Statistical Analysis Plan

NCT Number: NCT04842643

Title: A Phase 3, Open-label, Non-controlled, Multi-dose, Extension Study to Evaluate the Long-term Safety and Tolerability of IGSC, 20% in Japanese Subjects with Primary Immunodeficiency Disease (PID)

Study Number: TAK-664-3002

Document Version and Date: Final 3.0 / 23-Mar-2023

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STATISTICAL ANALYSIS PLAN

Study Number: TAK-664-3002

Study Title: A Phase 3, Open-label, Non-controlled, Multi-dose, Extension Study to Evaluate the Long-term Safety and Tolerability of IGSC, 20% in Japanese Subjects with Primary Immunodeficiency Disease (PID)

Phase: 3

Version: Final 3.0

Date: 23-Mar-2023

Prepared by: [redacted]

Based on:

Protocol Version: Protocol Amendment 3.0

Protocol Date: 28 Nov 2022

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original version	*07-Apr-2021*	[Not Applicable]
Version 2.0	*20-Aug-2021*	• Section 5.0 Analysis set definition updated to keep consistency with core study. • Section 6.3 Protocol deviation section updated to keep consistency with protocol deviation management plan. • Section 6.6.1 Adverse event section updated to add previously missing description of certain summary tables. • Section 6.6.1 Adverse event section updated to remove by treatment summary. • Section 6.6.6 Study drug administration updated to correct the definition of parameters. • Section 6.8.7 Treatment preference updated to clarify the analysis sets. • Section 6.9.2 Serum trough level of specific antibodies section added. • Other error corrections.
Version 3.0	*23-Mar-2023*	• Section 5.0: Duplicate expressions removed. • Section 6.1.3: Consistent with the description in Section 6.8. • Section 6.1.5.3: Imputation of missing medical history start dates added. • Section 6.1.5.6: Table of Convention for Converting Non-Standard Laboratory Results updated. • Section 6.4.1: Age categories added and clarified the definition of age. • Section 6.6.1: Occurrence and number of TEAEs section updated to add additional summary tables. Calculation formula of days of exposure corrected. • Section 6.6.1.1: Added missing items to the overall table to match endpoint. Summary tables for age categories and dosing interval added. • Section 6.6.1.2: Summary tables for age categories and dosing interval added. • Section 6.6.2: Description of summary table of specific antibody test results added. • Section 6.6.5: "Days of exposure" updated to "Days in study" to distinguish from the days of exposure for adverse events, the concept of total dose (mg) received replaced by average dose (mg/kg/week). • Section 6.6.6: Analysis of study drug administration parameters clarified. Calculation formula of duration of infusion added. • Section 6.8.2: Definition of infections updated to accommodate the change of medical dictionary version. • Section 6.8.5: Description of Poisson estimates added for total length of stay per subject. • Section 6.8.6: Concept of number of acute physician visits OR emergency room visits updated. Description of Poisson estimates added.

		• Section 6.9: Parameters of descriptive statistics updated. • Section 6.9.1: Liner and semi logarithmic scale plots for total IgG and IgG subclass added. • Section 6.10: Description of interim analysis updated.

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ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ASBI	acute serious bacterial infection
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BUN	blood urea nitrogen
CI	confidence interval
CTMS	clinical trial management system
eCRF	electronic case report form
EOS	end of study
HBV	Hepatitis B Virus
HIB	Haemophilus influenzae
IgG	immunoglobulin G
IGIV	intravenous immunoglobulin
IGSC	subcutaneous immunoglobulin
IGSC, 20%	Immune Globulin Subcutaneous (Human), 20% Solution
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PID	primary immunodeficiency disease
PK	pharmacokinetic
PT	Preferred Term
SAP	statistical analysis plan
SAS	Safety Analysis Set
SC	subcutaneous(ly)
SD	standard deviation
SOC	System Organ Class
TEAE	treatment-emergent adverse event
WBC	white blood cell count
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1.0 OBJECTIVES AND ENDPOINTS

1.1 Objectives

1.1.1 Primary Objective

The primary objective *is to evaluate the long-term safety and tolerability of subcutaneous immunoglobulin (IGSC), 20% in Japanese subjects with primary immunodeficiency disease (PID).*

1.1.2 Secondary Objectives

The secondary objectives are listed as below:

- *To assess serum trough immunoglobulin G (IgG) and subclasses concentrations following weekly or biweekly administration of immune globulin subcutaneous (Human), 20% solution (IGSC, 20%) in Japanese subjects with PID*
- *To evaluate the efficacy of IGSC, 20% in Japanese subjects with PID*
- *To assess treatment preference of Japanese subjects with PID*

1.2 Endpoints

1.2.1 Primary Endpoint

The primary endpoint *is occurrence of treatment-emergent adverse events (TEAEs), including but not limited to: study drug-related and non-related, serious, nonserious, severe, local and systemic TEAEs, as well as TEAEs leading to premature discontinuation from study, and infusion associated TEAEs.*

1.2.2 Secondary Endpoints

1.2.2.1 Pharmacokinetic Endpoints

The pharmacokinetic (PK) endpoints are:

Measurement of serum trough IgG and subclasses concentrations following weekly or biweekly administration of IGSC, 20% in Japanese subjects with PID

1.2.2.2 Efficacy Endpoints

The efficacy endpoints are listed as below:

- Annual rate of validated acute serious bacterial infections (ASBIs) per subject
- Annual rate of all infections per subject
- Health Resource Utilization:
- Days not able to attend school/work or to perform normal daily activities due to

illness/infection

- Days on antibiotics
- Number of hospitalizations due to illness/infection and length of stay (in days)
- Number of acute (urgent or unscheduled) physician visits due to illness/infection
- Treatment Preference

1.2.2.3 Safety and Tolerability Endpoints

The safety endpoints are listed as below:

- Clinical laboratory outcomes: raw (actual) values and change from baseline
- Vital signs: raw (actual) values and change from baseline and change from pre-infusion to post-infusion

The tolerability endpoint is occurrence of tolerability events related to the infusion of study drug.

2.0 STUDY DESIGN

This is a phase 3, prospective, multicenter, open-label, non-controlled, single-arm extension study.

Approximately 10 to 15 study sites planned, located in Japan. A total of 16 subjects will be enrolled in Study TAK-664-3001, of whom 12 subjects are expected to complete Epoch 2. A subset of 7 subjects will continue into Epoch 3, of whom 5 subjects are expected to complete.

This study will enroll Japanese subjects with PID who complete Study TAK-664-3001 successfully.

Subjects are considered to have completed Study TAK-664-3001 successfully if they fulfill 1 of the following 2 criteria:

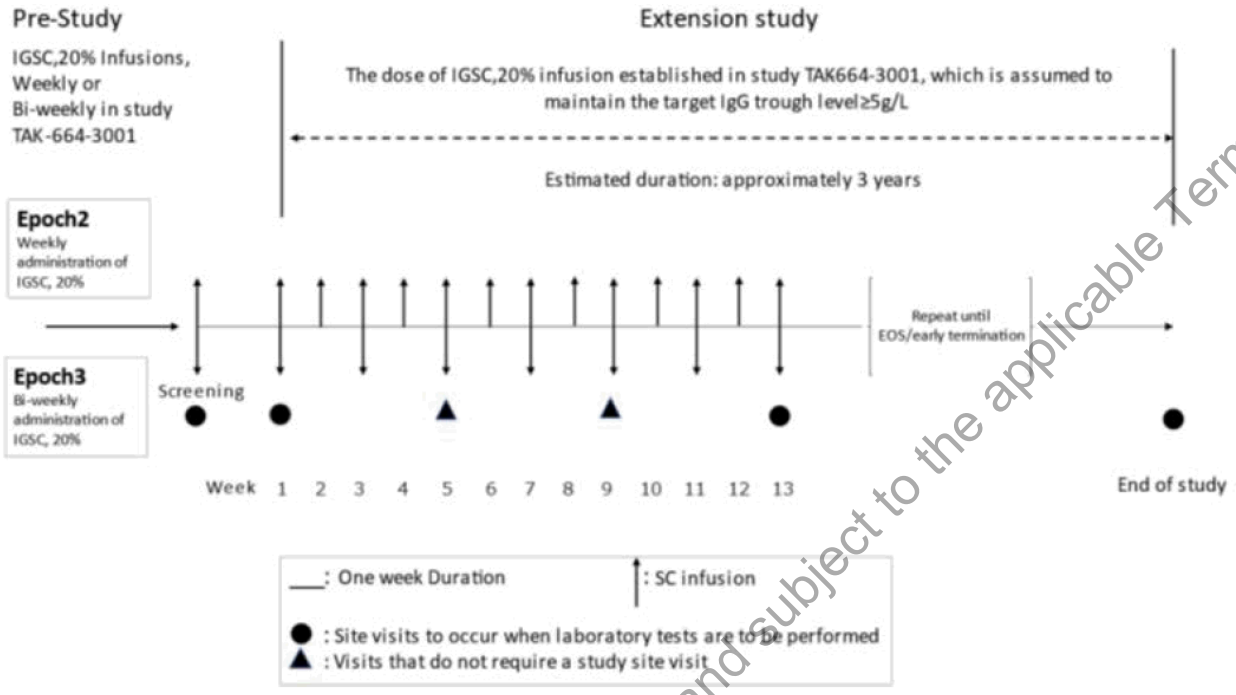
1. Subjects complete Epoch 2, in which IGSC, 20% is administered weekly, and do not enter Epoch 3.

2. Subjects complete Epoch 3, in which IGSC, 20% is administered biweekly.

Subjects who successfully complete Epoch 2 and enter Epoch 3, but do not successfully complete Epoch 3 will not be eligible to enter this study.

A schematic of the study design is provided in Figure 1.

Figure 1 Schematic of Study Design



Abbreviations: EOS=End of Study, IgG= immunoglobulin G, IGSC= subcutaneous immunoglobulin, SC=subcutaneous.

The study consists of the following periods:

- Screening/Baseline Period

Informed consent is expected to be obtained at last visit or prior to last visit of Study TAK-664-3001.The subjects will undergo screening/baseline procedures for determination of eligibility before infusion of IGSC, 20%.

- IGSC, 20% Treatment Period

Eligible subjects will receive IGSC, 20% until the commercial IGSC, 20% is available at each study site or study termination (estimated duration: approximately 3 years).

The number of infusion visits and study site visits during the subcutaneous (SC) treatment period will depend on where the SC injection is administered. Infusions between mandatory study site visits are recommended to be home treatments. The decision where the SC injection is administered is made during Study TAK-664-3001, however the location of injection administration can be changed based on the investigator's and subject's agreement.

Subjects should come to the study site for visits when laboratory test samples are to be collected every 12 weeks. Subjects are not required to come to the study site if all procedures/assessments can be performed at home.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

No statistical hypothesis testing will be performed.

3.1 Statistical Hypotheses

Not applicable.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

No formal sample size calculation has been performed in this extension study. A sample size of approximately 16 subjects is the estimated maximal number of subjects who can enroll from the previous TAK-664-3001 study.

5.0 ANALYSIS SETS

5.1 Screened Set

The Screened Set will consist of *all subjects who have signed informed consent* in TAK-664-3002 study.

5.2 Core Study Screened Set

The Core Study Screened Set will consist of all subjects who have signed informed consent in TAK-664-3001 study.

5.3 Enrolled Set

The Enrolled Set will contain all subjects in the Screened Set for whom an enrollment number has been assigned in TAK-664-3002 study.

5.4 Core Study Enrolled Set

Core Study Enrolled Set will consist of all screened subjects for whom an enrollment number has been assigned in TAK-664-3001 study.

5.5 All-Treated Set

The All-Treated Set will contain all subjects in the Enrolled Set who received IGSC, 20% administration at least once in TAK-664-3002. This will be efficacy analysis set.

5.6 Core Study All-Treated Set

The Core Study All-Treated Set will contain all subjects in the Core Study Enrolled Set who received at least 1 dose of study drug (IGIV or IGSC) in TAK-664-3001.

5.7 Safety Analysis Set

The Safety Analysis Set (SAS) will contain all subjects in the Core Study Enrolled Set who received at least 1 dose of study drug (IGIV or IGSC) in TAK-664-3001.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

The combined data from the core study TAK-664-3001 and the extension TAK-664-3002 will be analyzed. *Continuous endpoints/outcome measures (e.g., change from baseline) will be summarized using the following descriptive statistics: number of subjects (n), mean, median, standard deviation (SD), minimum value, maximum value. Categorical endpoints/outcome measures (e.g., adverse events [AEs]) will be summarized in terms of number and percent of subjects and number of occurrences in each category.*

6.1.1 Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of study drug (intravenous immunoglobulin [IGIV] or IGSC) in TAK-664-3001.

IGSC reference start date is defined as the day of the first dose of IGSC in TAK-664-3001.

Throughout the rest of this document, "first dose of study drug" refers to the first dose of study drug (IGIV or IGSC) in TAK-664-3001 unless otherwise stated.

If the date of the event is on or after the reference date, then:

- Study Day = (date of event – reference date) + 1.

If the date of the event is prior to the reference date, then:

- Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Section 6.1.5.

6.1.2 Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date and time (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date and time coincide, that measurement will be considered pre-baseline, but AEs and medications commencing on the reference start date and time will be considered post-baseline. If the time of an event or assessment is not available for events and assessments occurring on the same day as reference start date, only the dates will be

taken into account when determining whether an event or assessment is pre-baseline or post-baseline.

6.1.3 General Choice of Analysis Sets for Analyses

Background summaries (e.g., subject disposition) will be based on the Enrolled Set.

Analysis of efficacy will be based on Core Study All-treated Set unless otherwise stated, and analysis of PK data (serum IgG trough concentrations) will be based on the All-Treated Set.

Analysis of safety and tolerability will be based on the SAS.

6.1.4 Multicenter Study

This study will be conducted by multiple investigators at multiple centers. Data from all centers will be pooled together in the analyses and there are no plans to perform an analysis of homogeneity of the results across centers.

6.1.5 Handling of Missing, Unused, and Spurious Data

No imputation for missing data will be applied except for the partial dates for prior/concomitant medications and AEs, the missing severity for AEs and the missing relationship to study drug for AEs.

Imputed data will not be presented in the listings. The original missing data will be presented in the listings.

6.1.5.1 Missing Medication Dates

Partial or completely missing medication dates will be handled as described below to determine if the medications are prior or concomitant relative to the reference start date. Imputed medication dates will not be presented in the listings.

6.1.5.1.1 Incomplete Start Date

- Missing day and month:
    - If the year of the incomplete start date is the same as the year of the date of the first dose of study drug, then the day and month of the date of the first dose of study drug will be assigned to the missing fields.
    - If the year of the incomplete start date is before the year of the date of the first dose of study drug, then December 31 will be assigned to the missing fields.
    - If the year of the incomplete start date is after the year of the date of the first dose of study drug, then 01 January will be assigned to the missing fields.

- Missing month only:
    - The day will be treated as missing and both month and day will be replaced according to the above procedure.
- Missing day only:
    - If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of study drug, then the day of the date of the first dose of study drug will be assigned to the missing day.
    - If either the year is before the year of the date of the first dose of study drug or if both years are the same but the month is before the month of the date of the first dose of study drug, then the last day of the month will be assigned to the missing day.
    - If either the year is after the year of the date of the first dose of study drug or if both years are the same but the month is after the month of the date of the first dose of study drug, then the first day of the month will be assigned to the missing day.

6.1.5.1.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

- Missing Day and Month
    - 31 December will be assigned to the missing fields.
- Missing Month only
    - The day will be treated as missing and both month and day will be replaced according to the above procedure.
- Missing Day only
- The last day of the month will be assigned to the missing day.

6.1.5.2 Missing AE Dates

The following approaches will be applied for missing AE dates:

- To facilitate categorization of AEs as treatment-emergent, imputation of dates will be used.
- If an AE start date is completely missing, then the AE will be considered treatment-emergent.
- For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to first study drug administration (e.g., AE start

year and month are the same as the year and month of the first dose of study drug), then the AE will be classified as treatment-emergent.

- To facilitate categorization of AEs as treatment-emergent, the same imputation of start date used for medication dates will be used of AE start date. See Section 6.1.5.1.1 for details. AE stop dates will not be imputed.

6.1.5.3 Missing Medical History Start Dates

Partial or completely missing medical history start dates will be handled same as missing AE start dates to determine whether a medical history is concurrent or not.

6.1.5.4 Missing Relationship to Study Drug for AEs

If the relationship to study drug is missing for an AE starting on or after the date of the first dose of study drug, a causality of "Related" will be assigned. The imputed values for relationship to study drug will be used for incidence summaries, while the actual values will be presented in data listings.

6.1.5.5 Missing Severity for AEs

If severity is missing for an AE starting prior to the date of the first dose of study drug, then no imputation will be applied. If the severity is missing for an AE starting on or after the date and time of the first dose of study drug, then the worst severity will be assigned, i.e., "Severe". The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

6.1.5.6 Character Values of Clinical Laboratory Variables

Any non-standard laboratory results will be converted to numeric values using the example rules shown in Table 1.

Table 1. Convention for Converting Non-Standard Laboratory Results

Non-Standard Lab Values	Standardized Numeric Values
<0.2	Deduct 0.01 from the reference value. i.e., 0.19
<0.1	Deduct 0.01 from the reference value. i.e., 0.09
>1.045	Add 0.001 to the reference value. i.e., 1.046
<3	Deduct 0.1 from the reference value. i.e., 2.9

6.2 Disposition of Subjects

Number of subjects screened/enrolled in TAK-664-3001 will be presented for the Core Study Screened Set. Number and percentage of subjects with screen failure in TAK-664-3001 will also be presented based on the Core Study Screened Set.

Number of subjects screened/enrolled in TAK-664-3002 will be presented for the Screened Set. Number and percentage of subjects with screen failure in TAK-664-3002 and reason for screen failure will also be presented based on the Screened Set.

Number and percentages of subjects treated, ongoing on treatment (for dry runs only), who completed/discontinued early from treatment (including reason for withdrawal), and who completed/discontinued early from the study (including reason for withdrawal) will be provided based on the All-Treated Set.

Similarly, number of subjects included and excluded from each analysis set (including reason for exclusion) will be summarized based on the Core Study Enrolled set. A listing showing inclusion and exclusion of each subject from each analysis set will be provided.

6.3 Protocol Deviations

Protocol deviations as obtained from a clinical trial management system (CTMS) will be assessed throughout the study. All identified deviations will be reported in the CTMS. Protocol deviations from the CTMS will be coded to severity categories ("major" and "minor") and provided as part of the CTMS transfer to Biostatistics.

Protocol deviations will be collected at both the site and subject level. Deviations at the site level will be applied to all subjects who were enrolled at that site at the time of the deviation.

Protocol deviations happened in TAK-664-3001 will be summarized by deviation type and severity for the Core Study Enrolled Set. Protocol deviations happened across TAK-664-3001 and TAK-664-3002 will be summarized by deviation type and severity for the Enrolled Set. All protocol deviations will be included in a subject listing. In particular, protocol deviations identified as related to the impact of COVID-19 will be flagged in the subject listings.

6.4 Demographic and Other Baseline Characteristics

6.4.1 Demographics and Other Baseline Characteristics

The following baseline demographic and other baseline characteristics collected in TAK-664-3001 will be reported for this study:

- Age (years)
- Age categories (<18 years / >=18 years)
- Sex
- Ethnicity
- Race

- Epoch Treatment at the End of TAK-664-3001 study (Epoch 2/Epoch 3)
- Weight at baseline (kg)
- Height at baseline (cm)
- BMI at baseline (kg/m^2) - calculated as weight (kg)/ [height $(m)^2$]

Age is the age at informed consent date.

Continuous demographic and other characteristics will be summarized using descriptive statistics based on the Core Study All-Treated Set and Enrolled Set. For categorical demographics, number and percentage of subjects in each category will be provided based on the Core Study All-Treated Set and Enrolled Set. Epoch Treatment at the End of TAK-664-3001 study (Epoch 2/Epoch 3) which is collected at the Screening/Baseline Visit of TAK-664-3002 study will only summarized for All-Treated Set.

The baseline demographic and other baseline characteristics will be presented in subject listing for Core Study All-Treated Set.

The demographic and other baseline characteristics collected at the Screening/Baseline Visit of TAK-664-3002 will be presented in subject listing for All-Treated Set.

6.4.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0 or newer, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) based on the Core Study All-Treated Set and Enrolled Set. A subject having more than one surgery/medical condition/disease within the same SOC/PT will be counted only once for that SOC or PT.

All medical history will be listed. Medical histories that started before first dose of study drug AND were on going at the time of the first dose of study drug or ended on the first dose of study drug will be flagged as “ongoing” in the listing.

6.5 Prior and Concomitant Medications/Procedures/Therapies

6.5.1 Prior Medications/Procedures/Therapies

Prior medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) dated 2020 Mar or newer. Prior therapies and procedures will be coded using MedDRA Version 23.0 or newer.

Prior medications/procedures/therapies are defined as any medication/procedure/therapy that started and stopped prior to the first dose of study drug.

Partial date imputation for medications is described in Section 6.1.5.1.

The prior medications will be summarized by the number and proportion of subjects within each Anatomical Therapeutic Chemical (ATC) Level 2 therapeutic class and PT for the Core Study All-Treated Set and All-Treated Set. The prior therapies and procedures will be summarized by the number and proportion of subjects within each SOC and PT for the Core Study All-Treated Set and All-Treated Set. Multiple medication usage by a subject in the same category (i.e., therapeutic class or PT) will be counted only once.

All prior therapies, procedures and medication will be listed for the Core Study All-Treated Set.

6.5.2 Concomitant Medications/Procedures/Therapies

Concomitant medications will be coded using the WHO Drug Dictionary dated 01 Mar 2020 or newer. Concomitant therapies and procedures will be coded using MedDRA Version 23.0 or newer.

Concomitant medications/procedures/therapies are defined as any medication/procedure/therapy that:

- started prior to, on or after the first dose of study drug (IGIV or IGSC) in TAK-664-3001 and started no later than the EOS/Early Termination Visit of TAK-664-3002,
- OR ended on or after the date of first dose of study drug (IGIV or IGSC) in TAK-664-3001 or were ongoing at the EOS of TAK-664-3002.

Partial date imputation for medications is described in Section 6.1.5.1.

Concomitant medications will be summarized by the number and proportion of subjects within each ATC Level 2 therapeutic class and PT for the Core Study All-Treated Set and All-Treated Set. The concomitant therapies and procedures will be summarized by the number and proportion of subjects within each SOC and PT for the Core Study All-Treated Set and All-Treated Set. Multiple medication usage by a subject in the same category (i.e., therapeutic class or PT) will be counted only once.

All concomitant therapies, procedures and medication will be listed for the Core Study All-Treated Set.

6.6 Safety Analysis

All safety summaries will be based on the SAS.

The definition of baseline is provided in Section 6.1.2.

All safety data, including derived data, will be presented in subject data listings.

6.6.1 Adverse Events

AEs will be coded using MedDRA Version 23.0 or newer.

TEAEs are defined as AEs with onset after date/time of first dose of study drug (IGIV or IGSC) in Study-TAK-664-3001 or Study-TAK-664-3002, or medical conditions present prior to the start of study drug Study-TAK-664-3001 or Study-TAK-664-3002 but increased in severity or relationship after date/time of first dose of study drug in Study-TAK-664-3001 or Study-TAK-664-3002.

IGSC TEAEs are defined as AEs with onset after date/time of first dose of IGSC in Study-TAK-664-3001 or Study-TAK-664-3002, or medical conditions present prior to the start of IGSC in Study-TAK-664-3001 or Study-TAK-664-3002 but increased in severity or relationship after date/time of first dose of IGSC in Study-TAK-664-3001 or Study-TAK-664-3002.

AEs with missing start/stop dates will be imputed as described in Section 6.1.5.2.

Only TEAEs will be analyzed. Non-TEAEs will be listed only.

Related AEs are defined as *any AE that is recorded as "possibly related" or "probably related" to study drug.*

Unrelated AEs are defined as *any AE recorded as "unlikely related" or "not related".*

Temporally associated AEs are defined as any AE that begin during study drug administration or within 72 hours of completion of study drug administration.

Missing relationship to study drug imputation is described in Section 6.1.5.4.

Missing severity imputation is described in Section 6.1.5.5.

The summaries described below will be based on the AEs happened across TAK-664-3001 and TAK-664-3002.

6.6.1.1 Occurrence and Number of TEAEs and IGSC TEAEs

An overall summary of number and percentage of subjects with any TEAE, any local/systemic TEAE, any related/unrelated local TEAE, any related/unrelated systemic TEAE, any related TEAE, any unrelated TEAE, any severe TEAE, any severe related TEAE, any serious TEAE, any nonserious TEAE, any serious related TEAE, any temporally associated TEAEs, any

temporally associated and related TEAEs, any TEAE leading to study discontinuation, any TEAE leading to study drug withdrawn and any TEAE leading to death as well as the total number of events for each category will be provided.

The number and percentage of subjects with any TEAE including and excluding infections (the definition of infection is provided in Section 6.8.2), as well as the total number of TEAEs, will be summarized by SOC and PT. This summary will be repeated for local TEAEs, systemic TEAEs, related TEAEs, related/unrelated TEAEs excluding infections, severe TEAEs, mild/moderate/severe related TEAEs excluding infections, serious TEAEs including and excluding infections, serious related/unrelated TEAEs including and excluding infections, local TEAEs including and excluding infections, local related/unrelated TEAEs excluding infections, mild/moderate/severe related local TEAEs excluding infections, systemic TEAEs excluding infections, systemic related/unrelated TEAEs excluding infections, mild/moderate/severe related systemic TEAEs excluding infections, temporally associated TEAEs including and excluding infections, related and temporally associated TEAEs including and excluding infections, related or temporally associated TEAEs including and excluding infections, TEAEs leading to study discontinuation excluding infections, and TEAEs leading to death for overall. In the summaries, SOC will be sorted alphabetically, and PT will be sorted within each SOC in descending frequency of the Total column.

The number and percentage of subjects with any TEAE, as well as the total number of TEAEs, will be summarized by PT. This summary will be repeated for TEAEs excluding infections and infection TEAEs. In the summaries, PT will be sorted in decreasing frequency.

A comprehensive summary table of number of subjects, number of events, number of events per infusion and number of events per subject will be provided for any TEAE including infections by PT, location (systemic or local), relationship and severity.

In AE incidence summaries, subjects with multiple events in the same category will be counted only once in the AE category. Subjects with events in more than one category will be counted once in each of the categories.

In AE count summaries, multiple occurrences of the same AE will be counted multiple times.

Subject with multiple severities of the same AE, the maximum severity (most serious severity) will be used in analysis. Similarly, in subjects with multiple relationships of the same AE, the worst relationship will be used in the analysis. If a subject experiences multiple severity of the same AE (e.g., 3 occurrences: 1 mild, 1 moderate, 1 severe) all categorized under the same causality assessment (e.g., all related to study drug), the AE with the maximum severity (AE that is severe) will be used in analysis.

If more than 1 AE occurs within the same Preferred Term (PT) for the same subject, then the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug. For example, if a subject experienced a mild headache not related to the study drug, and a moderate headache related to the study drug, then the subject will be counted once for headache using the moderate headache related to the study drug.

All the summaries above will be repeated for IGSC TEAEs. All AEs will be provided in subject listings. Study days relative to both reference start date and IGSC reference start date will be provided in the listings.

The following tables (an overall summary and summaries by SOC and PT) for TEAEs will also be provided by age categories (<18 years / >=18 years) and by dosing interval (weekly / biweekly). All the summaries above will be repeated for IGSC TEAEs.

An overall summary of number and percentage of subjects with any TEAE, any local/systemic TEAE, any related/unrelated local TEAE, any related/unrelated systemic TEAE, any related TEAE, any unrelated TEAE, any severe TEAE, any severe related TEAE, any serious TEAE, any nonserious TEAE, any serious related TEAE, any temporally associated TEAEs, any temporally associated and related TEAEs, any TEAE leading to study discontinuation, any TEAE leading to study drug withdrawn and any TEAE leading to death as well as the total number of events for each category will be provided.

The number and percentage of subjects with any TEAE including and excluding infections, as well as the total number of TEAEs, will be summarized by SOC and PT.

This summary will be repeated for local TEAEs, systemic TEAEs and related TEAEs.

6.6.1.2 TEAEs per Infusion, per Subject, per Subject-Year and IGSC TEAEs per Infusion, per Subject, per Subject-Year

The following summaries will be provided for overall:

- Number of TEAEs per infusion, by SOC and PT
- Number of TEAEs per subject, by SOC and PT
- Number of TEAEs per subject-year, by SOC and PT

Number of TEAEs per infusion is number of TEAEs divided by total number of infusions administered.

Number of TEAEs per subject is number of TEAEs divided by total number of subjects.

Number of TEAEs per subject-year is number of TEAEs divided by total number of days of exposure, converted into years. Days of exposure will be calculated as (last date in study - date of first dose of study drug [IGIV or IGSC] in TAK-664-3001) + 1.

The summaries above will be repeated for TEAEs excluding infections, related/unrelated TEAEs excluding infections, local TEAEs including and excluding infections, related/unrelated local TEAEs excluding infections, systemic TEAEs excluding infections, related/unrelated systemic TEAEs excluding infections, mild/moderate/severe related TEAEs excluding infections, serious TEAEs including and excluding infections, serious related/unrelated TEAEs including and excluding infections, temporally associated TEAEs including and excluding infections, related and temporally associated TEAEs including and excluding infections, and related or temporally associated TEAEs including and excluding infections for overall. In the summaries, SOC will be sorted alphabetically, and PT will be sorted within each SOC in descending frequency of the Total column.

All the summaries above will be repeated for IGSC TEAEs. For the calculation of number of IGSC TEAEs per subject-year, days of exposure for IGSC TEAE will be calculated as (last date in study - date of first dose of IGSC in TAK-664-3001) + 1.

The following summary for TEAEs will also be provided by age categories (<18 years / >=18 years) and by dosing interval (weekly / biweekly). The summary above will be repeated for IGSC TEAEs.

- Number of TEAEs per subject-year, by SOC and PT

6.6.2 Clinical Laboratory Outcomes

Laboratory evaluations that are performed at study site visits will be collected and processed via a central laboratory and presented in International System of Units (SI Units).

Clinical laboratory outcomes to be evaluated include the following:

Hematology	hemoglobin, hematocrit, erythrocytes (i.e., red blood cell count), leukocytes (i.e., white blood cell count [WBC]) and differential - basophils, eosinophils, lymphocytes, monocytes, neutrophils, platelet counts, absolute neutrophil counts (ANCs).
Chemistry	sodium, potassium, chloride, bicarbonate, protein, albumin, alanine transaminase (ALT), serum total bilirubin, aspartate transaminase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), serum creatinine, creatinine phosphokinase (CPK), glucose, haptoglobin, lipase.
Urinalysis	color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination.
Hemolysis*	direct antiglobulin test, urine hemosiderin

	*Hemolysis test will only be performed in subjects aged 12 years and older.
Specialty Tests	Hepatitis B Surface Antigen (HbsAg), Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV)-1/2.
Specific Antibody Tests	Clostridium tetani toxoid, Haemophilus influenzae Type B (HIB), Hepatitis B virus (HBV)

Hematology, chemistry, urinalysis, hemolysis and specific antibody results will be summarized as described below. Specialty test results will be listed only.

Raw (actual) clinical laboratory values and changes in raw values from baseline at each post-baseline assessment time point will be summarized for continuous variables. If more than one laboratory result is reported per study visit per parameter, the last non-missing result will be selected for analysis.

Shift from baseline (shift table) to minimum and maximum post-baseline assessment result will be provided for categorical variables. *Summaries of shift-from-baseline will be produced for each laboratory parameter that has a reference range, using the categories: low (below the lower limit of the reference range), normal (within the reference range), high (above the upper limit of the reference range), and missing. Missing data will not be imputed.*

Laboratory values for abnormalities for the following parameters will be classified according to a 5-point (Grades 0-4) toxicity grading scale provided in protocol Appendix D: ALP, ALT, AST, BUN, hemoglobin, lymphocytes, neutrophils, platelet count, potassium, serum creatinine, sodium, serum total bilirubin, WBC. The classification of abnormalities will be performed by the central laboratory and the toxicity grades will be provided in the raw datasets.

Shift-from-baseline to each post-baseline assessment time point and shift-from-baseline to the worse post-baseline assessment will be produced for the parameters above by toxicity grade.

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable (e.g., "<X"), a coded value will be used in the analysis instead as specified in Section 6.1.5.6. However, the actual values as reported in the database will be presented in data listings.

All laboratory test results will be presented in subject listings. Subjects with clinically significant abnormal laboratory test results will be listed. This listing will include all results of the laboratory parameter that was abnormal and determined to be clinically significant by the investigator for a subject across study visits to identify any trends.

6.6.3 Vital Signs

The following vital signs will be measured:

- Height (cm)
- Weight (kg)
- Body temperature (°C)
- Respiratory rate (breaths/min)
- Pulse rate (beats/min)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

Raw (actual) vital signs, and changes in raw values from baseline at each post-baseline assessment time point, will be summarized.

If more than one vital sign result is reported per time point per parameter, the last non-missing result will be selected for analysis.

6.6.4 Other Safety Data

6.6.4.1 Pregnancy Test

Pregnancy test results will be listed by study visit.

6.6.4.2 Physical Examination

Physical examination will be listed by study visit.

6.6.5 Extent of Exposure and Compliance

Extent of exposure will be summarized in terms of days in study (days) and total dose received (mg).

Days in study will be calculated as number of number of days from the first dose of study drug to the date of EOS Visit.

Average dose (mg/kg/week) will be calculated as the average of subject's dose (mg/kg) received at each visit during the corresponding period, while the dose received at each visit will be calculated as planned dose (mg/kg) [volume administered at the visit (mL) / planned volume (mL)] / dosing interval (weeks)].Treatment compliance (%) is defined as the percentage of planned doses received by the subject and will be calculated as number of doses received / number of planned doses * 100.

The number of planned doses is the number of doses planned to be administered up to the date of the EOS or early termination.

Descriptive statistics of days in study, total dose received, total number of doses received by the subject, treatment compliance, and the number and percentage of subjects that received at least 80% of planned doses (defined as treatment compliance >= 80%) will be presented.

6.6.6 Study Drug Administration

Number of infusions per subject, number of infusions per subject-year, number of infusions per month, number of infusion sites per infusion and number of infusion sites per month will be summarized.

Number of infusions per month will be calculated as [total number of infusions during the corresponding period / days of exposure] * 30.4 days per month.

Number of infusion sites per infusion will be calculated as total number of infusion sites during the corresponding period / total number of infusions.

Number of infusion sites per month will be calculated as total number of infusion sites /(duration in treatment (days) / 30.4 days per month).

Descriptive statistics of percentage of infusions completed as planned / with infusion rate reduced / interrupted / stopped / with infusion rate reduced or interrupted or stopped will be summarized. Descriptive statistics of duration of infusion (mins), maximum infusion rate per infusion site, infusion volume per infusion site will be presented.

Duration of infusion (mins) will be calculated as (infusion stop time – infusion start time), without considering the interruption.

A listing of study drug administration and injection report will be provided.

6.7 Tolerability Analysis

6.7.1 Tolerability Events

Tolerability events will be measured in terms of the number and percentage of subjects for which the infusion was not tolerable.

An infusion is considered tolerable if the infusion rate was not reduced, or the infusion was not interrupted or stopped, due to a TEAE related to study drug infusion.

Descriptive statistics of number and percentage of subjects with the following tolerability events as well as the total number of tolerability events will be provided for the SAS:

- Any study drug administration with the infusion rate reduced for tolerability concerns or for AEs
- Any study drug administration with the infusion interrupted for tolerability concerns or for AEs
- Any study drug administration with the infusion stopped for tolerability concerns or for AEs
- Any study drug administration with the infusion rate was reduced or interrupted or stopped for tolerability concerns or for AEs

Study drug administration with the infusion rate reduced/infusion interrupted/infusion stopped for tolerability concerns or for AEs are the corresponding events collected by the CRF page "Study Drug Administration – Subcutaneous" with "Reason infusion not completed as planned" = "Adverse Event" OR "Device Malfunction" OR "Other Reason".

Descriptive statistics of number and percentage of subjects with the following events as well as the total number of events will be provided for the SAS:

- Any study drug administration with the infusion rate reduced/infusion stopped with "Reason infusion not completed as planned" = "Adverse Event"
- Any study drug administration with the infusion rate reduced/infusion stopped with "Reason infusion not completed as planned" = "Device Malfunction"
- Any study drug administration with the infusion rate reduced/infusion stopped with "Reason infusion not completed as planned" = "Other Reason"

6.8 Efficacy Analysis

All efficacy summaries will be based on the Core Study All-Treated Set unless otherwise stated.

Efficacy data, including derived efficacy parameters defined in the subsections below, will be presented in subject data listings.

6.8.1 Annual Rate of Validated ASBIs per Subject

ASBIs will include bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess that are caused by a recognized bacterial pathogen. The diagnostic criteria for ASBIs are included in protocol Appendix E.

The annual rate of validated ASBIs will be calculated as the mean number of ASBIs per subject per year and be summarized using descriptive statistics.

Number of ASBIs per subject per year will be calculated as below:

- Number of ASBIs / duration of study * 365.25 days per year, where duration in study is calculated as the number of days from the first dose of study drug to the date of EOS/Early Termination Visit

Additionally, the generalized linear model procedure for Poisson regression with log link will be used via the SAS procedure PROC GENMOD to estimate ASBI rate per person per year and its one-sided 99% upper confidence bound (or equivalently, the upper bound of the two-sided 98% confidence interval). Subject-year will be calculated for each subject as (duration of study in days/365.25), and the natural log-transformed subject-year will be used in the generalized linear model as an offset variable. To handle over-dispersion, the exponential distribution dispersion parameter will be assumed to be given by the deviance divided by the degrees of freedom and all statistics will be adjusted accordingly. No covariates other than the intercept term will be included in the model. The estimated intercept term and the upper bound of its two-sided 98% CI will be transformed by using the natural exponential function, to provide the point estimate of the ASBI rate per person per year and its one-sided 99% upper confidence bound.

The number and percentage of subjects with bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess will be summarized.

The diagnosis of ASBIs will be presented in subject listings.

6.8.2 Annual Rate of All Infections per Subject

The preferred terms from MedDRA 23.0 SOC or newer “Infections and infestations” will be used to identify infections.

The annual rate of all infections will be calculated as the mean number of all infections per subject per year and be summarized using descriptive statistics. Point-estimate and 95% CI of the annual rate of all infections calculated using a Poisson model with subject-year in study as the offset variable will be provided.

Number of infections per subject per year will be calculated as below:

- Number of infections / duration of study * 365.25 days per year, where duration in study is calculated as the number of days from the first dose of study drug to the date of EOS/Early Termination Visit

6.8.3 Days Not Able to Attend School/Work or to Perform Normal Daily Activities Due to Illness/Infection

The days not able to attend school/work or perform normal daily activities due to illness/infection will be collected on the electronic case report form (eCRF) and standardized to per year (365.25 days), and will be calculated as below:

- Sum of days not able to attend school/work or perform normal daily activities due to illness/infection per subject / duration of study * 365.25 days per year, where duration in study is calculated as the number of days from the first dose of study drug to the date of EOS/Early Termination Visit

The mean of days not able to attend school/work or perform normal daily activities due to illness/infection per year will be summarized using descriptive statistics. Point-estimate and 95% CI of calculated using a Poisson model with subject-year in study as the offset variable will also be provided.

6.8.4 Days on Antibiotics

Antibiotics are defined as any medication under ATC Level 2 therapeutic class "ANTIBACTERIALS FOR SYSTEMIC USE".

Number of days on antibiotics is defined as the number of days that antibiotics were taken as concomitant medications and will be standardized to per year (365.25 days) and will be calculated as below:

- Sum of the actual number of distinct days that antibiotics were taken per subject / duration of study * 365.25 days per year, where duration in study is calculated as the number of days from the first dose of study drug to the date of EOS/Early Termination Visit

If a subject took multiple antibiotics on a single day, that day will be counted for only once. Partial date imputation for medications is described in Section 6.1.5.1.

The mean of days on antibiotics per year will be summarized using descriptive statistics. Point-estimate and 95% CI of calculated using a Poisson model with subject-year in study as the offset variable will also be provided.

6.8.5 Number of Hospitalizations Due to Illness/Infection and Length of stay

Number of hospitalizations will be collected on the eCRF.

Length of stay is defined as the duration of hospitalization and will be calculated as (date of hospital discharge - date of hospital admission) + 1. If the hospitalization is ongoing at the time

of EOS/Early Termination Visit, then the hospital discharge date will be imputed with the data cut-off date for the analysis.

Number of subjects with hospitalizations, number of hospitalizations, length of stay per stay and total length of stay per subject will be summarized descriptive statistics.

Number of subjects with hospitalization / number of hospitalizations / length of stay per stay / total length of stay per subject will also be standardized to per year (365.25 days) and will be calculated as below:

- Number of subjects with hospitalization OR number of hospitalizations OR number of days per stay OR number of days of total length of stay per subject / duration of study * 365.25 days per year, where duration in study is calculated as the number of days from the first dose of study drug to the date of EOS/Early Termination Visit

Point-estimate and 95% CI of number of hospitalizations per year / total length of stay per subject calculated using a Poisson model with subject-year in study as the offset variable will also be provided.

6.8.6 Number of Acute Physician Visits Due to Illness/Infection

Number of acute physician visits and emergency room visits will be collected on the eCRF and summarized descriptive statistics.

Number of acute physician visits / emergency room visits per subject will also be standardized to per year (365.25 days) as below:

- Number of acute physician visits OR emergency room visits per subject / duration of study * 365.25 days per year, where duration in study is calculated as the number of days from the first dose of study drug to the date of EOS/Early Termination Visit

Point-estimate and 95% CI of number of acute physician visits OR emergency room visits per subject calculated using a Poisson model with subject-year in study as the offset variable will also be provided by epoch and overall based on the All-Treated Set.

6.8.7 Treatment Preference

Treatment preference will be assessed at the EOS/Early Termination Visit.

Treatment preference assessed at the EOS/Early Termination Visit of TAK-664-3001 will be analyzed separately for the age groups 2-13 years (observer: parent) and 14 years and older

(observer: subject) for Core Study All-Treated Set. Age will be defined as the age at the Screening Visit of TAK-664-3001.

Treatment preference assessed at the EOS/Early Termination Visit of TAK-664-3002 will be analyzed separately for the age groups 2-13 years (observer: parent) and 14 years and older (observer: subject) for All-Treated Set. Age will be defined as the age at the Screening/Baseline Visit of TAK-664-3002.

Descriptive statistics of each question of treatment preference will be presented by visit and age groups (2-12 years; 13 years and older).

6.9 Pharmacokinetic Analysis

The PK analysis (total serum IgG trough concentrations and serum trough level of specific antibodies) will be based on the Core Study All-Treated Set.

6.9.1 Serum IgG Trough Analysis

The total serum trough levels of IgG (total serum trough total IgG antibodies and IgG subclasses) will be listed and summarized.

Values below the lower limit of quantitation (LLOQ) will be replaced as zero for descriptive statistics of serum IgG PK concentrations.

All serum IgG concentration data will be summarized by total IgG, IgG subclass (or specific antibodies) and/or scheduled timepoint, as appropriate. For the 3002 study data, mean (±SD) trough concentrations for IgG and IgG subclass will be presented by weekly or biweekly administration in a concentration-time plot on linear and semi-logarithmic (without SD) scale. Repeated and unscheduled measurements are included in the listings but not used for statistical analysis or summary tables, unless the repeated measurement was performed due to unreliable values/technical reasons, e.g., clotted samples.

Individual subject's serum trough levels of total IgG and IgG subclasses and actual sampling time will be listed by nominal sampling timepoint and summarized by dose, IgG, and IgG subclass with descriptive statistics such as number of observations (n), arithmetic mean, SD, coefficient of variation, minimum, maximum, median, first quartile (Q1), third quartile (Q3), interquartile range (IQR), geometric mean, geometric coefficient of variation and 2-sided 95% confidence interval (CI) of the geometric mean.

6.9.2 Serum Trough Level of Specific Antibodies

The serum trough levels of specific antibodies to relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae Type B [HIB] and HBV) will be listed and summarized.

Values below the lower limit of quantitation (LLOQ) will be replaced as zero for descriptive statistics of serum IgG PK concentrations.

All serum concentration data will be summarized by specific antibody status to relevant pathogens and scheduled timepoint, as appropriate. Repeated and unscheduled measurements are included in the listings but not used for statistical analysis or summary tables, unless the repeated measurement was performed due to unreliable values/technical reasons, e.g., clotted samples.

Individual subject's serum trough levels of specific antibody and actual sampling time will be listed by nominal sampling timepoint and summarized by specific antibody status to relevant pathogens with descriptive statistics such as n, arithmetic mean, SD, coefficient of variation, minimum, maximum, median, first quartile (Q1), third quartile (Q3), interquartile range (IQR), geometric mean, geometric coefficient of variation and 2-sided 95% confidence interval (CI) of the geometric mean.

6.10 Interim Analysis

An interim analysis of study data will be undertaken to support the Japanese New Drug Application submission as described below. It will summarize PK (Serum IgG trough levels), safety, efficacy, and tolerability of treatment with IGSC, 20% in all subjects with PID in this study. The snapshot date will be stated in the SAP. The target data will be all subject data obtained at snapshot date in this study. No adaptive design or data monitoring committee is planned for this study.

An interim analysis will be performed using the cut-off data of January 31, 2023.

6.11 Data Monitoring Committee

No data monitoring committee (DMC) is planned for this study.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

[Change 1] In protocol, it was stated that *for laboratory and vital sign analyses, baseline will be defined as the last non-missing value before the time of participation in this study.*

In this SAP, the definition of baseline is defined as the last non-missing measurement taken prior to reference start date and time, while reference start date is defined as the day of the first dose of study drug (IGIV or IGSC) in TAK-664-3001.

[Change 2] In protocol, it was stated that *Shift from baseline (shift table) to each post-baseline assessment time point will be provided for laboratory categorical variables.*

In this SAP, instead of shift from baseline to each post-baseline assessment time point, shift from baseline to minimum and maximum assessment result is proposed.

9.0 APPENDIX

9.1 Changes from the Previous Version of the SAP

Not Applicable.

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

9.2.1.1 Dates & Times

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

9.2.1.2 Spelling format

English US.

9.2.1.3 Paper Size, Orientation, and Margins

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

9.2.1.4 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.

9.2.1.5 Descriptive Statistics

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

- Minimum and maximum: N;
- Mean, median, lower and upper bounds of two-sided CI: N + 1;
- SD: N + 2.

9.2.1.6 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' and percentages <100.0 but >99.9 which will be presented as '>99.9'.

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

9.2.1.7 Listings

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

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

9.2.2 Definition of Baseline

Definition of baseline is provided in Section 6.1.2.

9.2.3 Definition of Visit Windows

No visit windowing will be performed for this study.

9.2.4 Presentation of Nominal Visits

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

Study	Study Visit	Label
TAK-664-3001	Screening/Baseline Visit	Screening
	Epoch 1 Week X	Epoch 1 Week X
	Epoch 2 Week X	Epoch 2 Week X
	Epoch 3 Week X	Epoch 3 Week X
TAK-664-3002	Screening/Baseline Visit	Ex Screening
	Week X	Ex Week

Ex = Extension

9.3 Analysis Software

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