# Statistical Analysis Plan

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Study Number: TAK-743-5007

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

**STATISTICAL ANALYSIS PLAN**

Study Number: TAK-743-5007

Study Title: Open-arm, Japan Expanded Access Program with Lanadelumab (TAK-743) for Japanese Patients with Hereditary Angioedema

Phase: Japan Expanded Access Program

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## ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine transaminase |
| AST | aspartate transaminase |
| ATC | Anatomical Therapeutic Chemical |
| BILI | Total bilirubin |
| BP | blood pressure |
| C1-INH | C1 esterase inhibitor |
| C1q | complement component 1q |
| C4 | complement component 4 |
| CI | confidence interval |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| FAS | full analysis set |
| HAAARP | HAE Attack Assessment and Reporting Procedures |
| HAE | hereditary angioedema |
| HR | heart rate |
| IP | investigational product |
| ISR | injection site reaction |
| KM | Kaplan-Meier |
| LLN | lower limit of normal |
| LTP | long-term prophylaxis |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PT | Preferred Term (MedDRA) |
| RR | respiratory rate |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SC | subcutaneous(ly) |
| SD | standard deviation |
| SMQ | Standardized MedDRA Queries |
| SOC | System Organ Class |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| WHO | World Health Organization |

# 1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

## 1.1 Objectives

### 1.1.1 Primary Objective

*The primary objective is to ensure access to lanadelumab in Japanese subjects with hereditary angioedema (HAE) who meet the criteria for expanded access.*

### 1.1.2 Secondary Objectives

- *To evaluate the long-term safety of repeated subcutaneous (SC) administration of lanadelumab.*
- *To evaluate the long-term efficacy of lanadelumab in preventing HAE attacks.*

## 1.2 Endpoints

### 1.2.1 Safety Endpoints

The following safety endpoints are to be evaluated:

- *Number and percentage of subjects with treatment-emergent adverse events (AEs), including serious adverse event (SAE)s and adverse events of special interest (AESIs).*
- *Number of subjects with clinically significant abnormal laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis).*
- *Number of subjects with clinically significant vital signs including blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR).*

### 1.2.2 Efficacy Endpoints

The following efficacy endpoint is to be evaluated:

- *Non-rollover Subjects: Time to first HAE attack after Day 0 for the efficacy evaluation period of Day 0 through Day 182.*

## 1.3 Estimand

Not Applicable.

# 2.0 STUDY DESIGN

*This is an open-label, Japan Expanded Access Program with lanadelumab (TAK-743) for Japanese patients with Type I or II HAE. Two types of subjects will be enrolled into this study:*

- *Subjects who rollover from Study SHP643-302.*
- *Subjects who are non-rollovers (ie, were not participants in Study SHP643-302).*

*Rollovers from Study SHP643-302*

*Subjects from Study SHP643-302 are permitted to rollover and enroll into this study if:*

1. *They have completed the treatment period of Study SHP643-302; and*
2. *They have consented to enter Study TAK-743-5007 on or before Day 350 of the SHP643-302 study (since Day 378 of Study SHP643-302 is also Day 0 of Study TAK-743-5007, informed consent may be completed on Day 364 or this visit, if not already provided).*

*Subjects who discontinue from Study SHP643-302 after providing informed consent are not eligible to enroll in Study TAK-743-5007.*

*There is no screening period for rollover subjects. The first study visit for rollover subjects (Day 0) is to occur on the same day as the Study SHP643-302 Day 378 study visit. Rollover subjects will complete all Study SHP643-302 final study assessments (Day 378) at which time they will be discharged from that study. Results of the final SHP643-302 assessments on Day 378 will be used as the predose results for Day 0 of Study TAK-743-5007.*

*Following informed consent and predose assessments, rollover subjects will continue with an open-label dose of 300 mg lanadelumab administered SC on Day 0. Rollover subjects will receive SC administration of lanadelumab 300 mg q2w or q4w at the discretion of the Investigator, with optional consultation with the sponsor, if they have been well-controlled (eg, attack free for 26 weeks). Rollovers from Study SHP643-302 who have been self-administering the study drug at the time of screening will be permitted to continue self-administration of lanadelumab.*

*<u>Non-rollover subjects</u>*

*Subjects with historical baseline HAE attack of at least 1 attack per 4 weeks in the recent year who have not participated in Study SHP643-302 (non-rollovers) are permitted to enroll if they meet the eligibility requirements for expanded access.*

*Screening of some subjects is allowed following discussion with the sponsor: ie, subjects who screen failed out of the run-in period for Study SHP643-302 when enrollment for that study closed.*

*Once all screening assessments are completed and eligibility confirmed, non-rollover subjects will arrive at the study site and, following predose assessments, will receive an open-label dose of 300 mg lanadelumab administered SC on Day 0. Non-rollover subjects will receive SC administration lanadelumab 300 mg q2w or q4w if they have been well-controlled (eg, attack free for 26 weeks) and at the discretion of the Investigator with optional consultation with the sponsor.*

*All doses are to fall within the accepted ± 4 days window around study visits. From Day 0 to Day 182, visits will occur q2w. After Day 182, study visits will occur every 12 weeks, and site personnel are to call subjects q2w to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.*

*All subjects who are considered suitable candidates will be allowed to self-administer treatment throughout the study. Subjects are required to complete appropriate training by the Investigator*

*or designee and have their understanding of the procedures confirmed by the Investigator or designee.*

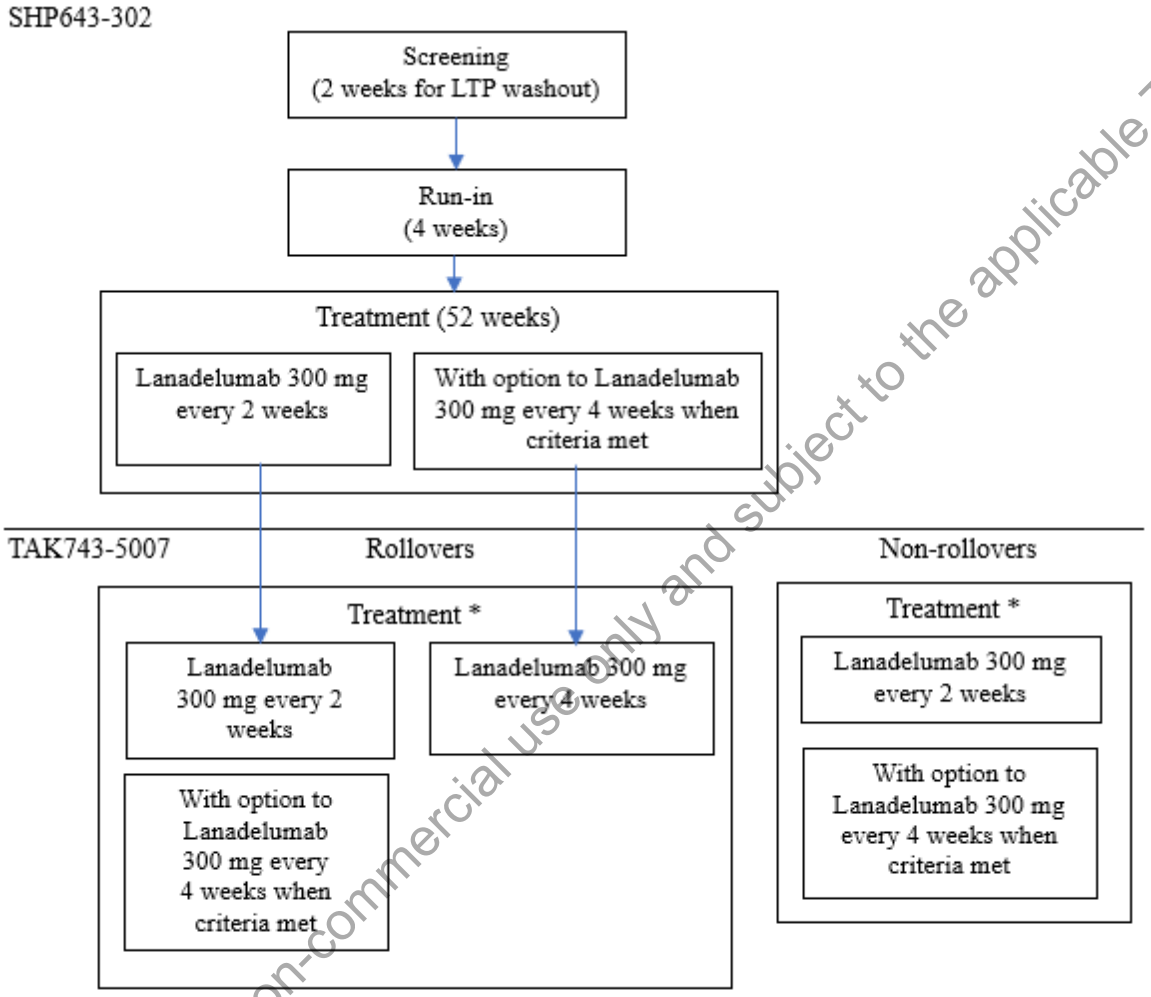
*The treatment period is to last up to lanadelumab manufacturing and sale, discontinued development, or withdrawal of new drug application.*

*If a subject experiences an acute angioedema attack at any time during the study that in the opinion of the Investigator requires medical intervention, standard of care therapy is to be provided based on subject's medical history and per locally approved product information.*

*Administration of lanadelumab and study procedures is to continue without alteration to Appendix A in the protocol, even if a subject receives treatment for a breakthrough angioedema attack on the day of a scheduled dose of study drug (if self-administering) or scheduled study visit.*

*An overview of the study design scheme is provided in* Figure 1. *All study procedures are detailed in the schedule of assessments (Appendix A in the protocol).*

**Figure 1 Schematic of Study Design**




*Until moment of lanadelumab manufacturing and sale, development discontinued, or withdraw of new drug application

LTP = long-term prophylaxis

# 3.0 STATISTICAL HYPOTHESES AND DECISION RULES

## 3.1 Statistical Hypotheses

Not Applicable.

## 3.2 Statistical Decision Rules

Not Applicable.

## 3.3 Multiplicity Adjustment

Not Applicable.

# 4.0 SAMPLE-SIZE DETERMINATION

*This study is designed to expand access of lanadelumab and evaluate the safety of open-label treatment with lanadelumab in subjects with HAE who participated in SHP643-302 (rollover subjects) and individuals who are not otherwise able to participate in SHP643-302 (non-rollover subjects). Therefore, no formal sample size calculation was performed.*

# 5.0 ANALYSIS SETS

## 5.1 Screened Set

The Screened Set is defined as all subjects who have signed informed consent.

## 5.2 Enrolled Set

The Enrolled Set is defined as all subjects who have signed informed consent and also passed inclusion/exclusion criteria, i.e., the subjects not identified as screen failure on the study completion/early termination electronic case report form (eCRF).

## 5.3 Full Analysis Set

Full Analysis Set (FAS) is defined as all subjects who received at least 1 dose of lanadelumab. All safety and efficacy analyses will be based on the FAS and each subset in FAS defined below. Unless otherwise specified, summary tabulations conducted using FAS will be presented by each subset and overall.

- Rollover subjects in FAS: the subset of subjects who participated in Study SHP643-302 and received any study drug after entering Study TAK-743-5007.
- Non-rollover subjects in FAS: the subset of subjects who entered Study TAK-743-5007 directly and received any study drug after entering Study TAK-743-5007.

# 6.0 STATISTICAL ANALYSIS

## 6.1 General Considerations

### 6.1.1 Analysis Approach for Continuous Variables

Continuous variables will be summarized using the descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum) unless stated otherwise in the section specific to an endpoint.

### 6.1.2 Analysis Approach for Binary Variables

Binary and categorical variables will be summarized using the number and percentage of subjects unless stated otherwise in the section specific to an endpoint.

### 6.1.3 Analysis Approach for Time-to-Event Variables

Time-to-event variables will be summarized using Kaplan-Meier (KM) estimates of the 25th, 50th (median), and 75th percentiles with associated two-sided 95% confidence interval (CI), as well as percentage of events and censored observations unless stated otherwise in the section specific to an endpoint.

In addition, KM plots detailing each subject's contribution to the analysis will be provided.

## 6.2 Disposition of Subjects

### 6.2.1 Disposition of Subjects

The number of subjects who were included in each defined analysis set (i.e., Screened, Enrolled, and FAS) will be summarized for the Screened Set by rollover, non-rollover and overall.

The number and percentage of subjects who completed or prematurely discontinued the study will be presented for FAS. Reasons for premature discontinuation from study will be summarized (number and percentage) for the FAS.

Disposition of all subjects, including screen failures, will be presented in a listing for the Screened Set. Inclusion criteria not met and exclusion criteria met will be listed.

### 6.2.2 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 ("critical", "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 FAS. All protocol deviations will be included in a subject listing. In particular, protocol deviations identified as related to the impact of COVID-19 will be flagged in the subject listings.

## 6.3 Demographic and Other Baseline Characteristics

### 6.3.1 Demographics and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented for FAS.

The following demographic characteristics will be summarized:

- Age at informed consent date (years),
- Age category (<18, 18 to <40, 40 to <65, ≥65 years),
- Sex (Male, Female),
- Weight (kg),
- Weight category (<50, 50 to <75, 75 to <100, ≥100 kg),
- Height (cm),
- Body mass index (BMI) (kg/m$^2$), calculated as 10000*weight (kg)/ height (cm)$^2$,
- BMI group for subjects ≥ 18 years of age (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m$^2$),
- BMI percentile group for subjects < 18 years of age based on growth charts from the Centers for Disease Control and Prevention (CDC) (Underweight: <5th percentile, Healthy or Overweight: 5th to <95th percentile, Obese: >=95th percentile),
    - Official and validated SAS programs created by CDC will be used to calculate the percentile of BMI. For more information on the CDC SAS programs, see http://www.cdc.gov/growthcharts/computer_programs.htm.

The following baseline HAE characteristics will be summarized in a separate table:

- Age at onset of HAE symptoms (years),
- HAE type (Type I, Type II, Unspecified- Type I or Type II),
- History of laryngeal attacks,
- Primary attack location,
- Number of attacks in the last 1 and 12 months prior to screening,
- Average attack duration (in days) in the last 12 months prior to screening,
- Average severity of HAE attacks in the last 12 months prior to screening,
- LTP therapy use before entering the run-in or treatment period of study (yes or no) as recorded on the LTP Therapy Discontinuation eCRF,
- Type of LTP therapy before entering the run-in or treatment period (C1-INH, Androgens, Anti-fibrinolytics, or not on LTP)

For rollover subjects, the data of the LTP (C1-INH, Androgens, or Anti-fibrinolytics) treatment a subject was on prior to the run-in period in SHP643-302 study will be used. For non-rollover subjects, the LTP treatment a subject was on prior to the treatment period will be determined by applying the algorithm below to prior medications (i.e., medications with start and stop date prior to the start date of the treatment period, imputing partial dates as described in Section 9.2.6.2) reported for that subject that lasted for ⩾4 days:

| LTP | Algorithm to Identify Medications |
|---|---|
| C1-INH | ATC level 4 in ('B06AC') and preferred drug name not in ('icatibant', 'ecallantide', 'icatibant acetate') |
| Androgens | ATC level 4 in ('G03BA', 'G03BB', 'A14AA') or preferred drug name in ('danazol', 'oxandrolone') |
| Anti-fibrinolytics | ATC level 4 in ('B02AA', 'B02AB') |

All baseline and demographic data will be presented in subject listings.

### 6.3.2 Medical History and Concurrent Medical Conditions

This section will be applied to non-rollover subjects in FAS only.

Medical history will be collected at the Screening Visit and will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or newer.

The medical history will be summarized by system organ class (SOC) and preferred term (PT) for non-rollover subjects in FAS. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency.

All medical history will be presented in subject listings for non-rollover subjects in FAS.

## 6.4 Medication History and Concomitant Medications

### 6.4.1 Prior Medications

This section will be applied to non-rollover subjects in FAS only.

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

Prior medication/therapy/procedure is defined as any medication/therapy/procedure with the start date and time prior to the date and time of the first dose of investigational product (IP).

Partial date imputation for medications is described in Section 9.2.6.2.

The prior medications will be summarized by the number and proportion of subjects within each Anatomical Therapeutic Chemical (ATC) Level 2 therapeutic class and PT for non-rollover subjects in FAS. The prior therapies and procedures will be summarized by the number and

proportion of subjects within each SOC and PT for non-rollover subjects in FAS. Tabulations will be presented sorted by therapeutic class in alphabetical order and by PT within each therapeutic class by descending frequency. Multiple medication usage by a subject in the same category (i.e., therapeutic class or PT) will be counted only once.

All prior therapies, procedures and medication will be listed for non-rollover subjects in FAS.

### 6.4.2 Concomitant Medications

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

Concomitant medication/therapy is defined as any medication/therapy with a start date and time prior to the date and time of the first dose of IP and continuing after the first dose of IP or with a start date and time between the dates and times of the first dose of IP and end of the treatment, inclusive. Concomitant procedure is defined as any procedure with a start date and time between the dates and times of the first dose of IP and end of the treatment, inclusive.

Any medication/therapy/procedure with a start date after the end of the treatment will not be considered a concomitant medication/therapy/procedure. Partial date imputation for medications is described in Section 9.2.6.2.

The summaries of concomitant medication/therapy/procedure will be presented separately for:

- Concomitant Medications/therapies/procedures (excluding those taken for an HAE Attack)
- Concomitant Medications/therapies/procedures taken for an HAE Attack

The concomitant medications will be summarized by the number and proportion of subjects within each ATC Level 2 therapeutic class and PT for FAS. Tabulations will be presented sorted by therapeutic class in alphabetical order and by PT within each therapeutic class by descending frequency. The concomitant therapies and procedure will be summarized by the number and proportion of subjects within each SOC and PT for FAS. Tabulations will be presented sorted by therapeutic class in SOC and by PT within each SOC by descending frequency. Multiple medication usage by a subject in the same category (i.e., therapeutic class or PT) will be counted only once.

All concomitant therapies, procedures and medication will be listed for FAS.

## 6.5 Efficacy Analysis

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

### 6.5.1 Time to First HAE Attack

This analysis will be conducted in non-rollover subjects in FAS only.

The time to the first investigator-confirmed HAE attack (days) after Day 0 for the efficacy evaluation period of Day 0 through Day 182 will be calculated from the date and time of the first dose of lanadelumab for that efficacy evaluation period to the date and time of the first investigator-confirmed HAE attack after the first dose for that efficacy evaluation period.

Subjects who do not experience any attacks during the efficacy evaluation period will be censored at the date and time of the end of the period, i.e., visit date of Day 182 visit and time of 23:59. Subjects who discontinue the study during the efficacy evaluation period prior to experiencing their first on-study investigator-confirmed HAE attack will be censored at the date of study discontinuation and time of 23:59.

Time to the first investigator-confirmed HAE attack will be summarized using Kaplan-Meier (KM) estimates of the 25th, 50th (median), and 75th percentiles with associated two-sided 95% CI, as well as percentage of events and censored observations.

In addition, KM plots detailing each subject's contribution to the analysis will be provided.

### 6.5.2 Achievement of Attack-free Status by interval (1 month, 2 months, 3 months, …, until the Day 182 Visit)

This analysis will be conducted in non-rollover subjects in FAS only.

The definition of attack free is given in Section 6.5.3.

The number and percentage of subjects achieving attack-free status will be summarized for the following intervals: 1 month (i.e., Day 0 to Day 28 visit date minus one day), 2 months (Day 0 to Day 56 visit date minus one day), 3 months (i.e., Day 0 to Day 84 visit date minus one day), …, Day 0 through Day 182 (as defined in Section 9.2.3.1) A two-sided 95% CI for the proportion of subjects achieving attack-free will be derived using the exact method.

A subject is considered as attack free during an interval if the subject has no investigator-confirmed HAE attacks during that interval. For subjects who discontinue the study during an interval, the evaluation period will end at the date of study discontinuation with time 23:59 and attack-free status will be evaluated for the period of time that the subject was in the evaluation period.

The number and percentage of subjects achieving attack-free status after Day 182 will be only listed for the following intervals: 266 days (i.e., Day 0 to Day 266 visit date minus one day), 350 days (Day 0 to Day 350 visit date minus one day).

### 6.5.3 Number of investigator-confirmed HAE attacks during Day 0 through Day 182

The total number of investigator-confirmed HAE attacks reported and subject-time in months that each subject contributed during Day 0 through Day 182 will be summarized in rollover subjects in FAS and non-rollover subjects in FAS (not be summarized in FAS).

A listing of all investigator confirmed HAE attacks will be presented.

**Normalized Number of Investigator-confirmed Hereditary Angioedema Attacks (NNA)**

The investigator-confirmed NNA per 4 weeks during Day 0 through Day 182 will be expressed as a monthly (4 weeks, i.e., 28 days) HAE attack rate for each subject. In what follows, for conciseness, HAE attack rate refers to NNA per 4 weeks.

For Rollover subjects in FAS, the data of the baseline investigator-confirmed HAE attack rate in SHP643-302 study will be used.

For non-rollover subjects in FAS, the number of HAE attacks in last 1 month prior to screening collected by CRF divided by the number of days of the month prior to screening multiplied by 28 days will be used as baseline. As a note, this HAE attacks prior to screening are not investigator-confirmed.

The treatment period investigator-confirmed HAE attack rate will be calculated as the number of HAE attacks occurring during that treatment period divided by number of days the subject contributed to that treatment period multiplied by 28 days.

The treatment period HAE attack rate percentage change from baseline will be calculated for each subject as the difference in attack rates, treatment period attack rate minus run-in period attack rate, divided by the run-in period attack rate or prior screening attack rate.

The baseline attack rate, as well as the treatment period investigator-confirmed attack rate, change from baseline, and percent change from baseline will be summarized using descriptive statistics.

In addition, the number of investigator-confirmed HAE attacks per month (defined as 28 days) will be summarized by study month (per 28-day interval). The summary will include descriptive statistics for run-in period investigator-confirmed attack rate or prior screening attack rate, as well as monthly treatment period investigator-confirmed attack rates, monthly change from baseline, and monthly percent change from baseline. Investigator-confirmed HAE attacks will be grouped into 28-day intervals using the start date of the HAE attack. In particular, if a HAE attack starts during an interval and is ongoing at the start of the next interval, that HAE attack will be counted only once for the interval during which it started. The first study drug administration date and time in this study will be used as the start of the first interval and end of the interval will be the first study drug administration date and time in this study plus 28 days. Each successive interval will start the last day of the prior interval plus 1 day (24 hours) and end 28 days later.

Similar summary tables except the summary of attack rate per month will be presented for the following clinical outcome measures:

- Number of investigator-confirmed HAE attacks requiring acute treatment:

  Investigator-confirmed HAE attacks requiring acute treatment are defined as those attacks with ‘Has the subject received any of the following acute HAE therapy treatment for this reported attack?’ marked as ‘Yes’ on the CRF.

- Number of moderate or severe investigator-confirmed HAE attacks:

  Moderate and severe investigator-confirmed HAE attacks are defined as those attacks that were classified as of moderate or severe according to the HAE Attack Assessment and Reporting Procedures (HAARP) defined severity and reported as such on the CRF.

- Number of high-morbidity investigator-confirmed HAE attacks:

  High morbidity HAE attack is defined as any attack that has at least 1 of the following characteristics as reported on the HAE acute attack CRF: severe based on HAARP, results in hospitalization (except hospitalization for observation <24 hours), hemodynamically significant (systolic blood pressure <90, requires IV hydration, or associated with syncope or near syncope) or laryngeal (based on primary or secondary HAE attack location).

If the length of hospitalization cannot be determined due to missing dates and times, then that hospitalization will be conservatively counted as being greater than 24 hours.

## 6.6 Safety Analysis

No statistical hypothesis testing will be performed. All safety summaries will be based on the FAS. Safety endpoints include AEs, clinical laboratory variables, vital signs, and electrocardiogram (ECG) variables.

The definition of baseline is provided in Section 9.2.2.

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

### 6.6.1 Adverse Events

AEs will be coded using MedDRA Version 23.0 or newer.

Treatment-emergent AEs (TEAEs) are defined as AEs with onset at the time of or following the first exposure to lanadelumab in this study, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. For AEs with partial onset times, 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 as to when the AE occurred relative to study drug administration, then the AE will be classified as treatment-emergent. Partial date imputation for AE is described in Section 9.2.6.3.

The analyses described in this section will be based on TEAEs only; plainly referred to as AEs in this section for brevity. All AEs (TEAEs and non-TEAEs) will be provided in the AE subject listing.

Related AEs are AEs classified as related to study drug by the investigator. Missing relationship to study drug imputation is described in Section 9.2.6.5.

Severe AEs are AEs classified as severe (grade 3) or life threatening (grade 4) by the investigator. Missing severity imputation is described in Section 9.2.6.4.

The collection of tabulations described in this section (with the exception of the analyses of AESI and injection site reaction [ISR]) will be produced for 2 mutually exclusive subgroups of AEs based on whether the AE was identified in EDC as a subject-reported HAE attack or not, and defined as follows:

Non-HAE attack reported AEs will include the subset of AEs identified in EDC as not a reported HAE attack. Essentially, this will be all AEs excluding HAE attack reported events.

HAE reported AEs will include the subset of AEs identified in EDC as a reported HAE attack. Note that this includes investigator-confirmed HAE attacks; all investigator-confirmed HAE attacks will be coded to the PT of angioedema.

The number and percentage of subjects with any AE, any related AE, any SAE, any related SAE, any severe AE, any related severe AE, and any investigator-reported AESI, as well as the total number of events for each category will be summarized. The number of deaths due to an AE, hospitalization due to an AE and study discontinuation due to an AE will be summarized.

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized by SOC, and PT. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, related severe AEs, and investigator-reported AESI. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency.

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized by PT. This tabulation will be repeated for related AEs and serious AEs. Tabulations will be presented sorted by PT by descending frequency.

All AEs will be provided in subject listings. In addition, subject listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs, related AEs, severe AEs, and investigator-reported AESIs will be produced.

### 6.6.2 Adverse Events of Special Interest

AESI for this study are hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events). The preferred terms from MedDRA 23.0 Standardized MedDRA Queries (SMQ) will be used to identify an SMQ-defined AESI. Table 1 shows the SMQs used to identify AESI of hypersensitivity, hypercoagulable, and bleeding.

**Table 1. SMQ Used to Identify AESI**

| AESI | SMQ |
|---|---|
| Hypersensitivity | Hypersensitivity |
| Hypercoagulable | Embolic and thrombotic events, arterial<br>Embolic and thrombotic events, venous<br>Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous |
| Bleeding | Haemorrhage laboratory terms<br>Haemorrhage terms (excl laboratory terms) |

The number and percentage of subjects with any AESI, any related AESI, any serious AESI, any related serious AESI, any severe AESI, and any related severe AESI, as well as the total number

of events for each category will be summarized. The number of deaths due to an AESI, hospitalization due to an AESI and study discontinuation due to an AESI will be summarized.

The number and percentage of subjects with SMQ-defined AESI, as well as the total number of SMQ-defined AESIs, will be summarized by SOC and PT. Separate summary tables will be created for each AESI category and for those events with the SMQ-defined AESIs classified as related, serious, related serious, severe, and related severe. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency. A listing detailing the PT within the SMQ will be provided.

### 6.6.3 Injection Site Reaction AEs

ISR AEs will be identified by adverse events with the preferred terms starting with 'Injection site', 'Application site', or 'Administration site'.

The number and percentage of subjects with any ISR AE, any related ISR AE, any serious ISR AE, any related serious ISR AE, any severe ISR AE, and any related severe ISR AE, as well as the total number of events for each category will be summarized. The number of deaths due to an ISR AE, hospitalization due to an ISR AE and study discontinuation due to an ISR AE will be summarized.

The number and percentage of subjects with an ISR AE, as well as the total number of ISR AEs, will be summarized by SOC, and PT.

The number and percentage of subjects with an ISR AE will be summarized by SOC, PT and maximum severity.

The number of ISR events and the percentage of ISR events calculated based on total number of injections, will be summarized by PT and overall. Descriptive statistics (n, mean, SD, minimum, median, and maximum) will be presented to describe the ISR duration (hours). ISR duration will also be summarized by category (0-0.5 hour, >0.5 - 1 hour, >1 – 12 hour, >12 – 24 hour, <= 1 Day - Unclear, > 1 Day: >1-14 Days, >14 Days).

A listing of ISR AEs will be provided.

#### *6.6.3.1 Duration of Injection Site Reaction AEs*

Duration of ISR AEs is calculated as 'stop date/time – start date/time' for the ISR AEs with non-missing start and stop date/time.

The missing start or stop date/time for ISR AEs will not be imputed. ISR AEs with missing start or stop date/time will be excluded from the summary statistics analysis and reported as number missing in the continuous analysis of ISR AE duration. For the categorical analyses on ISR AE duration, the following rules will be applied:

- ISR AE with non-missing start and stop date/time: duration of the AE will be calculated as 'stop date/time – start date/time' and mapped to a duration category.

- ISR AE with non-missing start and stop dates and missing time: duration of the AE will be calculated as 'stop date – start date +1'. If the calculated duration is 1 day, then the duration category for this AE is <= 1 day - unclear. If the calculated duration is greater than 1 day, then it will be mapped to a >1 day category.

- ISR AE with missing start or stop date: The ISR AE will be excluded from the categorical analyses on duration and will be listed in the missing category.

### 6.6.4 Clinical Laboratory Data

Laboratory evaluations that are done at study site visits will be collected and processed via a central laboratory, and presented in conventional units.

Clinical laboratory parameters to be evaluated include the following:

| | |
|---|---|
| **Hematology** | Hemoglobin, hematocrit, red blood cells (RBC), white blood cells (WBC) count total and differential - neutrophils, lymphocytes, monocytes, eosinophils, basophils, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), absolute platelet count. |
| **Chemistry** | Albumin, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin (total and direct), blood urea nitrogen (BUN), calcium, carbon dioxide (CO2), chloride, creatinine, creatine phosphokinase (CPK), glucose, phosphate, magnesium, potassium, sodium, total protein. |
| **Coagulation** | Prothrombin time, activated partial thromboplastin time (aPTT), international normalized ratio (INR) |
| **Urinalysis** | Bilirubin, glucose, ketones, blood, nitrite, potential hydrogen (pH), protein, specific gravity, microscopy (if indicated by macroscopic findings). |
| **Virology** | Hepatitis B Surface Antigen (HbsAg); Hepatitis C Virus (HCV); Human Immunodeficiency Virus (HIV) |

Hematology, Chemistry, Coagulation, and Urinalysis results will be summarized as described below. Virology results will be listed only.

Actual values and change from baseline in clinical laboratory tests will be summarized by study visit. If more than one laboratory result is reported per study visit per parameter, the last non-missing result will be selected for analysis.

Categorical laboratory test results (urinalysis excluding pH) will be summarized by study visit. If more than one laboratory result is reported per study visit per parameter, the result yielding the most severe classification will be selected for analysis.

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. The number of subjects with a non-missing result, and the number and percentage of subjects with a clinically significant result less than the lower limit of normal (LLN), non-clinically significant result less than the LLN, within the normal range, non-clinically significant result more than the upper limit of normal (ULN), and clinically significant result more than the ULN will be summarized by study visit. If more than one laboratory result is reported per study visit per parameter, the result yielding the most severe classification will be selected for analysis.

Among chemistry parameters, additional analyses in Table 1 will be conducted on liver function tests for the FAS using the highest pre-treatment and highest overall treatment period measurements. The number and percentage of subjects with highest results falling into the categories of normal (<=1 x ULN), >1 – <=3 x ULN, >3 – <=5 x ULN, and greater than >5 x ULN on the liver function tests for ALT/AST will be summarized for all pre-treatment measurements and overall treatment period measurements. Total bilirubin (BILI) will be summarized by the number and percentage of subjects with highest results falling into the categories of <=2 x ULN and >2 x ULN for all pre-treatment measurements and overall treatment period measurements. Additionally, for the FAS, a shift table summarizing the shift in categories from highest pre-treatment measurements to the highest overall treatment period measurements will be created for the liver function tests including ALT, AST and BILI.

**Table 1. Lab Parameter Criteria Categories**

| Parameter | Criteria Categories | | | |
|---|---|---|---|---|
| Liver Function Tests | | | | |
| ALT (U/L) | Normal (<=1 x ULN) | >1 – <=3 x ULN | >3 – <=5 x ULN | >5 x ULN |
| AST (U/L) | Normal (<=1 x ULN) | >1 – <=3 x ULN | >3 – <=5 x ULN | >5 x ULN |
| Bilirubin (umol/L) | | <=2.0 x ULN | >2 x ULN | - |

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable (e.g., "<X"), a coded value will be used in the analysis instead as specified in Section 9.2.6.6. However, the actual values as reported in the database will be presented in data listings.

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

### 6.6.5 Vital Signs

The following vital signs will be measured:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

- HR (beats per minute)
- Body temperature (°C)
- RR (breaths per minute)

Actual values and changes from baseline in vital signs will be summarized by study visit and study time point. If more than one vital sign result is reported per study visit and study time point per parameter, the last non-missing result will be selected for analysis.

Vital sign values will be classified according to clinical significance as determined by the investigator. The number of subjects with a non-missing result, and the number and percentage of subjects with a non-clinically significant result and clinically significant result will be summarized by study visit and study time point. If more than one vital sign result is reported per study visit and study time point per parameter, the result yielding the most severe classification will be selected for analysis.

All vital sign data will be presented in subject listings. Subjects with clinically significant vital sign values will be listed. This listing will include all results of the vital sign parameter that was determined by the investigator to be clinically significant for a subject across study time points to identify any trends.

### 6.6.6 Electrocardiogram (ECG)

A standard 12-lead ECG (single recording) will be performed at screening visit, final visit/early termination, and when clinically indicated.

The following ECG variables will be measured:

- HR (beats per minute)
- RR duration (millisecond [msec])
- PR duration (msec)
- QRS duration (msec)
- QT duration (msec)

All ECG data will be presented in subject listings.

### 6.6.7 Other Safety Analysis

#### *6.6.7.1 Biomarker Test*

C1 esterase inhibitor (C1-INH), complement component 4 (C4), and complement component 1q (C1q) assays will be obtained at screening for eligibility assessment. Samples need not be obtained at screening for eligibility assessment if they were already collected as part of Study SHP643-302.

The C1-INH, C1q, and C4 testing results at screening will be listed for non-rollover subjects in FAS. The corresponding reference ranges will be provided in the same listing.

*6.6.7.2 Pregnancy Test*

Pregnancy test results will be listed by study visit.

*6.6.7.3 Physical Examination*

Physical examination will be listed by study visit.

### 6.6.8 Extent of Exposure and Compliance

*6.6.8.1 Exposure to Investigational Product (IP)*

Exposure to IP for the FAS will be summarized and overall in terms of time on treatment (month) and total dose received (mg).

Time on treatment (month) will be calculated as (number of days from the date of the first dose to the earliest of the data cut date, early discontinuation date, or the date of the end of the treatment, inclusively)/28.

Total dose received (mg) will be calculated as the sum of subject's dose (mg) received at each visit, i.e., 150 mg/mL*study drug volume (mL) administered at the visit.

For the summaries, these quantities will be calculated from the first dose to the earliest of the data cut date, early discontinuation date, or the date of the end of the treatment.

Descriptive statistics (n, mean, SD, minimum, median, and maximum) will be presented for time on treatment and total dose received. In addition, time on treatment will be summarized by category (<1 Month, 1 -< 3 Months, 3 -< 6 Months, 6 -< 9 Months, 9 -< 12 Months, >= 12 Months).

A listing of study drug administration, injection report and dose frequency modifications will be provided.

*6.6.8.2 Measurements of Treatment Compliance*

Treatment compliance is defined as the percentage of planned doses received by the subject and will be calculated as follows:

Treatment compliance (%) = number of doses received / number of planned doses * 100.

The number of planned doses is the number of doses planned to be administered up to study completion or early termination, i.e., the number of records entered using the study drug administration CRF regardless of whether the study drug was indicated to be administered or not.

Descriptive statistics (n, mean, SD, minimum, median, and maximum) of total number of doses received by the subject, treatment compliance, and the number and percentage of subjects that received at least 80% of planned doses will be presented for FAS.

#### *6.6.8.3 Study Drug Administration and Injection Report*

*All subjects who are considered suitable candidates will be allowed to self-administer treatment throughout the study.*

An Injection Report will be completed by the subject (or parent/caregiver) following each dose of IP, according to the assessment schedule in protocol Appendix A. The Injection Report will collect information on the subject's experience with SC injection and self-administration of IP.

The number and percentage of subjects who performed study drug administration via study staff administration in-clinic, self-administration in-clinic (including "Self-administration in the study clinic under supervision by study staff" and "Parent/ caregiver administration in the study clinic under supervision by study staff"), or self-administration at home (including "Self-administration at home or other outside clinic location" and "Parent/ caregiver administration at home or other outside clinic location"), as well as the total number of injections in each category and in each category by study visit, will be tabulated for the FAS.

Additionally, the number and percentage of subjects who received 0, 1-5, 6-10, 11-20, or >20 study staff administration in-clinic, self-administration in-clinic, or self-administration at home will be summarized for the FAS.

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

## 6.7 Interim Analyses

Interim summary may be produced during the study to support regulatory reporting if requested by the authority.

# 7.0 REFERENCES

Not Applicable.

# 8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not Applicable.

# 9.0 APPENDIX

## 9.1 Changes From the Previous Version of the Statistical Analysis Plan (SAP)

Not Applicable.

## 9.2 Data Handling Conventions

### 9.2.1 General Data Reporting Conventions

For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, SD, minimum, and maximum values will be presented.

For the summary statistics of all numerical variables, unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. SD will be displayed to two levels of precision greater than the data collected.

Percentages shall be reported to 1 decimal place, except when the percentage equals exactly 100 where it shall be displayed as an integer (100). For zero, only count and no percentage will be displayed. The denominator for all percentages will be the number of subjects within the population of interest, unless otherwise specified.

BMI will be rounded to 1 decimal place and normalized number of HAE attacks will be rounded to 2 decimal places for reporting.

Listings will be sorted by subject ID, visit (when available), assessment/event start date (when available), assessment/event end date (when available) and alphabetically by preferred term/name (when available), unless otherwise specified.

### 9.2.2 Definition of Baseline

For safety analyses, baseline is defined as the last non-missing value prior to first exposure to study drug (based on date or date/time) in this study.

For efficacy analyses, refer to baseline attack rate defined in Section 6.5.4.

### 9.2.3 Definition of Visit Windows

Although there is a visit window of ± 4 days around the expected visit date, nominal visits will be used for the per-visit analyses. Therefore, no windowing of visits by study day will be done for data obtained at the scheduled visits.

For the analysis, study day will be calculated as follows:

If the assessment date is on or after the date of first dose of IP:

Study day = assessment date – first dosing date + 1

If the assessment date is before the date of first dose of IP:

Study day = assessment date – first dosing date

#### *9.2.3.1 Analysis Periods*

The efficacy evaluation period of Day 0 through Day 182 is defined as the interval of time:

[*date/time of first exposure to study drug*, *date of Day 182 visit at 23:59*]

### 9.2.4 Derived Efficacy Endpoints

#### *9.2.4.1 Unique HAE Attacks*

To be counted as a unique attack distinct from the previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.

Specifically, there must be at least 24 hours between the stop date/time of the first event and the start date/time of the next event, for the attacks to be considered distinct. If there is less than 24 hours between the stop date/time of the first event and the start date/time of the next event, the events will be counted as one attack.

When two or more attacks are combined for efficacy analysis, the parameters of the attacks will be conservatively chosen. The start date and time of the combined attack will take the earliest start date and time from the individual attacks; and the end date and time of the combined attack will take the latest end date and time of the individual attacks. If there are two attacks within 24 hours, but the start date of the later attack occurs after the end of the efficacy evaluation period, the attacks will be combined and counted as one attack that occurs within the efficacy evaluation period of the start time. The severity of the combined attack will take the highest severity from the individual attacks. The primary location of the combined attack will be determined by the primary location of the individual attacks, and by following the hierarchy of laryngeal attack, abdominal attack, and peripheral attack. One primary location will be taken; and all the other primary location(s) and secondary locations will be considered as secondary location for the combined attack. The rescue medications and supportive treatment for the combined attack will include all the records from individual attacks. Also, the combined attack will be considered as an investigator-confirmed attack if any of the individual attack being combined is an investigator-confirmed attack.

The duration of an HAE attack is calculated as stop date/time – start date/time.

The imputation rules for partial start or end date and time for HAE attacks date/time is described in Section 9.2.6.1.

### 9.2.5 Repeated or Unscheduled assessments of Safety Parameters

Unscheduled measurements will not be included in by-visit summaries, however if a subject has repeated assessments before the start of IP, then the results from the final assessment made prior to the start of IP will be used as baseline. If EOS/ET assessments are repeated or unscheduled, the last post-baseline assessment will be used as the EOS/ET assessment for generating descriptive statistics. All post-baseline assessments will be presented in the data listings.

### 9.2.6 Handling of Missing, Unused, and Spurious Data

All subjects in the analysis sets defined in Section 5.0 will be included in the associated analyses.

No imputation for missing data (e.g., last observation carried forward) will be applied except for the missing date/time for HAE attacks, the partial dates for AEs and prior/concomitant medications, the missing severity for AEs and the missing relationship to IP for AEs.

Imputed dates will not be presented in the listings. The original missing date/time will be presented in the listings.

#### *9.2.6.1 Missing Start or End Date and Time for HAE Attacks*

The following rules apply to the handling of HAE attack data for efficacy analyses only.

In general, missing start date/time and end date/time will be imputed as described in Section 9.2.6.3. However, the following rules will be applied for the attacks satisfying the corresponding conditions, in order to conservatively classify the attacks as separate, distinct attacks with at least 24 hours in-between:

- For HAE attacks with a missing start time and a non-missing start date one calendar day after the end date of the previous attack, the start time will be imputed using the end time of the previous HAE attack to ensure there are 24 hours in between the two attacks.
- For HAE attacks with a missing start time and a non-missing end date/time within 24 hours from the end date/time of the previous attack, the attack should be considered as one attack with the previous attack (see Section 9.2.4.1 for details on combining HAE attacks)
- For HAE attacks with missing end time and a non-missing end date one calendar day before the start date of the next attack, the end time will be imputed as the start time of the next HAE attack to ensure there are 24 hours in between the two attacks.
- For HAE attacks with a missing end time and non-missing start date/time within 24 hours from the start date/time of the next attack, the attack should be considered as one attack with the next attack (see Section 9.2.4.1 for details on combining HAE attacks)

For HAE attacks with a non-missing start date and time and a missing stop date and time:

- If the event is not indicated as ongoing, the stop date and time will be imputed as start date and time + 48 hours or 24 hours before the start date and time of the next attack, whichever is earlier.
- If the event is indicated as ongoing, the stop date and time will be imputed as the earliest of the following two date and time:
    - Start date and time + 48 hours or study completion date and the stop time of 23:59, whichever is later.
    - 24 hours before the start date and time of the next attack.

#### *9.2.6.2 Missing Date/Time Information for Prior or Concomitant Medications/Therapies/Procedures*

For prior or concomitant medications (and/or therapies/procedures), including rescue medications, incomplete (i.e., partially missing) start date/time and/or stop date/time will be imputed. When the start date/time and the stop date/time are both incomplete for a subject, impute the start date/time first.

##### *9.2.6.2.1 Incomplete Start Date/Time*

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

###### *9.2.6.2.1.1 Missing Time*

- If the start time is missing and the start date is equal to the date of first study drug administration (before or after imputation), then the time of first study drug administration will be assigned to the missing time.
- For any other cases, the missing time will be imputed as 0:00.

###### *9.2.6.2.1.2 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 IP, then the day and month of the date of the first dose of IP 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 IP, 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 IP, then 01 January will be assigned to the missing fields.

###### *9.2.6.2.1.3 Missing Month only*

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

###### *9.2.6.2.1.4 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 IP, then the day of the date of the first dose of IP will be assigned to the missing day

- If either the year is before the year of the date of the first dose of IP or if both years are the same but the month is before the month of the date of the first dose of IP, 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 IP or if both years are the same but the month is after the month of the date of the first dose of IP, then the first day of the month will be assigned to the missing day.

*9.2.6.2.2 Incomplete Stop Date/Time*

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.

*9.2.6.2.2.1 Missing Time*

If the stop time is missing, the missing time will be imputed as 23:59.

*9.2.6.2.2.2 Missing Day and Month*

31 December will be assigned to the missing fields

*9.2.6.2.2.3 Missing Month only*

The day will be treated as missing and both month and day will be replaced according to the above procedure.

*9.2.6.2.2.4 Missing Day only*

The last day of the month will be assigned to the missing day

*9.2.6.3 Missing Date/Time Information for Adverse Events*

For AEs with partial start date/time, non-missing date/time 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/time parts as to when the AE occurred relative to study drug administration, e.g. AE start year and month are the same as the year and month of the first dose of IP, then the AE will be classified as treatment-emergent.

To facilitate categorization of AEs as treatment emergent, imputation of start date/time will be used. Stop date/time will not be imputed.

#### *9.2.6.3.1 Incomplete Start Date/Time*

Follow the same rules as in Section 9.2.6.2.1.

#### *9.2.6.3.2 Incomplete Stop Date/Time*

Not applicable.

### *9.2.6.4 Missing Severity assessment for Adverse Events*

If severity is missing for an AE starting prior to the date of the first dose of IP, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of IP, then the worst severity will be assigned, i.e., "life threatening (grade 4)". The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

This rule applies also to HAARP severity for HAE attacks for which the worst severity is "Severe".

### *9.2.6.5 Missing Relationship to IP for Adverse Events*

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

### *9.2.6.6 Character Values of Clinical Laboratory Variables*

The non-standard laboratory results will be converted to numeric values using the rules shown in Table 4.

**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 |
| <3 | Deduct 0.1 from the reference value, i.e., 2.9 |
| <2 | Deduct 0.1 from the reference value, i.e., 1.9 |

## 9.3 Analysis Software

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.