARS-CoV-2 as measured by pseudovirus neutralization assays on Day 29, Day 43, Day 57, Day 209, and Day 394.*

Post hoc exploratory immunogenicity data such as serum bAb levels against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 nucleocapsid protein may be generated using the residual of serum samples.

1.2 Endpoints

1.2.1 Primary Endpoint(s)

Safety:

- *Percentage of subjects with reported solicited local AEs: injection site pain, erythema/redness, swelling, induration, and lymphadenopathy (axillary (underarm) swelling or tenderness ipsilateral to the side of injection) for 7 days following each vaccination (day of vaccination + 6 subsequent days).*
- *Percentage of subjects with solicited systemic AEs: headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, and fever for 7 days following each vaccination (day of vaccination + 6 subsequent days).*
- *Percentage of subjects with unsolicited AEs for 28 days after each vaccination.*
- *Percentage of subjects with SAE until Day 57.*
- *Percentage of subjects with MAAEs until Day 57.*
- *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 57.*
- *Percentage of subjects with SARS-CoV-2 infection until Day 57.*

Immunogenicity:

- *Geometric mean titers (GMT), geometric mean fold rise (GMFR) and seroconversion rate (SCR; defined at percentage of subjects with a change from below the limit of detection (LOD) or the lower limit of quantification [LLOQ] to equal to or above LOD or LLOQ, OR, ≥ 4-fold rises from baseline) of serum bAb against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 S protein on Day 57.*

1.2.2 Secondary Endpoint(s)

Safety:

- *Percentage of subjects with SAE 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 and SCR of serum bAb against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 S protein on Day 29, Day 43, Day 209, and Day 394.*
- *GMT, GMFR and SCR (defined at percentage of subjects with a change from below the LOD or LLOQ to equal to or above LOD or LLOQ, OR, ≥ 4-fold rises from baseline) of serum nAb against SARS-CoV-2 as measured by assay specific to wild-type virus on Day 29, Day 43, Day 57, Day 209, and Day 394.*

1.2.3 Exploratory Endpoint(s)

- *GMT, GMFR and SCR (defined at percentage of subjects with a change from below LOD or LLOQ to equal to or above LOD or LLOQ, OR, ≥ 4-fold rises from baseline) of serum nAb against SARS-CoV-2 as measured by pseudovirus neutralization assays on Day 29, Day 43, Day 57, Day 209, and Day 394.*

Additional immunogenicity data such as serum bAb levels against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 nucleocapsid protein may be evaluated using the residual of serum samples.

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-919 by IM injection in healthy Japanese male and female adults, given 28 days apart.

The trial is planned to enroll 200 subjects (150 subjects in the TAK-919 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-919 arm and 40 subjects in the placebo arm), and 60 subjects will be stratified by age as ≥ 65 years (50 subjects in the TAK-919 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-919 or saline placebo by IM injection on Day 1, and receive the second dose of TAK-919 or saline placebo after 28 days of the first vaccination (Day 29). All subjects will be followed up for safety and immunogenicity for 12 months after the last trial vaccination.

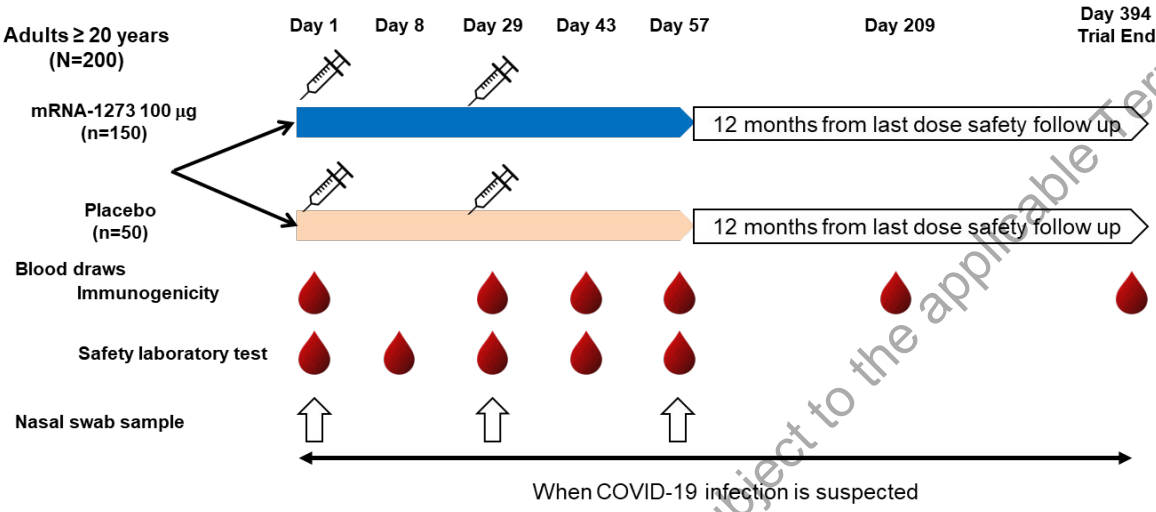
Each subject will be provided with an electronic diary (eDiary). Oral body temperature, and solicited local and systemic AEs will be recorded in the eDiary by the subjects for 7 days after each vaccination (including the day of vaccination). All subjects will be followed for unsolicited AEs for 28 days following each vaccination (day of vaccination +27 subsequent days). All subjects will be followed for SAEs, MAAEs, and AEs leading to trial withdrawal or discontinuation of dosing during the trial. All subjects will also be tested for SARS-CoV-2 infection at prespecified time points (Day 1, Day 29, Day 57) and in case of suspected for COVID-19 clinical symptoms throughout the trial.

The primary analysis will be performed for safety and immunogenicity after all subjects have completed the Day 57 visit. After the primary analysis, the trial will be unblinded for Sponsor personnel. The Investigator, site staff and subjects will remain blinded to the investigational medicinal product (IMP) for 12 months after the last trial vaccination.

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-919 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-919 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-919".

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 57

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 and SCR 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. Same manner is applied for LOD. 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 28 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)
- Seropositive status at baseline determined by serologic titer against SARS-CoV-2 nucleocapsid (Seronegative at baseline is defined as below limit of detection [LOD] or lower limit of quantification [LLOQ]) at Day 1. Seropositive at baseline is defined as equal to or above LOD or LLOQ at Day 1): Positive, Negative

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) and seroconversion rate (SCR; defined at percentage of subjects with a change from below the limit of detection (LOD) or the limit of quantification (LLOQ) to equal to or above LOD or LLOQ, OR, ≥ 4-fold rises from baseline) of serum bAb against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 S protein on Day 57.

6.5.1.1 Derivation of Endpoint(s)

Analyses will be conducted using the PPS and FAS.

SCR at Day 57 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 57 will be calculated in each treatment group.

6.5.1.2 Main Analytical Approach

6.5.1.2.1 Seroconversion Rate

Seroconversion is a binary outcome where a success is when subjects with a change from below the LOD or LLOQ to equal to or above LOD or LLOQ, OR, ≥4-fold rises from baseline.

The number and proportion of subjects who have a seroconversion at Day 57 will be summarized for each treatment group. The summary will also include the 95% CI of the proportion of subjects achieving seroconversion at Day 57, calculated based on the Clopper-Pearson method. The number and percentage of subjects with fold-rise ≥ 2, fold-rise ≥3, and fold- rise ≥4 from baseline will be summarized with 95% CI calculated based on the Clopper-Pearson method.

6.5.1.2.2 GMT and GMFR

GMT and GMFR will be calculated and will be summarized at Day 57.

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), i.e., 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 and SCR of serum bAb against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 S protein on Day 29, Day 43, Day 209, and Day 394.*
- *GMT, GMFR and SCR (defined at percentage of subjects with a change from below LLOQ to equal to or above LLOQ, OR, ≥ 4-fold rises from baseline) of serum nAb against SARS-CoV-2 as measured by assay specific to wild-type virus on Day 29, Day 43, Day 57, Day 209, and Day 394.*

6.5.2.1 Derivation of Endpoint(s)

Analyses will be conducted using the PPS and FAS.

Seroconversion rate 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

Seroconversion of serum bAb against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 S protein is defined in Section 6.5.1.2.1.

Seroconversion of serum nAb against SARS-CoV-2 as measured by assay specific to wild-type virus is defined is a binary outcome where a success is when subjects with a change from below LOD or LLOQ to equal to or above LOD or LLOQ, OR, ≥ 4-fold rises from baseline.

SCR 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. The number and percentage of subjects with fold-rise ≥ 2, fold-rise ≥3, and fold- rise ≥4 from baseline at Day 29 and Day 57 will be summarized with 95% CI calculated based on the Clopper-Pearson method.

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.

6.5.2.2.3 Mixed Model For Repeated Measures (MMRM)

The following analysis is performed only for bAb against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 S protein.

Mixed Effect Model for longitudinal data with fold increase from baseline in log transformed anti-body titers as dependent variable, and treatment groups, visit, treatment-by-visit, age group, and baseline log-transformed anti-body titers as independent variables and subject as a random effect. This analysis will be performed only when the proportion of subjects whose value of immunogenicity is LLOQ is less than 50% at any visit and any treatment group.

An unstructured covariance structure will be used to model the within-subject errors. A Kenward-Roger approximation will be used for the denominator degrees of freedom. If there is a convergence issue due to the unstructured covariance matrix, a compound symmetry covariance structure will be used to model the within-subject errors.

The geometric least squares mean (GLSM) and corresponding 2-sided 95% CI for the antibody titers for each treatment group will be provided by visit.

In addition, the ratio of GLSM and the corresponding 2-sided 95% CI will be provided to assess the treatment difference (TAK-919 vs. Placebo) at each visit. The GLSM, and corresponding 95% CI results in log transformed scale estimated from the model will be back transformed to obtain these estimates in the original scale. Geometric mean ratio (GMR), estimated by the ratio of GLSM and the corresponding 2 sided 95% CI will be provided to assess the treatment difference between TAK-919 group vs. placebo group at each visit.

6.5.3 Exploratory Endpoints Analysis

- *GMT, GMFR and SCR (defined at percentage of subjects with a change from below LOD or LLOQ to equal to or above LOD or LLOQ, OR, ≥ 4-fold rises from baseline) of serum nAb against SARS-CoV-2 as measured by pseudovirus neutralization assays on Day 29, Day 43, Day 57, Day 209, and Day 394.*

6.5.3.1 Derivation of Endpoint(s)

Analyses will be conducted using the PPS and FAS.

Seroconversion rate 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.

6.5.3.2 Main Analytical Approach

6.5.3.2.1 Seroconversion Rate

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

6.5.3.2.2 GMTs and GMFRs

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

6.5.3.3 Assessment of the potential relationship between serum bAb antibody against SARS-CoV-2 and serum nAb antibody against SARS-CoV-2

Spearman's rank correlation and Scatter plot for common log transformed serum bAb antibody titer and common log transformed serum nAb antibody titer will be provided using PPS by each Visit by Treatment group and age group.

6.5.4 Subgroup Analyses

Perform subgroup analyses on the items described in Section 6.5.1, Section 6.5.2.2.1 and Section 6.5.2.2.2. Subgroup analyses will be conducted using the PPS.

The subgroup is:

- Age group (years): 20 $<$ 65 and $\geq$ 65
- Sex: Male, Female
- Seropositive status at baseline determined by serologic titer against SARS-CoV-2 nucleocapsid (Seronegative at baseline is defined as below limit of detection [LOD] or lower limit of quantification [LLOQ]) at Day 1. Seropositive at baseline is defined as equal to or above LOD or LLOQ at Day 1): Positive, Negative

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, erythema/redness, swelling, induration, and* lymphadenopathy (*axillary (underarm) swelling or tenderness ipsilateral to the side of injection*) *for 7 days following each vaccination (day of vaccination + 6 subsequent days).*
- *Percentage of subjects with solicited systemic AEs: headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills and fever for 7 days following each vaccination (day of vaccination + 6 subsequent days).*
- *Percentage of subjects with unsolicited AEs for 28 days after each vaccination.*
- *Percentage of subjects with SAE until Day 57.*
- *Percentage of subjects with MAAEs until Day 57.*
- *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 57.*
- *Percentage of subjects with SARS-CoV-2 infection until Day 57.*

The secondary safety endpoints are:

- *Percentage of subjects with SAE 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 10.2. 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
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
Lymphadenopathy (Axillary swelling or tenderness at the same side of injection site)	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
Solicited Systemic AEs				
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
Fatigue	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, requires outpatient intravenous hydration	Emergency room visit or hospitalization for hypotensive shock
Chills	No interference with activity	Some interference with activity, but no treatment required	Prevents daily activity or treatment required	Emergency room visit or hospitalization
Fever [b]	38.0°C – 38.4°C	38.5°C – 38.9°C	39.0°C – 40.0°C	> 40.0°C

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

a In addition to grading the measure 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 plus 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 (e.g., 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 28 Days After Each 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 each dose for 28 days post each dose of study intervention.

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 28 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 listing of all unsolicited AEs will be provided.

6.6.2.3 Occurrence of Serious AEs Until Day 57

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 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 Medically-Attended Adverse Events Until Day 57

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 28 days interval post each dose (based on the start date of the event).

A listing of all MAAEs will be provided.

6.6.2.5 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 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.

6.6.2.6 AEs Leading to Subject's Withdrawal From the Trial Until Day 57

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 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.

6.6.2.7 SARS-CoV-2 Infection Until Day 57.

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 testing of SARS-CoV-2 infection is considered as having SARS-CoV-2 infection.

A listing of the PCR 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 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.

6.6.3.3 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.

6.6.3.4 This analysis will be conducted only at the Final analysis. 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 6.6.2.7.

A subject who is found to be positive to COVID-19 based on the PCR testing of SARS-CoV-2 infection or seroconversion in serum bAb levels against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 nucleocapsid protein is considered as having SARS-CoV-2 infection.

Seroconversion in serum bAb levels against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 nucleocapsid protein is defined differently for participants who were seropositive or seronegative at baseline as below:

• Participants seronegative at Baseline (below limit of detection [LOD] or lower limit of quantification [LLOQ] in serum bAb levels against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 nucleocapsid protein): seropositive as measured by serum bAb levels against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 nucleocapsid protein on study

• Participants seropositive at Baseline: 4-fold or more increase in serum bAb levels against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 nucleocapsid protein

A listing of the PCR testing of SARS-CoV-2 infection and subjects who seroconversion subjects 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.b lists the clinical safety laboratory tests that will be performed.

Table 6.b Lists the Clinical Safety Laboratory Tests

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

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

- Grade 1 (i.e., mild);
- Grade 2 (i.e., moderate);
- Grade 3 (i.e., severe)
- Grade 4 (i.e., 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 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): $20 \leq < 65$ and ≥ 65
- Sex: Male, Female
- Seropositive status at baseline determined by serologic titer against SARS-CoV-2 nucleocapsid (Seronegative at baseline is defined as below limit of detection [LOD] or lower limit of quantification [LLOQ]) at Day 1. Seropositive at baseline is defined as equal to or above LOD or LLOQ at Day 1) : Positive, Negative

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 57 visit. After the primary analysis, the trial will be unblinded only for the

Sponsor personnel. The Investigator, site staff and subjects will remain blinded to the IMP until trial end (Day 394).

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

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

The definition of Seroconversion Rate for serum bAb against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 S protein

Before the change

Seroconversion of serum bAb against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 S protein is defined is a binary outcome where a success is when subjects with a change from below LOD to equal to or above LOD, OR, ≥ 4-fold rises from baseline.

After the change

Seroconversion of serum bAb against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 S protein is defined is a binary outcome where a success is when subjects with a change from below LOD or LLOQ to equal to or above LOD or LLOQ, OR, ≥ 4-fold rises from baseline.

Reason for the change

According to the immunogenicity data to be reported from serology laboratories, the definition of SCR was updated to ‘the percentage of subjects with a change from below the limit of detection [LOD] or the lower limit of quantification [LLOQ] to equal to or above LOD or LLOQ, OR, ⩾ 4-fold rises from baseline’

The definition of Seroconversion Rate for serum nAb against SARS-CoV-2 as measured by assay specific to wild-type virus

Before the change

Seroconversion of serum nAb against SARS-CoV-2 as measured by assay specific to wild-type virus is defined is a binary outcome where a success is when subjects with a change from below LLOQ to equal to or above LLOQ, OR, ≥ 4-fold rises from baseline.

After the change

Seroconversion of serum nAb against SARS-CoV-2 as measured by assay specific to wild-type virus is defined is a binary outcome where a success is when subjects with a change from below LOD or LLOQ to equal to or above LOD or LLOQ, OR, ≥ 4-fold rises from baseline.

Reason for the change

According to the immunogenicity data to be reported from serology laboratories, the definition of SCR was updated to ‘the percentage of subjects with a change from below the limit of detection [LOD] or the lower limit of quantification [LLOQ] to equal to or above LOD or LLOQ, OR, ⩾ 4-fold rises from baseline’

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.

Start Date	Stop Date	Action
	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.
	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.

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 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 (e.g. 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:

1. A window of +/- 7 days from the target day is applied to the following visits: Study Days 29, 43, 57 (for Day 29, the date and time of second dose of study intervention can be used as upper bound);

2. A window of +/- 30 days from the target day is applied to the following visits: Study Day 209 and Day 394;

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 29	29	22 - 36
Period 2 (Relative to Dose 2)	Day 43	15	8 - 21
	Day 57	29	22 - 105
	Day 209	181	106 - 273
	Day 394	366	274 - 380

(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 in the tables below for a full list of preferred terms.

PT Code	PT Term(English)
10081035	Acquired C1 inhibitor deficiency
10048799	Acute generalised exanthematous pustulosis
10069773	Administration related reaction
10075096	Administration site dermatitis
10075099	Administration site eczema
10075102	Administration site hypersensitivity
10071156	Administration site rash
10075964	Administration site recall reaction
10075109	Administration site urticaria
10075969	Administration site vasculitis
10052613	Allergic bronchitis

PT Code	PT Term(English)
10059447	Allergic colitis
10053779	Allergic cough
10051394	Allergic cystitis
10075185	Allergic eosinophilia
10075308	Allergic gastroenteritis
10071198	Allergic hepatitis
10057380	Allergic keratitis
10060934	Allergic oedema
10075072	Allergic otitis externa
10061557	Allergic otitis media
10050639	Allergic pharyngitis
10078853	Allergic reaction to excipient
10063532	Allergic respiratory disease
10063527	Allergic respiratory symptom
10049153	Allergic sinusitis
10079554	Allergic stomatitis
10066173	Allergic transfusion reaction
10075479	Allergy alert test positive
10056352	Allergy test positive
10074079	Allergy to immunoglobulin therapy
10077279	Allergy to surgical sutures
10055048	Allergy to vaccine
10078682	Anal eczema
10002198	Anaphylactic reaction
10002199	Anaphylactic shock
10067113	Anaphylactic transfusion reaction
10002216	Anaphylactoid reaction
10063119	Anaphylactoid shock
10002222	Anaphylaxis treatment
10002424	Angioedema

PT Code	PT Term(English)
10064059	Antiallergic therapy
10065514	Antiendomysial antibody positive
10050894	Anti-neutrophil cytoplasmic antibody positive vasculitis
10003036	Application site dermatitis
10050099	Application site eczema
10063683	Application site hypersensitivity
10003054	Application site rash
10076024	Application site recall reaction
10050104	Application site urticaria
10076027	Application site vasculitis
10061430	Arthritis allergic
10075084	Aspirin-exacerbated respiratory disease
10081492	Atopic cough
10003645	Atopy
10005149	Blepharitis allergic
10005589	Blood immunoglobulin E abnormal
10005591	Blood immunoglobulin E increased
10006404	Bromoderma
10006482	Bronchospasm
10083809	Bullous haemorrhagic dermatosis
10073992	Catheter site dermatitis
10073995	Catheter site eczema
10073998	Catheter site hypersensitivity
10052271	Catheter site rash
10052272	Catheter site urticaria
10074014	Catheter site vasculitis
10071399	Chronic eosinophilic rhinosinusitis
10071380	Chronic hyperplastic eosinophilic sinusitis
10009192	Circulatory collapse
10052250	Circumoral oedema

PT Code	PT Term(English)
10081703	Circumoral swelling
10010726	Conjunctival oedema
10010744	Conjunctivitis allergic
10067510	Contact stomatitis
10066973	Contrast media allergy
10010836	Contrast media reaction
10011033	Corneal oedema
10011686	Cutaneous vasculitis
10062918	Dennie-Morgan fold
10012431	Dermatitis
10012432	Dermatitis acneiform
10012434	Dermatitis allergic
10012438	Dermatitis atopic
10012441	Dermatitis bullous
10012442	Dermatitis contact
10012455	Dermatitis exfoliative
10012456	Dermatitis exfoliative generalised
10012468	Dermatitis herpetiformis
10012470	Dermatitis infected
10058675	Dermatitis psoriasiform
10072867	Device allergy
10076665	Dialysis membrane reaction
10070559	Distributive shock
10076470	Documented hypersensitivity to administered product
10013687	Drug eruption
10013700	Drug hypersensitivity
10074350	Drug provocation test
10073508	Drug reaction with eosinophilia and systemic symptoms
10014184	Eczema
10014198	Eczema infantile

PT Code	PT Term(English)
10014201	Eczema nummular
10066042	Eczema vaccinatum
10058681	Eczema vesicular
10055182	Eczema weeping
10056387	Encephalitis allergic
10014627	Encephalopathy allergic
10078117	Eosinophilic granulomatosis with polyangiitis
10059284	Epidermal necrosis
10053177	Epidermolysis
10014989	Epidermolysis bullosa
10015029	Epiglottic oedema
10015218	Erythema multiforme
10015226	Erythema nodosum
10064579	Exfoliative rash
10015907	Eye allergy
10052139	Eye oedema
10015967	Eye swelling
10015993	Eyelid oedema
10016029	Face oedema
10016741	Fixed eruption
10018258	Giant papillary conjunctivitis
10049305	Gingival oedema
10018291	Gingival swelling
10066837	Gleich's syndrome
10059499	Haemorrhagic urticaria
10058898	Hand dermatitis
10019617	Henoch-Schonlein purpura
10069440	Henoch-Schonlein purpura nephritis
10062506	Heparin-induced thrombocytopenia
10019860	Hereditary angioedema

PT Code	PT Term(English)
10080955	Hereditary angioedema with C1 esterase inhibitor deficiency
10020751	Hypersensitivity
10081004	Hypersensitivity myocarditis
10081988	Hypersensitivity pneumonitis
10020764	Hypersensitivity vasculitis
10021247	Idiopathic urticaria
10067142	Immediate post-injection reaction
10083842	Immune thrombocytopenia
10070581	Immune tolerance induction
10063855	Implant site dermatitis
10063858	Implant site hypersensitivity
10063786	Implant site rash
10063787	Implant site urticaria
10073168	Incision site dermatitis
10073411	Incision site rash
10082742	Infusion related hypersensitivity reaction
10051792	Infusion related reaction
10065458	Infusion site dermatitis
10074850	Infusion site eczema
10065471	Infusion site hypersensitivity
10059830	Infusion site rash
10076085	Infusion site recall reaction
10065490	Infusion site urticaria
10074851	Infusion site vasculitis
10071152	Injection related reaction
10022056	Injection site dermatitis
10066221	Injection site eczema
10022071	Injection site hypersensitivity
10022094	Injection site rash

PT Code	PT Term(English)
10066797	Injection site recall reaction
10022107	Injection site urticaria
10067995	Injection site vasculitis
10073612	Instillation site hypersensitivity
10073622	Instillation site rash
10073627	Instillation site urticaria
10067972	Interstitial granulomatous dermatitis
10076229	Intestinal angioedema
10052098	Iodine allergy
10051891	Kaposi's varicelliform eruption
10069167	Kounis syndrome
10023845	Laryngeal oedema
10064866	Laryngitis allergic
10023891	Laryngospasm
10023893	Laryngotracheal oedema
10070492	Limbal swelling
10024558	Lip oedema
10024570	Lip swelling
10076606	Mast cell degranulation present
10075572	Medical device site dermatitis
10075575	Medical device site eczema
10075579	Medical device site hypersensitivity
10075585	Medical device site rash
10076140	Medical device site recall reaction
10075588	Medical device site urticaria
10075203	Mouth swelling
10056671	Mucocutaneous rash
10028164	Multiple allergies
10029120	Nephritis allergic
10029415	Nikolsky's sign

PT Code	PT Term(English)
10075807	Nodular rash
10084049	Nutritional supplement allergy
10030081	Oculomucocutaneous syndrome
10067317	Oculorespiratory syndrome
10030110	Oedema mouth
10068355	Oral allergy syndrome
10067950	Oropharyngeal blistering
10078783	Oropharyngeal oedema
10031111	Oropharyngeal spasm
10031118	Oropharyngeal swelling
10056998	Palatal oedema
10074403	Palatal swelling
10068809	Palisaded neutrophilic granulomatous dermatitis
10056872	Palpable purpura
10074332	Pathergy reaction
10034541	Perioral dermatitis
10034545	Periorbital oedema
10056647	Periorbital swelling
10034829	Pharyngeal oedema
10082270	Pharyngeal swelling
10080894	Procedural shock
10063438	Pruritus allergic
10037789	Radioallergosorbent test positive
10037844	Rash
10037855	Rash erythematous
10037857	Rash follicular
10037867	Rash macular
10037868	Rash maculo-papular
10050004	Rash maculovesicular
10037870	Rash morbilliform

PT Code	PT Term(English)
10037871	Rash neonatal
10037879	Rash papulosquamous
10037884	Rash pruritic
10037888	Rash pustular
10057984	Rash rubelliform
10037890	Rash scarlatiniform
10037898	Rash vesicular
10037973	Reaction to azo-dyes
10037974	Reaction to colouring
10079925	Reaction to excipient
10037977	Reaction to food additive
10064788	Reaction to preservatives
10038192	Red man syndrome
10039085	Rhinitis allergic
10057431	Scleral oedema
10051126	Scleritis allergic
10083260	Scrotal dermatitis
10039755	Scrotal oedema
10040400	Serum sickness
10040402	Serum sickness-like reaction
10040560	Shock
10040581	Shock symptom
10083164	SJS-TEN overlap
10040893	Skin necrosis
10040914	Skin reaction
10040934	Skin test positive
10041307	Solar urticaria
10041316	Solvent sensitivity
10042033	Stevens-Johnson syndrome
10074509	Stoma site hypersensitivity

PT Code	PT Term(English)
10059071	Stoma site rash
10042682	Swelling face
10042690	Swelling of eyelid
10042727	Swollen tongue
10078325	Symmetrical drug-related intertriginous and flexural exanthema
10079645	Therapeutic product cross-reactivity
10043967	Tongue oedema
10044223	Toxic epidermal necrolysis
10057970	Toxic skin eruption
10044296	Tracheal oedema
10045240	Type I hypersensitivity
10054000	Type II hypersensitivity
10053614	Type III immune complex mediated reaction
10053613	Type IV hypersensitivity reaction
10046735	Urticaria
10046740	Urticaria cholinergic
10052568	Urticaria chronic
10046742	Urticaria contact
10046750	Urticaria papular
10046751	Urticaria physical
10046752	Urticaria pigmentosa
10046755	Urticaria vesiculosa
10082290	Urticarial dermatitis
10048820	Urticarial vasculitis
10069477	Vaccination site dermatitis
10076161	Vaccination site eczema
10069489	Vaccination site exfoliation
10068880	Vaccination site hypersensitivity
10069482	Vaccination site rash
10076188	Vaccination site recall reaction

PT Code	PT Term(English)
10069622	Vaccination site urticaria
10076191	Vaccination site vasculitis
10069623	Vaccination site vesicles
10046943	Vaginal ulceration
10047111	Vasculitic rash
10081000	Vernal keratoconjunctivitis
10077117	Vessel puncture site rash
10077813	Vessel puncture site vesicles
10066273	Vulval eczema
10047768	Vulval ulceration
10071588	Vulvovaginal rash
10050181	Vulvovaginal ulceration
10080783	Vulvovaginitis allergic

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-919	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 29	D29
Day 43	D43
Day 57	D57
Day 209	D209
Day 394	D394

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.