



Statistical Analysis Plan

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Title: A Phase 3, Open-label, Non-controlled, Extension Study to Evaluate the Longterm Safety of TAK-771 in Japanese Patients With Primary Immunodeficiency Disease (PID)

Study Number: TAK-771-3005

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STATISTICAL ANALYSIS PLAN

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Study Title: A Phase 3, Open-label, Non-controlled, Extension Study to Evaluate the
Long-term Safety of TAK-771 in Japanese Patients with Primary
Immunodeficiency Disease (PID)

Phase: Phase 3

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Prepared by: [REDACTED]

Based on:

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
1.0	26APR2022	Not Applicable
2.0	19MAR2024	<ul style="list-style-type: none"> • Updated protocol version. • The same description as in Protocol was changed to italics. • Section 5: Added Epoch 2 Safety Analysis Set, Epoch 2 Full Analysis Set and Full Analysis Set for Extension Study, and unnecessary statements were removed from the PKAS description. • Revised the wording in each section to clarify whether it refers to "Epoch 2 of Study TAK-771-3004 or later" or "Study TAK-771-3005 or later". • Section 6.3.1: Primary Immunodeficiency Diagnosis was added. • Section 6.4, 6.4.1 and 6.4.2: Added the term "Procedures/Surgeries". Updated the term "therapy" to "surgery", as was done in Protocol 2.0. • Section 6.5.1.1: Added the types of tables to be analyzed and revised the derivations of local/systemic TEAE. • Section 6.5.1.2: Moved the relevant description to Section 6.5.1.1 because the contents of Section 6.5.1.1 were mixed up. The title of section 6.5.1.2 was also revised to match the description. • Section 6.5.1.3: Added a new section for subgroup analysis. • Section 6.5.2: Deleted unnecessary description regarding listings. • Section 6.5.4.1: Stated the definition of abnormal or above standard values of anti-rHuPH20 titer. • Section 6.6: Added EXFAS tables. • Section 6.6.1, 6.6.2: Added additional analysis. • Section 6.6.3: <ul style="list-style-type: none"> - Deleted number of subjects with hospitalizations and length of stay per stay. - Added derivation for the number of acute physician visits / emergency room visits. • Section 6.6.4: Revised the whole description. • Section 6.6.5: Added a new section. • Section 6.7: Since it was decided not to create a separate Clinical Pharmacology Analysis Plan, added a description about PK analysis. • Section 6.8: <ul style="list-style-type: none"> - For the number (percentage) of subjects for whom the infusion rate was reduced/interrupted/stopped for tolerability concerns or for AEs, derivation was revised.

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		<ul style="list-style-type: none">- Reference page in eCRF has changed from “Dosing Injection rHuPH20” to “Dosing Injection 10%IGI”.- Stated the definition of “subjects whose treatment interval from Study TAK-771-3004 in Epoch 2 through TAK-771-3005” and “subjects who maintained a treatment interval of 3 or 4 weeks for 48 weeks”.• Section 6.9: Changed the end of exposure as the end of treatment instead of the end of Epoch or study and deleted Total dose received.• Section 9.2.6: Added the logic of the end of Epoch 1 for subjects who completed Epoch 1 and continued to Epoch 2.• Section 9.2.7: Added the visit windows for home records of vital sign and PK/specific antibody measurements.
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ABBREVIATIONS

AE	adverse event
AGT	antiglobulin test
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASBI	acute serious bacterial infection
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
B19V	Parvovirus B19
BUN	blood urea nitrogen
COVID-19	Coronavirus disease 2019
CK	creatinine phosphokinase
cSCIG	conventional subcutaneous immunoglobulin
CTMS	clinical trial management system
DMC	Data Monitoring Committee
EOS	end of study
ET	early termination
EXSAS	Safety Analysis Set for Extension Study
FAS	full analysis set
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HIB	hepatitis B virus
HIV	human immunodeficiency virus
IgG	immunoglobulin G
IGI	immune globulin infusion
IVIG	intravenous immunoglobulin
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
n	number of subjects
PCR	polymerase chain reaction
PID	primary immunodeficiency diseases
PK	pharmacokinetic
PKAS	pharmacokinetic analysis set
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred Term
SAS	safety analysis set
SC	subcutaneous

SD	standard deviation
SI units	International System of Units
SOC	System Organ Class
SY	subject-year
TEAE	treatment-emergent adverse event
US	United States
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary

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1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

The primary objective of the study is to evaluate the long-term safety of TAK-771 in Japanese patients with primary immunodeficiency diseases (PID).

1.1.2 Exploratory Objectives

The exploratory objectives of this study are listed below:

- *To evaluate the efficacy of TAK-771 in Japanese patients with PID*
- *To assess serum trough immunoglobulin G (IgG) concentrations following 3- or 4-week intervals administration of TAK-771 in Japanese patients with PID*
- *To evaluate the tolerability of TAK-771 in Japanese patients with PID*
- *To assess treatment preference of Japanese patients with PID*
- *To evaluate the actual status of infusion in Japanese patients with PID*

1.2 Endpoints

1.2.1 Primary Endpoints

The primary endpoints of this study are listed below:

1.2.1.1 Safety endpoints

- *Occurrence of treatment-emergent adverse events (TEAEs)*
- *Development of positive titer ($\geq 1:160$) binding antibodies to Recombinant Human Hyaluronidase (rHuPH20) and development of positive neutralizing antibodies to rHuPH20*

1.2.2 Exploratory Endpoints

The exploratory endpoints of this study are listed below:

1.2.2.1 Efficacy Endpoints

- *Annual rate of validated acute serious bacterial infections (ASBIs) per subject*
- *Annual rate of all infections per subject*
- *Healthcare 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*

1.2.2.2 Pharmacokinetic Endpoints

- *Serum trough levels of total IgG measured in the treatment period*

1.2.2.3 Safety Endpoints

- Changes in clinical laboratory parameters
 - Changes in vital signs and body weight
 - Relationship between anti-rHuPH20 antibody titer (elevated, not elevated) and the occurrence of adverse events (AE)s
- It will be assessed if at least 5 subjects have elevated titers cumulatively from the preceding Study TAK-771-3004. Subjects who have two consecutive anti-rHuPH20 binding antibody titers of $\geq 1:160$ which are elevated from the subject's titers at baseline in the preceding Study TAK-771-3004 are defined as having elevated titers.*

1.2.2.4 Tolerability Endpoints

- Occurrence of tolerability events related to the infusion of TAK-771 in the treatment period.
- Ability to maintain a regular treatment interval of 3 or 4 weeks

1.2.2.5 Other Endpoints

- Treatment preference assessed by a Patient Preference Questionnaire at End-of-Study (EOS)/Early termination (ET)
- Mode of administrations, including but not limited to: number of infusions per month, number of infusion sites per infusion, number of infusion sites per month, duration of individual infusions, maximum infusion rate/site, and infusion volume/site.

1.3 Estimand

Not applicable.

2.0 STUDY DESIGN

This is a phase 3, prospective, multicenter, open-label, non-controlled, single-arm extension study to evaluate the long-term safety of TAK-771 in Japanese patients with PID. This study will enroll patients with PID who successfully complete Study TAK-771-3004 and wish to continue TAK-771 administration. Of the 15 subjects to be enrolled in the Study TAK-771-3004, 12 subjects are expected to complete the study and approximately 10 subjects are expected to be enrolled in this Study TAK-771-3005. Up to 10 clinical sites located in Japan are planned.

The study consists of signing informed (e)Consent, Screening/Baseline visit, treatment period, and EOS/ET visit.

Informed consent for this Study TAK-771-3005 is expected to be obtained prior to or at the last visit of the preceding Study TAK-771-3004.

Screening/Baseline Visit

After informed consent has been obtained, the subjects will undergo procedures for the determination of eligibility before the first administration of TAK-771 in this extension study. Baseline can correspond to the EOS visit of Study TAK-771-3004. In such a case, the Screening/Baseline visit and the EOS visit of Study TAK-771-3004 should be on the same day. If those visits happen on separate dates for a compelling reason, the Screening/Baseline visit in

this study must be within 6 days at a maximum (it should be aligned with the timepoint of SC infusion) from the EOS visit in Study TAK-771-3004 and the assessments at both visits can still be combined. After confirming the eligibility, proficiency of the subject (and/or, as applicable, a caregiver who may assist the subject with self-administration) in self-infusion procedures will be verified by the investigator/designee using a proficiency checklist. If a subject (and/or a caregiver) had already been verified to be proficient to have self-infusion in the preceding Study TAK-771-3004, the initial administration of TAK-771 in this study can be self-infusion at home.

Treatment Period

Subjects will continue TAK-771 administration at the same dose and frequency they had in the Study TAK-771-3004 until the commercial TAK-771 becomes available at each study site or study termination (estimated duration: approximately 3 years). The dose of TAK-771 will be adjusted to maintain the target IgG trough level of ≥ 5 g/L and the dosing intervals will be either 3 or 4 weeks, changeable on a case-by-case basis if necessary.

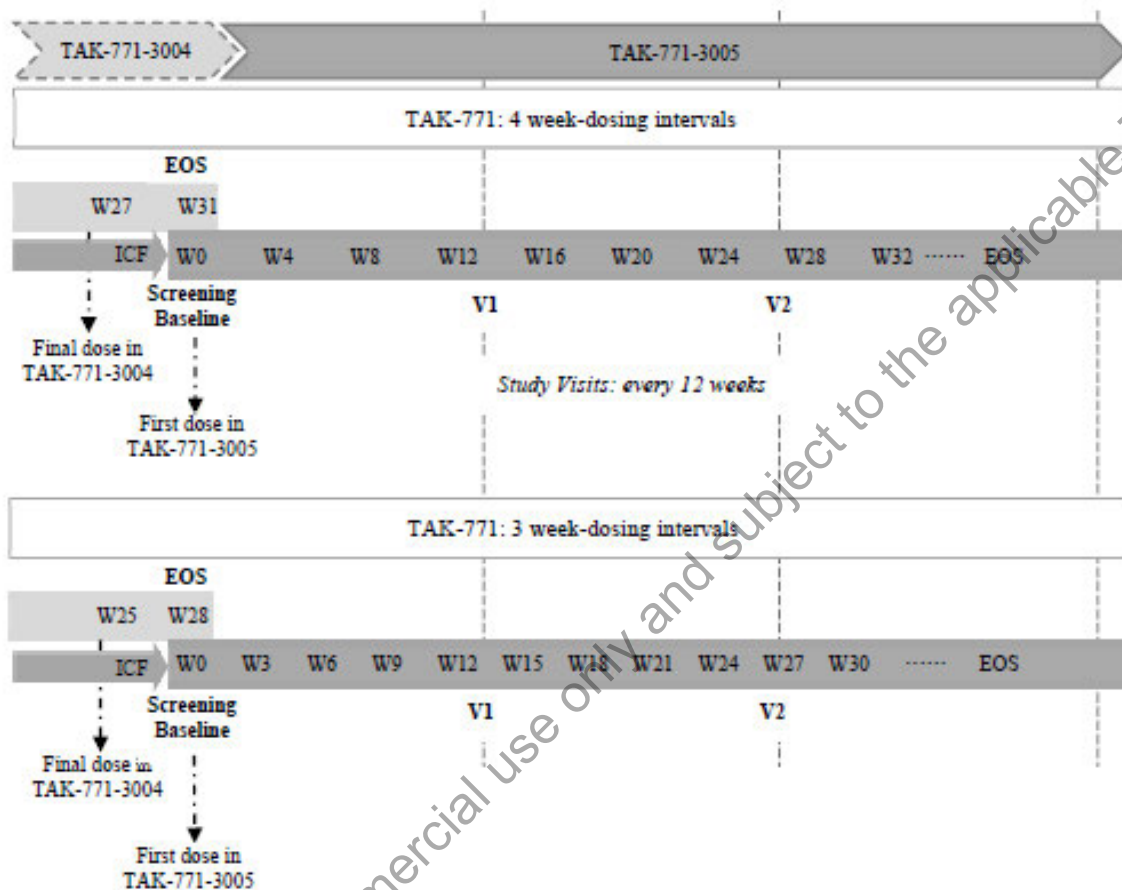
Mandatory study site visits are scheduled every 12 weeks for clinical and laboratory examination. Infusions between the mandatory study site visits are recommended to be home treatments for subjects whose proficiency in self-infusion procedures is verified. The study subject should be well trained for self-infusion process before they will do self-infusion at home. Investigator should confirm that the subject has enough knowledge and skill for self-infusion and need to record it. When infusions are self-administered at home, the infusion related data will be recorded in subject diary and assessments to be conducted on the day of administration (ie, vital signs and body weight) will also be conducted at home and recorded in the diary. Subjects who have not been confirmed to be proficient enough to have self-administration need to visit study site every 3 or 4 weeks for the study drug administration until the self-administration proficiency is verified. In such a case, the infusion related data will be recorded in the subject's source document and electronic case report form (eCRF) at study site. Other assessments to be conducted on the day of administration will also be measured/collected at study site and recorded in the subject's source documents and eCRFs.

End-of-Study/Early Termination Visit

All study subjects completing or exiting the study should complete the EOS/ET procedures at the EOS/ET visit.

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

Figure 1. Schematic of Study Design



Abbreviations: EOS=end-of-study; ICF=informed consent form; V=visit; W=week

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

A sample size of approximately 10 subjects is the estimated number of subjects who can enroll from the previous Study TAK-771-3004. Of the 15 subjects to be enrolled in Study TAK-771-3004, 12 subjects are expected to complete treatment period of Study TAK-771-3004, assuming a dropout rate of 20%.

5.0 ANALYSIS SETS

Analysis of safety and tolerability, efficacy, and PK data will be based on the following analysis sets (analysis populations), as defined:

5.1 Enrolled Set

The Enrolled Set will contain *all enrolled subjects who have signed informed (e)Consent in Study TAK-771-3004 and are assigned to subject identifier.*

5.2 Safety Analysis Set

The Safety Analysis Set (SAS) will contain *all enrolled subjects who received investigational drug in Study TAK-771-3004 at least once.*

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

Moreover, Epoch 2 Safety Analysis Set contains subjects that meet the above criteria for Safety Analysis Set in Epoch 2.

5.3 Safety Analysis Set for Extension Study

The EXSAS will contain *all enrolled subjects who received investigational drug in TAK-771-3005 at least once.*

Some of the analyses for SAS will be based on the EXSAS as well. The data after the start of TAK-771-3005 study will be included in these analyses.

5.4 Full Analysis Set

The Full Analysis Set (FAS) will contain *all enrolled subjects who received investigational drug in Study TAK-771-3004 at least once.*

Analysis of efficacy will be based on the FAS.

Moreover, Epoch 2 Full Analysis Set contains subjects that meet the above criteria for Full Analysis Set in Epoch 2.

5.5 Full Analysis Set for Extension Study

The EXFAS will contain *all enrolled subjects who received investigational drug in TAK-771-3005 at least once.*

Some of the analyses for FAS will be based on the EXFAS as well. The data after the start of TAK-771-3005 study will be included in these analyses.

5.6 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PKAS) will contain *all enrolled subjects who received investigational drug at least once in Study TAK-771-3004, have had at least 1 evaluable serum IgG concentration, and no major protocol deviations or events that would affect the serum IgG concentration analysis results.*

Analysis of serum IgG trough concentrations will be based on the PKAS.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Efficacy, safety and tolerability endpoints will be analyzed using descriptive statistics for continuous endpoints/outcome measures (e.g., change from baseline): number of subjects (n), mean, median, standard deviation (SD), minimum value, maximum value, 1st quartile (Q1) and 3rd quartile (Q3). Minimum and maximum values will be presented with the same number of decimal places as the recorded data. Means, medians, Q1 and Q3 will be presented to 1 more decimal place than the recorded data. The SDs will be presented to 2 more decimal places than the recorded data. Descriptive statistics will be summarized by Epoch and overall treatment period, where Epoch 1 is Epoch 1 from TAK-771-3004 study and Epoch 2 includes Epoch 2 from TAK-771-3004 study and TAK-771-3005 study (a continuation of TAK-771-3004 study). Summaries will be provided by treatment period, visit/timepoint, and overall treatment period, where applicable.

For the categorical endpoints/outcome measures of safety and tolerability assessments, the numbers and percentages of each possible value will be tabulated by Epoch and overall treatment period. The denominator for the percentage will be based on the number of subjects who provided non-missing responses to the categorical variable.

Analysis will be performed with pooled data from this study and the preceding Study TAK-771-3004.

6.2 Disposition of Subjects

The number of subjects screened for Study TAK-771-3005, the number and percentage of subjects with screen failure and reason for screen failure will be presented for all subjects who signed the Informed Consent Form for Study TAK-771-3005.

The number and percentage of subjects ongoing on treatment (only to be provided at Interim Analysis and Dry Run of Final Analysis), who completed/discontinued early from treatment (including reason for withdrawal), ongoing in study (only to be provided at Interim Analysis and Dry Run of Final Analysis), and who completed/discontinued early from the study (including reason for withdrawal) will be provided based on the EXSAS.

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

6.2.1 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 for Study TAK-771-3005 will be summarized by deviation type and severity for the EXSAS. All protocol deviations will be presented in a listing. In particular, protocol deviations identified as exclusion from the PKAS will be flagged in the listings.

6.2.2 COVID-19

A separate table of protocol deviations related to the Coronavirus disease 2019 (COVID-19) pandemic will be presented for TAK-771-3005 period. All protocol deviations related to the Coronavirus disease 2019 (COVID-19) pandemic will be presented in a listing. Missing data due to the COVID-19 pandemic will not be handled any differently than missing data for other reasons.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

The following subject demographic and baseline characteristics will all be collected in the preceding Study TAK-771-3004, and presented for the EXSAS:

- Age at informed consent obtained from TAK-771-3004 (years)
- Sex
- Ethnicity
- Race
- Weight at TAK-771-3004 baseline (kg)
- Height at TAK-771-3004 baseline (cm)
- BMI at TAK-771-3004 baseline (kg/m²)
- Dosing frequency per interval in TAK-771-3004 – 4-week dosing interval or 3-week dosing interval
- Prior treatment at consent obtained from TAK-771-3004 – IVIG, cSCIG or TAK-664
- Primary Immunodeficiency Diagnosis from TAK-771-3004 (see all the categories below)
 - Congenital Agammaglobulinemia - XLA
 - Agammaglobulinemia - AR
 - X-Linked Hyper IgM (XHIM)
 - Hyper-IgM - AR
 - Severe Combined Immune Deficiency
 - Common Variable Deficiency
 - Wiskott Aldrich Syndrome
 - Specific Antibody Deficiency

- Specific Antibody Deficiency with IgG Subclass Deficiency
- Specific Antibody Deficiency with Low IgG
- Ataxia Telangiectasia
- Muccocutaneous Candidiasis
- Complete DiGeorge Syndrome
- Other

Continuous measurements will be summarized using descriptive statistics, and categorical data will be presented by number and percentage of subjects in each category.

6.3.2 Medical History and Concurrent Conditions

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher and will be summarized by System Organ Class (SOC) and Preferred Term (PT) based on the EXSAS. A subject having more than one medical/surgical event 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 the date of informed consent in TAK-771-3004 study AND were on going at the time of the date of informed consent in TAK-771-3004 study or ended on the date of informed consent in TAK-771-3004 study will be flagged as “ongoing” in the listing.

6.4 Prior Medications and Concomitant Medications/Procedures/Surgeries

6.4.1 Prior Medications/Procedures/Surgeries

No prior treatment information will be collected in this study.

Prior medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) dated 01 Mar 2021 or newer. Prior surgeries and procedures will be coded using MedDRA version 24.0 or higher.

Prior medications/procedures/surgeries are defined as any medication/procedure/ surgery that started and stopped prior to the first dose of investigational drug in TAK-771-3004.

Partial date imputation for medications is described in [Section 9.2.3.1](#).

The prior medications/procedures/surgeries will be summarized by the number and percentage of subjects within each Preferred Term of a medical product, procedure/surgery name for the EXSAS. Multiple medication usage by a subject in the same category (i.e., Preferred Term of a medical product name) will be counted only once.

All prior surgeries, procedures and medications will be listed for the EXSAS.

6.4.2 Concomitant Medications/Procedures/Surgeries

Concomitant medications will be coded using the WHO-DD dated 01 Mar 2021 or newer. Concomitant surgeries and procedures will be coded using MedDRA version 24.0 or higher.

Concomitant medications/procedures/surgeries refer to all treatment taken between the dates of the first dose of investigational product in TAK-771-3004 and study completion/termination up to TAK-771-3005 study, inclusive.

Partial date imputation for medications is described in [Section 9.2.3.1](#).

Concomitant medications/procedures/surgeries will be summarized by the number and percentage of subjects within each medical product/procedure/surgery name for the EXSAS. Multiple medication usage by a subject in the same category (i.e., medical product name) will be counted only once.

All concomitant surgeries, procedures and medications will be listed for the EXSAS.

6.5 Safety Analysis

Safety summaries will be based on the SAS. All safety data, including derived data, will be presented in listings. However partial or missing date will appear as partial or missing in the listings.

In addition, safety summaries for AEs that occurred after the initial dose of investigational drug in TAK-771-3005 will be based on the EXSAS.

When analyzing each visit by dosing interval, the analysis continues with the first dosing interval information, even if a switch in dosing interval occurs in the middle of Epoch 2.

6.5.1 Adverse Events

All AEs will be coded using the MedDRA version 24.0 or higher and then reported by MedDRA SOC and PT, and overall. Only TEAEs will be analyzed.

Treatment-emergent adverse events, defined as AEs onset after date-time of first dose of investigational drug or medical conditions present prior to the start of investigational drug but increased in severity or relationship after date-time of first dose of investigational drug. Because all participants in this study have completed the first dose of investigational product in preceding Study TAK-771-3004, all of AEs collected in this study will be considered as TEAEs. Adverse events in this study will be collected from the completion of EOS visit in Study TAK-771-3004 until EOS/ET visit of this study.

Related TEAEs, defined as TEAEs causally related to investigational product.

Multiple Severities and Relationships: Subject with multiple severities of the same AE, the maximum severity (most serious severity) will be used in analysis, and similarly with multiple relationships of the same AE, the worst relationship will be used. If a subject experiences multiple severities 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 investigational drug), the AE with the maximum severity (AE that is severe) will be used in analysis.

Related AEs: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases,

complications, concomitant medications and concurrent treatments, may also be responsible. Relationship (causality) to study procedures should also be determined for all AEs. The relationship should be assessed as “Related” if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as “Not Related”.

Recurrent AEs: If more than 1 AE occurs within the same 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 investigational drug. For example, if a subject experienced a mild headache not related to the investigational drug, and a moderate headache related to investigational drug, then the subject will be counted once for headache using the moderate headache related to investigational drug.

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.

Summaries by SOC and PT: In the summaries, SOC will be sorted alphabetically, and PT will be sorted within each SOC in descending frequency in the Total column (i.e., the column of all subjects will be sorted in descending order after the sorting by SOC and PT).

Summaries by PT only: In the summaries, PT will be sorted in decreasing frequency in the table Total column.

6.5.1.1 Summaries of Treatment-Emergent Adverse Events

A TEAE will be counted for a specific Epoch, only if that TEAE started during that Epoch. For AE summaries by Epoch, the number of subjects reaching that Epoch will be presented and will be used as denominator for percentage calculation.

An overall summary of the number and percentage of subjects with any TEAE, any local TEAE, any local TEAE related to IP, any systemic TEAE, any systemic TEAE related to IP, any related/non-related TEAE, any severe TEAE, any severe related TEAE, any serious TEAE, any serious related TEAE, any infusion-associated TEAE, any TEAE leading to study discontinuation, and any TEAE leading to death, as well as the total number of events for TAK-771-3005 period and overall treatment period.

Derivation of Local TEAEs and systemic TEAEs are as follows:

- Local TEAEs: Injection Site Reaction Flag is checked as “Yes” from “Adverse Events” or “Adverse Events - 3005” page in eCRF (herein after called “Adverse Events page of eCRF”).
- Systemic TEAEs: Injection Site Reaction Flag is not checked as “Yes” from Adverse Event page of eCRF page in eCRF.

Infusion-associated TEAEs are captured in the Adverse Event page of eCRF as ‘Infusion-Related Reaction Flag’ checked as “Yes”.

The number and percentage of subjects with any TEAE, as well as the number of TEAEs, will be summarized by SOC, PT, TAK-771-3005 period and overall treatment period for IP related TEAEs. The summary by SOC, PT, TAK-771-3005 period and overall treatment period will be repeated for IP-related serious TEAEs and IP-related local/systemic TEAEs.

Additionally, the number and percentage of subjects with any TEAE, as well as the number of TEAEs, will be summarized by relationship to IP, SOC, PT, TAK-771-3005 period and overall treatment period. The same summary will be repeated for serious TEAEs, non-serious TEAEs, TEAEs leading to study discontinuation, TEAEs leading to death (overall treatment period only), TEAEs related to study procedure, Infusion associated TEAEs, local TEAEs and Systemic TEAEs.

The number and percentage of subjects with any TEAE, as well as the number of TEAEs, will be summarized by Severity, SOC, PT, TAK-771-3005 period and overall treatment period.

Similarly, the summary is repeated by Severity, SOC, PT, TAK-771-3005 period overall treatment period for related/non-related TEAEs.

6.5.1.2 Adverse Events per Infusion, per Subject, per Subject Year

The following summaries will be provided for TAK-771-3005 period and overall treatment period:

- *Number of TEAEs per infusion, by SOC and PT*
 $TEAEs \text{ per infusion} = \text{number of TEAEs} / \text{total number of infusions administered to subjects in the analysis set, SAS}$
- *Number of TEAEs per subject, by SOC and PT*
 $TEAEs \text{ per subject} = \text{number of TEAEs} / \text{total number of subjects in the analysis set, SAS}$
- *Number of TEAEs per Subject-Year (SY), by SOC and PT*
 $TEAEs \text{ per SY} = \text{number of TEAEs} / \text{total number of days of exposure, i.e., the sum of duration of treatment for all subjects in the analysis set, SAS, converted into years}$
Where duration of treatment is calculated as the number of days from the first dose of investigational drug to the end date of the Epoch with last treatment. (See [Section 9.2.6](#) for the definition of start date/end date of an Epoch).
- *Number of TEAEs per 1000 SYs will be provided for all TEAEs (if analyzable), by primary SOC and PT*
 $TEAEs \text{ per 1000 SYs} = 1000 \times (\text{Total Number of TEAEs in the study for all subjects} / \text{Total SYs in the study})$
Where Total SYs will be calculated by summing subjects' durations in the study. Each subject's duration will be calculated as the number of days from the first dose of investigational drug to the date of EOS/Early termination visit. If the subject's last date is missing, then the date of last dose of investigational drug will be used if available. This item is provided only for analyses for overall treatment period.

The above-mentioned summaries will be repeated for local/systemic TEAEs, related TEAEs, local/systemic related TEAEs, serious TEAEs, serious related TEAEs, infusion-associated TEAEs, serious infusion-associated TEAEs, severe infusion-associated TEAEs, related infusion-associated TEAEs, related severe infusion-associated TEAEs, related serious infusion-associated TEAEs.

6.5.1.3 Subgroup Analysis for Treatment-Emergent Adverse Events

The TEAE summaries in [Section 6.5.1.1](#) are provided for the following subgroups.

Subgroup: Age group [<18 , ≥ 18 years old]

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Summary: An overall summary, summary of TEAEs by SOC and PT, summary of related TEAEs by SOC and PT and summary of TEAEs by relationship to IP, SOC and PT

6.5.2 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).

The hematology panel will consist of complete blood count (hemoglobin, hematocrit, erythrocytes [i.e., red blood cell count], and leukocytes [i.e., white blood cell {WBC} count]) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. In addition, absolute neutrophil count (ANCs) will be determined by laboratory calculation.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, protein, albumin, alanine aminotransferase (ALT), serum total bilirubin, aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), serum creatinine, creatinine phosphokinase (CK), glucose, haptoglobin, lipase.

Urinalysis includes: color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination.

Specialty tests include: hepatitis B surface antigen (HBsAg), polymerase chain reaction (PCR) for hepatitis C virus (HCV) and PCR for human immunodeficiency virus (HIV)-1/2. For a schedule of laboratory test blood drawings, see Appendix 2 of clinical study protocol. These assessments will be performed at the central laboratory.

Additional specialty tests may be performed if required to establish the etiology of an AE or of abnormal laboratory results, such as tests for HIV, hepatitis A virus (HAV), hepatitis B virus (HBV), HCV, hepatitis E virus (HEV), or Parvovirus B19 (B19V).

Tests for hemolysis:

Scheduled tests will only be performed in subjects aged 12 years and older.

- *If hemolysis tests are scheduled when routine hematology and clinical chemistry are already being assessed at the visit, then tests for hemolysis will consist of:*
 - *direct antiglobulin test (Coombs-test or AGT)*
 - *urine hemosiderin*
- *If hemolysis tests are scheduled when routine hematology and clinical chemistry are Not being assessed at the visit, then tests for hemolysis will consist of:*
 - *direct antiglobulin test (Coombs-test or AGT)*
 - *urine hemosiderin*
 - *hemoglobin*
 - *lactate dehydrogenase*
 - *serum haptoglobin*

Hematology, clinical chemistry, urinalysis and hemolysis results will be summarized by visit for overall treatment period as described below. Specialty test results will be listed only.

Raw (actual) clinical laboratory values (in SI units) and changes in raw values from baseline in Study TAK-771-3004 at each post-baseline assessment time point will be summarized as continuous variables. See [Section 9.2.2](#) for definition of baseline. 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 in Study TAK-771-3004 (shift table) to each post-baseline assessment timepoint 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. In addition, shift-from-baseline summaries will be produced by toxicity grade.

Clinical laboratory values for abnormalities for the following parameters will be classified according to a 5-point (Grades 0-4) toxicity grading scale provided in Appendix 6 of clinical study protocol, and programming instruction can be found in [Appendix 9.4](#): ALP, ALT, AST, BUN, hemoglobin, lymphocytes, neutrophils, platelet count, potassium, serum creatinine, sodium, serum total bilirubin, WBC count. The classification of abnormalities will be performed by the central laboratory and the toxicity grades will be provided in the raw datasets.

If the reported value of a clinical laboratory parameter 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 9.2.3.5](#). However, the actual values as reported in the database will be presented in listings.

All clinical laboratory test results will be presented in listings.

6.5.3 Vital Signs

Vital signs include body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Blood pressure measurements will be taken after subjects remain sitting in an upright position for at least one minute.

Vital sign values are to be recorded on the appropriate eCRF.

Raw (actual) vital signs and body weight, and changes in raw values from baseline in Study TAK-771-3004 at each post-baseline assessment time point will be summarized by visit for overall treatment period.

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

6.5.4 Anti-rHuPH20 Antibodies

All subjects will be monitored for the formation of anti-rHuPH20 antibodies using validated anti-rHuPH20 antibody detection assay (also known as the Screening and Confirmatory Binding Assay). Samples with binding antibody titers $\geq 1:160$ will be analyzed for the presence of

neutralizing antibodies using a validated assay based on neutralization of rHuPH20 activity at the central laboratory.

Number and percentage of subjects who develop anti-rHuPH20 binding antibody titers of $\geq 1:160$ will be summarized. Samples with anti-rHuPH20 binding antibody titers $\geq 1:160$ will be analyzed for the presence of neutralizing antibodies, and the number and percentage of subjects who develop neutralizing antibodies to rHuPH20 will be summarized for the EXSAS.

The number and percentage of subject with any interpretation of hyaluronidase antibody test results will also be presented by categories of interpretation.

6.5.4.1 Exploratory Analysis

Subjects are defined as having elevated anti-rHuPH20 antibody titers if they have two consecutive anti-rHuPH20 binding antibody titers of $\geq 1:160$ which are elevated from the subject's titers at baseline in the preceding Study TAK-771-3004. If at least 5 subjects have elevated titers cumulatively from the preceding Study TAK-771-3004, then an exploratory analysis will be conducted to assess if there is any evidence of relationship between anti-rHuPH20 antibody titer (elevated, not elevated) and the occurrence of AEs. In addition, an exploratory analysis of any treatment-emergent abnormal titer or rises above baseline in the preceding Study TAK-771-3004 in anti-rHuPH20 antibody titer will be performed to assess if there is any evidence of relationship between anti-rHuPH20 antibody titer (elevated, not elevated) and the occurrence of AEs.

Anti-rHuPH20 titer that is abnormal or rises above baseline is defined as those with (1) those with any post-baseline values $\geq 1:160$ and with missing value in baseline or (2) those with post-baseline values is greater than the maximum value between baseline and 1:160.

For the analyses described above, the number and percentage of subjects with any TEAE by SOC and PT, will be provided by anti-rHuPH20 titer classification for TAK-771-3005 period based on the EXSAS. .

Subjects with multiple events in the same category (SOC/PT) will be counted only once in the AE category overall, and subjects with multiple events in the same category across different anti-rHuPH20 titer classification will be counted once per anti-rHuPH20 titer classification.

6.6 Efficacy Analysis

All efficacy analyses will be based on the FAS and EXFAS. Efficacy data, including derived efficacy parameters defined in the subsections below, will be presented in listings.

6.6.1 Annual Rate of Validated Acute Serious Bacterial Infections

Acute Serious Bacterial Infections 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 Appendix 5 of clinical study protocol.

The annual rate of validated ASBIs will be calculated as the mean number of validated ASBIs per subject per year and be summarized using descriptive statistics for TAK-771-3005 Period based on the EXFAS and overall treatment period based on the FAS.

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

- For TAK-771-3005 Period: number of ASBIs / duration of TAK-771-3005 Period * 365.25 days per year, where duration of TAK-771-3005 Period is calculated as the end date of the TAK-771-3005 Period – the start date of the TAK-771-3005 Period + 1 (See [Section 9.2.6](#) for the definition of start date/end date of an Epoch).
- For overall treatment period: number of validated ASBIs / duration of study * 365.25 days per year, where duration in study is calculated as the EOS/Early termination visit – the date of first dose of investigational drug in Study TAK-771-3004 + 1.

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 validated ASBIs will be presented in listings.

6.6.2 Annual Rate of All Infections

All infections will be reported as AEs and are defined as all PTs under the “Infections and infestations” SOC of MedDRA version 24.0 or higher.

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 for TAK-771-3005 Period based on the EXFAS and overall treatment period based on the FAS. 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 for TAK-771-3005 Period based on the EXFAS and overall treatment period based on FAS.

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

- For TAK-771-3005 Period: Number of infections / duration of TAK-771-3005 Period * 365.25 days per year, where duration of TAK-771-3005 Period is calculated as the end date of the TAK-771-3005 Period – the start date of the TAK-771-3005 Period + 1 (See [Section 9.2.6](#) for the definition of start date/end date of an Epoch).
- For overall treatment period: Number of infections / duration of study * 365.25 days per year, where duration of study is calculated as EOS/Early termination visit – date of first dose of investigational drug in Study TAK-771-3004 + 1.

The number and percentage of subjects with any infections will be summarized.

6.6.3 Healthcare Resource Utilization

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

Number of days not able to attend school/work or perform normal daily activities due to illness/infection will be collected using diaries or other source data options throughout the study and will be transcribed to electronic case report form (eCRF) and calculated as below:

- For TAK-771-3005 Period: Sum of days not able to attend school/work or perform normal daily activities due to illness/infection per subject / duration of TAK-771-3005 Period * 365.25 days per year, where duration of TAK-771-3005 Period is calculated as the end date of the TAK-771-3005 Period – the start date of the TAK-771-3005 Period + 1 (See [Section 9.2.6](#) for the definition of start date/end date of an Epoch).
- For overall treatment period: 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 of study is calculated as the end date of EOS/Early termination visit – date of first dose of investigational drug in Study TAK-771-3004 + 1.

The mean 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 calculation using Poisson model with subject-year in study as the offset variable by TAK-771-3005 Period based on the EXFAS and overall treatment period based on the FAS.

6.6.3.2 Days on Antibiotics

Number of days on antibiotics will be collected in the “Concomitant Medications” eCRF page. Antibiotics are defined as any medication coded under ATC Level 2 therapeutic class “Antibacterial for Systematic Use”.

Number of days on antibiotics is defined as the number of days that antibiotics were taken as concomitant medications and will be calculated as below:

- For TAK-771-3005 Period: Sum of the actual number of distinct days that antibiotics were taken per subject / duration of TAK-771-3005 Period * 365.25 days per year, where duration of TAK-771-3005 Period is calculated as the end date of the TAK-771-3005 Period – the start date of the TAK-771-3005 Period + 1 (See [Section 9.2.6](#) for the definition of start date/end date of an Epoch).
- For overall treatment period: Sum of the actual number of distinct days that antibiotics were taken per subject / duration of study * 365.25 days per year, where duration of study is calculated as the EOS/Early termination visit – date of first dose of investigational drug in Study TAK-771-3004 + 1.

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 9.2.3.1](#).

The mean days on antibiotics per year will be summarized using descriptive statistics, Point-estimate and 95% CI of calculation using Poisson model with subject-year in study as the offset variable by TAK-771-3005 Period based on the EXFAS and overall treatment period based on the FAS.

6.6.3.3 *Number of Hospitalizations Due to Illness/Infection and Length of Stay*

Admissions to a hospital as an inpatient and the number of days in hospital will be collected using diaries or other source data options throughout the study and will be transcribed to eCRFs.

Number of hospitalizations and total length of stay per subject will be summarized using descriptive statistics, Point-estimate and 95% CI of calculation using Poisson model with subject-year in study as the offset variable by TAK-771-3005 Period based on the EXFAS and overall treatment period based on the FAS.

Number of hospitalizations and total length of stay per subject will be calculated as below:

- For TAK-771-3005 Period: Number of hospitalizations OR number of days of total length of stay per subject / duration of TAK-771-3005 Period * 365.25 days per year, where duration of TAK-771-3005 Period is calculated as the end date of the TAK-771-3005 Period – the start date of the TAK-771-3005 Period + 1 (See [Section 9.2.6](#) for the definition of start date/end date of an Epoch).
- For overall treatment period: Number of hospitalizations OR number of days of total length of stay per subject / duration of study* 365.25 days per year, where duration of study is calculated as EOS/Early termination visit– the date of first dose of investigational drug in Study TAK-771-3004 + 1.

6.6.3.4 *Number of Acute (Urgent or Unscheduled) Physician Visits Due to Illness/Infection*

Acute (urgent or unscheduled) physician visits due to illness/infection, will be collected using diaries or other source data options throughout the study and will be transcribed to eCRFs.

Number of acute physician visits due to illness/infection will be summarized using descriptive statistics, Point-estimate and 95% CI of calculation using Poisson model with subject-year in study as the offset variable by TAK-771-3005 Period based on the EXFAS and overall treatment period based on the FAS.

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

- For TAK-771-3005 Period: Number of acute physician visits OR emergency room visits per subject / duration of TAK-771-3005 Period * 365.25 days per year, where duration of TAK-771-3005 Period is calculated as the start date of the TAK-771-3005 Period – the end date of the TAK-771-3005 Period + 1 (See [Section 9.2.6](#) for the definition of start/end of epoch).
- For overall treatment period: 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.

6.6.4 **Infusion Parameters in Epoch 2 and/or TAK-771-3005 Period**

Mode of administration will be summarized descriptively by TAK-771-3005 Period based on FAS and TAK-771-3004 in Epoch 2 through TAK-771-3005 based on EXFAS. The parameters may include but not limited to the following:

For TAK-771-3005 Period:

Derivation for number of infusion sites per infusion, duration of infusion, maximum infusion rate/site and infusion volume/site is also performed for each Dosing Interval.

- Number of infusions per month
Total number of infusions administered in each dosing interval on TAK-771-3005 Period / (duration of each dosing interval on TAK-771-3005 Period / 30.4375), where duration of each dosing interval on TAK-771-3005 Period is calculated as the sum of (the end date of the visit - start date of the visit + 1) for each visit per subject per dosing interval on TAK-771-3005 Period
(i.e: if a subject switches the dosing interval in the middle of TAK-771-3005 Period, the above sum will be calculated for 3 week dosing interval and 4 week dosing interval separately, instead of simply calculating it as the last date of the applicable dosing interval – first date of the applicable dosing interval + 1).
- Number of infusion sites per infusion
Total number of infusion sites injected on TAK-771-3005 Period / Total number of infusions administered on TAK-771-3005 Period.
- Number of infusion sites per month
Total number of infusion sites injected in each dosing interval on TAK-771-3005 Period / (duration of each dosing interval on TAK-771-3005 Period / 30.4375), where duration of each dosing interval on TAK-771-3005 Period is calculated as the sum of (the end date of the visit - start date of the visit + 1) for each visit per subject per dosing interval on TAK-771-3005 Period
(i.e: if a subject switches the dosing interval in the middle of TAK-771-3005 Period, the above sum will be calculated for 3 week dosing interval and 4 week dosing interval separately, instead of simply calculating it as the last date of the applicable dosing interval – first date of the applicable dosing interval + 1).
- Duration of infusion
End date and time of infusion on TAK-771-3005 Period– Start date and time of infusion on TAK-771-3005 Period for each infusion per subject.
- Maximum infusion rate/site
Maximum Infusion Rate results from CRF / number of infusion sites/body.
- Infusion volume/site
Scheduled Dose results from CRF / number of infusion sites/body.

For TAK-771-3004 in Epoch 2 through TAK-771-3005:

Derivation for number of infusion sites per infusion, duration of infusion, maximum infusion rate/site and infusion volume/site is also performed for each Dosing Interval.

- Number of infusions per month
Total number of infusions administered in each dosing interval on TAK-771-3004 in Epoch 2 through TAK-771-3005 / (duration in each dosing interval of TAK-771-3004 in Epoch 2 through TAK-771-3005 / 30.4375), where duration in each dosing interval of TAK-771-3004 in Epoch 2 through TAK-771-3005 is calculated as the sum of (the end date of visit - visit - start date of the visit + 1) for each visit per subject per dosing interval in Epoch 2 on TAK-771-3004 and TAK-771-3005.
(i.e: if a subject switches the dosing interval in the middle of Epoch 2 on TAK-771-3004 in Epoch 2 through TAK-771-3005, the above sum will be calculated for 3 week dosing interval and 4 week dosing interval separately, instead of simply calculating it as the last date of the applicable dosing interval – first date of the applicable dosing interval + 1).
- Number of infusion sites per infusion
Total number of infusion sites injected on TAK-771-3004 in Epoch 2 through TAK-771-3005 / Total number of infusions administered on TAK-771-3004 in Epoch 2 through TAK-771-3005.
- Number of infusion sites per month
Total number of infusion sites injected in each dosing interval on TAK-771-3004 in Epoch 2 through TAK-771-3005 / (duration in each dosing interval of TAK-771-3004 in Epoch 2 through TAK-771-3005 / 30.4375), where duration in each dosing interval of TAK-771-3004 in Epoch 2 through TAK-771-3005 is calculated as the sum of (the end date of visit - start date of the visit + 1) for each visit per subject per dosing interval in Epoch 2 on TAK-771-3004 and TAK-771-3005

(i.e: if a subject switches the dosing interval in the middle of TAK-771-3004 in Epoch 2 through TAK-771-3005, the above sum will be calculated for 3 week dosing interval and 4 week dosing interval separately, instead of simply calculating it as the last date of the applicable dosing interval – first date of the applicable dosing interval + 1).

- Duration of infusion
End date and time of infusion in TAK-771-3004 in Epoch 2 or TAK-771-3005 – Start date and time of infusion in Epoch 2 on TAK-771-3004 for each infusion per subject.
- Maximum infusion rate/site
Maximum Infusion Rate results from CRF / number of infusion sites/body.
- Infusion volume/site
Scheduled Dose results from CRF / number of infusion sites/body.

6.6.5 Dose/Week Administered

Dose/week administered is calculated as dose received/body weight/week (g/kg/week) using the latest weight at the time of that dose for each record of a subject. It will be summarized for Epoch 1, Epoch 2 in Study TAK-771-3004, TAK-771-3005 Period, Study TAK-771-3004 in Epoch 2 through TAK-771-3005 and overall treatment period, and the following age group:

- Subjects aged 2 to < 12 years
- Subjects aged 12 years and older
- Total

For dose/week administered, the number of subjects included in each categories, mean and SD will be calculated.

6.7 Pharmacokinetic Analysis

The total serum trough levels of IgG antibodies will be listed and summarized by dosing interval for TAK-771-3005 period, and the following age group.

- Total
- Subjects aged 2 to < 12 years
- Subjects aged 12 years and older

Similarly, specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae [HIB], Hepatitis B virus [HBV]) will be listed and summarized by dosing interval, Epoch and scheduled time point.

Descriptive statistics including geometric mean and the corresponding 2-sided 95% confidence interval will be presented.

Values below the lower limit of quantitation (LLOQ) will be considered as zero for descriptive statistics of serum IgG PK concentrations. LLOQ for total serum trough levels of IgG is 1.72 g/L.

Total serum IgG concentration data will be summarized by dosing interval for TAK-771-3005 period.

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. All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimals the data carry.

For the reporting of descriptive statistics for PK concentrations, the mean (and GeoMean where applicable) and SD, will be presented to one digit more precision than the source data. The minimum, median, and maximum will be presented to the same precision as the source data. Coefficient of variation (and GeoCV %) will always be reported to 1 decimal place. 2-sided 95% CIs of mean and GeoMean will be reported to the same precision as the mean and GeoMean.

For listings, the number of decimal places should be displayed as reported from Bioanalytical vendor.

6.8 Tolerability Analysis

A tolerability event is considered to have occurred if an infusion was not tolerable, which is defined as any changes in dosing of TAK-771 such as reduction of infusion rate, interruption or discontinuation of TAK-771 due to TEAEs related to TAK-771. Tolerability events will be measured based on EXSAS in terms of the number and percentage of subjects for which the infusion was not tolerable.

In addition, for all the summaries besides percentage of subjects who maintained a treatment interval of 3 or 4 weeks throughout the study participation, percentage of subjects who maintained a treatment interval of 3 or 4 weeks for 48 weeks from the start of Epoch 2 in Study TAK-771-3004 through TAK-771-3005, and maximum duration of maintaining a regular treatment interval of 3 or 4 weeks, tolerability analysis for after the initial dose of investigational drug in TAK-771-3005 will be summarized for SAS.

The following summaries will be provided:

- *Number (percentage) of subjects for whom the infusion rate was reduced for tolerability concerns or for AEs* Infusion rates reduced are collected as “Dose Reduced” or “Dose Rate Reduced” under the item of “Action Taken with Study Treatment”, as well as the “Reason for Dose Adjustment” is “Adverse Event” or “Intolerability” in either the “Dosing Injection 10%IGI” or 10%IGI part of “Dosing Injection” eCRF page. This summary will be provided by Epoch and overall treatment period.
- *Number (percentage) of subjects for whom the infusion was interrupted for tolerability concerns or for AEs* Infusion rates interrupted are collected as “Drug Interrupted” under the item of “Action Taken With Study Treatment”, as well as the “Reason for Dose Adjustment” is “Adverse Event” or “Intolerability” in either the “Dosing Injection 10%IGI” or 10%IGI part of “Dosing Injection” eCRF page. This summary will be provided by Epoch and overall treatment period.
- *Number (percentage) of subjects for whom the infusion was stopped for tolerability concerns or for AEs* Infusion rates stopped are collected as “Drug Withdrawn” under the item of “Action Taken With Study Treatment”, as well as the “Reason for Dose Adjustment” is “Adverse Event” or “Intolerability” in either the “Dosing Injection 10%IGI” or 10%IGI part of “Dosing Injection” eCRF page. This summary will be provided by Epoch and overall treatment period.
- *Number (percentage) of subjects for whom the infusion rate was reduced or interrupted or stopped for tolerability concerns or for AEs.* This summary will be provided by Epoch and overall treatment period.
- *Percentage of subjects who maintained a treatment interval of 3 or 4 weeks throughout the*

study participation. These subjects are defined as subjects whose treatment interval from Study TAK-771-3004 in Epoch 2 through TAK-771-3005 have not been changed in dose due to adverse events or tolerability. This summary will be provided for TAK-771-3005 Period and overall treatment period.

- *Percentage of subjects who maintained a treatment interval of 3 or 4 weeks for 48 weeks from the start of Epoch 2 in Study TAK-771-3004 through TAK-771-3005*
These subjects are defined as subjects who did not experience a change in treatment interval due to adverse events or tolerability from Epoch 2 of TAK-771-3004 to Week 24 of TAK-771-3005.
This summary will be provided for overall treatment period.
- *Maximum duration of maintaining a regular treatment interval of 3 or 4 weeks*
Maximum duration of maintaining a regular treatment interval is defined as the period of time at the regular treatment interval before a change in treatment interval due to adverse events or tolerability.
This summary will be provided for TAK-771-3005 Period and overall treatment period.

6.9 Extent of Exposure and Infusion Compliance

Extent of exposure will be summarized by TAK-771-3005 Period and overall treatment period in terms of days of exposure and number of infusions for the SAS and EXSAS.

Days of exposure will be calculated as below:

- For TAK-771-3005 Period: Number of days from the date of the first dose of investigational drug on TAK-771-3005 Period to the date of the end of treatment on TAK-771-3005 Period (See [Section 9.2.6](#) for the definition of start date/end date of an Epoch).
- For overall treatment period: Number of days from the date of the first dose of investigational drug in Study TAK-771-3004 to the end date of the end of treatment

Infusion compliance will be summarized by TAK-771-3005 Period and overall treatment period for the SAS and EXSAS.

Infusion compliance is calculated as the total number of applied infusions including completed, interrupted, and stopped infusions, divided by the number of expected infusions, multiplied by 100. The number of expected infusions is based on the following:

- Overall treatment period: Based on the number of infusions per dosing interval regimen (expected infusions from the start of Epoch 1 to the end of study).
- TAK-771-3005 period: Based on the number of infusions per dosing interval regimen from the start to end of TAK-771-3005, if Study TAK-771-3005 is completed (expected infusions from the start of TAK-771-3005 to end of TAK-771-3005).

Extent of exposure and compliance will be presented in listings. For 10% IGI, the details of overdose for the overall treatment period will also be presented in the listing.

6.10 Treatment Preference

Treatment preference will be analyzed separately for the age groups of 2 to 13 years (observer: parent) and 14 years and older (observer: subject). Age will be defined as the age at screening in Study TAK-771-3004.

Number and percentage of subjects per answer to each question of treatment preference will be presented based on the EXFAS by age groups (2-13 years; 14 years and older) at EOS/Early termination visit of TAK-771-3005 Period.

6.11 Other Safety Analysis

6.11.1 Physical Examination

Physical examination will be performed on the following body systems being described as normal or abnormal: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological.

All physical examination data will be listed only.

6.11.2 Pregnancy Test

A urine pregnancy test will be performed on all females of childbearing potential at the Screening/Baseline visit as well as distinct study visits (every 24 weeks), and EOS/ET visit. If the pregnancy test is performed at the EOS visit in the preceding Study TAK-771-3004, it can be used to determine the pregnancy status at the Screening/Baseline visit of this study and there will be no need to repeat the test in this study.

All pregnancy test data will be listed only.

6.12 Interim Analyses

Interim analysis will be performed within approximately 2 months from the regulatory submission for the approval of TAK-771 in Japan to present the most up-to-date data on the long-term safety of TAK-771 in Japanese subjects with PID to the Pharmaceuticals and Medical Devices Agency (PMDA) to support the data submitted for the approval. No adaptive design or data monitoring committee (DMC) is planned for this study.

7.0 REFERENCES

None

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

- Added the logic of the end of Epoch 1 on Section 9.2.6 for subjects who completed Epoch 1 and continued to Epoch 2.

9.0 APPENDIX

9.1 Changes from the Previous Version of the SAP

See REVISION HISTORY.

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 and median: 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):

- Subject ID,
- Parameter, when applicable
- Date/Time, when applicable
- Timepoint, when applicable.

9.2.2 Definition of Baseline

Unless otherwise specified, baseline is defined as the non-missing value before initial dose of study drug in Study TAK-771-3004. In the case where the timing of last non-missing value coincidence with the date of initial dose of investigational drug, the last non-missing value will be considered as pre-baseline.

9.2.3 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 investigational drug for AEs.

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

9.2.3.1 Missing medication dates

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

9.2.3.1.1 Incomplete Start Date

- If a medication start date is completely missing, then the medication will be considered concomitant.
- Missing day and month:
 - If the year of the incomplete start date is the same as the year of the date of informed consent in Study TAK-771-3004, then the day and month of informed consent in Study TAK-771-3004 will be assigned to the missing fields.
 - If the year of the incomplete start date is before the year of the date of informed consent in Study TAK-771-3004, 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 informed consent in Study TAK-771-3004, 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 informed consent in Study TAK-771-3004, then the day of the date of informed consent will be assigned to the missing day.
 - If either the year is before the year of the date of informed consent or if both years are the same but the month is before the month of the date of informed consent in Study TAK-771-3004, 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 informed consent in Study TAK-771-3004 or if both years are the same but the month is after the month of the date of informed consent in Study TAK-771-3004, then the first day of the month will be assigned to the missing day.

9.2.3.1.2 *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.

9.2.3.2 *Missing Adverse Event 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 and the database is from TAK-771-3004 study, then the AE will be considered treatment-emergent in Epoch 1, and the date of onset will be identified as the start date of Epoch 1. If an AE start date is completely missing and the database is from TAK-771-3005 study, then the AE will be considered treatment-emergent in Epoch 2, and the date of onset will be identified as the start date of Epoch 2 in TAK-771-3004.
- For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. The following rules will be applied to impute the missing numerical fields, and if the imputed date is before the start date of Epoch 2 in TAK-771-3004, then the AE will be considered treatment-emergent in Epoch 1. If the imputed onset date is before the treatment start date, then the onset date will be equal to the treatment start date. Otherwise, the AE will be considered treatment-emergent in Epoch 2.
 - Missing Day and Month: 1 January will be assigned to the missing fields.
 - Missing Day only: Day 1 will be assigned.

9.2.3.3 *Missing Relationship to Study Drug for Adverse Events*

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

9.2.3.4 *Missing Severity for Adverse Events*

If severity is missing for an AE starting prior to the date of the first dose of investigational 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 investigational drug in Study TAK-771-3004, 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 listings.

9.2.3.5 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

9.2.4 Reference Start Date and Study Day

Reference start date is defined as the day of the first dose of investigational drug, TAK-771-3004.

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

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

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

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

- Study Day = (date of event – reference start 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 9.2.3](#).

9.2.5 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.

9.2.6 Date of Start/End of Epoch

The start date of Epoch 1 is defined as the date of first investigational drug administration in TAK-771-3004 study, and the start date of Epoch 2 is defined as the date of Epoch 2 entry in TAK-771-3004 study.

The end date of an Epoch is defined as follow:

For Epoch 1:

- For subjects who completed Epoch 1 but did not continue to Epoch 2, end date is defined as, The date of last investigational drug administration +
(13 days if subjects are on the 3-week dosing regimen; or
20 days if subjects are on the 4-week dosing regimen)

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- For subjects who completed Epoch 1 and continued to Epoch 2, end date is defined as the date of first investigational drug administration in Epoch 2 - 1.

For Epoch 2:

- For subjects who completed Epoch 2 on Study TAK-771-3004 but did not enter Study TAK-771-3005 end date is defined as,
The date of last investigational drug administration in Study TAK-771-3004+
(20 days if subjects are on the 3-week dosing regimen; or
27 days if subjects are on the 4-week dosing regimen.
- For subjects who completed Epoch 2 on Study TAK-771-3005, end date is defined as,
The date of EOS/ET visit.

For subjects who discontinued the study during the corresponding Epoch, the early discontinuation date will be set as the end date of the corresponding Epoch.

9.2.7 Definition of Visit Windows

In general, there are no visit windowing is defined for this study.

However, for home treatment records of vital signs and PK/specific antibody measurements only, derive the visit as in the following (for Baseline visit, please refer to Section 9.2.2). If there are more than one results reported per subject in the same parameter and analysis visit, the last non-missing result will be selected for analysis. Target Day for records of TAK-771-3005 study is the date of first investigational drug administration in TAK-771-3005 study.

Table 2. Visit Windows for 4-week Dosing Interval, IVIG and cSCIG Subjects

Analysis Visit	Target Day	Allowance	Derivation
R-1 WEEK 1	1	-	For non-PK/specific antibody: Analysis Day of vital sign measurement =1 and Planned Timepoint is not Pre-dose. For PK/specific antibody: Analysis Day of PK/specific antibody measurement =1.
R-2 WEEK 2	8	-	Analysis Day of vital sign measurement =8
R-3 WEEK 4	22	-	Day of vital sign measurement =22
VISIT 1 WEEK 7	43	± 3	40 \leq Analysis Day of vital sign/PK measurement \leq 46
VISIT 2 WEEK 11	71	± 3	68 \leq Analysis Day of vital sign/PK measurement \leq 74
VISIT 3 WEEK 15	99	± 3	96 \leq Analysis Day of vital sign/PK measurement \leq 102

Analysis Visit	Target Day	Allowance	Derivation
VISIT 4 WEEK 19	127	± 3	124 \leq Analysis Day of vital sign/PK measurement \leq 130
VISIT 5 WEEK 23	155	± 3	152 \leq Analysis Day of vital sign/PK/specific antibody measurement \leq 158
VISIT 6 WEEK 27	183	± 3	180 \leq Analysis Day of vital sign/PK/specific antibody measurement \leq 186
TAK-771-3004 EOS/ET	211	-	For non-PK/specific antibody: Original visit of vital sign data is 'EOS/ET' in Study TAK-771-3004 data. For PK/specific antibody: 208 \leq Analysis Day of PK/specific antibody measurement \leq 214
TAK-771-3005 WEEK 0	1	-	For non-PK: Analysis Day of Study TAK-771-3005 vital sign measurement =1 and Planned Timepoint is not Pre-dose. For PK: Analysis Day of PK measurement =1.
TAK-771-3005 WEEK 4	29	± 3	26 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 32
TAK-771-3005 WEEK 8	57	± 3	54 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 60
TAK-771-3005 VISIT 1 WEEK 12	85	± 3	82 \leq Analysis Day of Study TAK-771-3005 vital sign/PK measurement \leq 88
TAK-771-3005 WEEK 16	113	± 3	110 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 116
TAK-771-3005 WEEK 20	141	± 3	138 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 144
TAK-771-3005 VISIT 2	169	± 3	166 \leq Analysis Day of Study TAK-771-3005 vital sign/PK measurement \leq 172

Analysis Visit	Target Day	Allowance	Derivation
WEEK 24			
TAK-771-3005 WEEK 28	197	± 3	194 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 200
TAK-771-3005 WEEK 32	225	± 3	222 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 228
TAK-771-3005 VISIT X WEEK XX*	XX*7 + 1	± 3	Target Day -3 to Target Day +3. For PK: AVISITS are provided for each "VISIT X".
TAK-771-3005 EOS/ET	For non-PK/specific antibody: - For PK/specific antibody: 28 days after the last dose	-	For non-PK/specific antibody: Original visit of vital sign data is 'EOS/ET' in Study TAK-771-3005 data. For PK/specific antibody: 25 days after the last dose to 31 days after the last dose.
End of Study	-	-	Original visit of vital sign data is 'END OF STUDY' in Study TAK-771-3005 data

* X appears every 12 weeks and means the number of study visit after "VISIT 3"(X: 3, 4, 5, ...).

XX appears every 4 weeks and means the number of weeks after WEEK 32 (XX: 32, 36, 40...).

Table 3. Visit Windows for 4-week Dosing Interval, TAK664 Subjects

Analysis Visit	Target Day	Allowance	Derivation
R-1 WEEK 1	1	-	For non-PK/specific antibody: Analysis Day of vital sign measurement =1 and Planned Timepoint is not Pre-dose. For PK/specific antibody: Analysis Day of PK/specific antibody measurement =1.
R-2 WEEK 2	8	-	Analysis Day of vital sign measurement =8
R-3 WEEK 4	22	-	Day of vital sign measurement =22
VISIT 1 WEEK 7	43	± 3	40 \leq Analysis Day of vital sign/PK measurement \leq 46

Analysis Visit	Target Day	Allowance	Derivation
VISIT 2 WEEK 11	71	± 3	68 \leq Analysis Day of vital sign/PK measurement \leq 74
VISIT 3 WEEK 15	99	± 3	96 \leq Analysis Day of vital sign/PK measurement \leq 102
VISIT 4 WEEK 19	127	± 3	124 \leq Analysis Day of vital sign/PK measurement \leq 130
VISIT 5 WEEK 23	155	± 3	152 \leq Analysis Day of vital sign/PK/specific antibody measurement \leq 158
VISIT 6 WEEK 27	183	± 3	180 \leq Analysis Day of vital sign/PK/specific antibody measurement \leq 186
TAK-771-3004 EOS/ET	211	-	For non-PK/specific antibody: Original visit of vital sign data is 'EOS/ET' in Study TAK-771-3004 data. For PK/specific antibody: 208 \leq Analysis Day of PK/specific antibody measurement \leq 214.
TAK-771-3005 WEEK 0	1	-	For non-PK: Analysis Day of Study TAK-771-3005 vital sign measurement =1 and Planned Timepoint is not Pre-dose. For PK: Analysis Day of PK measurement =1.
TAK-771-3005 WEEK 4	29	± 3	26 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 32
TAK-771-3005 WEEK 8	57	± 3	54 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 60
TAK-771-3005 VISIT 1 WEEK 12	85	± 3	82 \leq Analysis Day of Study TAK-771-3005 vital sign/PK measurement \leq 88
TAK-771-3005 WEEK 16	113	± 3	110 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 116
TAK-771-3005 WEEK 20	141	± 3	138 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 144

Analysis Visit	Target Day	Allowance	Derivation
TAK-771-3005 VISIT 2 WEEK 24	169	± 3	166 \leq Analysis Day of Study TAK-771-3005 vital sign/PK measurement \leq 172
TAK-771-3005 WEEK 28	197	± 3	194 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 200
TAK-771-3005 WEEK 32	225	± 3	222 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 228
TAK-771-3005 VISIT X WEEK XX*	XX*7 + 1	± 3	Target Day -3 to Target Day +3. For PK: AVISITS are provided for each "VISIT X".
TAK-771-3005 EOS/ET	For non-PK/specific antibody: - For PK/specific antibody: 28 days after the last dose	-	For non-PK/specific antibody: Original visit of vital sign data is 'EOS/ET' in Study TAK-771-3005 data. For PK/specific antibody: 25 days after the last dose to 31 days after the last dose.
End of Study	-	-	Original visit of vital sign data is 'END OF STUDY' in Study TAK-771-3005 data

* X appears every 12 weeks and means the number of study visit after "VISIT 3"(X: 3, 4, 5, ...).

XX appears every 4 weeks and means the number of weeks after WEEK 32 (XX: 32, 36, 40...).

Table 4. Visit Windows for 3-week Dosing Interval, IVIG and cSCIG Subjects

Analysis Visit	Target Day	Allowance	Derivation
R-1 WEEK 1	1	-	For non-PK/specific antibody: Analysis Day of vital sign measurement =1 and Planned Timepoint is not Pre-dose. For PK/specific antibody: Analysis Day of PK/specific antibody measurement =1.

Analysis Visit	Target Day	Allowance	Derivation
R-2 WEEK 2	8	-	Analysis Day of vital sign measurement =8
VISIT 1 WEEK 4	22	± 3	19 \leq Analysis Day of vital sign/PK measurement \leq 25
VISIT 2 WEEK 7	43	± 3	40 \leq Analysis Day of vital sign/PK measurement \leq 46
VISIT 3 WEEK 10	64	± 3	61 \leq Analysis Day of vital sign/PK measurement \leq 67
VISIT 4 WEEK 13	85	± 3	82 \leq Analysis Day of vital sign/PK measurement \leq 88
VISIT 5 WEEK 16	106	± 3	103 \leq Analysis Day of vital sign/PK measurement \leq 109
VISIT 6 WEEK 19	127	± 3	124 \leq Analysis Day of vital sign/PK measurement \leq 130
VISIT 7 WEEK 22	148	± 3	145 \leq Analysis Day of vital sign/PK/specific antibody measurement \leq 151
VISIT 8 WEEK 25	169	± 3	166 \leq Analysis Day of vital sign/PK/specific antibody measurement \leq 172
TAK-771-3004 EOS/ET	190	-	For non-PK/specific antibody: Original visit of vital sign data is 'EOS/ET' in Study TAK-771-3004 data. For PK/specific antibody: 187 \leq Analysis Day of PK/specific antibody measurement \leq 193.
TAK-771-3005 WEEK 0	1	-	For non-PK: Analysis Day of Study TAK-771-3005 vital sign/PK measurement =1 and Planned Timepoint is not Pre-dose. For PK: Analysis Day of PK measurement =1.
TAK-771-3005 WEEK 3	22	± 3	19 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 25

Analysis Visit	Target Day	Allowance	Derivation
TAK-771-3005 WEEK 6	43	± 3	40 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 46
TAK-771-3005 WEEK 9	64	± 3	61 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 67
TAK-771-3005 VISIT 1 WEEK 12	85	± 3	82 \leq Analysis Day of Study TAK-771-3005 vital sign/PK measurement \leq 88
TAK-771-3005 WEEK 15	106	± 3	103 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 109
TAK-771-3005 WEEK 18	127	± 3	124 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 130
TAK-771-3005 WEEK 21	148	± 3	145 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 151
TAK-771-3005 VISIT 2 WEEK 24	169	± 3	166 \leq Analysis Day of Study TAK-771-3005 vital sign/PK measurement \leq 172
TAK-771-3005 WEEK 27	190	± 3	187 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 193
TAK-771-3005 WEEK 30	211	± 3	208 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 214
TAK-771-3005 WEEK 33	232	± 3	229 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 235
TAK-771-3005 VISIT X WEEK XX*	XX*7 + 1	± 3	Target Day -3 to Target Day +3. For PK: AVISITS are provided for each "VISIT X".
TAK-771-3005 EOS/ET	For non-PK/specific antibody: - For PK/specific antibody: -	-	For non-PK/specific antibody: Original visit of vital sign data is 'EOS/ET' in Study TAK-771-3005 data. For PK/specific antibody: 18 days after the last dose to 24 days after the last dose.

Analysis Visit	Target Day	Allowance	Derivation
	21 days after the last dose		
End of Study	-	-	Original visit of vital sign data is 'END OF STUDY' in Study TAK-771-3005 data

* X appears every 12 weeks and means the number of study visit after "VISIT 3" (X: 3, 4, 5, ...).

XX appears every 3 weeks and means the number of weeks after WEEK 33 (XX: 36, 39, 42, ...).

Table 5. Visit Windows for 3-week Dosing Interval, TAK664 Subjects

Analysis Visit	Target Day	Allowance	Derivation
R-1 WEEK 1	1	-	For non-PK/specific antibody: Analysis Day of vital sign measurement =1 and Planned Timepoint is not Pre-dose. For PK/specific antibody: Analysis Day of PK/specific antibody measurement =1.
R-2 WEEK 2	8	-	Analysis Day of vital sign measurement =8
VISIT 1 WEEK 4	22	± 3	19 <= Analysis Day of vital sign/PK measurement <= 25
VISIT 2 WEEK 7	43	± 3	40 <= Analysis Day of vital sign/PK measurement <= 46
VISIT 3 WEEK 10	64	± 3	61 <= Analysis Day of vital sign/PK measurement <= 67
VISIT 4 WEEK 13	85	± 3	82 <= Analysis Day of vital sign/PK measurement <= 88
VISIT 5 WEEK 16	106	± 3	103 <= Analysis Day of vital sign/PK measurement <= 109
VISIT 6 WEEK 19	127	± 3	124 <= Analysis Day of vital sign/PK measurement <= 130
VISIT 7 WEEK 22	148	± 3	145 <= Analysis Day of vital sign/PK/specific antibody measurement <= 151

Analysis Visit	Target Day	Allowance	Derivation
VISIT 8 WEEK 25	169	± 3	166 \leq Analysis Day of vital sign/PK/specific antibody measurement \leq 172
TAK-771-3004 EOS/ET	190	-	For non-PK/specific antibody: Original visit of vital sign data is 'EOS/ET' in Study TAK-771-3004 data. For PK/specific antibody: 187 \leq Analysis Day of PK/specific antibody measurement \leq 193.
TAK-771-3005 WEEK 0	1	-	For non-PK: Analysis Day of Study TAK-771-3005 vital sign measurement =1 and Planned Timepoint is not Pre-dose. For PK: Analysis Day of PK measurement =1.
TAK-771-3005 WEEK 3	22	± 3	19 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 25
TAK-771-3005 WEEK 6	43	± 3	40 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 46
TAK-771-3005 WEEK 9	64	± 3	61 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 67
TAK-771-3005 VISIT 1 WEEK 12	85	± 3	82 \leq Analysis Day of Study TAK-771-3005 vital sign/PK measurement \leq 88
TAK-771-3005 WEEK 15	106	± 3	103 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 109
TAK-771-3005 WEEK 18	127	± 3	124 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 130
TAK-771-3005 WEEK 21	148	± 3	145 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 151
TAK-771-3005 VISIT 2 WEEK 24	169	± 3	166 \leq Analysis Day of Study TAK-771-3005 vital sign/PK measurement \leq 172

Analysis Visit	Target Day	Allowance	Derivation
TAK-771-3005 WEEK 27	190	± 3	187 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 193
TAK-771-3005 WEEK 30	211	± 3	208 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 214
TAK-771-3005 WEEK 33	232	± 3	229 \leq Analysis Day of Study TAK-771-3005 vital sign measurement \leq 235
TAK-771-3005 VISIT X WEEK XX*	XX*7 + 1	± 3	Target Day -3 to Target Day +3. For PK: AVISITS are provided for each "VISIT X"
TAK-771-3005 EOS/ET	For non-PK/specific antibody: - For PK/specific antibody: 21 days after the last dose		For non-PK/specific antibody: Original visit of vital sign data is 'EOS/ET' in Study TAK-771-3005 data. For PK/specific antibody: 18 days after the last dose to 24 days after the last dose.
End of Study	-	-	Original visit of vital sign data is 'END OF STUDY' in Study TAK-771-3005 data

* X appears every 12 weeks and means the number of study visit after "VISIT 3" (X: 3, 4, 5, ...).

XX appears every 3 weeks and means the number of weeks after WEEK 33 (XX: 36, 39, 42, ...).

9.3 Analysis Software

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

9.4 Programming Notes for Lab Toxicity Grading

The following table represents the protocol-specified grading criteria after the updates have been made to support good programming practice. It is planned to use these final updated criteria for the lab toxicity grading.

Protocol-Specified Toxicity Grading Scale for Laboratory Values – Version for programming														
Analyte	Direction	WNL is Grade 0	No Grade 1	Units	Grade 0 ^a		Grade 1 ^a		Grade 2 ^a		Grade 3 ^a		Grade 4 ^a	
					Low	High	Low	High	Low	High	Low	High	Low	High
ALP	Increase	YES	NO	ULN	.	.	.	<=2.5	>2.5	<=5.0	>5.0	<=20	>20.0	.
ALT	Increase	YES	NO	ULN	.	.	.	<=2.5	>2.5	<=5.0	>5.0	<=20	>20.0	.
AST	Increase	YES	NO	ULN	.	.	.	<=2.5	>2.5	<=5.0	>5.0	<=20	>20.0	.
LDH	Increase	YES	NO	ULN	.	.	.	<=2.5	>2.5	<=5.0	>5.0	<=20	>20.0	.
BUN	Increase	NO	NO	ULN	0.0	<=1.4	>1.4	<=2.5	>2.5	<=5.0	>5.0	<=10	>10.0	.
Hemoglobin	Decrease	YES	NO	g/dL	.	.	>=10.0		>=8.0	<10.0	>=6.5	<8.0	>=0.0	<6.5
Lymphocytes	Decrease	NO	NO	x10 ³ /uL	>=2.0	.	>=1.5	<2.0	>=1.0	<1.5	>=0.5	<1.0	>=0.0	<0.5
Neutrophils	Decrease	NO	NO	x10 ³ /uL	>=2.0	.	>=1.5	<2.0	>=1.0	<1.5	>=0.5	<1.0	>=0.0	<0.5
Platelet Count	Decrease	YES	NO	x10 ³ /uL	.	.	>=75		>=50.0	<75.0	>=25	<50.0	>=0.0	<25.0
Potassium	Decrease	NO	NO	mmol/L	>=3.5	.	>=3.0	<3.5	>=2.5	<3.0	>=2.0	<2.5	>=0.0	<2.0
Potassium	Increase	NO	NO	mmol/L	0.0	<=5.5	>5.5	<=6.0	>6.0	<=6.5	>6.5	<=7.0	>7.0	.
Serum Creatinine	Increase	YES	NO	ULN	.	.	.	<=1.5	>1.5	<=3.0	>3.0	<=6.0	>6.0	.
Sodium	Decrease	NO	NO	mmol/L	>=136	.	>=130	<136	>=123	<130	>=116	<123	>=0.0	<116
Sodium	Increase	NO	NO	mmol/L	0.0	<=145	>145	<=150	>150	<=157	>157	<=165	>165	.
Serum Total Bilirubin	Increase	YES	YES	ULN	<=1.5	>1.5	<=3.0	>3.0	.
WBC	Decrease	NO	NO	x10 ³ /uL	>=4.0	.	>=3.0	<4.0	>=2.0	<3.0	>=1.0	<2.0	>=0.0	<1.0

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, WBC=white blood cell, WNL=within normal limits, ULN=upper limit of normal, ECOG=Eastern Cooperative Oncology Group, WHO=World Health Organization

^a The toxicity scale is defined as: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening. Grading scale criteria taken from ECOG and WHO guidelines, with the exception of LDH which uses the same thresholds as defined for ALT and AST.