Statistical Analysis Plan

NCT Number: NCT05150340

Title: A Phase 3, Open-label, Non-controlled Study to Evaluate the Pharmacokinetics, Safety and Tolerability, and Efficacy of TAK-771 in Japanese Subjects with Primary Immunodeficiency Diseases (PID)

Study Number: TAK-771-3004

Document Version and Date: Version 2.0 / 21-Sep-2023

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STATISTICAL ANALYSIS PLAN

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Phase: Phase 3

Version: Final 2.0

Date: 21-Sep-2023

Prepared by: [redacted]

Based on:

Protocol Version: Protocol Version 2.0

Protocol Date: 17-May-2022

REVISION HISTORY

Version		Approval Date	Primary Rationale for Revision
1.0		29Oct2021	Not Applicable
2.0		21Sep2023	Updated protocol version. Deleted clinically significant changes in laboratory evaluations, vital signs and weight throughout SAP since these are no longer endpoints in Protocol Ver 2.0. Section 5.0: Added Epoch 2 Safety Analysis Set and Epoch 2 Full Analysis Set and added a description about PK Analysis Set. Section 6.3.1: Primary Immunodeficiency Diagnosis was added and revised the Analysis Set. Section 6.4: Updated the term "therapy" to "surgery", as was done in Protocol 2.0. Section 6.4.2: Revised the definition of concomitant according to Protocol 2.0. Section 6.6.1, Section 6.6.2: Clarification of analysis content. Section 6.6.3: - 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: Added derivations for maximum infusion rate/site and infusion volume/site. Section 6.7.1.1: Added the types of tables to be analyzed and revised the derivations of local/systemic TEAE. Section 6.7.3: Description has changed to the following, and also mentioned in Section 8.0. "For vital signs, change from pre infusion to post-infusion will also be summarized by Epoch and overall treatment period"→ "For vital signs, change from pre infusion to post-infusion will also be summarized for Epoch 1". Section 6.7.4.1: Revised the description according to Protocol 2.0 and added the logic for anti-rHuPH20 titer that is abnormal or rises above baseline. Removed the section for Life Quality Index, since it was removed from the Protocol. Section 6.8: - Added a derivation for the number of weeks to reach final dose interval (3 weeks or 4 weeks) in Epoch 1 and percentage of subjects who achieve a treatment interval of 3 or 4 weeks in Epoch 2 and reasons for

			dose adjustment for the number (percentage) of subjects for whom the infusion rate was reduced/interrupted/stopped for tolerability concerns or for AEs. - For the number (percentage) of subjects for whom the infusion rate was reduced/interrupted/stopped for tolerability concerns or for AEs, derivation was revised. - Reference page in eCRF has changed from "Dosing Injection rHuPH20" to "Dosing Injection 10%IGI". 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. Added Number of infusions. Section 6.10.1.2: Changed the description to calculate SF-36 using special software. Section 6.10.3: Revised to calculate number and percentage of subjects in each category, instead of descriptive statistics. 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.

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ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASBI	acute serious bacterial infection
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
B19V	Parvovirus B19
BP	bodily pain
BUN	blood urea nitrogen
CL/F	apparent total clearance
C_{max}	maximum concentration
C_{min}	minimum concentration
COVID-19	coronavirus 2019
CPK	creatinine phosphokinase
cSCIG	conventional subcutaneous immunoglobulin
CTMS	clinical trial management system
eCRF	electronic case report form
EOS	end of study
FAS	full analysis set
GH	general health
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
HRQoL	health-related quality of life
IG	immunoglobulin
IgG	immunoglobulin G
IGI	immune globulin infusion
IVIG	intravenous immunoglobulin
LDH	lactate dehydrogenase
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MH	mental health
n	number of subjects

PCR	polymerase chain reaction
PCS	physical component summary
PF	physical functioning
PID	primary immunodeficiency diseases
PK	pharmacokinetic
PKAS	pharmacokinetic analysis set
PT	Preferred Term
RCS	role/social component summary
RE	role emotional
RP	role physical
SAS	safety analysis set
SC	subcutaneous
SCIG	subcutaneous immunoglobulin
SD	standard deviation
SF	social functioning
SI units	International System of Units
SOC	System Organ Class
SY	subject-year
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TSQM	Treatment Satisfaction Questionnaire for Medication
VAS	visual analogue scale
VT	vitality
V_z/F	apparent volume of distribution
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

The primary objective of the study is to assess serum trough levels of total immunoglobulin G (IgG) when using TAK-771 as maintenance therapy in Japanese subjects with Primary Immunodeficiency Diseases (PID).

1.1.2 Secondary Objectives

The secondary objectives of this study are listed below:

- To characterize the pharmacokinetic (PK) profiles of TAK-771 in Japanese subjects with PID following TAK-771 administration.
- To evaluate the safety and tolerability of TAK-771 in Japanese subjects with PID.
- To evaluate the efficacy of TAK-771 in Japanese subjects with PID.
- To assess disease activity and health-related quality of life (HRQoL) in Japanese subjects with PID following TAK-771 administration.

1.2 Endpoints

1.2.1 Primary Endpoint

The primary endpoint for the study is the serum trough levels of total IgG (total serum trough IgG antibodies) measured during the trough evaluation period of Epoch 2 (administration of TAK-771).

1.2.2 Secondary Endpoints

Secondary endpoints cover PK, safety and tolerability, efficacy, and disease activity and HRQoL.

1.2.2.1 Pharmacokinetic Endpoints

Pharmacokinetic endpoints and parameters:

- PK parameters for total serum levels of IgG and for IgG subclasses in PK assessment period in Epoch 2 (in a subset of 5 to 7 subjects aged 12 years and older), which may include but not limited to the following: maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve (AUC), half-life, apparent total clearance (CL/F), apparent volume of distribution (V_z/F), minimum concentration (C_{min}).
- Serum trough levels of IgG subclasses in the trough evaluation period of Epoch 2.

- Trough levels of specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae [HIB], Hepatitis B virus [HBV]) in Epoch 1 and 2.

1.2.2.2 Safety and Tolerability Endpoints

Safety endpoints/outcome measures:

- Occurrence of treatment-emergent adverse events (TEAEs) in Epoch 1 and 2, including but not limited to: TAK-771-related and non-related, serious, non-serious, severe, local and systemic TEAEs, as well as TEAEs leading to premature discontinuation from study, and infusion-associated TEAEs.
- Changes in clinical laboratory parameters in Epoch 1 and 2.
- Changes in vital signs and body weight in Epoch 1 and Epoch 2. Change from baseline in vital signs and body weight, and change from pre-infusion to post-infusion in vital signs.
- Development of positive titer (≥1:160) binding antibodies, and development of neutralizing antibodies, to Recombinant Human Hyaluronidase (rHuPH20) in Epoch 2.
  Number and percentage of subjects who develop anti-rHuPH20 binding antibody titers of ≥1:160.
  Number and percentage of subjects who develop neutralizing antibodies to rHuPH20.

Tolerability endpoints/outcome measures:

- Occurrence of tolerability events related to the infusion of TAK-771 in Epoch 1 and 2.
  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. Number and percentage of subjects who experienced tolerability events will be measured.
- Number of weeks to reach final dose interval (3 weeks or 4 weeks) in Epoch 1.
- Percentage of subjects who achieve a treatment interval of 3 or 4 weeks in Epoch 2.
- Percentage of subjects who maintain a treatment interval of 3 or 4 weeks in Epoch 2.

1.2.2.3 Efficacy Endpoints

Efficacy endpoints/outcome measures:

- Annual rate of validated acute serious bacterial infections (ASBIs) per subject in Epoch 1 and 2.
- Annual rate of all infections per subject in Epoch 1 and 2.
- Healthcare Resource Utilization in Epoch 1 and 2:
  - 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.
- Infusion parameters in Epoch 2, 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.

1.2.2.4 Disease Activity and Health-Related Quality of Life Endpoints

- QoL: PEDS-QL (Varni et al. 1999), SF-36 v2 (Ware and Sherbourne 1992), EQ-5D-3L Health Questionnaire (Shaw et al. 2005) in Epoch 1 and 2.
- Treatment Satisfaction (Treatment Satisfaction Questionnaire for Medication-9 [TSQM-9]) (Daly et al. 1991) in Epoch 1 and 2.
- Treatment Preference at End-of-study (EOS)/Early termination.

[redacted]

1.3 Estimand

Not applicable.

2.0 STUDY DESIGN

This is a phase 3, open-label, non-controlled, multi-dose, multicenter study to evaluate serum trough levels of IgG, PK, efficacy, safety and tolerability of TAK-771 in Japanese subjects with PID, as well as to assess disease activity and HRQoL. A total of 15 subjects aged 2 years or older will be enrolled, of whom 12 subjects are expected to complete the study. Approximately 10 to 15 study sites are planned, located in Japan.

This study will enroll patients with a confirmed diagnosis of PID, who have been receiving a consistent dose of intravenous immunoglobulin (IVIG), subcutaneous immunoglobulin (SCIG) or TAK-664*NOTE 1 at least 3 months prior to screening. The diagnosis must be confirmed by the Medical Director prior to TAK-771 treatment.

The study consists of signing informed (e)Consent, screening, treatment period (Epoch 1: dose ramp-up period, Epoch 2: dose adjustment period and trough evaluation period), and EOS/Early termination visit.

After informed consent has been obtained, subjects will undergo screening to determine the eligibility.

Screening

Subjects who are switching from IVIG or conventional subcutaneous immunoglobulin (cSCIG) will enter screening period for up to 13 weeks to undergo procedures for the determination of eligibility and will continue to receive their own immunoglobulin treatment at the same dose and dosing frequency as prescribed prior to their entry into this study. During the screening period, subjects will have IgG trough levels measured at least 2 timepoints. After confirming the eligibility, subjects will enter the Epoch 1 and receive the initial dosing of TAK-771 subcutaneous (SC) 1 week after the last IVIG or cSCIG administration.

Subjects who have been receiving TAK-664 and are switching from Study TAK-664-3001 or TAK-664-3002 (TAK-664 studies, hereafter) will directly move on to the treatment period without entering the screening period. To determine the eligibility, the data including the latest laboratory data and IgG trough levels collected in the TAK-664 studies will be used. After confirming the eligibility, subjects will enter the Epoch 1 and receive the initial dosing of TAK-771 SC 1 week (for subjects switching from TAK-664 weekly dosing) or 2 weeks (for subjects switching from TAK-664 bi-weekly dosing) after the last TAK-664 administration.

Epoch 1

For all subjects, TAK-771 will be started with the ramp-up infusion (3 to 6 weeks), see Section 6.3.3.1 of clinical study protocol for details.

Epoch 2

TAK-771 will be administered subcutaneously at 3- or 4-weeks dosing intervals after the ramp-up. Subjects will remain on this dosing interval until the end of 24-week treatment period.

PK assessment will be performed in 5 to 7 subjects aged 12 years and older. PK assessment will be started just before the last SC infusion (Week 27 [Visit 6] for 4-week dosing interval, and Week 25 [Visit 8] for 3-week dosing interval, depending on the subject's treatment schedule, see Figure 2 in clinical study protocol for details) and serum samples will be collected at 7 time points in total until the EOS visit. Alternatively, PK assessment can be started at 1 visit earlier (at Week 23 [Visit 5] for 4-week dosing interval, and Week 22 [Visit 7] for 3-week dosing interval, depending on the subject's treatment schedule) and completed just before the last SC infusion at the discretion of investigator. A schedule of PK assessment is provided in Appendix 2 of clinical study protocol.

All study subjects completing or exiting the study should complete the EOS/Early termination procedures. The visit will be 21 days after the last dose for 3-week dosing intervals and 28 days after the last dose for 4-week dosing intervals. This will mark the subjects' completion of the study. The recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first.

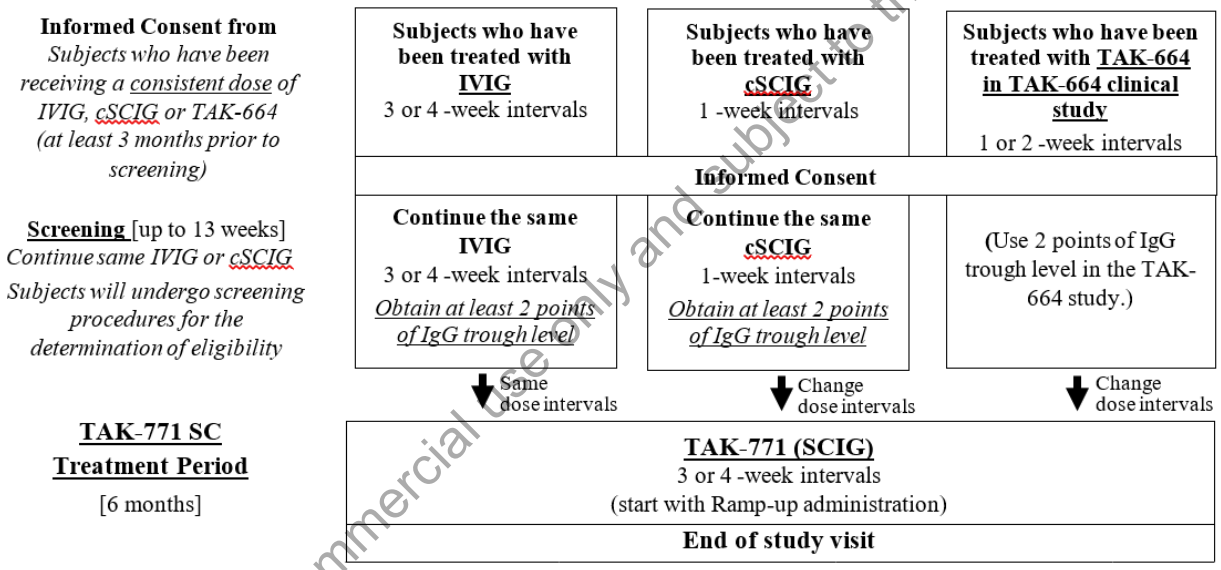
**NOTE 1: TAK-664 (20% immune globulin infusion [IGI]) is another immune globulin (IG) preparation for SC use that is currently under development. In Japan, there are 2 ongoing clinical studies in patients with PID; pivotal study (Study TAK-664-3001) and the extension study (Study TAK-664-3002).*

A schematic of the study design is shown in Figure 1. A schedule of assessments is listed in Section 1.3 of clinical study protocol.

Primary analysis will be performed, at database release after Last Participant Last Visit, at 100% primary endpoint data availability.

No interim analysis, adaptive design, or data monitoring committee are planned for this study.

Figure 1 Schematic of Study Design



IVIG: intravenous immunoglobulin; SC: subcutaneous; SCIG: subcutaneous immunoglobulin; cSCIG: conventional subcutaneous immunoglobulin; IgG: immunoglobulin G

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

The planned total sample size for this study is 15 subjects (enrolled subjects).

Of the 15 subjects to be enrolled, 12 subjects are expected to complete treatment period of the study, assuming a dropout rate of 20%. Subjects who prematurely discontinue the study will not be replaced. The number of subjects expected to complete treatment period (12 subjects) is considered adequate for the evaluation of serum trough IgG levels, safety and tolerability, and efficacy of TAK-771, as well as for the assessment of disease activity and HRQoL.

This study is not designed for statistical hypothesis testing and therefore the sample size is not based on statistical considerations such as study power, but instead mainly on consideration of the small size of the Japanese patient population with PID, a group of rare diseases. In Japan, the estimated prevalence of PIDs is 2 to 3 per 100,000 people and the estimated number of people affected is 2,900 to 3,500. Of the number of PID patients (2,900 to 3,500), an estimated 1,450 to 1,750 would be potential targets for IG replacement therapy. In clinical practice, most patients requiring a switch to SCIG (as is required by the study design) are already being treated with the approved SCIG product (Hizentra®). In the Hizentra® New Drug Application review report, the estimated number of patients who could receive IG replacement therapy was 1,155, which is lower than the estimated 1,450 to 1,750 patients. Even if all patients who are treated with IVIG or Hizentra® can participate in this study, the number of potentially eligible patients for the planned study is extremely limited, making it infeasible to enroll a large sample size. Therefore, the applicant made the study design that PID patients who complete ongoing clinical trials (TAK-664 studies) of TAK-664 (20% SCIG) are able to enroll in this study.

Based on feasibility and the sponsor's clinical experience with IgG products, a total sample size of 15 subjects (12 completers) is considered suitable for providing adequate estimates of trough levels (study primary objective), as well as adequate estimates of safety and tolerability, efficacy, disease activity and HRQoL (secondary objectives).

5.0 ANALYSIS SETS

Analysis of serum trough levels of IgG, efficacy, safety and tolerability, and disease activity and HRQoL data will be based on the following analysis sets (analysis populations).

5.1 Enrolled Set

The Enrolled Set will contain all enrolled subjects who have signed informed (e)Consent and are assigned to subject identification codes.

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

5.2 Safety Analysis Set

The Safety Analysis Set (SAS) will contain all enrolled subjects who received investigational drug 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 Full Analysis Set

The Full Analysis Set (FAS) will contain all enrolled subjects who received investigational drug at least once.

Analysis of efficacy, disease activity and HRQoL 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.

5.4 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PKAS) will contain all enrolled subjects who received investigational drug at least once, 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 and analysis of PK profiles will be based on the subset of 5 to 7 subjects aged 12 years and older in the PKAS.

For more information on PKAS, see Clinical Pharmacology Analysis Plan version 2.0. (Also see there for details on PKAS1 and PKAS2.)

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. Summaries will also 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.

6.2 Disposition of Subjects

The number of subjects screened, 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.

The number and percentage of subjects eligible for Epoch 1, treated, ongoing on treatment (only to be provided at dry run), who completed/discontinued early from treatment (including reason for withdrawal), ongoing in study by Epoch (only to be provided at dry run), and who completed/discontinued early from the study (including reason for withdrawal) will be provided by Epoch and overall treatment period based on the Enrolled Set.

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 will be summarized by deviation type and severity for the SAS. 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 and listing of protocol deviations related to the Coronavirus disease 2019 (COVID-19) pandemic will be presented for each epoch. 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 be presented for the SAS and PKAS1:

- Age at informed consent (years)
- Sex
- Ethnicity
- Race

- Weight at baseline (kg)
- Height at baseline (cm)
- BMI at baseline (kg/m^2)
- Dosing frequency per interval – 4-week dosing interval or 3-week dosing interval
- Prior treatment at consent –IVIG, cSCIG or TAK-664
- Primary Immunodeficiency Diagnosis (see all the categories below)
  - Congenital Agamma - XLA 21
  - 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 Medical 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 SAS. 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 first dose of investigational drug AND were on going at the time of the first dose of investigational drug or ended on the first dose of investigational drug will be flagged as “ongoing” in the listing.

6.4 Medication History and Concomitant Medications/Procedures/Surgeries

6.4.1 Prior Medications/Procedures/Surgeries

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.

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 SAS. 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 SAS.

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 and study completion/termination, 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 SAS. 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 SAS.

6.5 Pharmacokinetic Analysis

6.5.1 Primary and Secondary Pharmacokinetics Endpoints Analysis

The analyses of primary and secondary PK endpoints will be described in the Clinical Pharmacology Analysis Plan, which will be produced by [redacted] Clinical Pharmacology team.

6.6 Efficacy Analysis

All efficacy analyses will be based on the FAS. 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 ASBIs per subject per year and be summarized using descriptive statistics for Epoch 1 and overall treatment period based on the FAS.

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

- For Epoch 1: number of ASBIs / duration of in Epoch 1 * 365.25 days per year, where duration of Epoch 1 is calculated as the end date of Epoch 1 – the start date of Epoch 1 + 1 (See Section 9.2.6 for the definition of start date/end date of an Epoch).
- For overall treatment period: number of ASBIs / duration of study * 365.25 days per year, where duration in study is calculated as the date of EOS/Early termination visit – the date of first dose of investigational drug + 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 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 Epoch 1 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 Epoch 1 and overall treatment period based on FAS.

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

- For Epoch 1: number of infections / duration of in Epoch 1 * 365.25 days per year, where duration of Epoch 1 is calculated as the end date of Epoch 1 – the start date of Epoch 1 + 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 in study is calculated as the date of EOS/Early termination visit - the date of first dose of investigational drug + 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:

- By Epoch: sum of days not able to attend school/work or perform normal daily activities due to illness/infection per subject / duration of each Epoch * 365.25 days per year, where duration of each Epoch is calculated as the end date of the Epoch – the start date of the Epoch + 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 in study is calculated as the date of EOS/Early termination visit - the date of first dose of investigational drug + 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 by Epoch 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:

- By Epoch: sum of the actual number of distinct days that antibiotics were taken per subject / duration of each Epoch * 365.25 days per year, where duration of each Epoch is calculated as the end date of the Epoch – the start date of the Epoch + 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 in study is calculated as the date of EOS/Early termination visit - the date of first dose of investigational drug + 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 by Epoch 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 by Epoch and overall treatment period based on the FAS.

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

- By Epoch: number of hospitalizations OR number of days of total length of stay per subject / duration of each Epoch * 365.25 days per year, where duration of each Epoch is calculated as the end date of the Epoch – the start date of the Epoch + 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 in study is calculated as the date of EOS/Early termination visit - the date of first dose of investigational drug + 1.

A hospitalization will be counted for a specific Epoch only if that hospitalization started during that Epoch.

6.6.3.4 Number of Acute (Urgent of 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 by Epoch and overall treatment period based on the FAS.

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

- By Epoch: Number of acute physician visits OR emergency room visits per subject / duration of each epoch * 365.25 days per year, where duration of each epoch is calculated as the start date of the epoch – the end date of the epoch + 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

Infusion parameters in Epoch 2 will be summarized descriptively based on FAS. The parameters may include but not limited to the following:

- Number of infusions per month
- Total number of infusions administered in Epoch 2 / (duration of Epoch 2 / 30.4375), where duration of Epoch 2 is calculated as the end date of the Epoch 2 – the start date of the Epoch 2 + 1 (See Section 9.2.6 for the definition of start date/end date of an Epoch).
- Number of infusion sites per infusion
- Total number of infusion sites injected in Epoch 2 / Total number of infusions administered in Epoch 2.
- Number of infusion sites per month
- Total number of infusion sites injected in Epoch 2 / (duration of Epoch 2 / 30.4375), where duration of Epoch 2 is calculated as the end date of the Epoch 2 – the start date of the Epoch 2 + 1 (See Section 9.2.6 for the definition of start date/end date of an Epoch).
- Duration of infusion
- End date and time of infusion in Epoch 2 – Start date and time of infusion in Epoch 2, 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.

6.7 Safety Analysis

All 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.

6.7.1 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. Non-TEAEs will be listed only.

Treatment-emergent adverse events, defined as AEs with onset after date-time of first dose of investigational drug but before EOS/Early termination visit, 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.

Non-TEAEs, defined as AEs with onset before date-time of first dose of investigational drug, or medical conditions present prior to the start of investigational drug but did not increase in severity or relationship after date-time of first dose of investigational drug.

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 Total column 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.

6.7.1.1 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 each category will be provided for each Epoch, 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" page in eCRF.
- Systemic TEAEs: Injection Site Reaction Flag is not checked as "Yes" from "Adverse Events" page in eCRF.

Infusion-associated TEAEs are captured in the "Adverse Events" eCRF page 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, Epoch and overall treatment period for IP related TEAEs. The summary by SOC, PT 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, Epoch 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, Epoch and overall treatment period. Similarly, the same summary by Severity, SOC, PT and overall treatment period is repeated for related/non-related TEAEs.

6.7.1.2 Adverse Events per Infusion, per Subject, per Subject Year

The following summaries will be provided for overall treatment period:

- Number of TEAEs per infusion, by SOC and PT
- TEAEs per infusion = number of TEAEs / total number of infusions administered to subjects in the analysis set, SAS
- Number of TEAEs per subject, by SOC and PT
- TEAEs per subject = number of TEAEs / total number of subjects in the analysis set, SAS
- Number of TEAEs per Subject-Year (SY), by SOC and PT
- TEAEs per SY = number of TEAEs / 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 per 1000 SYs = 1000 × (Total Number of TEAEs in the study for all subjects / 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.

The above-mentioned summaries will be repeated for TEAEs, 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.

6.7.1.3 Subgroup Analysis for Treatment-Emergent Adverse Events

The TEAE summaries in Section 6.7.1.1 are provided for the following subgroups.

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

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

6.7.2 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 (CPK), 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 Epoch and overall treatment period as described below. Specialty test results will be listed only.

Raw (actual) clinical laboratory values (SI units) and changes in raw values from baseline 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 (shift table) to each post-baseline assessment time point 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. 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.

6.7.3 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 at each post-baseline assessment time point will be summarized by Epoch and overall treatment period. For vital signs, change from pre-infusion to post-infusion will also be summarized for Epoch 1.

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

6.7.4 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 ≥ 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 ≥1:160 in Epoch 2 will be summarized. Samples with anti-rHuPH20 binding antibody titers ≥1:160 will be analyzed for the presence of neutralizing antibodies, and the number and percentage of subjects who develop neutralizing antibodies to rHuPH20 in Epoch 2 will be summarized. The number and percentage of subject with any interpretation of hyaluronidase antibody test results will also be presented by categories of interpretation.

6.8 Tolerability Analysis

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 TAK-771 infusion. A tolerability event is considered to have occurred if an infusion was not tolerable. Tolerability events will be measured in terms of the number and percentage of subjects for which the infusion was not tolerable.

The following summaries will be provided:

- Number (percentage) of subjects for whom the infusion rate was reduced for tolerability concerns or for AEs and reasons for dose adjustment.
- 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 duration.
- 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 duration.
- 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 duration.
- 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 duration.
- Number of weeks to reach final dose interval (3 weeks or 4 weeks) in Epoch 1
- For subjects with E2 dosing start date, the number of weeks to reach final dose interval is defined as treatment duration of Epoch 1 /7
- Percentage of subjects who achieve a treatment interval of 3 or 4 weeks in Epoch 2
- Subjects who achieve a treatment interval of 3 or 4 weeks are the number of subjects with Epoch 2 dosing start date.
- Percentage of subjects who maintain a treatment interval of 3 or 4 weeks in Epoch 2
- Subjects who maintain a treatment interval are subjects whose regimen in Epoch 2 are retained the same as determined at the end of Epoch 1.

6.9 Extent of Exposure and Infusion Compliance

Extent of exposure will be summarized by Epoch and overall treatment period in terms of days of exposure and number of infusions for the SAS.

Days of exposure will be calculated as below:

- By Epoch: number of days from the date of the first dose of investigational drug in each Epoch to the date of the end of treatment in each Epoch (See Section 9.2.6 for the definition of start date/end date of an Epoch).
- For overall treatment period: number of number of days from the first dose of investigational drug to the date of the end of treatment.

Infusion compliance will be summarized by Epoch and overall treatment period for the SAS.

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 for each Epoch is based on the number of infusions per dosing interval regimen if each Epoch is completed.

Extent of exposure and infusion 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 Disease Activity and Health-related Quality of Life

All disease activity and HRQoL summaries will be based on the FAS, and all data will be provided in listings.

6.10.1 Quality of Life

Quality of life will be analyzed separately for the age groups of 2 to 7 years (PEDS-QL, observer: parent), 8 to13 years (PEDS-QL, observer: subject), and 14 years and older (SF-36, observer: subject). Additionally, all subjects will complete the EQ-5D-3L Health Questionnaire, analyzed separately for the age groups: 2 to11 years EQ-5D-3L (observer: parent) and 12 years and older EQ-5D-3L (observer: subject). Age will be defined as the age at screening. The observer should remain constant for the duration of subject participation. In the event that the language/age group is not available, the assessment in the closest language/age group will be used.

6.10.1.1 PEDS-QL

The PEDS-QL Inventory is a 23-item, brief measure of health-related quality of life in children and young people. The measure can be completed by parents as well as children and young people.

The 23 items in the PEDS-QL comprise 4 Generic Core Scales:

- Physical Functioning (8 items)
- Emotional Functioning (5 items)
- Social Functioning (5 items)
- School Functioning (5 items)

Items on the PEDS-QL will be reverse scored and transformed to a 0-100 scale using the following rules: 0 (Never) = 100; 1 (Almost Never) = 75; 2 (Sometimes) = 50; 3 (Often) = 25; 4 (Almost Always) = 0.

Scale scores will be calculated as the sum of the items over the number of items answered (to account for missing data). If more than 50% of items are missing, the scale score will not be computed.

Total scale score will be calculated as the mean of all items.

Descriptive statistics of total scale score of PEDS-QL and change from baseline (if both scores are available) will be presented by treatment interval, visit, and age groups (2-7 years; 8-13 years).

6.10.1.2 SF-36

SF-36 is a 36-item, patient-reported survey of patient health.

SF-36 measures eight scales: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH).

Two sets of scores will be derived from the SF-36: eight scale scores, and three summary scores: physical component summary (PCS) score, mental component summary (MCS) scores and role/social component summary (RCS).

PCS score, MCS score and RCS score can be calculated using Web Tool mentioned in Section 9.3. Use the latest PCS score, MCS score and RCS score (use “3PCS”, “3MCS” AND “3RCS” variables in the software output results file). Descriptive statistics of the PCS score, MCS score and RCS score, and the corresponding changes from baseline will be presented by treatment interval, visit for subjects with age of 14 years and older at screening.

6.10.1.3 EQ-5D-3L Health Questionnaire

EQ-5D-3L Health Questionnaire consists of 2 parts: the EQ-5D descriptive system and the EQ visual analogue scale (VAS).

EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems (Level 1), some problems (Level 2), and extreme problems (Level 3). This part of the EQ-5D-3L provides a descriptive profile that can be used to generate a health state profile. Each health state profile can be assigned a health state index score based on societal preference weights for the health state. Health state index scores generally range from less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than death) to 1 (perfect health), with higher scores indicating higher health utility. The health state index score will be calculated from individual health profiles using Japanese value set as listed in Table 1.

The health state index score h will be calculated using the following formula:

$$h = 1 - (\alpha + \Sigma_d \Sigma_l \beta_{dl} x_{dl})$$

where x_{dl} represents ten dummy variables that indicate the presence of either a Level 2 or a Level 3 in a given dimension of the evaluated state. In other words, d stands for the dimensions: M for mobility, SC for self-care, UA for usual activities, PD for pain or discomfort, AD for anxiety or depression; and l stands for either Level 2 or Level 3. α is constant term representing any move away from perfect health.

For example, assuming there is a subject with health state profile = 11223. The health state index for this subject is calculated as: 1 – 0.152 – 0.044 – 0.080 – 0.112 = 0.612.

Table 1 Japanese Value Set for EQ-5D-3L Health State Index Score

Coefficient	Value
α	0.152
β_{M2} β_{M3}	0.075 0.418
β_{SC2} β_{SC3}	0.054 0.102
β_{UA2} β_{UA3}	0.044 0.133
β_{PD2} β_{PD3}	0.080 0.194
β_{AD2} β_{AD3}	0.063 0.112

EQ VAS is a 0-100 scale where the subjects are asked to self-rate health. The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgement.

Descriptive statistics of the health state index score of ED-5D and ED VAS score and change from baseline (if both scores are available) will be presented by treatment interval, visit, and age groups (2-11 years; 12 years and older).

6.10.2 Treatment Satisfaction

Treatment Satisfaction Questionnaire for Medication (TSQM-9) will be assessed at Week 1, 12 weeks after the ramp-up in treatment period (Week 19 for 4-week dosing interval regimen and Week 16 for 3-week dosing interval regimen), and at the EOS/Early termination visit.

Data will be analyzed separately for the age groups of 2 to 12 years (observer: parent) and 13 years and older (observer: subject). Age will be defined as the age at screening. The observer should remain constant for the duration of subject participation. In the event that the language/age group is not available, the assessment in the closest language/age group will be used.

6.10.2.1 Treatment Satisfaction Questionnaire for Medication-9

Treatment Satisfaction Questionnaire for Medication-9 is a self-administered, 9-item, validated measure that assesses treatment satisfaction in the following 3 domains: effectiveness (items 1-3), convenience (items 4-6), and global satisfaction (items 7-9).

Items 1-6 and Item 9 will be coded on a scale of 1-7. Items 7 and 8 will be coded on a scale of 1 to 5. The scores of TSQM-9 domains are calculated by summing up item values within each domain and transforming them into scores ranging from 0 to 100 using the following formula:

- Effectiveness
  - If all items are completed: = [(item1 + item2 + item3) - 3]/18*100
  - If one item is missing: = [sum of completed items - 2]/12*100
- Convenience
  - If all items are completed: = [(item4 + item5 + item6) - 3]/18*100
  - If one item is missing: = [sum of completed items - 2]/12*100
- Global satisfaction
  - If all items are completed = [(item7 + item8 + item9) - 3]/14*100
  - If either Item 7 or 8 is missing: = [sum of completed items - 2]/10*100
  - If item 9 is missing: = [(item 7 + item 8) -2]/8*100

The TSQM-9 domain scores range from 0 to 100, where higher scores represent better satisfaction on that domain. A score can be computed for a domain only if no more than one item is missing from that domain.

Descriptive statistics of TSQM-9 domain scores and change from baseline will be presented by treatment interval, Epoch, visit, and age groups (2-12 years; 13 years and older).

6.10.3 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.

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

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 will be listed only.

6.11.2 Pregnancy Test

A urine pregnancy test will be performed on all females of childbearing potential at screening for subjects switching from IVIG or cSCIG treatment, and at pre-infusion at Week 1 for subjects switching from TAK-664 studies. All pregnancies are reported from the time informed (e)Consent is signed until EOS/Early termination visit.

All pregnancy test will be listed only.

6.12 Interim Analyses

No interim analysis, adaptive design, or data monitoring committee is planned for this study.

7.0 REFERENCES

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8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

· Description has changed to the following on Section 6.7.3.

"*For vital signs, change from pre infusion to post-infusion will also be summarized by Epoch and overall treatment period*" → "*For vital signs, change from pre infusion to post-infusion will also be summarized for Epoch 1*"

· 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):

- Allocated treatment group;
- 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 last non-missing value (including unscheduled assessments) before the start of initial dose of investigational drug. 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 the first dose of investigational drug, then the day and month of the date of the first dose of investigational 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 investigational 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 investigational 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 investigational drug, then the day of the date of the first dose of investigational drug will be assigned to the missing day.
  - If either the year is before the year of the date of the first dose of investigational drug or if both years are the same but the month is before the month of the date of the first dose of investigational 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 investigational drug or if both years are the same but the month is after the month of the date of the first dose of investigational drug, 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, then the AE will be considered treatment-emergent in Epoch 1.

- 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 investigational drug administration in Epoch 1 or Epoch 2 (e.g., AE start year and month are the same as the year and month of the first dose of investigational 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 9.2.3.1 for details.

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, 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 2.

Table 2 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.

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 an Epoch is defined as the date of first investigational drug administration in the corresponding Epoch.

The end date of an Epoch is defined as follow:

- 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)
- 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 subjects who completed Epoch 2, end date is defined as,

  The date of last investigational drug administration +

  (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 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, derive the visit as in the following (for Baseline visit, please refer to Section 9.2.2):

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

Analysis Visit	Target Day	Allowance	Derivation
R-1 WEEK 1	1	-	Analysis Day of vital sign measurement =1 and Planned Timepoint is not Pre-dose
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 <= Analysis Day of vital sign measurement <= 46
VISIT 2 WEEK 11	71	±3	68 <= Analysis Day of vital sign measurement <= 74
VISIT 3 WEEK 15	99	±3	96 <= Analysis Day of vital sign measurement <= 102
VISIT 4 WEEK 19	127	±3	124 <= Analysis Day of vital sign measurement <= 130
VISIT 5 WEEK 23	155	±3	152 <= Analysis Day of vital sign measurement <= 158
VISIT 6 WEEK 27	183	±3	180 <= Analysis Day of vital sign measurement <= 186
EOS/ET	211	-	Original visit of vital sign data is 'EOS/ET'
End of Study		-	Original visit of vital sign data is 'END OF STUDY'

Table 4 Visit Windows for 4-week Dosing Interval, TAK-664 Subjects

Analysis Visit	Target Day	Allowance	Derivation
R-1 WEEK 1	1	-	Analysis Day of vital sign measurement =1 and Planned Timepoint is not Pre-dose
R-2 WEEK 2	8	-	Analysis Day of vital sign measurement =8
R-3 WEEK 4	22	-	Analysis Day of vital sign measurement =22
VISIT 1 WEEK 7	43	±3	40 <= Analysis Day of vital sign measurement <= 46
VISIT 2 WEEK 11	71	±3	68 <= Analysis Day of vital sign measurement <= 74
VISIT 3 WEEK 15	99	±3	96 <= Analysis Day of vital sign measurement <= 102
VISIT 4 WEEK 19	127	±3	124 <= Analysis Day of vital sign measurement <= 130
VISIT 5 WEEK 23	155	±3	152 <= Analysis Day of vital sign measurement <= 158
VISIT 6 WEEK 27	183	±3	180 <= Analysis Day of vital sign measurement <= 186
EOS/ET	211	-	Original visit of vital sign data is 'EOS/ET'
End of Study		-	Original visit of vital sign data is 'END OF STUDY'

Table 5 Visit Windows for 3-week Dosing Interval, IVIG and cSCIG Subjects

Analysis Visit	Target Day	Allowance	Derivation
R-1 WEEK 1	1	-	Analysis Day of vital sign measurement =1 and Planned Timepoint is not Pre-dose
R-2 WEEK 2	8	-	Analysis Day of vital sign measurement =8
VISIT 1 WEEK 4	22	-	Analysis Day of vital sign measurement =22
VISIT 2 WEEK 7	43	±3	40 <= Analysis Day of vital sign measurement <= 46
VISIT 3 WEEK 10	64	±3	61 <= Analysis Day of vital sign measurement <= 67
VISIT 4 WEEK 13	85	±3	82 <= Analysis Day of vital sign measurement <= 88
VISIT 5 WEEK 16	106	±3	103 <= Analysis Day of vital sign measurement <= 109
VISIT 6 WEEK 19	127	±3	124 <= Analysis Day of vital sign measurement <= 130
VISIT 7 WEEK 22	148	±3	145 <= Analysis Day of vital sign measurement <= 151
VISIT 8 WEEK 25	169	±3	166 <= Analysis Day of vital sign measurement <= 172
EOS/ET	190	-	Original visit of vital sign data is 'EOS/ET'
End of Study		-	Original visit of vital sign data is 'END OF STUDY'

Table 6 Visit Windows for 3-week Dosing Interval, TAK-664 Subjects

Analysis Visit	Target Day	Allowance	Derivation
R-1 WEEK 1	1	-	Analysis Day of vital sign measurement =1 and Planned Timepoint is not Pre-dose
R-2 WEEK 2	8	-	Analysis Day of vital sign measurement =8
VISIT 1 WEEK 4	22	±3	19 <= Analysis Day of vital sign measurement <= 25
VISIT 2 WEEK 7	43	±3	40 <= Analysis Day of vital sign measurement <= 46
VISIT 3 WEEK 10	64	±3	61 <= Analysis Day of vital sign measurement <= 67
VISIT 4 WEEK 13	85	±3	82 <= Analysis Day of vital sign measurement <= 88
VISIT 5 WEEK 16	106	±3	103 <= Analysis Day of vital sign measurement <= 109
VISIT 6 WEEK 19	127	±3	124 <= Analysis Day of vital sign measurement <= 130
VISIT 7 WEEK 22	148	±3	145 <= Analysis Day of vital sign measurement <= 151
VISIT 8 WEEK 25	169	±3	166 <= Analysis Day of vital sign measurement <= 172
EOS/ET	190	-	Original visit of vital sign data is 'EOS/ET'
End of Study		-	Original visit of vital sign data is 'END OF STUDY'

9.3 Analysis Software

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

In addition, for SF-36 calculation, QualiTest's web tool (where population mean and standard deviation for Japanese population in 2017 are applied) are used.

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	<=1.5	>1.5	<=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

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.