# Statistical Analysis Plan

NCT Number: NCT05460325

Title: A Multi-center, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of Lanadelumab (SHP643) in Chinese Subjects With Hereditary Angioedema

Study Number: SHP643-304

Document Version and Date: Version 2.0, 10 July 2023

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# STATISTICAL ANALYSIS PLAN

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Study Title: A Multi-center, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of Lanadelumab (SHP643) in Chinese Subjects with Hereditary Angioedema

Phase: 3

Version: 2.0

Date: *10 July 2023*



Prepared by: [redacted]

Based on:

Protocol Version: Amendment 2.0

Protocol Date: 09 FEB 2023

## REVISION HISTORY

| Version | SAP Section | Primary Rationale for Revision |
|---|---|---|
| 2.0 | 2.0 Study Design | Revised to align with Protocol Amendment 2.0 |
| | 5.3 Per-Protocol Analysis Set (PPAS) | Added per-protocol analysis set to support sensitivity analysis of the efficacy endpoints |
| | 6.2 Disposition of Subjects | Added re-screening subjects in the disposition of all subjects. |
| | 6.3.1 Demographics and Baseline Characteristics | Updated the age category of "<18" to "≥12 to <18". |
| | 6.3.3 Baseline HAE Characteristics | Updated the Run-in period HAE attack rate categories to 1 to <2, 2 to <3, ≥3 attacks/4 week. |
| | 6.5.4 Sensitivity Analysis | Included sensitivity analysis of secondary efficacy endpoints using investigator-reported HAE attacks for PPAS. |
| | 6.6.1.2 Injection Site Reaction (ISR) AEs | Updated category of summary to align with the study data collection |
| | 6.6.7.2 Measurements of Treatment Compliance | Added a listing of measurements of treatment compliance and exposure. |
| | 6.9.2 Protocol deviations | Updated to describe the handling of the site level deviations and important protocol deviations. |
| | 6.10 Interim Analyses | Added the interim analysis to align with the protocol amendment 2.0 |
| Original version 1.0 | Not Applicable | Not Applicable |

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## ABBREVIATIONS

| | |
|---|---|
| ADA | Anti-drug Antibody |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALT | Alanine Transaminase |
| AST | Aspartate Transaminase |
| ATC | Anatomical Therapeutic Chemical |
| BILI | Bilirubin |
| BMI | Body Mass Index |
| cHMWK | Cleaved High Molecular Weight Kininogen |
| C1-INH | C1 Esterase Inhibitor |
| C1q | Complement Component 1q |
| C4 | Complement Component 4 |
| CDC | Centers for Disease Control and Prevention |
| CI | Confidence Interval |
| COVID-19 | Coronavirus disease 2019 |
| CRF | Case Report Form |
| CS | Clinical Significance |
| CTMS | Clinical Trial Management System |
| CV% | Coefficient of Variation |
| ECG | Electrocardiogram |
| EOS | End of Study |
| EOT | End of Treatment |
| ET | Early Termination |
| FAS | Full analysis set |
| HAARP | HAE Attack Assessment and Reporting Procedures |
| HAE | Hereditary angioedema |
| HR | Heart Rate |
| IP | Investigational Product |
| ISR | Injection Site Reaction |
| IV | Intravenous |
| KM | Kaplan-Meier |
| LLN | Lower Limit of Normal |
| LTP | Long-term Prophylaxis |
| MedDRA | Medical Dictionary for Regulatory Activities |
| msec | Millisecond |
| NCS | Non-Clinical Significance |
| NNA | Normalized Number of Attacks |
| PD | Pharmacodynamic |

| | |
|---|---|
| PK | Pharmacokinetic |
| pKal | Plasma kallikrein |
| PPAS | Per-Protocol Analysis Set |
| PT | Preferred Term (MedDRA®) |
| RR | Respiratory Rate |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| SD | Standard Deviation |
| SMQ | Standardized MedDRA® Query |
| SOC | System Organ Class |
| SPD | Significant Protocol Deviation |
| TEAE | Treatment-emergent Adverse Event |
| ULN | Upper Limit of Normal |
| WHO-DD | World Health Organization Drug Dictionary |

# 1.0 OBJECTIVES, END POINTS AND ESTIMANDS

## 1.1 Objectives

### 1.1.1 Primary Objective

The primary objective of this study is *to evaluate the safety of repeated subcutaneous (SC) administrations of lanadelumab in Chinese subjects with hereditary angioedema (HAE).*

### 1.1.2 Secondary Objective(s)

The secondary objectives of this study are:

- *To evaluate the pharmacokinetic (PK) of repeated SC administrations of lanadelumab in Chinese subjects with HAE*
- *To evaluate the pharmacodynamic (PD) of repeated SC administrations of lanadelumab in Chinese subjects with HAE*
- *To evaluate the efficacy of repeated SC administrations of lanadelumab in Chinese subjects with HAE*
- *To evaluate the immunogenicity of repeated SC administration of lanadelumab and the effect on lanadelumab PK, PD, efficacy, and safety*



### 1.1.3 Exploratory Objective(s)

Not applicable

## 1.2 Endpoints

**Table 1. Objectives and Endpoints**

| Objective | Endpoint(s) |
|---|---|
| **Primary** | |
| • *To evaluate the safety of repeated SC administrations of lanadelumab in Chinese subjects with HAE.* | • *Treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and adverse events of special interest (AESIs)*<br>• *Clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis)* |

## Table 1. Objectives and Endpoints

| Objective | Endpoint(s) |
|---|---|
| | • *Vital signs including blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR)*<br>• *12-lead electrocardiogram (ECG)*<br>• *Physical examination* |
| **Secondary** | |
| • *To evaluate the PK of repeated SC administrations of lanadelumab in Chinese subjects with HAE.* | • *Plasma concentrations of lanadelumab* |
| • *To evaluate the PD of repeated SC administrations of lanadelumab in Chinese subjects with HAE.* | • *Plasma kallikrein (pKal) activity as measured by cleaved high molecular weight kininogen (cHMWK) level (ie, plasma concentrations of cHMWK)* |
| • *To evaluate the efficacy of repeated SC administrations of lanadelumab in Chinese subjects with HAE.* | • *Number of investigator-confirmed HAE attacks during the efficacy evaluation periods*<br>• *Number of investigator-confirmed HAE attacks requiring acute treatment during the efficacy evaluation periods*<br>• *Number of investigator-confirmed moderate or severe HAE attacks during the efficacy evaluation periods*<br>• *Maximum attack severity during the efficacy evaluations periods.*<br>• *Time to first HAE attack during the efficacy evaluation periods*<br>• *Achievement of attack-free status during the efficacy evaluation periods*<br>• *Number and percentage of subjects meeting the criterion of at least a 50%, 70%, 90% and 100% reduction in the investigator-confirmed normalized number of attacks (NNA) per 4 weeks relative to the run-in period NNA, and the number and percentage of subjects achieving NNA < 1.0 per 4 weeks* |
| • *To evaluate the immunogenicity of repeated SC administration of lanadelumab and the effect on lanadelumab PK, PD, efficacy, and safety.* | • *Presence or absence of antidrug antibody (ADA) in plasma (neutralizing or non-neutralizing antibodies in plasma)*<br>• *Effect on:*<br>  • *Lanadelumab plasma concentrations*<br>  • *cHMWK level* |

## Table 1. Objectives and Endpoints

| Objective | Endpoint(s) |
|---|---|
| | • *Number of investigator-confirmed HAE attacks during the efficacy evaluation periods* |

## 1.3 Estimand(s)

**Table 2. Estimand Framework**

| Estimand: Primary | | | | | |
|---|---|---|---|---|---|
| | **Attributes** | | | | |
| **Definition** | **Treatment** | **Population** | **Variable (or Endpoint)** | **Strategy for Addressing Intercurrent Event** | **Population-Level Summary** |
| Proportion of Chinese patients with HAE who develop TEAEs including each AESI (Hypersensitivity reactions and events of disordered coagulation [Bleeding AESI，Hypercoagulable AESI]) and all SAEs after exposure to Lanadelumab during the Treatment Period | 300 mg lanadelumab q2wks administered for 26 weeks for a total of 14 doses during the Treatment Period | ≥ 12-year-old Chinese patients with HAE defined through inclusion and exclusion criteria as stated in the protocol and who received at least 1 dose of lanadelumab during the study | Occurrence of TEAEs following first lanadelumab dose | 1) Premature study discontinuation related/or unrelated to investigational product while on treatment: TEAEs occurring while the subject is on the study will be counted.<br>2) Investigational product interruption: TEAEs occurring during the interruption while the subject is on the study will be counted.<br>3) Use rescue medication: TEAEs occurring during the use of rescue medications/supportive treatments while the subject is on the study will be counted. | Number and proportion of patients who experience TEAEs during Treatment Period |

## Table 2. Estimand Framework (Continued)

| Estimand: Secondary | | | | | |
|---|---|---|---|---|---|
| | **Attributes** | | | | |
| **Definition** | **Treatment** | **Population** | **Variable (or Endpoint)** | **Strategy for Addressing Intercurrent Event** | **Population-Level Summary** |
| Investigator-confirmed normalized number of attacks (NNA) per 4 weeks, while on lanadelumab during each of the efficacy evaluation periods. | 300 mg lanadelumab q2wks for 26 weeks administered for a total of 14 doses during the Treatment Period | ≥ 12-year-old Chinese patients with HAE defined through inclusion and exclusion criteria as stated in the protocol and who received at least 1 dose of lanadelumab during the study | Number of investigator-confirmed HAE attacks during the efficacy evaluation periods | 1) Premature study discontinuation related/or unrelated to investigational product while on treatment: HAE attacks occurring while the subject is on study up to study discontinuation will be counted.<br>2) Investigational product interruption: HAE attacks occurring during the interruption will be counted.<br>3) Use rescue medication: HAE attacks are counted regardless of whether the subject uses rescue medications/supportive treatments. | Investigator-confirmed normalized number of attacks per 4 weeks during each efficacy evaluation period and comparison to investigator-confirmed normalized number of attacks per 4 weeks during Run-in Period |

## Table 2. Estimand Framework (Continued)

| Estimand: Secondary | | | | | |
|---|---|---|---|---|---|
| | **Attributes** | | | | |
| **Definition** | **Treatment** | **Population** | **Variable (or Endpoint)** | **Strategy for Addressing Intercurrent Event** | **Population-Level Summary** |
| Time to first HAE attack during each of the efficacy evaluation periods. | 300 mg lanadelumab q2wks administered for 26 weeks for a total of 14 doses during the Treatment Period | ≥ 12-year-old Chinese patients with HAE defined through inclusion and exclusion criteria as stated in the protocol and who received at least 1 dose of lanadelumab during the study | Time to first HAE attack during each of the efficacy evaluation periods. | 1) Premature study discontinuation related/or unrelated to investigational product with no attack before the end of the efficacy evaluation period: If the subject discontinues prior to having an HAE attack, the subject will be censored at the time of study discontinuation.<br>2) Investigational product interruption: HAE attack occurring during the interruption will be counted as an event.<br>3) Use rescue medication: HAE attacks are counted as events regardless of whether the subject uses rescue medications/supportive treatments. | Kaplan-Meier (KM) estimates of time to first HAE attack will be summarized using the 25th, 50th (median), and 75th percentiles with associated two-sided 95% CI, as well as percentage of events and censored observations during each efficacy evaluation period |

## Table 2. Estimand Framework (Continued)

| Estimand: Secondary | | | | | |
|---|---|---|---|---|---|
| | **Attributes** | | | | |
| **Definition** | **Treatment** | **Population** | **Variable (or Endpoint)** | **Strategy for Addressing Intercurrent Event** | **Population-Level Summary** |
| Achievement of HAE attack free status during each of the efficacy evaluation periods | 300 mg lanadelumab q2wks administered for 26 weeks for a total of 14 doses during the Treatment Period. | ≥ 12-year-old Chinese patients with HAE defined through inclusion and exclusion criteria as stated in the protocol and who received at least 1 dose of lanadelumab during the study | Achievement of attack-free status during the efficacy evaluation periods | 1) Premature study discontinuation related/or unrelated to investigational product of the efficacy evaluation with no attack before the end of the efficacy evaluation period: The subject will be counted as attack-free<br>2) Investigational product interruption: HAE attacks occurring during the interruption will be counted as events.<br>3) Use rescue medication: HAE attacks are counted as events regardless of whether the subject uses rescue medications/supportive treatments. | Proportion of subjects achieving attack-free status for each of the efficacy evaluation periods of Day 0 through Day 182 and Day 70 through Day 182 and corresponding exact 95% CI. |

AESI = Adverse Event of Special Interest; CI = confidence interval; HAE = Hereditary angioedema; q2wks = once every two weeks; SAE = Serious Adverse Event; TEAE = Treatment-emergent Adverse Event

## 2.0 STUDY DESIGN

*This open-label study will enroll Chinese subjects of 12 years of age or older with a confirmed diagnosis of HAE (Type I or II).*

*The study includes a screening period that may require screening of 4 weeks, a washout period of 2 weeks, a run-in period of 4 to 8 weeks, a treatment period of 26 weeks, and a follow-up period of 4 weeks. Maximum study period will be 44 weeks.*

Screening Visit and Washout Period:

*Following informed consent, subjects will undergo screening assessments. Screened adult subjects who are on long-term prophylaxis (LTP) (eg, androgens) for HAE are required to undergo a minimum 2-week washout period prior to the run-in period. This LTP washout period is permitted as long as the investigator determines that doing so would not place the subject in any undue safety risk and that the subject is at least 18 years of age (ie, LTP washout is not required in adolescent subjects [≥12 to <18 years of age]). Subjects who fail screening due to a single laboratory test result that does not meet eligibility criteria may have that laboratory test repeated at the discretion of the investigator. This will include a repeat of only the failed assessment rather than a repeat of all screening assessments.*



Run-in Period:

*Screened subjects who are not on LTP therapy for HAE or who have completed the required washout period will enroll and enter a run-in period of 4 to 8 weeks to determine their baseline attack rate. Only subjects meeting a minimum baseline attack rate of at least 1 investigator-confirmed attack per 4 weeks will be eligible for treatment. Subjects who experience 3 or more investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to the treatment period. Subjects without at least 1 investigator-confirmed attack after 4 weeks will have their run-in period extended by 4 weeks, during which time they need to have at least 2 investigator-confirmed attacks in 8 weeks to be eligible for treatment. Subjects who do not meet the minimum attack rate during the run-in period or are otherwise determined to be ineligible due to screening assessments will not be allowed to enter the treatment period of the study and will be replaced with new HAE subjects until approximately 20 subjects have entered the treatment period. Subjects who are found to be ineligible during the run-in period will not be allowed to rescreen into the study.*

Treatment Period:

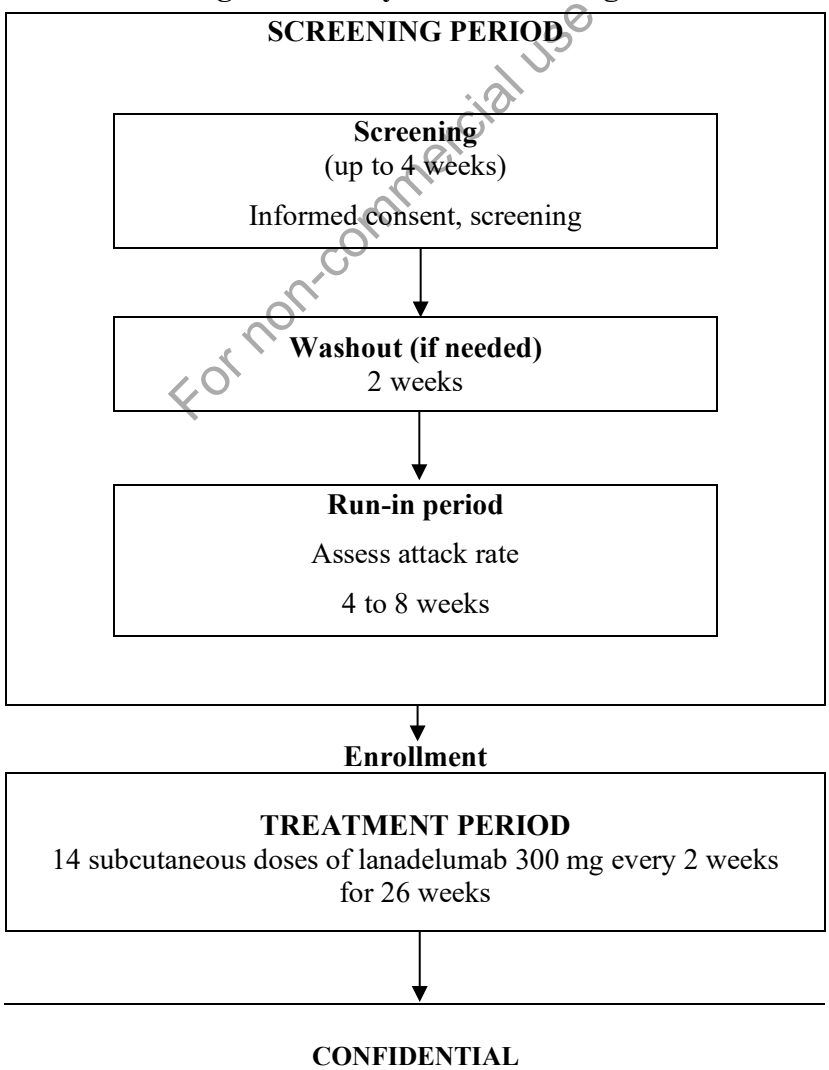
*Subjects who enter the treatment period will receive lanadelumab 300 mg every two weeks (q2wks) for 26 weeks. Subjects who complete the run-in period will receive a total of 14 doses of lanadelumab from Day 0 to Day 182 (±3 days).*

Follow-up Period:

*After completion of the 26 weeks treatment period, subjects will be followed for an additional 4 weeks and will attend the follow-up visit on Day 210 (±3 days).*

*All study procedures are detailed in the study schematic diagram (Figure 1) and schedule of study activities (*Appendix 9.4 Table 6*).*

**Figure 1. Study Schematic Diagram**



**FOLLOW-UP PERIOD**
4 weeks

## 3.0 STATISTICAL HYPOTHESES AND DECISION RULES

*No statistical hypothesis testing will be performed.*

## 4.0 SAMPLE-SIZE DETERMINATION

*The planned total sample size for this study is approximately 20 subjects.*

*The sample size is considered adequate based on the objectives of the study and was based on clinical judgment and precedent studies of similar design and similar subject population and not on statistical considerations such as study power. With a sample size of 20 subjects exposed to lanadelumab, the probability of observing an event that occurs within the population at a rate of 10% is approximately 87%.*



## 5.0 ANALYSIS SETS

Analysis of study data will be based on the following analysis sets:

### 5.1 Screened Set

All subjects who have signed informed consent.

### 5.2 Full Analysis Set (FAS)

*All subjects who received at least 1 dose of lanadelumab (investigational product [IP]). All safety and efficacy analyses will be based on the FAS.*

### 5.3 Per-Protocol Analysis Set (PPAS)

The per-protocol analysis set (PPAS) will consist of all subjects in the FAS who met all study entry criteria and who had no significant protocol violations that might impact efficacy. Significant or important protocol deviations are defined in the latest version of the Protocol Deviation Management Plan. Protocol deviations will be reported in the IQVIA clinical trial management system (CTMS) throughout the study. It should be noted that not all significant protocol deviations will lead to the subject's exclusion from the PPAS as some or all significant deviations will not necessarily have any influence on the efficacy.

Prior to conducting any analysis of the PPAS, a cross-functional protocol deviations review meeting of CTMS data will be held to determine final subject exclusions.

### 5.4 Pharmacokinetic Set (PK set)

*All subjects in the FAS who have at least 1 evaluable post-dose PK concentration value. All PK analyses will be based on the PK set.*

### 5.5 Pharmacodynamic Set (PD set)

*All subjects in the FAS who have at least 1 evaluable post-dose PD concentration value. All PD analyses will be based on the PD set.*

## 6.0 STATISTICAL ANALYSIS

### 6.1 General Considerations

All variables in this study will use the analysis method below unless stated otherwise in the section specific to an endpoint. Where applicable, variables will be summarized descriptively by study visit.



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.

The definition of baseline is provided in Section 9.2.2.

A windowing convention will be used to determine the analysis value for a given study visit for observed data analyses. See Section 9.2.3 for details.

#### 6.1.1 Handling of Treatment Misallocations

Not applicable.

#### 6.1.2 Analysis Approach for Continuous Variables

All continuous endpoints in this study will be summarized descriptively using number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum value. See Section 9.2.1 for details.

### 6.1.3 Analysis Approach for Categorical Variables

All categorical endpoints in this study will be summarized descriptively using count and percentage. See Section 9.2.1 for details.

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

Time-to-event variables (e.g., time to the first HAE attack) will be analyzed using Kaplan-Meier (KM) estimates. Summaries will include median time and quartiles, if estimable, and corresponding 95% CI. See Section 6.5.2.3 for analysis details.

## 6.2 Disposition of Subjects

The number of subjects who were included in each defined analysis population (i.e., Screened, FAS, PK, and PD) will be summarized.

The summary for study disposition will include the count/percentage of subjects who have completed the study, and the count/percentage of subjects who have prematurely withdrawn from the study, as well as the primary reasons for study withdrawal, and will be presented for the FAS. Additionally, the subjects who completed the entire treatment period will be summarized (count and percentage).

Completing the treatment period is defined as those subjects who complete Visit 14/Day 182.

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

## 6.3 Demographic and Other Baseline Characteristics

### 6.3.1 Demographics and Baseline Characteristics

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

The following demographics and baseline characteristics will be summarized:

- Age at informed consent date (years),
- Age category (≥12 to <18, 18 to <40, 40 to <65, ≥65 years),
- Sex (Male, Female),

- Race (Asian, Chinese),
- Weight (kg),
- Weight group (<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$^2$), and
- 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.

All demographic and baseline characteristic data will be presented in subject listings for the Screened Set.



### 6.3.2 Medical History and Concurrent Medical Conditions

Medical history will be collected at the Screening Visit and will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0 or newer.

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

All medical history will be presented in subject listings for the Screened Set.

### 6.3.3 Baseline HAE Characteristics

The following baseline HAE characteristics will be summarized descriptively for the FAS:

- Age at onset of HAE symptoms (years),
- HAE type (Type I, Type II, Unspecified- Type I or Type II),
- History of laryngeal attacks (yes, no),
- Primary HAE attack location (laryngeal, abdominal, peripheral, or a combination of these locations),

- Number of HAE attacks in the last 1, 3, and 12 months prior to screening,
- Average HAE 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 (mild, moderate, severe),
- Number of HAE attacks of different severity (mild, moderate, severe) in the last 3 months prior to screening,
- Average HAE attack duration category (less than 12 hours, 12-24 hours, 24-48 hours, greater than 48 hours, not applicable) in the last 3 months prior to screening,
- Run-in period HAE attack rate (attacks/4 weeks),
- Run-in period HAE attack rate categories (1 to <2, 2 to <3, ≥3 attacks/4 weeks),
- Type of LTP therapy use before entering the run-in period (C1 esterase inhibitor [C1-INH], Androgens, Anti-fibrinolytics, or not on LTP).



The LTP (C1-INH, Androgens, or Anti-fibrinolytics) treatment a subject was on prior to the run-in 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 run-in period, imputing partial dates as described in Section 9.2.7.2) 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') |

Run-in period HAE attack rate (attacks/months) will be calculated as the number of HAE attacks during the run-in period divided by the number of days the subject contributed to the run-in period multiplied by 28 days.

All baseline HAE characteristics data will be presented in subject listings for the Screened Set.

## 6.4 Medication History and Concomitant Medications

### 6.4.1 Prior Medication/therapy/procedure

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

Partial date imputation for medications is described in Section 9.2.7.2.

Prior medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) dated 01 Mar 2022 or newer. Prior therapies and procedures will be coded using MedDRA Version 25.0 or newer.

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 FAS. The prior therapies and procedures (excluding those taken for an HAE attack) 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 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 preferred name) will be counted only once.



All prior medications, therapies, and procedures will be listed for Screened Set.

### 6.4.2 Concomitant Medication/therapy/procedure

Concomitant medication/therapy/procedure 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 follow-up period, 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 follow-up period, inclusive.

Concomitant medications will be coded using the WHO-DD dated 01 Mar 2022 or newer. Concomitant therapies and procedures will be coded using MedDRA Version 25.0 or newer.

Concomitant medications will be summarized by the number and proportion of subjects within each ATC Level 2 therapeutic class and PT for the FAS population. Tabulations will be presented sorted by therapeutic class in alphabetical order and by PT within each therapeutic class by descending frequency for FAS. The concomitant therapies and procedures 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 preferred name) will be counted only once.

Concomitant medications/therapies/procedures (excluding those taken for an HAE attack) will be summarized by treatment period, follow-up period, and overall study period. Detailed definition of these analysis periods is given in Section 9.2.4. Partial date imputation for medications is described in Section 9.2.7.2. All concomitant medications, therapies, and procedures will be listed for the FAS.

### 6.4.3 Rescue Medications and Supportive Treatments

Rescue medications and supportive treatments as a subset of prior or concomitant medication/therapies/procedures are defined as any medication/therapy/procedure identified by the investigator as given for an HAE attack. They will be reported in HAE Acute Attack CRF. The types of rescue medications are Firazyr (icatibant), fresh frozen plasma, and other acute HAE therapy treatment; and the types of supportive treatments are intravenous (IV) fluids, pain medication, oxygen, anti-emetic, and other acute HAE supportive treatment.



The rescue medications will be summarized by the number and proportion of subjects within each ATC Level 2 therapeutic class and PT for FAS. The therapies and procedures performed for HAE attack 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 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 preferred name) will be counted only once.

Rescue medications and supportive treatments will be summarized by run-in period, treatment Period, follow-up period, and overall study period (including those taken for an HAE attack from screening period through follow-up period). Partial date imputation for medications is described in Section 9.2.7.2.

Additional analysis details on HAE attack rescue medications and supportive treatments use can be found in Section 6.5.3.1.2.2 and Section 6.5.3.1.2.3.

All rescue medications and supportive treatments will be included in the listings of prior or concomitant medications/therapies procedures, respectively.

## 6.5 Efficacy Analysis

*No statistical hypothesis testing will be performed.* The totality of results across all efficacy endpoints will be the measure of overall treatment benefit.

*All efficacy summaries will be based on the FAS. Efficacy data, including derived data, will be presented in subject data listings.*

*Efficacy endpoints will be evaluated for the following 2 efficacy evaluation periods:*

- *Day 0 (after study drug administration) through Day 182*
- *Presumed steady-state period from Day 70 through Day 182*

Detailed definition of these periods is given in Section 9.2.4. For efficacy evaluation periods starting from Day 70, only subjects who reach the visit of Day 70 will be included in the analysis and this number of subjects will be used as denominator for percentage calculation.

A HAE attack will be counted for a specific efficacy evaluation period only if that HAE attack started during that period. For example, if a HAE attack starts before Day 70 and is ongoing after Day 70, it will not be counted for the efficacy period Day 70 through Day 182.

For all efficacy analyses, unique HAE attacks, as defined in Section 9.2.5.1, will be used.

The definition of baseline for efficacy analyses is provided in Section 9.2.2.

Handling of missing start or end date and time for HAE attacks is described in Section 9.2.7.1.



### 6.5.1 Primary Endpoint(s) Analysis

The primary objective for this study is safety. All efficacy endpoints are secondary.

### 6.5.2 Secondary Endpoints Analysis

#### 6.5.2.1 *Number of Investigator-confirmed HAE Attacks during the efficacy evaluations periods*

Investigator-confirmed HAE attacks are those that the primary investigator confirmed as meeting the HAE Attack Assessment and Reporting Procedures (HAARP) criteria for an HAE attack and reported on the CRF.

The number of investigator-confirmed HAE attacks during each efficacy evaluation period will be expressed as a normalized monthly (4 weeks, i.e., 28 days). The HAE attack rate in this statistical analysis plan (SAP) refers to investigator-confirmed normalized number of HAE attacks (normalized number of attacks [NNA]) per 4 weeks.

The baseline investigator-confirmed HAE attack rate will be calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the baseline run-in period divided by the number of days the subject contributed to the run-in period multiplied by 28 days. The run-in period is defined in more details in Section 9.2.4.

For each treatment efficacy evaluation period, the investigator-confirmed HAE attack rate will be calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the efficacy evaluation period divided by the number of days the subject contributed to the efficacy evaluation period multiplied by 28 days.

The baseline investigator-confirmed attack rate, as well as the treatment period investigator-confirmed attack rate, change from baseline, and percent change from baseline for each efficacy evaluation period will be summarized for the FAS. In addition to the descriptive statistics for attack rates, the summary will include the total number of investigator-confirmed HAE attacks reported during each period and subject-time in months that each subject contributed to each period.



Figures plotting the investigator-confirmed HAE attacks reported during each efficacy evaluation period with timing relative to first study drug administration day for each subject will be created (i.e., birds on a wire plots).

In addition, the number of investigator-confirmed HAE attacks per month (i.e., 28 days) will be summarized by month (per 28-day interval) for the FAS. The summary will include descriptive statistics for baseline investigator-confirmed attack rate, as well as monthly investigator-confirmed attack rates, monthly change from baseline, and monthly percent change from baseline for each efficacy evaluation period. 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. For the overall treatment period, the date of the first exposure to study drug in this study will be used as the start of the first interval and end of the interval will be the date of first exposure to study drug in this study

plus 27 days. For the presumed steady state period, the Day 70 will be used as the start of the first interval. The end of the interval will be the start of the interval plus 27 days. Each successive interval will start the last day of the prior interval plus 1 day and end 28 days later.

Similar summary tables except the summary of attack rate per month for each efficacy evaluation period will be presented for the following efficacy endpoints for the FAS:

- Number of investigator-confirmed HAE attacks requiring acute treatment during the efficacy evaluation periods:

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

- Number of investigator-confirmed moderate or severe HAE attacks during the efficacy evaluation periods:

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



#### 6.5.2.2 *Maximum attack severity during the efficacy evaluations periods*

Hereditary angioedema attack severity level is based on HAARP (see Section 9.2.5.3 for details on handling HAE attack severity). The number and percentage of subjects will be tabulated by maximum attack severity (no attacks, mild, moderate, and severe) for each efficacy evaluation period.

Additional analyses of HAE attack severity for subject level HAE attack characteristics can be found in Section 6.5.3.1.1.2.

#### 6.5.2.3 *Time to first HAE attack during the efficacy evaluation periods*

The time to the first investigator-confirmed HAE attack (days) after Day 0 for the efficacy evaluation period of Day 0 through Day 182 and Day 70 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. See Section 9.2.4 for detailed definition of these periods.

Subjects with attacks will be analyzed as events, with the date and time of the first HAE attack during the efficacy evaluation period taken as the time of the event. 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 KM estimates of the 25th, 50th (median), and 75th percentiles, if estimable, and 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.*



6.5.2.4 *Achievement of attack-free status during the efficacy evaluation periods*

A subject is considered as attack free during an efficacy evaluation period if the subject has no investigator-confirmed HAE attacks during that efficacy evaluation period. For subjects who discontinue the study during an efficacy evaluation period, 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 for the efficacy evaluation period will be summarized for the FAS. A two-sided 95% CI for the proportion of subjects achieving attack-free will be derived using the exact method.

6.5.2.5 *Number and percentage of subjects meeting the criterion of at least a 50%, 70%, 90% and 100% reduction in the investigator-confirmed normalized number of attacks (NNA) per 4 weeks relative to the run-in period NNA*

There will be four classes of responders based on pre-specified percentage reduction in the investigator-confirmed NNA per 4 weeks (i.e., monthly, 28 days) from the run-in period: 50% or more reduction, 70% or more reduction, 90% or more reduction, and 100% reduction.

For each efficacy evaluation period, the percentage reduction will be calculated as the run-in period HAE attack rate minus the treatment period HAE attack rate divided by the run-in period HAE attack rate. Number and percentage of subjects achieving each of the four predefined

thresholds will be summarized for each efficacy evaluation period. The four classes of responders are nested within each other and not mutually exclusive.

6.5.2.6 *Number and percentage of subjects achieving NNA < 1.0 per 4 weeks*

There will be one class of responder based on pre-specified investigator-confirmed NNA per 4 weeks (i.e., monthly, 28 days) for each of the efficacy evaluation periods: <1.0 per 4 weeks.

The number and percentage of subjects achieving the predefined threshold will be summarized for each efficacy evaluation period.

### 6.5.3 Other Supportive Efficacy Endpoints

6.5.3.1 *Characteristics of investigator-confirmed HAE attacks*

Characteristics of investigator-confirmed HAE attacks will be summarized for the run-in period and each efficacy evaluation period at both the subject level and event-level. The calculations described below will be conducted for clinical outcomes data partitioned within each efficacy evaluation period.



*6.5.3.1.1 Subject Level HAE Attack Characteristics*

*6.5.3.1.1.1 HAE Attack Duration*

For each subject, the mean duration of all investigator-confirmed HAE attacks will be calculated in hours and summarized. See Section 9.2.5.2 for details on handling HAE attack duration and Section 9.2.7.1 for handling of missing date/time of HAE attacks.

The subject-level average attack duration will be categorized into 12-hour intervals and tabulated by category (<12 hours, 12-24 hours, >24-48 hours, and >48 hours).

*6.5.3.1.1.2 HAE Attack Severity*

The mean attack severity will be calculated using a numerical rating (0=No attack, 1=Mild, 2=Moderate, and 3=Severe) and summarized for all subjects, as well as only subjects with HAE attacks. See Section 9.2.5.3 for details on handling HAE attack severity.

The categorical analyses on HAE maximum attack severity can be found in Section 6.5.2.2.

#### *6.5.3.1.2 Event Level HAE Attack Characteristics*

##### *6.5.3.1.2.1 HAE Attack Location*

The number and percentage of subjects with attacks, as well as the number of events, will be tabulated by the primary attack location (peripheral, abdominal, and laryngeal) as determined by the investigator. See Section 9.2.5.1 for details on handling HAE primary attack location.

Additionally, the attack location will be re-classified and summarized with an emphasis on the laryngeal attack. In this summary, an attack with either the primary or secondary location(s) identified as laryngeal will be considered as a laryngeal attack; otherwise, attacks will be classified by their reported primary attack location.



##### *6.5.3.1.2.2 Rescue Medication Use*

The number and percentage of subjects with rescue medication use for an HAE attack, as well as the number of events (number of rescue medications used), will be tabulated by type of rescue medication [FIRAZYR (icatibant), fresh frozen plasma, and other local standard of care] as reported in the HAE Acute Attack CRF.

See Section 9.2.5.1 for additional details on handling HAE attack rescue medication use.

##### *6.5.3.1.2.3 Supportive Treatment Use*

The number and percentage of subjects with supportive treatment use for an HAE attack, as well as the number of events, will be tabulated by type of supportive treatment (IV fluids, pain medication, oxygen, anti-emetic, and other) as reported in the HAE Acute Attack CRF.

See Section 9.2.5.1 for additional details on handling HAE attack supportive treatment use.

### 6.5.3.2 *Percentage of Attack-Free Days*

An attack-free day is defined as a calendar day with no investigator-confirmed HAE attack.

The percentage of HAE attack free days during each efficacy evaluation period will be calculated by counting the number of days in the efficacy evaluation period without an HAE attack and dividing by the number of days the subject was in the efficacy evaluation period.

Descriptive statistics for the percentage of HAE attack free days will be summarized for each efficacy evaluation period.

### 6.5.4 Sensitivity Analysis

*Sensitivity analysis will be performed to evaluate the robustness of the efficacy results during each efficacy evaluation period. All efficacy analyses will be repeated using all subject-reported HAE attacks instead of limiting the analysis to those attacks that were investigator-confirmed* for the FAS. All analyses for secondary efficacy endpoints will also be conducted using investigator-reported HAE attacks for the PPAS.

### 6.5.5 Subgroup Analyses

No subgroup analyses are planned for efficacy endpoints.

## 6.6 Safety Analysis

Safety analysis is the primary analysis for this study. Safety endpoints include adverse events (AEs), clinical laboratory variables, vital signs, electrocardiogram (ECG) variables, and physical examination.

*No statistical hypothesis testing will be performed. All safety summaries will be based on the FAS. All safety data, including derived data, will be presented in subject data listings.*

The definition of baseline is provided in Section 9.2.2.



### 6.6.1 Adverse Events (AE)

Adverse events will be coded using MedDRA Version 25.0 or newer.

*Treatment-emergent adverse event (TEAE) is defined as AE with onset at the time of or following initial dosing with study drug (lanadelumab), or medical conditions present prior to the start of study drug but increasing in severity or relationship at the time of or following the start of treatment, up to the last follow-up visit. 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 9.2.7.3.

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 9.2.7.6.

*Severe AEs are AEs classified as severe (grade 3) or life threatening (grade 4) by the investigator.* Missing severity imputation is described in Section 9.2.7.5.

The collection of tabulations described in this section (with the exception of the analyses of adverse event of special interest (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 attack 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.

For AE summaries, AEs will be classified to one of two analysis periods unless stated otherwise in the specific section:

- *Treatment Period AEs will include all AEs starting at or after the first exposure to lanadelumab in this study to those starting before or at the subject's last visit date during the treatment period in this study (AEs starting at or after treatment on Day 0 through Day 182 visit).*



*Follow-up Period AEs will include all AEs starting at or after the subject's last visit date of the treatment period in this study (AEs starting after the Day 182 visit).The number and percentage of subjects with any AE, any related AE, any serious adverse event (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 for each analysis period. The number of deaths due to an AE, hospitalization due to an AE and study discontinuation due to an AE will be summarized for each analysis period.*

In addition, an overall AE during the treatment period will be summarized by the run-in period HAE attack rate categories and by whether or not use LTP therapy, respectively.

*The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized by SOC and PT for each analysis period. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, and related severe AEs. Similar summary tables for investigator-reported AESIs, or determined by the search tool of relevant Standardized*

*MedDRA Queries, will also be generated.* 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 for treatment period AEs only. This tabulation will be repeated for related AEs and SAEs for treatment period AEs.* Tabulations will be presented sorted by PT by descending frequency.

*All AEs will be provided in subject listings. Listings will be presented separately for each analysis period. In addition, subject listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs, related AEs, severe AEs, and AESIs will be produced.*



#### 6.6.1.1 *Adverse Events of Special Interest (AESI)*

Adverse event of special interest for this study are hypersensitivity reactions and events of disordered coagulation (hypercoagulability events and bleeding events). The preferred terms from MedDRA 25.0 or newer Standardized MedDRA Queries (Standardized MedDRA® Query [SMQ]) will be used to identify an SMQ-defined AESI. Table 3 shows the SMQs used to identify AESI of hypersensitivity, hypercoagulable, and bleeding.

**Table 3. 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) |

AESI = Adverse Event of Special Interest; SMQ = Standardized MedDRA® Query

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 for each analysis period. The number of

deaths due to an AESI, hospitalization due to an AESI and study discontinuation due to an AESI will be summarized for each analysis period.

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 for each analysis period. 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.

#### 6.6.1.2 *Injection Site Reaction (ISR) AEs*

Injection site reaction AEs will be identified by AEs 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 for each analysis period. 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 for the treatment period.

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 for the treatment period.

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

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 for the treatment period. Injection site reaction duration will also be summarized by category (<= 1 Day - Unclear, > 1 Day: >1-14 Days, >14 Days).

Refer to Section 9.2.7.4 for algorithm to derive duration of ISR AEs. A listing of ISR AEs will be provided.

### 6.6.2 Clinical Laboratory Evaluation

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

Clinical laboratory parameters to be evaluated include the following:

***Clinical Chemistry***

- *Albumin*
- *Alkaline phosphatase*
- *Alanine aminotransferase (ALT; SGPT)*
- *Aspartate aminotransferase (AST; SGOT)*
- *Bilirubin (total and direct)*
- *Blood urea nitrogen*
- *Calcium*
- *Carbon dioxide*
- *Chloride*
- *Creatinine*
- *Creatine phosphokinase (CPK)*
- *Glucose*
- *Phosphate*
- *Magnesium*
- *Potassium*
- *Sodium*
- *Total protein*
- *Uric acid*

***Hematology***

- *Hemoglobin*
- *Hematocrit*
- *Red blood cell count*
- *White blood cell count with differential*
- *Mean corpuscular volume*
- *Mean corpuscular hemoglobin*
- *Mean corpuscular hemoglobin concentration*
- *Absolute platelet count*

***Coagulation***

- *Prothrombin time*
- *Activated partial thromboplastin time (aPTT)*
- *International Normalized Ratio (INR)*

***Urinalysis***

- *Bilirubin*
- *Glucose*
- *Ketones*
- *Blood*
- *Nitrite*
- *pH*
- *Protein*
- *Specific gravity*
- *Microscopy (if indicated by macroscopic findings)*

***Serology***

- *HBsAg*
- *HCV*
- *HIV*

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

Descriptive statistics for clinical laboratory values and changes from baseline at each study visit, combined all scheduled study visits, combined all unscheduled visits, and combined all visits including both scheduled and unscheduled visits will be presented.



For continuous laboratory test results, if more than one laboratory result is reported per study visit per parameter, the last non-missing result will be selected for analysis. For categorical laboratory test results, 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 (CS) 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 below the lower limit of normal (LLN), non-clinically significant result below the LLN, within the normal range, non-clinically significant result above the upper limit of normal (ULN), and clinically significant result above the ULN will be summarized by study visit and overall post-baseline scheduled/unscheduled visits. 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. Post-baseline analysis is summarized on non-missing post-baseline most severe results per subject and per parameter. Clinical significance attributions for laboratory results are described in Section 9.2.7.7.

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 9.2.8. 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.

Among chemistry parameters, additional analyses in Table 4 will be conducted on liver function tests using the highest pre-treatment, highest treatment period, and follow-up 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 alanine transaminase (ALT), aspartate transaminase (AST) will be summarized for all pre-treatment measurements, treatment period, and follow-up 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, treatment period, and follow-up period measurements. Additionally, a shift table summarizing the shift in categories from highest pre-treatment measurements to the highest treatment period and follow-up period measurements will be created for the liver function tests including ALT, AST and BILI.



**Table 4. Lab Parameter Criteria Categories**

| Parameter | Criteria Categories | | | |
|---|---|---|---|---|
| Liver Function Tests | | | | |
| Alanine transaminase (U/L) | Normal (<=1 x ULN) | >1 – <=3 x ULN | >3 – <=5 x ULN | >5 x ULN |
| Aspartate transaminase (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 | - |

ULN = upper limit of normal

### 6.6.3 Vital Signs

The following vital signs will be measured:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (HR) (beats per minute)
- Body temperature (°C)
- Respiratory rate (RR) (breaths per minute)

Actual values and changes from baseline in vital signs will be summarized by study visit, study time point, overall post-baseline scheduled visits, overall post-baseline unscheduled visits, and

overall post-baseline visits including both scheduled and unscheduled visits for each parameter. 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 CS 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, study time point, overall post-baseline scheduled visits, overall post-baseline unscheduled visits, and overall post-baseline visits including both scheduled and unscheduled visits for each parameter. 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.



### 6.6.4 Electrocardiography

The following ECG variables will be measured:

- HR (beats per minute)
- PR interval (millisecond [msec])
- QRS duration (msec)
- QT interval (msec)
- Corrected QT interval (QTc) interval (msec)
- QTcF interval (msec)
- QTcB interval (msec)

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

Electrocardiogram overall assessments will be classified according to CS of ECG findings and abnormality as determined by the investigator. The number of subjects with a non-missing

result, and the number and percentage of subjects with a normal overall assessment, subjects with an abnormal overall assessment and all ECG findings not clinically significant, and subjects with an abnormal overall assessment and at least one clinically significant ECG finding will be summarized by study visit and overall post-baseline scheduled/unscheduled visits for subjects who have baseline results. If more than one ECG result is reported per study visit per parameter, the result yielding the most severe classification will be selected for analysis.

All ECG data will be presented in subject listings. Subjects with clinically significant abnormal ECG findings will be listed. This listing will include all ECG findings that were abnormal and determined to be clinically significant by the investigator for a subject across study time points to identify any trends.



### 6.6.5 Physical Examinations

Physical examination findings by body system will be classified as normal, abnormal not clinically significant, abnormal clinically significant, or not performed by the investigator, and will be summarized by study visit.

All physical examination data will be presented in subject listings Subjects with clinically significant abnormal physical examination findings will be listed. This listing will include all results of the body system that was determined by the investigator to be clinically significant for a subject across study visits to identify any trends.

### 6.6.6 Pregnancy Test

Pregnancy test results will be listed by study visit.

### 6.6.7 Extent of Exposure and Compliance

#### 6.6.7.1 *Exposure to Investigational Product (IP)*

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

Treatment duration (month) will be calculated as (number of days from the date of the first dose to the earlier of early discontinuation date, or the date of the end of the treatment period, 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.

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

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

#### 6.6.7.2 *Measurements of Treatment Compliance*

All planned study drug administrations will be recorded in the electronic case report form (eCRF). 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 a subject is scheduled to receive up to study completion or early termination (ET), based upon the dosing schedule.

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 summarized for FAS.

A listing of measurements of treatment compliance and exposure will be provided for FAS.



## 6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

A separate PK/PD modeling analysis plan will support the population PK/PD modeling approach on the characterization of PK/PD properties of lanadelumab in the Chinese population. The analysis results will be reported separately.

*No formal statistical hypothesis will be tested.*

*Tabular and graphical summaries will be analyzed based on the PK set and PD set, as appropriate.*

### 6.7.1 Pharmacokinetic Analysis

The plasma concentration data of lanadelumab will be provided in subject data listings and summarized using descriptive statistics (number of subjects, arithmetic mean, SD, coefficient of variation [CV%], median, minimum, maximum, geometric mean, and CV% of geometric mean) for each protocol scheduled sampling visit based on the PK set defined in Section 5.3.

Plasma concentrations below the lower limit of quantitation (LLOQ) will be set to zero in the calculation of summary statistics; they will not be imputed in the subject data listings.

Figures of individual and mean (± SD) concentration-time profiles for plasma lanadelumab will be generated.

### 6.7.2 Pharmacodynamic Analysis

The plasma kallikrein (pKal) activity will be measured by cleaved high molecular weight kininogen (cHMWK) level (i.e., plasma concentrations of cHMWK).

The cHMWK levels will be provided in subject data listing(s) and summarized using descriptive statistics (number of subjects, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and CV% of geometric mean) for each protocol scheduled sampling visit based on the PD Set defined in Section 5.4.

Figures of individual and mean (± SD) concentration-time profiles cHMWK will be generated.

### 6.7.3 Biomarker Analysis

C1 esterase inhibitor (C1-INH), complement component 4 (C4), and complement component 1q (C1q) assays will be obtained at screening for eligibility assessment.

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

## 6.8 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

Not applicable

## 6.9 Other Analyses

### 6.9.1 Immunogenicity Analyses

Immunogenicity will be measured based on the presence or absence of neutralizing or non-neutralizing anti-drug antibody (ADA) in plasma and will be analyzed using the FAS.

The ADA result (positive/negative/not evaluable) and neutralizing ADA result (reactive/non-reactive/not evaluable) will be summarized using descriptive statistics by study visit.

The ADA result, ADA titer result (quantitative) and neutralizing ADA result will be listed for each subject by study visit.

#### 6.9.1.1 *Analyses of Immunogenicity/Efficacy Relationships*

For each efficacy evaluation period, subjects will be grouped in two distinct categories: subjects who had at least one positive ADA result during or prior to the period, based on available tests and subjects who had no positive ADA result during the period.

Separately for these two ADA categories, the baseline investigator-confirmed attack rate, as well as the treatment period investigator-confirmed attack rate, change from baseline, and percent change from baseline for each efficacy evaluation period will be summarized using descriptive statistics. Subjects who only had non-reportable ADA results during the period will be excluded from the analysis.

The calculation of investigator-confirmed attack rate is detailed in Section 6.5.2.1.



#### 6.9.1.2 *Analyses of Immunogenicity/Pharmacokinetic Relationships*

The plasma lanadelumab concentration data will be summarized using descriptive statistics (number of subjects, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and CV% of geometric mean) for each sampling visit separately by ADA result (positive/negative/not evaluable) obtained at the same visit.

#### 6.9.1.3 *Analyses of Immunogenicity/Pharmacodynamic Relationships*

Cleaved high molecular weight kininogen levels will be summarized using descriptive statistics (number of subjects, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and CV% of geometric mean) for each sampling visit separately by ADA result (positive/negative/not evaluable) obtained at the same visit.

### 6.9.2 Protocol deviations

Protocol deviations as obtained from a 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 importance criteria (“yes”, “no”) aligned with Takeda significance categories (“significant protocol deviation [SPD]” and “non-SPD”), and provided as part of the CTMS transfer to Biostatistics.

Protocol deviations will be collected at both the site and subject level. Deviations at the site level will be tracked as non-compliance for all subjects who are enrolled at that site at the time of the deviation.

Subject level protocol deviations and study site non-compliances will be summarized by deviation type, severity, and overall for the FAS, respectively. A separate protocol deviation specific to coronavirus disease 2019 (COVID-19) will also be summarized.

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy and/or reliability of study data or that may significantly affect a subject's rights, safety, or well-being. These deviations will be identified with a flag in the listings, and a sub-category of important protocol deviations will also be summarized in the subject level protocol deviation and study site non-compliances table.

All subject protocol deviations and study site non-compliances will be included in separate listings for the screened set. Protocol deviations identified as related to the impact of COVID-19 will be flagged in the subject listings.



### 6.10 Interim Analyses

*An interim data analysis may be performed to support the supplementary New Drug Application (sNDA) submission for China pediatric indication. The interim analysis will at least summarize the efficacy, safety and PK of treatment with lanadelumab in Chinese subjects with HAE. The interim analysis will be conducted when approximately 10 subjects complete the 26 weeks treatment period and 4 weeks follow-up period.*

No adaptive design is planned for this study. A data cut not affecting study conduct may be performed to support regulatory request.

### 6.11 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

No data monitoring committee, internal review committee, or other data Review committees is planned for this study.

## 7.0 REFERENCES

Not applicable

## 8.0 NOT APPLICABLE CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable

# 9.0 APPENDIX

## 9.1 Changes From the Previous Version of the SAP

A summary of the changes for SAP 2.0 is provided in page 2 of Revision History. Any minor revisions in grammar, spelling, punctuation, and format are not reflected in the summary of changes.

## 9.2 Data Handling Conventions

### 9.2.1 General Data Reporting Conventions

Outputs will be presented according to Takeda Standard TLF Shells.

For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated. Mean and median will be presented to 1 more decimal place than the recorded data. Standard deviations will be presented to 2 more decimal places than the recorded data. Minimum and maximum will be displayed to the same level of precision as reported.



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. 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. This rule also applies to CV%. The denominator for all percentages will be based on the number of subjects within the population of interest who provided non-missing responses to the categorical variables, unless otherwise specified.

Body mass index will be rounded to 1 decimal place and normalized number of HAE attacks will be rounded to 2 decimal places for reporting. CIs will be presented using the same number of decimal places as the parameter estimate.

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, End of Treatment (EOT), and End of Study (EOS)

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

Baseline HAE attack rate for all efficacy analyses is defined as the monthly HAE attacks during run-in period.

If not otherwise specified, end of treatment (EOT) will be defined as the Day 182 visit.

If not otherwise specified, end of study (EOS) will be defined as the Day 210 visit.

### 9.2.3 Definition of Visit Windows

Although there is a visit window 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

Note that Day 0 will be equivalent to study day 1.



### 9.2.4 Definition of Analysis Periods

The run-in period is defined as the interval of time:

- If run-in end date < date of first dose of IP:

  [start date of run-in period at 0:00, end date of run-in period at 23:59]

- If run-in end date = date of first dose of IP:

  [start date of run-in period at 0:00, date/time of first dose of IP – 1 minute]

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

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

The efficacy presumed steady state evaluation period of Day 70 through Day 182 is defined as the interval of time:

[date/time of first dose of IP + 70 days, date of Day 182 visit at 23:59]

The follow-up period for AEs is defined as the interval of time:

[date of Day 182 visit + 1 day at 0:00, date of Day 210 visit at 23:59]

### 9.2.5 Derived Efficacy Endpoints

The following rules apply to the handling of HAE attack data for efficacy analyses only. Hereditary angioedema attacks starting prior to the run-in period are not processed by these rules.

#### 9.2.5.1 *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.

#### 9.2.5.2 *HAE Attack Duration*

The duration of an HAE attack is calculated (in hours) 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 9.2.7.1.

#### 9.2.5.3 *HAE Attack Severity*

The overall severity of the subject's attack was to be determined by the investigator using the following definitions provided as part of HAARP:

- Mild: Transient or mild discomfort
- Moderate: Mild to moderate limitation in activity - some assistance may be needed
- Severe: Marked limitation in activity, assistance required

The average attack severity will be calculated per subject by attributing a numeric value to each severity as follows: 0=No attack, 1=Mild, 2=Moderate, and 3=Severe. Higher values will indicate more severe attacks, while lower values will indicate less severe attacks.

#### 9.2.5.4 *HAE Attack Rate*

##### *9.2.5.4.1 Run-in Period HAE Attack Rate*

The run-in period HAE attack rate will be presented as the NNA per month (4 weeks) and calculated for each subject as number of HAE attacks occurring during the run-in period divided by the number of days the subject contributed to the run-in period multiplied by 28 days.



##### *9.2.5.4.2 Treatment Period HAE Attack Rate*

The treatment period HAE attack rate will be presented as the NNA per month and calculated for each subject as the number of HAE attacks occurring during the treatment period divided by number of days the subject contributed to the treatment period multiplied by 28 days. No assessment of treatment compliance will be considered for this calculation.

##### *9.2.5.4.3 Presumed Steady State Period HAE Attack Rate*

The presumed steady state period HAE attack rate will be presented as the NNA per month and calculated for each subject as the number of HAE attacks occurring during the presumed steady state period divided by number of days the subject contributed to the presumed steady state period multiplied by 28 days. If the subject did not contribute to the presumed steady state period, this rate will be missing. No assessment of treatment compliance will be considered for this calculation.

### 9.2.6 Repeated or Unscheduled Assessments of Safety Parameters

Unscheduled measurements will not be included in by-visit summaries unless specified, 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. However, all assessments will be presented in the data listings.

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

All subjects in the analysis sets defined in Section 5 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. Imputation of missing date/time for HAE attack data as described in Section 9.2.7.1 apply to efficacy analyses only. Hereditary angioedema attacks starting prior to the run-in period are not processed by these rules. For safety analyses, HAE attacks will be analyzed as reported, and missing date information will be handled as described for AEs in Section 9.2.7.3.



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

#### 9.2.7.1 *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 time will be imputed as described in Section 9.2.7.3. 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 9.2.5.1 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 9.2.5.1 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.



#### 9.2.7.2 *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 will be used to determine if the medication/therapy/procedure is concomitant or prior. If a determination cannot be made using the non-missing date parts as to when the medication/therapy/procedure occurred relative to study drug administration, then the medication/therapy/procedure will be classified as concomitant.

#### 9.2.7.3 *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.

#### 9.2.7.4 *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. Injection site reaction 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.



#### 9.2.7.5 *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 date of IP, then a severity of "Life threatening (grade 4)" will be assigned. 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".

#### 9.2.7.6 *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.

#### 9.2.7.7 *Clinical Significance (CS) Attributions for Laboratory Results*

Laboratory results will be classified as Normal, CS Low, Non-Clinical Significance (NCS) Low, NCS High, or CS High using a combination of the CS/NCS classification by the investigator and the Low/High classification based on the central laboratory reference range.

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

The non-standard laboratory results will be converted to numeric values using the rules shown in Table 5.

**Table 5. 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.

## 9.4 Schedule of Study Activities

**Table 6. Schedule of Study Activities**

| | Screening Period | | Treatment Period[b] *Grey columns indicate option for self-administration at the site[c]* | | | | | | | | | | | | | | | Follow-up Visit[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening Visit and Washout | Run-in Period[a] | | | | | | | | | | | | | | | | |
| **Visit No.** | | | 1 | Site Check-in[d] | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
| **Day No.** | | | 0 | 7 | 14 | 28 | 42 | 56 | 70 | 84 | 98 | 112 | 126 | 140 | 154 | 168 | 182/ET[e] | 210 |
| **Dose No.** | | | 1 | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | |
| Informed Consent[f] | X | | | | | | | | | | | | | | | | | |
| Eligibility Review | X | | X[g] | | | | | | | | | | | | | | | |
| LTP Therapy Washout[h] | X | | | | | | | | | | | | | | | | | |
| Lanadelumab 300 mg Treatment | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Injection Report[i] | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Diary Card[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Demographics | X | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | |
| C1-INH, C1q and C4 [k]Testing[k] | X | | | | | | | | | | | | | | | | | |
| Pregnancy Test[l](females) | X | | X | | | X | | X | | X | | X | | X | | | X | X |
| Vital Signs[m] | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination[n] | X | | X | | | X | | X | | | X | | | X | | | X | X |
| 12-Lead ECG[o] | X | | X | | | | | | | | | | | | | | X | |
| Clinical Laboratory Testing[p] | X | | X | | | X | | X | | | X | | | X | | | X | X |
| Serology Testing[q] | X | | | | | | | | | | | | | | | | | |
| Prior and Concomitant Therapy | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse Event[s] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HAE Symptoms or Attack Data[r,s] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PK Blood Sampling[t] | | | X | | X | | | X | | | X | | | X | | | X | X |
| PD Sample Collection[t] | | | X | | X | | | X | | | X | | | X | | | X | X |
| Plasma ADA Testing[t] | | | X | | | | | X | | | X | | | X | | | X | X |

ADA=antidrug antibody; AE= adverse event; AESI=an adverse event of special interest; BP=blood pressure; C1-INH=C1 esterase inhibitor; C1q = Complement Component 1q; C4 = Complement Component 4; ECG=electrocardiogram; eCRF=electronic case report form; ET=early termination; HAE=hereditary angioedema; HbsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HR=heart rate; LTP=long-term prophylaxis; PD=pharmacodynamic; PK=pharmacokinetic; RR=respiratory rate; SAE=serious adverse event; SC=subcutaneous.

[a] Subjects will undergo a run-in period to determine their baseline HAE attack rate. Only subjects with a baseline rate of at least 1 investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and treatment. Subjects who experienced 3 or more investigator-confirmed attacks before the end of the 4 weeks could exit the run-in period early and proceed to enrollment and treatment. Subjects without at least 1 investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 investigator-confirmed attacks in 8 weeks to proceed to enrollment and treatment. To be eligible for enrollment, subjects who have their run-in extended have to complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered as screen failures.

[b] Treatment period visits and follow-up visit will have a ±3-day window. Treatment period visits will have a maximum of 17 days or a minimum of 11 days between any 2 doses, starting with Dose 2, Day 14 through end of treatment.

[c] Subjects (and/or their parent/caregiver) are allowed to initiate self-administration under the investigator or designee supervision, after receiving the first 5 doses of lanadelumab at the study site administered by qualified personnel.

[d] Site personnel will contact the subject by phone to solicit for any attacks not already reported by the subject once between scheduled site visits or approximately 7 days after last contact with subject.

[e] In the event a subject prematurely discontinues from treatment and/or the study, ET visit procedures will be performed as soon as possible.

[f] For adolescent subjects (<18 years of age) enrolled in the study that reach 18 years of age during study periods, a consent using the most current version of the informed consent form by subject is required.

[g] Post run-in eligibility review must take place before Day 0 dosing.

[h] Adult subjects (≥18 years of age) who are on LTP therapy for HAE will be required to undergo a minimum 2-week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The investigator will confirm that the subject had successfully completed the 2-week washout period before they can enter the run-in period. Adolescent subjects (≥12 to <18 years of age) who are on LTP therapy for HAE are not required to undergo LTP washout.

[i] An injection report will be completed by the subject (or caregiver) following each dose of lanadelumab. The injection report will collect information on the subject's experience with SC injection of lanadelumab. Study personnel will document the subject's responses in the subject's medical record and eCRF.

[j] At the time of the screening visit, a diary card will be dispensed to the subject or caregiver. As soon as the subject enters the run-in period, the subject (or caregiver) should complete the diary card at the end of each day to record if an HAE attack happens or not. An HAE attack worksheet, part of the diary card, should be completed if the subject encounters any HAE attack. The investigator should check completion of diary card at each visit.

[k] Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment. Testing will be conducted by a central laboratory.

[l] The pregnancy test is only for females of childbearing potential. Test will be conducted at the local laboratory and could be serum or urine based.

[m] There will be a ±15-minute window for all vital signs. At study visits in which investigational product will be administered, vital signs including sitting or supine BP, HR, body temperature, and RR, are to be obtained prior to dosing and 1 hour after dosing.

[n] Height and weight will be collected at the screening visit only. The physical examination has to be performed prior to dosing of study drug. Physical examination findings by body system will be classified as normal, abnormal not clinically significant, abnormal clinically significant, or not performed by the investigator.

[o] Electrocardiograms (single recordings) will be performed and assessed by the local laboratory. The ECG has to be performed prior to dosing of study drug.

[p] Clinical laboratory testing will be conducted at the local laboratory and will include hematology (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, absolute platelet count), clinical chemistry (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin [total and direct], blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, creatine phosphokinase, glucose, phosphate, magnesium, potassium, sodium, total protein, uric acid), coagulation (prothrombin time, activated partial thromboplastin time, international normalized ratio), and urinalysis (bilirubin, glucose, ketones, blood, nitrite , pH, protein, specific gravity, microscopy [if indicated by macroscopic findings]). Blood samples for clinical laboratory testing will be collected pre-dose (ie, within 2 hours prior to dosing).

[q] Serology testing (HBsAg, HCV, and HIV) will be conducted at the local laboratory at screening.

[r] Historical attack information will be collected at screening. During the study, subjects (or caregivers, in the event the subject is <18 years old or is incapacitated) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack.

[s] Site personnel will also contact the subject once a week or at approximately 7 days after last contact with the subject during the run-in period and once between study visits or approximately 7 days after last contact with the subject during the treatment period in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not given through prior subject contact with the site.

[t] Blood samples for testing PK, PD and formation of antibodies to lanadelumab will be obtained at pre-dose (ie, within 2 hours prior to dosing) except on follow-up visit, with a window period of ±3 days for the corresponding visit except on Day 0. Testing for PK, PD, and ADAs will be conducted at a central laboratory.

Notes: If a subject experiences an SAE or an AESI, the investigator must report the event to the sponsor or CRO within 24 hours, by completing an SAE or AE or HAE acute attack eCRF in English or report via the paper safety report form (as back-up) within 24 hours of becoming aware of any SAE or AESI respectively.

Investigators are to report all SAEs to Takeda Global Patient Safety Evaluation (GPSE) Department through 30 days after the last dose of investigational product and SAEs considered related to investigational product >30 days after the last dose of investigational product.

Unscheduled visits may occur between the scheduled site visits as required. Assessments may be performed as clinically indicated at the discretion of the investigator.

Please see Protocol Section 8.1.7 for activities to be followed during an unanticipated situation like coronavirus disease 2019 outbreak.