Statistical Analysis Plan

NCT Number: NCT05299359

Title: A Phase 3, Single Arm, Open-Label Trial to Evaluate the Immunogenicity and Safety of a Single Heterologous Booster Vaccination of TAK-019 in Healthy Japanese Male and Female Adults Aged 20 Years and Older

Study Number: TAK-019-3001

Document Version and Date: Version 3.0 / 23-May-2023

Version Extension part 2.0 / 05-Dec-2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

Study Number: *TAK-019-3001*

Study Title: *A Phase 3, Single Arm, Open-Label Trial to Evaluate the Immunogenicity and Safety of a Single Heterologous Booster Vaccination of TAK-019 in Healthy Japanese Male and Female Adults Aged 20 Years and Older*

Phase: *3*

Version: *3.0*

Date: *23 May 2023*

Prepared by: [redacted]

Based on:

Protocol Version: *Amendment1*

Protocol Date: *29-July-2022*

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
[Original version]		[Not Applicable]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ANOVA	Analysis of Variance
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
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 immunogenicity and safety of a single heterologous booster vaccination of TAK-019 by IM injection in healthy Japanese male and female adults aged ⩾20 years.

Immunogenicity:

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

- *To assess non-inferiority of geometric mean titers (GMT) of neutralizing antibody titers to wild-type virus 14 days after a single booster vaccination (Day 15) compared with that observed 14 days after the second vaccination (Day 36) in Study TAK-019-1501.*

Safety:

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

- *Solicited local and systemic AEs for 7 days following booster vaccination (day of vaccination + 6 subsequent days).*
- *Unsolicited AEs for 28 days following booster vaccination (day of vaccination + 27 subsequent days).*
- *Serious adverse events (SAEs), adverse events of special interest (AESIs), medically attended AEs (MAAEs), AEs leading to trial withdrawal, and SARS-CoV-2 infection until Day 29.*

1.1.2 Secondary Objective(s)

Immunogenicity:

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

- *Serum immunoglobulin G (IgG) antibody levels to SARS-CoV-2 rS protein.*
- *Serum neutralizing antibody titers to the ancestral strain (wild-type virus).*

Safety:

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

- *SAEs, AESIs, MAAEs, AEs leading to trial withdrawal, and SARS-CoV-2 infection throughout the trial.*

1.1.3 Additional Objective(s)

1.1.3.1 [redacted]

[redacted]

1.2 Endpoints

1.2.1 Primary Endpoint(s)

Immunogenicity:

- *GMT ratio of neutralizing antibody titers to the ancestral strain (wild-type virus) on Day 15 after a single booster vaccination (14 days after the booster vaccination) compared with that observed on Day 36 (14 days after the second vaccination) in subjects from Study TAK-019-1501.*

Safety:

- *Percentage of subjects with reported solicited local AEs: injection site pain, tenderness, erythema/redness, induration, and swelling for 7 days following booster 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 booster vaccination (day of vaccination + 6 subsequent days).*
- *Percentage of subjects with unsolicited AEs for 28 days following booster vaccination (day of vaccination + 27 subsequent days).*
- *Percentage of subjects with SAEs until Day 29.*
- *Percentage of subjects with AESIs until Day 29.*
- *Percentage of subjects with MAAEs until Day 29.*
- *Percentage of subjects with any AEs leading to subject's withdrawal from the trial until Day 29.*
- *Percentage of subjects with SARS-CoV-2 infection until Day 29.*

1.2.2 Secondary Endpoint(s)

Immunogenicity:

- *GMT, geometric mean fold rise (GMFR), and seroconversion rate (SCR; defined at proportion of subjects with ≥4-fold rises from baseline [Day 1]) of serum IgG antibody levels to SARS-CoV-2 rS protein on Day 8, Day 15, Day 29, Day 91, Day 181, and Day 366.*
- *GMT, GMFR, and SCR of serum neutralizing antibody titers to the ancestral strain (wild-type virus) on Day 8, Day 15, Day 29, Day 91, Day 181, and Day 366.*

Safety:

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

1.2.3 [redacted]

[redacted]

1.3 Estimand(s)

Table 1.a Estimand Framework

Definition	The primary estimand is the vaccination effect of TAK-019 as a single heterologous booster vaccination compared to TAK-019 as primary vaccination in Healthy Japanese Male and Female Adults Aged 20 Years and Older who received planned vaccination appropriately.
Attribute	
Treatment	TAK-019 as single heterologous booster vaccination and TAK-019 as primary vaccination from historical 1501 study
Population	Healthy Japanese Male and Female Adults Aged 20 Years and Older (who meet inclusion/exclusion criteria)
Variable (or Endpoint)	serum neutralizing antibody titers to wild-type virus on Day 15 after single heterologous booster vaccination or on Day 36 after primary vaccination
Strategy for Addressing Intercurrent Event (IcE)	IcE1: Covid-19 infection Principal stratum strategy: antibody titers before Covid-19 infection is targeted variable. Subjects who developed a new positive PCR-confirmed SARS-CoV-2 infection occurring before primary immunogenicity sampling will be excluded from PPS. IcE2: Missed planned vaccination Principal stratum strategy: subjects who received the planned vaccination is targeted population. Subjects who missed planned vaccination will be excluded from PPS. IcE3: Usage of prohibited medications specified in the protocol Principal stratum strategy: subjects who received the TAK-019 only is targeted population. Subjects who received any other SARS-CoV-2 or other experimental novel coronavirus vaccine will be excluded from PPS. IcE4: Out of allowance of blood sampling for primary immunogenicity Principal stratum strategy: subjects who have appropriate immunogenicity data is targeted population. Subjects whose blood sampling date for primary immunogenicity (3001 study: on Day 15, 1501 study: on Day 36) is out of allowance will be excluded from PPS.
Population-Level Summary	Ratio in GMT of the variable between study groups

2.0 STUDY DESIGN

This is a phase 3, single arm, open-label trial to evaluate the immunogenicity and safety of a single heterologous booster vaccination of TAK-019 by IM injection in healthy Japanese male and female adults who completed 2 doses primary vaccinations with COMIRNATY intramuscular injection from 6 to 12 months before the trial vaccination.

The trial is planned to enroll 150 subjects (all in the TAK-019 arm). They will be stratified by age; 100 subjects as ≥20 years to <65 years, and 50 subjects as ≥65 years of age.

Once all screening assessments following informed consent are completed and eligibility is confirmed, the subject will receive a single booster vaccination of TAK-019 by IM injection. All subjects will be followed up for immunogenicity and safety for 12 months after the trial vaccination.

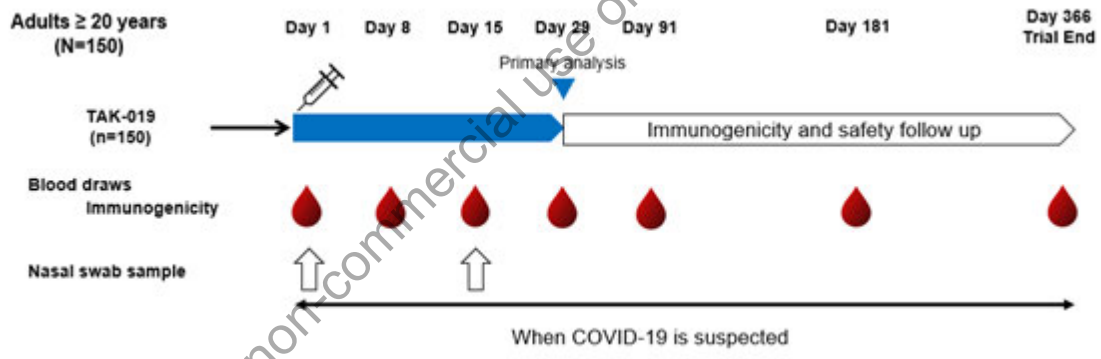
Each subject will be provided with an electronic diary (eDiary). Oral body temperature and solicited local and systemic AEs will be recorded in the eDiary by the subjects for 7 days after booster vaccination (including the day of vaccination). All subjects will be followed for unsolicited AEs for 28 days following booster vaccination (day of vaccination + 27 subsequent days).

All subjects will be followed for SAEs, AESIs, 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 and Day 15) or, in case of clinical symptoms suspected for COVID-19 throughout the trial.

The primary analysis will be performed for immunogenicity and safety after all subjects have completed the Day 29 visit.

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

Figure 2.a Schematic of Phase 3 Trial Design



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

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Non-inferiority of TAK-019 as a single heterologous booster vaccination on Day 15 to TAK-019 as a primary vaccination on Day 36 from historical 1501 study will be tested based on the following one-sided statistical hypotheses.

The null and alternative hypotheses in this case is defined as:

$$H_0: GMR < \Delta$$

$$H_1: GMR \geq \Delta$$

where GMR= (GMT of neutralizing antibody titers to the ancestral strain (wild-type virus) on Day 15 after a single booster vaccination in the subjects from this study) / (GMT of neutralizing antibody titers to the ancestral strain (wild-type virus) on Day 36 in subjects from TAK-019-1501 study), non-inferiority margin of $\Delta = 0.67$ [1].

If the lower bound of 95% CI will be equal or exceed the non-inferiority margin of 0.67, rejection of the null hypothesis and non-inferiority of TAK-019 as a single booster vaccination to TAK-019 as a primary vaccination from historical 1501 study is demonstrated.

3.2 Statistical Decision Rules

Not Applicable.

3.3 Multiplicity Adjustment

Not Applicable.

4.0 SAMPLE-SIZE DETERMINATION

In Study TAK-019-1501, GMT and geometric SD of serum neutralizing antibody titers to wild-type virus after the primary vaccinations on Day 36 (14 days after the 2nd vaccination) were 884.4 and 2.80 respectively in the vaccine group.

There is no immunogenicity data of serum neutralizing antibody titers to the ancestral strain (wild-type virus) after a booster vaccination of TAK-019 in Japanese subjects available. However, an estimate has been made on the results of the primary vaccination in Study TAK-019-1501 and the homoeologous booster vaccination in Study 2019nCoV-101 (Part 2). The assumption was made that neutralizing antibody titers on Day 15 in the proposed study would be equivalent to titers on Day 36 in Study TAK-019-1501 (ie, assuming GMT ratio to be 1 and geometric SD to be 2.80). With the guidance document, Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1) Evaluation of Vaccines Against Variants, issued by the PMDA [1], in mind, the non-inferiority margin of GMT ratio between booster vaccination group in the proposed study and the primary vaccination group in Study TAK-019-1501 is set as 0.67 fold. This results in 132 subjects be required as the number of evaluable subjects in PPS to ensure 90% power with the lower limit of 2-sided 95% CI of the GMT ratio exceeding the non-inferiority margin. Considering around 10% non-evaluable subjects, 150 subjects will be required into the proposed study.

5.0 ANALYSIS SETS

The Full Analysis Set (FAS), Per-protocol Set (PPS), and Safety Analysis Set (SAS) are defined for this trial. The FAS is defined as all enrolled subjects who receive at least 1 dose of the trial vaccination. 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 SAS defined as all subjects who receive at least 1 dose of the trial vaccination.

Subject evaluability criteria for each Analysis Set will be fixed before the database lock.

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 of the trial vaccination.

5.3 Full Analysis Set

FAS will consist of all enrolled subjects who receive at least 1 dose of the trial vaccination.

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.

- Missed dose of any planned injections. (1501 study only).
- Usage of prohibited medications specified in the protocol (section 7.3).
- Confirmation of SARS-CoV-2 infection before the vaccination. (3001 study: booster vaccination, 1501 study: 1st vaccination).
- Out of allowance of blood sampling for primary immunogenicity (3001 study: on Day 15, 1501 study: 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 medication.

All hypothesis tests will be and confidence intervals (CIs) will 2-sided. An alpha of 0.05 will be used for all statistical-testing, unless otherwise stated. All p-values reported will be 2-tailed and rounded to 3 decimal places prior to assessment of statistical significance.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. CIs intervals will be presented using the same number of decimal places as the parameter estimate.

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. 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 Group: This 3001 study and historical 1501 study.

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

Length of interval between the last Comirnaty injection and TAK-019 booster injection (Days) will be calculated as:

The date of TAK-019 booster vaccination - The date of the last vaccination (Comirnaty) + 1

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. 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

Main part is a part of original trial design for the first single booster vaccination of TAK-019. Extension part is designed to offer a second single booster vaccination of TAK-019 to participants who received the first single booster vaccination of TAK-019 in the Main Part and remained in study follow-up at least 5 months. The end of the Main Part is defined as the earlier of the completion of the final visit on Day 366 or the initiation of the Extension Part. Therefore, data of the Main Part will consist data of all subjects in the Main Part, data of the Extension Part will consist only data of subjects after the initiation of the Extension Part. The analysis plan of extension part is described in the SAP for extension part.

The final analysis will be performed at the end of the Main Part.

Only data through Day 366 or before Extension Part (2nd Booster phase) will be under consideration for this Main Part SAP.

6.1.1 Handling of Treatment Misallocations

Not Applicable.

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 and percentages of subjects vaccinated will be presented for the All Screened Subjects Analysis Set. Number and percentages of subjects 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:

- Number and percentages of subjects vaccinated, ongoing in study (for primary analysis only) after dose and discontinued early from the study (including reason for withdrawal) before Day 29 and who discontinued early from the study (including reason for withdrawal) after Day 29 (including Day 29) post dose will be presented based on the Safety Analysis Set.

The analysis of number of ongoing subjects after 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 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 as being major or critical, will be provided 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. For the result based on Safety Analysis Set, 3001 study group only will be provided.

The following demographic and other baseline characteristics will be reported by study group:

- Age (years) – at the date of signed informed consent.
- Age group (years): $20 \leq <65$ 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).
- Number of Prior Comirnaty Injection: 0, 1, 2
- Length of interval between the last Comirnaty injection and TAK-019 booster injection (days)
- Length of interval between the last Comirnaty injection and TAK-019 booster injection group (days): Min <= - < 168 days, 168 days <= - < 196 days, 196 days <= - < 224 days, 224 days <= - < 252 days, 252 days <= - < 280 days, 280 days <= - < 308 days, 308 days <= - < 336 days, 336 days <= - <= Max
- Length of interval between the last Comirnaty injection and TAK-019 booster injection group (days): Min <= - < 168 days, 168 days <= - < 196 days, 196 days <= - < 224 days, 224 days <= - < 252 days, 252 days <= - <= Max

Continuous demographic and other baseline characteristics will be summarised using descriptive statistics by study group. Categorical demographic and other baseline characteristics using number and percentages of patients in each category by study 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 24.0, 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.

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)

6.5.1 Primary Endpoint(s) Analysis

6.5.1.1 Derivation of Endpoint(s)

Primary endpoint is GMT ratio of neutralizing antibody titers to the ancestral strain (wild-type virus) on Day 15 after a single booster vaccination (14 days after the booster vaccination) compared with that observed on Day 36 (14 days after the second vaccination) in subjects from Study TAK-019-1501.

6.5.1.2 Main Analytical Approach

For GMT ratio of serum neutralizing antibody titers to the ancestral strain (wild-type virus) between booster vaccination group in the proposed study and the 2 doses primary vaccinations group in Study TAK-019-1501, point estimate and the two-sided 95% CIs will be provided using a 2-way analysis of variance (ANOVA) model. The 2-way ANOVA model will include log-transformed (common log) serum neutralizing antibody titers to the ancestral strain (wild-type virus) 14 days after vaccination as dependent variable, and categorized age (20<= - <65, 65<=) and study group as independent variable.

Each estimate by the model will be back transformed to the original scale. The lower limit of two-sided 95% CI of the GMT ratio will be compared with non-inferiority margin of 0.67 to assess the non-inferiority of neutralizing antibody titers to the ancestral strain (wild-type virus)

on Day 15 after a single booster vaccination compared with that observed on Day 36 (14 days after 2nd vaccination) in subjects from Study TAK-019-1501. If the lower limit of the 95% CI will be ≥0.67, the immune response to a single heterologous booster vaccination of TAK-019 will be considered to be non-inferior of that to the primary series of TAK-019.

For serum neutralizing antibody titers to the ancestral strain (wild-type virus), reverse cumulative distribution curve will be plotted by study group. Subgroup analysis will be conducted with Age group also.

6.5.1.3 Sensitivity Analysis

For primary endpoint, following statistical model will be used to explore the robustness of the model used for primary analysis.

Following each and all variables are added on the model used for primary analysis.

- Sex.
- BMI.

6.5.1.4 Supplementary Analyses

For primary endpoint, same analysis will be conducted based on the FAS.

6.5.2 Secondary Endpoint(s) Analysis

- GMT, GMFR, and SCR of serum IgG antibody levels to SARS-CoV-2 rS protein on Day 8, Day 15, Day 29, Day 91, Day 181, and Day 366.
- GMT, GMFR, and SCR of serum neutralizing antibody titers to the ancestral strain (wild-type virus) on Day 8, Day 15, Day 29, Day 91, Day 181, and Day 366.

Analyses will be conducted using the PPS. SCR of each immunogenicity endpoint at each time point will be calculated along with its 95% CI. For antibody titer values and GMFR from baseline, summary statistics, GMT, and the two-sided 95% CIs of each endpoint at each time point will be calculated.

6.5.3 [redacted]

[redacted]

[redacted]

6.5.4 Subgroup Analyses

Perform subgroup analyses on the items described in 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.
- Length of interval between the last Comirnaty injection and TAK-019 booster injection (days): Min <= - < 168 days, 168 days <= - < 196 days, 196 days <= - < 224 days, 224 days <= - < 252 days, 252 days <= - <= Max.

6.6 Safety Analysis

All safety summaries will be presented based on the Safety Analysis Set.

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 booster 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 booster vaccination (day of vaccination + 6 subsequent days).*
- *Percentage of subjects with unsolicited AEs for 28 days following booster vaccination (day of vaccination + 27 subsequent days).*
- *Percentage of subjects with SAEs until Day 29.*
- *Percentage of subjects with AESIs until Day 29.*
- *Percentage of subjects with MAAEs until Day 29.*
- *Percentage of subjects with any AEs leading to subject's withdrawal from the trial until Day 29.*
- *Percentage of subjects with SARS-CoV-2 infection until Day 29.*

The secondary safety endpoints are:

- *Percentage of subjects with SAEs throughout the trial.*
- *Percentage of subjects with AESIs throughout the trial.*

- *Percentage of subjects with MAAEs throughout the trial.*
- *Percentage of subjects with any AEs leading to subject's withdrawal from the trial from the day of the trial 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 24.0.

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 Booster Vaccination

Subjects will record solicited local and systemic AEs (Table 6.a), and oral body temperature, for 7 days following booster 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) [2].

If a solicited local or systemic AE continues beyond 7 days after booster dosing (including the day of administration), the solicited AEs 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

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Local Reaction to Injectable Product				
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)				
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 booster vaccination uses data collected by eDiary, on the other hands solicited AEs after 7 days following booster 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. 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). For the number of days a subject reported experiencing an event, histogram will be provided.

A listing of all solicited AEs will be provided.

6.6.2.2 Occurrence of Unsolicited AEs for 29 Days Following Booster 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 booster dose for 29 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 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 booster 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 29

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 presented.

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 29

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).
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.

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

Categories	Diagnoses (as MedDRA Preferred Terms)
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 [3].

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.

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 29

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.

A listing of all MAAEs will be provided.

6.6.2.6 AEs Leading to Subject's Withdrawal From the Trial Until Day 29

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.

6.6.2.7 SARS-CoV-2 Infection Until Day 29.

The incidence of the first SARS-CoV-2 infection will be summarized 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 6.6.2.7.

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.

This analysis will be conducted only at the Final analysis.

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 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.

6.6.5.1.1 Vital Sign Toxicity Grades

Vital sign 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 vital sign listed in Table 9.a:

- 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 vital sign results not meeting any of the 4 grades defined in the FDA toxicity grading system will be categorized as 'No Toxicity'. But Grade 4 is considered only for Fever due to the limited data collection.

6.6.6 Subgroup Analyses

Perform subgroup analyses on the items described in Section 6.6.2 ~ 6.6.3. Subgroup analyses will be conducted using the Safety Analysis Set.

The subgroup is:

- Age group (years): 20 ≤ <65 and ≥65.
- Sex: Male, Female.
- Length of interval between the last Comirnaty injection and TAK-019 booster injection (days): Min <= - < 168 days, 168 days <= - < 196 days, 196 days <= - < 224 days, 224 days <= - < 252 days, 252 days <= - <= Max.

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 29 visit.

7.0 REFERENCES

1. Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1) Evaluation of Vaccines Against Variants. Available from: https://www.pmda.go.jp/files/000240416.pdf
2. 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
3. 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

Section	Before Change	After Change	Reason
6.1 General Considerations		Main part is a part of original trial design for the first single booster vaccination of TAK-019. Extension part is designed to offer a second single booster vaccination of TAK-019 to participants who received the first single booster vaccination of TAK-019 in the Main Part and remained in study follow-up at least 5 months. The end of the Main Part is defined as the earlier of the completion of the final visit on Day 366 or the initiation of the Extension Part. Therefore, data of the Main Part will consist data of all subjects in the Main Part, data of the Extension Part will consist only data of subjects after the initiation of the Extension Part. The analysis plan of extension part is described in the SAP for extension part.	To make analysis target of main part clear.

		The final analysis will be performed at the end of the Main Part. Only data through Day 366 or before Extension Part (2nd Booster phase) will be under consideration for this Main Part SAP.	
6.3.1 Demographics	• Length of interval between the last Comirnaty injection and TAK-019 booster injection group (days): Min <= - < 168 days, 168 days <= - < 196 days, 196 days <= - < 224 days, 224 days <= - < 252 days, 252 days <= - < 280 days, 280 days <= - < 308 days, 308 days <= - < 336 days, 336 days <= - < Max Length of interval between the last Comirnaty injection and TAK-019 booster injection group (days): Min <= - < 168 days, 168 days <= - < 196 days, 196 days <= - < 224 days, 224 days <= - < 252 days, 252 days <= - < Max	• Length of interval between the last Comirnaty injection and TAK-019 booster injection group (days): Min <= - < 168 days, 168 days <= - < 196 days, 196 days <= - < 224 days, 224 days <= - < 252 days, 252 days <= - < 280 days, 280 days <= - < 308 days, 308 days <= - < 336 days, 336 days <= - <= Max Length of interval between the last Comirnaty injection and TAK-019 booster injection group (days): Min <= - < 168 days, 168 days <= - < 196 days, 196 days <= - < 224 days, 224 days <= - < 252 days, 252 days <= - <= Max	Error correction.
6.5.4 Subgroup Analyses	Length of interval between the last	Length of interval between the last	Error correction.

	Comirnaty injection and TAK-019 booster injection (days): Min <= - < 168 days, 168 days <= - < 196 days, 196 days <= - < 224 days, 224 days <= - < 252 days, 252 days <= - < Max.	Comirnaty injection and TAK-019 booster injection (days): Min <= - < 168 days, 168 days <= - < 196 days, 196 days <= - < 224 days, 224 days <= - < 252 days, 252 days <= - <= Max.	
6.6.6 Subgroup Analyses	Length of interval between the last Comirnaty injection and TAK-019 booster injection (days): Min <= - < 168 days, 168 days <= - < 196 days, 196 days <= - < 224 days, 224 days <= - < 252 days, 252 days <= - < Max.	Length of interval between the last Comirnaty injection and TAK-019 booster injection (days): Min <= - < 168 days, 168 days <= - < 196 days, 196 days <= - < 224 days, 224 days <= - < 252 days, 252 days <= - <= Max.	Error correction.

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.
	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 Definition of Visit Windows

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:

Visit	Day Relative to Dose within the Dosing Period [(b)]	Visit Window (Study Day) Relative to the Dosing Period
Baseline [(a)]	≤1	≤1
Day 8	8	8 – 11
Day 15	15	12 – 21
Day 29	29	22 – 60
Day 91	91	61 – 150
Day 181	181	151 – 335
Day 366	366	336 – 396

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 Vital Sign Abnormalities

The 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.

Table 9.a Tables for Vital Sign Abnormalities

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.

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 Study Groups

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

Study Group	Tables and Graphs	Listings
3001	1	1
1501	2	2

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 15	D15
Day 29	D29
Day 91	D91
Day 181	D181
Day 366	D366

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):

- 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.

STATISTICAL ANALYSIS PLAN

Study Number: *TAK-019-3001*

Study Title: *A Phase 3, Single Arm, Open-Label Trial to Evaluate the Immunogenicity and Safety of a Single Heterologous Booster Vaccination of TAK-019 in Healthy Japanese Male and Female Adults Aged 20 Years and Older*

Phase: *3*

Version: *Extension part 2.0*

Date: *05 December 2022*

Prepared by: [redacted]

Based on:

Protocol Version: *2.0*

Protocol Date: *29-Jul-2022*

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original version		Not Applicable

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
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
ULOQ	upper limit of quantification
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

Not Applicable.

1.1.2 Secondary Objective(s)

To evaluate the immunogenicity and safety of a second single booster vaccination of TAK-019 by IM injection in healthy Japanese male and female adults aged ≥20 years.

Immunogenicity:

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

- *Serum IgG antibody levels to SARS-CoV-2 rS protein.*
- *Serum neutralizing antibody titers to the ancestral strain (wild-type virus).*

Safety:

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

- *Solicited local and systemic AEs for 7 days following the second single booster vaccination (day of vaccination + 6 subsequent days).*
- *Unsolicited AEs for 28 days following the second single booster vaccination (day of vaccination + 27 subsequent days).*
- *SAEs, AESIs, MAAEs, AEs leading to trial withdrawal, and SARS-CoV-2 infection until* ***Extension Part*** *Day 29.*
- *SAEs, AESIs, MAAEs, AEs leading to trial withdrawal, and SARS-CoV-2 infection throughout the trial.*

1.1.3 Additional Objective(s)

1.1.3.1 [redacted]

[redacted]

1.2 Endpoints

1.2.1 Primary Endpoint(s)

Not Applicable

1.2.2 Secondary Endpoint(s)

Immunogenicity:

- *GMT, GMFR, and SCR (defined at proportion of subjects with ≥4-fold rises from baseline [**Extension Part** Day 1]) of serum IgG antibody levels to SARS-CoV-2 rS protein on **Extension Part** Day 15, Day 29, Day 91, Day 181, and Day 366.*
- *GMT, GMFR, and SCR of serum neutralizing antibody titers to the ancestral strain (wild-type virus) on **Extension Part** Day 15, Day 29, Day 91, Day 181, and Day 366.*

Safety:

- *Percentage of subjects with reported solicited local AEs: injection site pain, tenderness, erythema/redness, induration, and swelling for 7 days following the second single booster 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 the second single booster vaccination (day of vaccination + 6 subsequent days).*
- *Percentage of subjects with unsolicited AEs for 28 days following the second single booster vaccination (day of vaccination + 27 subsequent days).*
- *Percentage of subjects with SAEs until **Extension Part** Day 29.*
- *Percentage of subjects with AESIs until **Extension Part** Day 29.*
- *Percentage of subjects with MAAEs until **Extension Part** Day 29.*
- *Percentage of subjects with any AEs leading to subject's withdrawal from the trial until **Extension Part** Day 29.*
- *Percentage of subjects with SARS-CoV-2 infection until **Extension Part** Day 29.*
- *Percentage of subjects with SAEs throughout the trial.*
- *Percentage of subjects with AESIs throughout the trial.*
- *Percentage of subjects with MAAEs throughout the trial.*
- *Percentage of subjects with any AEs leading to subject's withdrawal from the trial from the day of the second single booster vaccination throughout the trial.*
- *Percentage of subjects with SARS-CoV-2 infection throughout the trial.*

1.2.3 [redacted]

[redacted]

[redacted]

1.3 Estimand(s)

As an extension of the TAK-019-3001 study, this is a single-arm trial rather than a confirmatory trial, the estimand framework is not applicable here.

2.0 STUDY DESIGN

Extension Part is designed to offer a second single booster vaccination of TAK-019 to participants who received the first single booster vaccination of TAK-019 in the Main Part and remained in study follow-up at least 5 months. The end of the Main Part is defined as the earlier of the completion of the final visit on Day 366 or the initiation of the Extension Part. Therefore, data of the Main Part will consist data of all subjects in the Main Part, data of the Extension Part will consist only data of subjects after the initiation of the Extension Part. The end of Extension Part is defined as the completion of the final visit on Extension Part Day 366. All analyses will be performed descriptively in the Extension Part.

*All subjects who are willing to proceed to the **Extension Part** and to receive a second booster vaccination of TAK-019 will be asked to schedule a Participant Decision Visit about 5 months after the first single booster vaccination.*

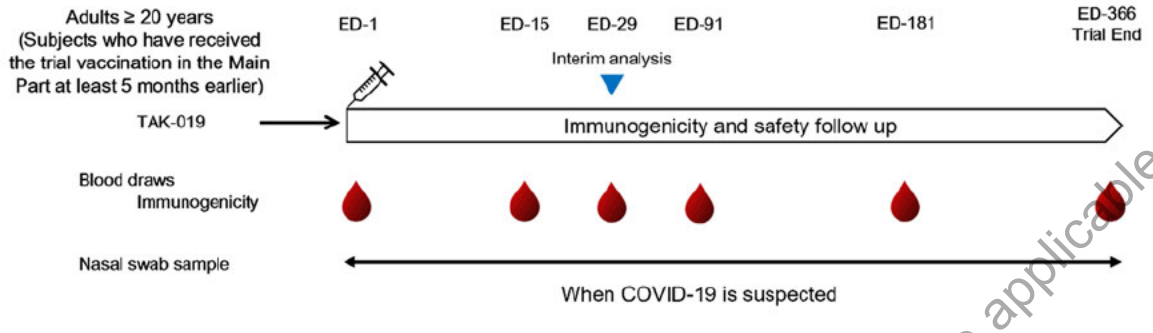
*All subjects who provide additional informed consent for the **Extension Part** at the Participant Decision Visit and are eligible for enrollment in the **Extension Part** will receive a second single booster vaccination of TAK-019, by IM injection (**Extension Part** Day 1). All subjects in the **Extension Part** will be followed up for immunogenicity and safety for 12 months after the **Extension Part** Day 1.*

*Each subject will be provided an eDiary. Oral body temperature and solicited local and systemic AEs will be recorded in the eDiary by the subjects for 7 days after the second booster vaccination (including the **Extension Part** Day 1). All subjects will be followed-up for unsolicited AEs for 28 days following the second booster vaccination (**Extension Part** Day 1 + 27 subsequent days).*

*All subjects will be followed-up for SAEs, AESIs, MAAEs, and AEs leading to trial withdrawal in the **Extension Part**. All subjects will also be tested for SARS-CoV-2 infection in case of clinical symptoms suspected for COVID-19 in the **Extension Part**.*

*An interim analysis will be performed for immunogenicity and safety after all subjects have completed the **Extension Part** Day 29 visit.*

Figure 2.a ***Schematic of Trial Design (Extension Part)***



*A schematic of the trial design for the **Extension Part** is included as Figure 2.a.*

Abbreviations: COVID-19: coronavirus disease 2019; ED: Extension Part Day.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not Applicable.

3.2 Statistical Decision Rules

Not Applicable.

3.3 Multiplicity Adjustment

Not Applicable

4.0 SAMPLE-SIZE DETERMINATION

*The number of subjects in this part is not based on statistical power considerations as this is an **Extension Part** of Study TAK-019-3001 following the **Main Part**.*

5.0 ANALYSIS SETS

The FAS, PPS, and Safety Analysis Set in Extension Part are defined for this trial. The FAS in Extension Part is defined as all subjects enrolled in Extension Part who receive at least 1 dose of the trial vaccination in Extension Part. Immunogenicity analysis will be conducted using the PPS in Extension Part defined to include subjects in the FAS in Extension Part and who have evaluable immunogenicity data and do not have significant protocol deviations which influence the immunogenicity assessment. Safety analysis will be conducted using the Safety Analysis Set in Extension Part defined as all subjects who receive at least 1 dose of the trial vaccination in Extension Part.

5.1 All Screened Subjects in Extension Part

The All Screened Subjects Analysis Set will consist of all subjects who had received the first booster dose in Main Part and provide additional informed consent for the Extension Part study,

to be used for reporting disposition and screening failures. Unless otherwise stated, All Screened Subjects in the following articles refers to the All Screened Subjects in the Extension Part.

5.2 Safety Analysis Set in Extension Part

The Safety Analysis Set will consist of all subjects who receive at least 1 dose of the trial vaccination in Extension Part. Unless otherwise stated, Safety Analysis Set in the following articles refers to the safety analysis set in the Extension Part.

5.3 Full Analysis Set in Extension Part

The FAS in Extension Part is defined as all subjects enrolled in Extension Part who receive at least 1 dose of the trial vaccination in Extension Part. Unless otherwise stated, FAS in the following articles refers to the full analysis set in the Extension Part.

5.4 Per-Protocol Analysis Set in Extension Part

PPS will consist of all subjects in the FAS in Extension Part and who have evaluable immunogenicity data and do not have significant protocol deviations which influence the immunogenicity assessment. Subjects with other protocol deviations might be excluded as necessary.

- Usage of prohibited medications specified in the protocol (section 7.3).
- Missed dose of planned injections in Main part.

Handling of the values of blood sampling for immunogenicity after confirmation of SARS-CoV-2 infection for immunogenicity analysis are described in section 6.5.2. Unless otherwise stated, PPS in the following articles refers to the per-protocol analysis set in the Extension Part.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Baseline values in **Extension Part** are defined as the last observed value before the second booster dose of study medication in the **Extension Part**.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. CIs intervals will be presented using the same number of decimal places as the parameter estimate.

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. 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 of the **Extension Part** 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 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. 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 9.2.3).

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

Not Applicable.

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 and percentages of subjects vaccinated will be presented for the All Screened Subjects Analysis Set. Number and percentages of subjects 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:

- Number and percentages of subjects vaccinated, ongoing in study (for interim analysis only) after dose and discontinued early from the study (including reason for withdrawal) before Extension Part Day 29 and who discontinued early from the study (including reason for withdrawal) after Extension Part Day 29 (including Extension Part Day 29) post dose will be presented based on the Safety Analysis Set.

The analysis of number of ongoing subjects after dose will only be presented for interim 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 based on screened subjects who received the second booster vaccine. 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 as being major or critical, will be provided 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:

- 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/m2).
- Length of interval between the first TAK-019 booster injection and the second TAK-019 booster injection (days)
- Length of interval between the first TAK-019 booster injection and the second TAK-019 booster injection group (days): Min <= - < =165 days, 165 days < - <= 175 days, 175 days < - < =Max.

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

6.3.2 Medical History and Concurrent Medical Conditions

Not Applicable.

6.4 Medication History and Concomitant Medications

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

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 and concomitant medications and concomitant procedures will be listed.

6.5 Efficacy Analysis

6.5.1 Primary Endpoint(s) Analysis

Not applicable.

6.5.1.1 Derivation of Endpoint(s)

Not applicable.

6.5.1.2 Main Analytical Approach

Not applicable.

6.5.1.3 Sensitivity Analysis

Not applicable.

6.5.1.4 Supplementary Analyses

Not applicable.

6.5.2 Secondary Endpoint(s) Analysis

- GMT, GMFR, and SCR (defined at proportion of subjects with ≥4-fold rises from baseline [**Extension Part** Day 1]) of serum IgG antibody levels to SARS-CoV-2 rS protein on **Extension Part** Day 15, Day 29, Day 91, Day 181, and Day 366.
- GMT, GMFR, and SCR of serum neutralizing antibody titers to the ancestral strain (wild-type virus) on **Extension Part** Day 15, Day 29, Day 91, Day 181, and Day 366.

We will conduct two different immunogenicity analysis based on PPS. For the first kind of analysis, values of blood sampling for immunogenicity will be excluded if the subject had already confirmed infection of SARS-CoV-2. For the second kind of analysis, if the subject had already confirmed infection of SARS-CoV-2, values of blood sampling for immunogenicity would be included, as a supplementary analysis. SCR of each immunogenicity endpoint at each time point will be calculated along with its 95% CI. For antibody titer values and GMFR from baseline, summary statistics, GMT, and the two-sided 95% CIs of each endpoint at each time point will be calculated. In addition to using **Extension Part** Day 1 as a baseline of GMFR and SCR, we present the results for GMFR and SCR using **Main Part** Day 1 as a baseline. We also use **Main Part** Day 15 as a baseline for GMFR of **Extension Part** Day 15. The result of Day 1 and Day 15 in the **Main Part** will be presented. For serum neutralizing antibody titers to the ancestral strain (wild-type virus) on **Extension Part** Day15, reverse cumulative distribution curve will be plotted. Subgroup analysis for reverse cumulative distribution curve will be conducted with Age group also.

6.5.3 [redacted]

[redacted]

6.5.4 Subgroup Analyses

Perform subgroup analyses on the items described in 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.
- Length of interval between the first TAK-019 booster injection and the second TAK-019 booster injection group (days): Min <= - < =165 days, 165 days < - <= 175 days, 175 days < - < =Max.

6.6 Safety Analysis

All safety summaries will be presented based on the Safety Analysis Set.

The secondary safety endpoints are:

- *Percentage of subjects with reported solicited local AEs: injection site pain, tenderness, erythema/redness, induration, and swelling for 7 days following the second booster 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 the second booster vaccination (day of vaccination + 6 subsequent days).*
- *Percentage of subjects with unsolicited AEs for 28 days following the second booster vaccination (day of vaccination + 27 subsequent days).*
- *Percentage of subjects with SAEs until Extension Part Day 29.*
- *Percentage of subjects with AESIs until Extension Part Day 29.*
- *Percentage of subjects with MAAEs until Extension Part Day 29.*
- *Percentage of subjects with any AEs leading to subject's withdrawal from the trial until Extension Part Day 29.*
- *Percentage of subjects with SARS-CoV-2 infection until Extension Part Day 29.*
- *Percentage of subjects with SAEs throughout the trial.*
- *Percentage of subjects with AESIs throughout the trial.*
- *Percentage of subjects with MAAEs throughout the trial.*
- *Percentage of subjects with any AEs leading to subject's withdrawal from the trial from the day of the second booster 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 24.0.

Only AEs that started or worsened in severity on or after the second booster of study intervention will be presented in the summary. A listing of all AEs including those prior to the second booster 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 related events will be counted for that SOC or PT.

6.6.2 Primary safety endpoints

Not applicable.

6.6.3 Secondary safety endpoints

6.6.3.1 Occurrence of Solicited AEs for 7 Days Following the Second Booster Vaccination

Subjects will record solicited local and systemic AEs (Table 6.a), and oral body temperature, for 7 days following the second booster 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 the second booster dosing (including the day of administration), the solicited AEs 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

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Local Reaction to Injectable Product				
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)				
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/	No interference with activity or 1–	Some interference with	Prevents daily activity, or	Emergency room visit or

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

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
vomiting	2 episodes/24 hours	activity or >2 episodes/24 hours	requires outpatient intravenous hydration	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 the second booster vaccination uses data collected by eDiary, on the other hands solicited AEs after 7 days following the second booster 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. Solicited AEs for 7 days following the first booster vaccination in the main part will be performed the same analysis based on the safety analysis set in the main part.

Also Solicited AEs persisting beyond 7 days after the second booster vaccination will be summarized by severity. 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). For the number of days a subject reported experiencing an event, histogram will be provided.

A listing of all solicited AEs after the second booster vaccination will be provided.

6.6.3.2 *Occurrence of Unsolicited AEs for 28 Days Following The Second Booster Vaccination*

All AEs are considered to be unsolicited AEs unless categorized as solicited AEs recorded in an eCRF. All unsolicited AEs will be recorded from the start of the second booster dose for 28 days (day of vaccination + 27 subsequent days).

Number and percentages of subjects with at least one unsolicited AE for 28 days following the second booster vaccination 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 for 28 days following the second booster vaccination 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 for 28 days following the second booster vaccination will be broken down 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 the second booster dose of study intervention will be presented by SOC and PT throughout the trial.

A listing of all unsolicited AEs for 28 days following the second booster vaccination will be provided.

6.6.3.3 *Occurrence of Serious AEs Until Extension Part Day 29*

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 second booster 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 from the second booster vaccination to Day 29 of extension part will be presented.

A listing of all SAEs a from the second booster vaccination to Day 29 of extension part including those prior to the second booster vaccination in extension part will be provided.

6.6.3.4 Occurrence of Adverse Event of Special Interest Until Extension Part Day 29

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).
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

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

Categories	Diagnoses (as MedDRA Preferred Terms)
	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 from the second booster vaccination to Day 29 of extension part 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.

A summary of related AESIs by Categories and PT from the second booster vaccination to Day 29 of extension part will be presented.

A listing of all AESIs from the second booster vaccination to Day 29 of extension part will be provided.

6.6.3.5 *Occurrence of Medically-Attended Adverse Events Until Extension Part Day 29*

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 from the second booster vaccination to Day 29 of extension part 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.

A listing of all MAAEs will be provided from the second booster vaccination to Day 29 of extension part.

6.6.3.6 *AEs Leading to Subject's Withdrawal From the Trial Until Extension Part Day 29*

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 between the second booster vaccination and Day 29 of extension part by SOC and PT will be presented.

A listing of all AEs leading to subject's withdrawal from the trial between the second booster vaccination and Day 29 of extension part will be provided.

6.6.3.7 *SARS-CoV-2 Infection Until Extension Part Day 29.*

The incidence of the first SARS-CoV-2 infection after the second booster vaccination until Day29 of extension part will be summarized 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 after the second booster vaccination until Day 29 of extension part will be provided.

6.6.3.8 *Occurrence of Serious AEs Throughout the Trial*

A summary of SAEs started on and after the second booster vaccination 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) after the second booster vaccination will be provided.

This analysis will be conducted only at the Final analysis.

6.6.3.9 *Occurrence of AESI Throughout the Trial*

A summary of AESIs by SOC and PT after the second booster vaccination 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 after the second booster vaccination will be provided.

This analysis will be conducted only at the Final analysis.

6.6.3.10 *Occurrence of MAAEs Throughout the Trial*

A summary of MAAEs by SOC and PT after the second booster vaccination 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 after the second booster vaccination will be provided.

This analysis will be conducted only at the Final analysis.

6.6.3.11 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 after the second booster vaccination will be provided.

This analysis will be conducted only at the Final analysis.

6.6.3.12 *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 6.6.3.7.

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 after the second booster vaccination will be provided.

This analysis will be conducted only at the Final analysis.

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 after the second booster vaccination with an outcome of death will be provided.

6.6.4.2 Unsolicited Adverse Events of Hypersensitivity until Extension Part Day 29

A summary of hypersensitivity AEs (refer to APPENDIX 9.2.5 for the list of SMQs) by PT after the second booster vaccination until Day 29 of extension part 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 after the second booster vaccination until Day 29 of extension part will be provided.

6.6.4.3 Unsolicited Adverse Events of Hypersensitivity through trial

A summary of hypersensitivity AEs by PT throughout the trial after the second booster vaccination 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 after the second booster vaccination will be provided.

6.6.4.4 Related Unsolicited Adverse Events of Hypersensitivity until Extension Part Day 29

A summary of related hypersensitivity AEs by PT after the second booster vaccination until Extension Part Day29 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 after the second booster vaccination until Day 29 of extension part will be provided.

6.6.4.5 Related Unsolicited Adverse Events of Hypersensitivity through trial

A summary of related hypersensitivity AEs by PT throughout the trial after the second booster vaccination 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 after the second booster vaccination will be provided.

6.6.5 Other Safety Analysis

6.6.5.1 Vital Sign Measurements

After the second single booster vaccination, 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 in extension part.

- Observed and change from extension part's 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 9.2.4) by visit.

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

6.6.5.1.1 Vital Sign Toxicity Grades

Vital sign with available FDA toxicity grades will be categorized as follows where higher grades representing a more severe toxicity (refer to APPENDIX 9.2.4 for each parameter toxicity grade criteria). FDA grading will be categorized for vital sign listed in Table 9.a:

- 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 vital sign results not meeting any of the 4 grades defined in the FDA toxicity grading system will be categorized as 'No Toxicity'. But Grade 4 is considered only for Fever due to the limited data collection.

6.6.6 Subgroup Analyses

Perform subgroup analyses on the items described in Section 6.6.2 ~ 6.6.3. Subgroup analyses will be conducted using the Safety Analysis Set.

The subgroup is:

- Age group (years): 20 ≤ <65 and ≥65.
- Sex: Male, Female.
- Length of interval between the first TAK-019 booster injection and the second TAK-019 booster injection group (days): Min <= - < =165 days, 165 days < - <= 175 days, 175 days < - < =Max. (Not applicable to the analysis in Section 6.6.3.1 about main part's results.)

6.7 Interim Analyses

An interim analysis of immunogenicity and safety is planned for the **Extension Part** after all subjects have completed **Extension Part** Day 29 (immunogenicity data through **Extension Part** Day 15 and safety data through **Extension Part** Day 29).

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

Section	Before Change	After Change	Reason
6.3.1 Demographics	Length of interval between the first TAK-019 booster injection and the second TAK-019 booster injection group (days): Min <= - < 140 days, 140 days <= - < 168 days, 168 days <= - < 196 days, 196 days<= - < Max.	Length of interval between the first TAK-019 booster injection and the second TAK-019 booster injection group (days): Min <= - < =165 days, 165 days < - <= 175 days, 175 days < - < =Max.	The previous settings about categories were inappropriate. Two of the categories have no observations.
6.5.4 Subgroup Analyses	Length of interval between the first TAK-019 booster injection and the second TAK-019 booster injection group (days): Min <= - < 140 days, 140 days <= - < 168 days, 168 days <= - < 196 days,	Length of interval between the first TAK-019 booster injection and the second TAK-019 booster injection group (days): Min <= - < =165 days, 165 days < - <= 175 days,	The previous settings about categories were inappropriate. Two of the categories have no observations.

	196 days<= - < Max.	175 days < - < =Max.	
6.6.6 Subgroup Analyses	Length of interval between the first TAK-019 booster injection and the second TAK-019 booster injection group (days): Min <= - < 140 days, 140 days <= - < 168 days, 168 days <= - < 196 days, 196 days<= - < Max.	Length of interval between the first TAK-019 booster injection and the second TAK-019 booster injection group (days): Min <= - < =165 days, 165 days < - <= 175 days, 175 days < - < =Max. (Not applicable to the analysis in Section 6.6.3.1 about main part's results.)	1. The previous settings about categories were inappropriate. Two of the categories have no observations. 2. The length of the interval is defined as the first TAK-019 booster injection and the second TAK-019 booster injection. It couldn't be used for analysis of the main part results.

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.

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 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 second booster dose of study intervention (including unscheduled assessments). In the case where the last non-missing measurement and the date and time of the second booster dose of study intervention coincide, that measurement will be considered pre-baseline, but AEs and medications commencing on the date of the second booster dose of study intervention will be considered post-baseline. The definition of the main part baseline is the same as the extension part, except that its timeline is based on the first single boost dose.

9.2.3 Definition of Visit Windows

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.

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:

Visit	Day Relative to Dose within the Dosing Period[j]	Visit Window (Study Day) Relative to the Dosing Period
Baseline	≤1	≤1
Day 15	15	8 – 21
Day 29	29	22 – 60
Day 91	91	61 – 150
Day 181	181	151 – 335
Day 366	366	336 – 396

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.

It is also necessary to visit on Day 8 in the main part, so the main part has a slightly different time window for Day 8 and Day 15. For main part Day 15, the visit window is defined between 12 days and 21 days after the first single booster dose.

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

9.2.4 Tables for Vital Sign Abnormalities

The 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.

Table 9.a Tables for Vital Sign Abnormalities

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.

9.2.5 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 Study Groups

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

– Treatment Group	– Tables and Graphs	– Listings
TAK-019	1	1

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 in main part	Base-m
Main Part Day 1	MD-1
Main Part Day 15	MD-15
Baseline in extension part	Base-ex
Extension Part Day 1	ED-1
Extension Part Day 15	ED-15
Extension Part Day 29	ED-29
Extension Part Day 91	ED-91
Extension Part Day 181	ED-181
Extension Part Day 366	ED-366

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, median, GMT, lower and upper bounds of two-sided 95% CI for GMT: N + 1;

- SD: N + 2.
- GMFR and two-sided 95% CI for GMFR: 2 decimal places.

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):

- 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.