Title: A Phase 3 Multi-center, Open-label Study to Evaluate the Efficacy and Safety of Lanadelumab (SHP643) in Japanese Subjects with Hereditary Angioedema

NCT Number: NCT04180163

Statistical analysis plan Approve Date: 23-Jan-2021

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Statistical Analysis Plan

Lanadelumab; TAK-743 (formerly SHP643, DX-2930)

Phase 3

A Phase 3 Multi-center, Open-label Study to Evaluate the Efficacy and Safety of Lanadelumab (SHP643) in Japanese Subjects with Hereditary Angioedema

Protocol Identifier: SHP643-302

Study Sponsor(s):	Dyax Corp., (a wholly-owned, indirect subsidiary of Shire plc) (Shire plc, a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited) 300 Shire Way, Lexington, MA 02421 USA
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Protocol:	Amendment 2 05 Oct 2020
SAP Version #:	Final 4.0
SAP Date:	23 Jun 2021
Status:	Final

VERSION HISTORY

Version	Issue Date	Summary of Changes
Final 1.0	16 Apr 2020	New Document
Final 2.0	18 Dec 2020	• LTP therapy use before entering the run-in period of study and type of LTP therapy before entering the run-in period moved from demographic to baseline HAE characteristics. • Clarified how to determine the analysis periods of AE and concomitant medication/therapy. • Protocol deviations linked to COVID-19 will be flagged in subject listings. • Clarified that summary tables of AE will be summarized for HAE attack reported AE and non-HAE attack reported AE separately. • Additional summaries of injection site reaction (ISR) AEs (overall summary table, summary table by SOC and PT, summary table by SOC, PT and maximum severity, and listing of ISR) added. • Clarified that summary table of number and duration of ISR will be summarized by PT for each analysis period. • Section of handling BLQ values for PD data removed as BLQ is not applicable for PD. • Antibody results "not reportable" changed to "not evaluable". Detailed definitions added for antibody results. • Run-in period interval definition updated. • Handling of unscheduled assessments of safety parameters updated. • Clarified that the definition of unique HAE attack will be applied for efficacy analysis only. • Clarified the handling of unique HAE attacks combined across efficacy evaluation periods. • Clarified that the handling of partial/missing date/time for both non-HAE and HAE AEs for safety analysis is defined in Section 12.6.3.

Version	Issue Date	Summary of Changes
		• Clarified that imputed dates will not be presented in the listings • Clarified the handling of missing severity for AEs. • SAS code for bird on wire removed as too programmatically technical for this SAP. • Revised the document following protocol amendment 2. • Added the endpoint "Achievement of attack-free status by interval. • Added subgroup analyses for the first interim analysis in Section 10.1. • Clarified the scope and data cutoff date of the first interim analysis in Section 11. • Revised Section 14 "Changes to analysis specified in protocol" as per protocol amendment 2. • Added 2 new values in Table 5 "Convention for Converting Non-Standard Laboratory Results" • Clarified that the immunogenicity analysis will be conducted for the full analysis set. • Corrected several typographical errors throughout the document. • Added additional laboratory analysis in section 7.2 for liver function tests: ALT, AST, Total Bilirubin. • Added "specific gravity" in section 7.2 for urinalysis' quantitative analysis. • Added section 5.6
Final 3.0	13 May 2021	• Updated section 5.8 on planned doses for those subjects whose dose frequency modified from 300 mg q2wks to 300 mg q4wks • Added section 10.1.2 to specify the contents added to the second interim analysis and final analysis due to subjects' dose frequency modification from 300 mg q2wks to 300 mg q4wks.

Version	Issue Date	Summary of Changes
		• Added HAE attack's missing subject reported end time imputation if more than one calendar day from the next HAE attack in section 12.6.1.
Final 4.0	23 Jun 2021	• Added wording "or newer" to anywhere SAP text contains "MedDRA Version 22.1" without text "or newer" to "MedDRA Version 22.1 or newer". • Added "and follow-up period" in SAP Section 7.2 for liver test. • Added wording "or later" by end of SAP text "World Health Organization Drug Dictionary dated (WHO-DD) 01 Sep 2019" and "WHO Drug Dictionary dated 01 Sep 2019".

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug Antibody
AE	Adverse Event
AE-QoL	Angioedema Quality of Life
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BILI	Bilirubin
BLQ	Below Limit of Quantitation
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
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
CO_2	Carbon Dioxide
CPK	Creatine Phosphokinase
CRF	Case Report Form
CTMS	Clinical Trial Management System
CV%	Coefficient of Variation
ECG	Electrocardiogram
EOS	End of Study
ET	Early Termination
FAS	Full Analysis Set
HAARP	HAE Attack Assessment and Reporting Procedures
HAE	Hereditary Angioedema
HR	Heart Rate

Abbreviation	Definition
HRQoL	Health-Related Quality of Life
INR	International Normalized Ratio
IP	Investigational Product
ISR	Injection Site Reaction
IV	Intravenous
JNDA	Japanese New Drug Application
KM	Kaplan-Meier
LLOQ	Lower Limit of Quantitation
LLN	Lower Limit of Normal
LTP	Long-term Prophylaxis
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
msec	Millisecond
NNA	Normalized Number of Attacks
PD	Pharmacodynamic
pH	Potential Hydrogen
PK	Pharmacokinetic
PT	Preferred Term (MedDRA®)
QoL	Quality of Life
RR	Respiratory Rate
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SMQ	Standardized MedDRA® Query
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal

Abbreviation	Definition
WBC	White Blood Cells
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety, and pharmacokinetic (PK)/pharmacodynamic (PD) data as described in the final study protocol dated 05 Oct 2020 incorporating most recent amendment 2.0. Specifications for tables, figures, and listings are contained in a separate document.

Population PK/PD modeling and simulation will be conducted to characterize PK/PD properties of lanadelumab in the Japanese population separately from this statistical analysis plan. A separate report detailing the methods and results will be generated.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock for any interim analysis.

2. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

2.1 Objectives

The objectives of the study are:

- To evaluate the efficacy of repeated subcutaneous (SC) administrations of lanadelumab in Japanese subjects with hereditary angioedema (HAE).
- To evaluate the safety of repeated SC administrations of lanadelumab in Japanese subjects with HAE.
- To evaluate the PK of repeated SC administrations of lanadelumab in Japanese subjects with HAE.
- To evaluate the effect of repeated SC administrations of lanadelumab on health-related quality of life (HRQoL) in Japanese subjects with HAE.
- To evaluate the PD of repeated SC administrations of lanadelumab in Japanese subjects with HAE.
- To evaluate the immunogenicity of repeated SC administration of lanadelumab and the effect on lanadelumab PK, PD, efficacy, and safety in Japanese subjects with HAE.

2.2 Estimands

The primary and secondary estimands are described in Table 1.

Table 1. List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable (or endpoint)**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Primary efficacy	The primary estimand is the effect of lanadelumab on achieving HAE attack free status during the efficacy evaluation period of Day 0 through Day 182.	>= 12-year-old Japanese subjects with HAE (Type I or II) 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 for the efficacy evaluation period of Day 0 through Day 182.	1/ Rescue medication: Regardless of whether or not rescue medication/supportive treatment use had occurred. 2/ Premature study discontinuation before the end of the efficacy evaluation period: Attack-free is evaluated up to study discontinuation.	Proportion of subjects achieving attack-free status for the efficacy evaluation period of Day 0 through Day 182 and corresponding exact 95% confidence interval (CI).
Other efficacy	A supportive estimand is the effect of lanadelumab on achieving HAE attack free status for each of the efficacy evaluation periods of Day 0 through Day 364, Day 70 through Day 182, and Day 70 through Day 364.	Same as primary efficacy estimand.	Achievement of attack-free status for each of the efficacy evaluation periods of Day 0 through Day 364, Day 70 through Day 182, and Day 70 through Day 364.	Same as primary efficacy estimand.	Proportion of subjects achieving attack-free status for each of the efficacy evaluation periods of Day 0 through Day 364, Day 70 through Day 182, and Day 70 through Day 364 as well as corresponding exact 95% CIs.

Table 1. List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable (or endpoint)**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Other efficacy	A supportive estimand is the effect of lanadelumab on the number of HAE attacks during each of the efficacy evaluation periods.	Same as primary efficacy estimand.	Number of investigator-confirmed HAE attacks during each of the efficacy evaluation periods	1/ Rescue medication: Regardless of whether or not rescue medication/supportive treatment use had occurred. 2/ Premature study discontinuation before the end of the efficacy evaluation period: HAE attacks up to study discontinuation are considered.	HAE attack rate per month during each of the efficacy evaluation period and comparison to HAE attack rate per month during run-in period.

Table 1. List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable (or endpoint)**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Other efficacy	A supportive estimand is the effect of lanadelumab on time to first HAE attack during each of the efficacy evaluation periods.	Same as primary efficacy estimand.	Time to first HAE attack during each of the efficacy evaluation periods.	1/ Rescue medication: Regardless of whether or not rescue medication/supportive treatment use had occurred. 2/ No attack before the end of the efficacy evaluation period: Time is censored at the end of the period. 3/ Premature study discontinuation with no attack before the end of the efficacy evaluation period: Time is censored at the time of study discontinuation.	Kaplan-Meier (KM) estimates of time to first HAE attack during each of the efficacy evaluation periods and corresponding 95% CI.

2.3 Endpoints

2.3.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the achievement of attack-free status for the efficacy evaluation period of Day 0 (after study drug administration) through Day 182.

The definition of attack free is given in Section 6.1.

2.3.2 Other Efficacy Endpoints

Other efficacy endpoints will be evaluated for the following 4 efficacy evaluation periods:

- Day 0 (after study drug administration) through Day 182 (the end of Treatment Period A)
- Day 0 (after study drug administration) through Day 364 (the end of Treatment Period B)
- Presumed steady-state period from Day 70 through Day 182
- Presumed steady-state period from Day 70 through Day 364

Other efficacy endpoints are as follows:

- Number of investigator-confirmed HAE attacks during each of the efficacy evaluation periods
- Number of investigator-confirmed HAE attacks requiring acute treatment during each of the efficacy evaluation periods
- Number of investigator-confirmed moderate or severe HAE attacks during each of the efficacy evaluation periods
- Maximum attack severity during each of the efficacy evaluation periods
- Number of investigator-confirmed high-morbidity attacks during each of the efficacy evaluation periods; a high morbidity HAE attack is defined as any attack that has at least 1 of the following characteristics: severe, results in hospitalization (except hospitalization for observation <24 hours), hemodynamically significant (systolic blood pressure <90, requires IV hydration, or associated with syncope or near syncope) or laryngeal
- Time to first HAE attack after Day 0 for the efficacy evaluation period of Day 0 through Day 182
- Time to first HAE attack after Day 0 for the efficacy evaluation period of Day 70 through Day 182

- Achievement of at least a 50%, 70% and 90% reduction in the investigator-confirmed normalized number of attacks (NNA) per 4 weeks relative to the run-in period NNA for each of the efficacy evaluation periods
- Achievement of an efficacy evaluation period NNA <1.0 per 4 weeks, <0.75 per 4 weeks, <0.50 per 4 weeks, and <0.25 per 4 weeks for each of the efficacy evaluations periods
- Achievement of attack-free status for each of the efficacy evaluation periods of Day 0 through Day 364, Day 70 through Day 182, and Day 70 through Day 364
- Achievement of attack-free status for monthly increments through Day 364 (i.e., attack free for Month 1, Month 2, Month 3, etc.)
- Achievement of attack-free status by interval (1 month, 2 months, 3 months, …, until the Day 182 Visit, 7 months, 8 months, …, until the Day 364 visit)
- Percentage of attack-free days during each of the efficacy evaluation period

2.3.3 Safety Endpoints

Safety endpoints are as follows:

- Treatment emergent adverse events (TEAEs), including adverse events of special interest (AESI) and serious adverse events (SAEs)
- Clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis)
- Vital signs including blood pressure, heart rate (HR), body temperature, and respiratory rate (RR)
- 12 lead-electrocardiogram (ECG)

2.3.4 Pharmacokinetic Endpoint

The PK endpoint is plasma concentrations of lanadelumab.

2.3.5 Pharmacodynamics Endpoint

The PD endpoint is plasma kallikrein activity as measured by cleaved high molecular weight kininogen (cHMWK) level (i.e., plasma concentrations of cHMWK).

2.3.6 Health-related Quality of Life (QoL) Endpoints

The health-related QoL endpoint will be measured by the AE-QoL questionnaire, which consists of 17 disease specific quality-of-life items, to produce a total AE-QoL score and 4 domain scores (functioning, fatigue/mood, fear/shame, and nutrition).

The health-related QoL endpoints are as follows:

- Change in total AE-QoL scores from baseline (Day 0) to Day 182
- Change in domain AE-QoL scores from baseline (Day 0) to Day 182
- Change in total AE-QoL scores from baseline (Day 0) to Day 364
- Change in domain AE-QoL scores from baseline (Day 0) to Day 364

2.3.7 Immunogenicity Endpoint

The immunogenicity endpoint is the presence or absence of anti-drug antibody (ADA) in plasma (neutralizing or non-neutralizing antibody in plasma).

3. STUDY DESIGN

3.1 General Description

This open-label, single arm, Phase 3 study will enroll approximately 8 Japanese subjects with HAE Type I or II. The study is composed of the following periods:

- Screening Period and Washout Period

All subjects will undergo screening assessments during a maximum 4-week screening period.

Eligible subjects who are on long-term prophylaxis (LTP) for HAE are required to undergo a minimum 2-week washout period prior to entering the run-in period. The washout period is included in the screening period.

- Run-in Period

Subjects who have completed the screening period will enroll and enter a run-in period of 4 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-week run-in period may exit the run-in period early and proceed to Treatment Period A. Subjects without at least 1 Investigator confirmed attack after 4 weeks of run-in may have their run-in period extended for another 4 weeks. Subjects who have their run-in extended must complete the full 8-week run-in period and must have at least 2 investigator-confirmed attacks during this time to be eligible to enter Treatment Period A. Subjects who do not meet the minimum attack rate during the run-in period, or are otherwise determined to be ineligible based on screening assessments, will be considered a screen failure

and will not be allowed to enter the treatment phase of the study; they will be replaced with new HAE subjects, until at least 8 subjects have entered Treatment Period A.

- Treatment Period A

Subjects who enter Treatment Period A will receive lanadelumab 300 mg q2wks for 26 weeks.

- Treatment Period B

After completion of the first 26-week treatment period, subjects will immediately continue into Treatment Period B.

Subjects who enter the Treatment Period B will receive lanadelumab for an additional 26 weeks (total of 52 weeks). During these additional 26 weeks, an individual subject may remain on the same dose regimen as Treatment Period A or may consider lanadelumab 300 mg q4wks if they have been well-controlled (e.g., attack free) for 26 consecutive weeks with lanadelumab treatment.

- Safety Follow-up Period

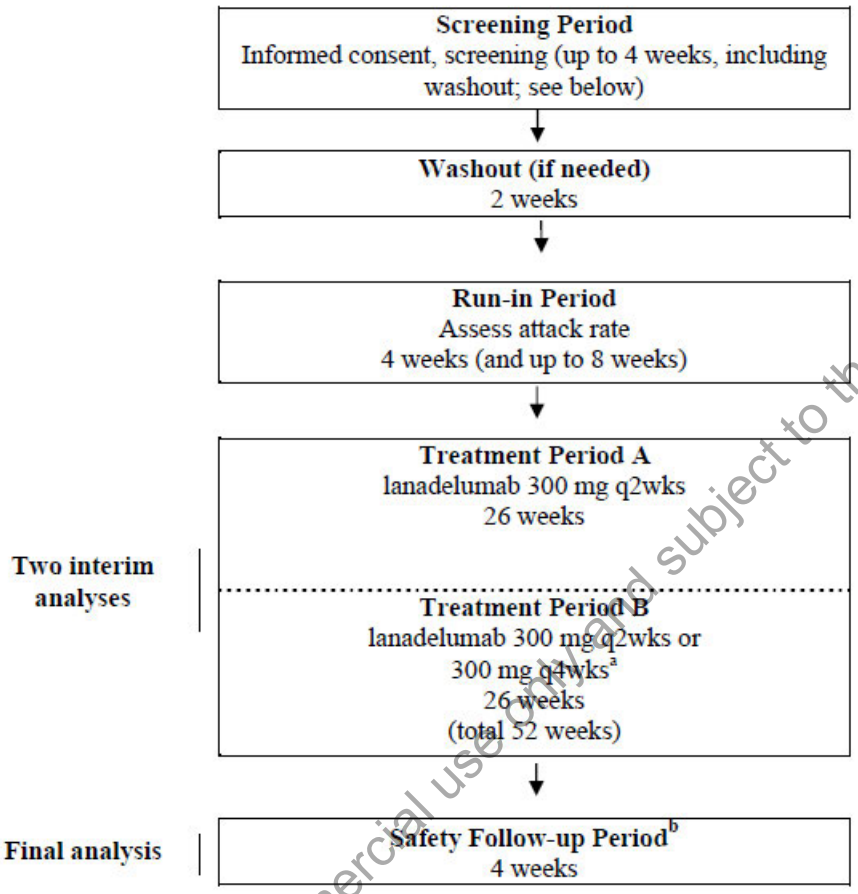
After completion of the second 26-week treatment (Treatment B) period, subjects may roll over into an expanded access study, Study TAK-743-5007. Subjects that elect to rollover to Study TAK-743-5007 will return on Day 378 to complete End of Study (EOS) assessments and will be discharged from this study. All other subjects will continue the study as originally planned and will be discharged from the study on Day 392 following completion of all EOS / Early Termination (ET) visit procedures.

A schematic representation of the study design is displayed in Figure 1. The study schedule of events can be found in Appendix 1 Schedule of Activities

Table and

Table .

Figure 1 Study Design



[a] During Treatment Period B, a subject may continue to receive lanadelumab 300 mg q2wks or, if the subject has been well-controlled (attack free) for 26 consecutive weeks with lanadelumab treatment, the subject may switch to a dose of 300 mg q4wks at the investigator's discretion and following approval by the sponsor's medical monitor.

[b] Subjects that complete the second 26-week treatment (Treatment B) period and choose to roll over into Study TAK-743-5007 will return on Day 378. All other subjects will continue the study as originally planned and will return on Day 392.

3.2 Sample Size and Power Considerations

The planned total sample size for this study is 8 subjects and is based on feasibility considerations. No formal sample size calculation was performed for this study.

4. STATISTICAL ANALYSIS SETS

4.1 Screened Set

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

4.2 Enrolled Set

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

4.3 Full Analysis Set

The Full Analysis Set (FAS) is defined as all subjects who received at least 1 dose of lanadelumab (investigational product [IP]). All safety, efficacy, and HRQoL analyses will be based on the FAS.

4.4 Pharmacokinetic (PK) Set

The PK Set is defined as 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.

4.5 Pharmacodynamic (PD) Set

The PD Set is defined all subjects in the FAS who have at least 1 evaluable post dose PD value. All PD analyses will be based on the PD set.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

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

The number and percentage of subjects who completed or prematurely discontinued the study will be presented for FAS. Completion of study refers to the completion of Visit 28/ Day 378 or Visit 28/Day 392. Reasons for premature discontinuation from study will be summarized (number and percentage) for the FAS. Additionally, the number and percentage of subjects who completed Treatment Period A (i.e., who completed Week 26 visit) and Treatment Period B (i.e., who completed Week 52 visit) will be presented.

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

5.2 Demographic and Other Baseline Characteristics

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

The following demographic characteristics will be summarized:

- Age at informed consent date (years),
- Age category (<18, 18 to <40, 40 to <65, ≥65 years),
- Sex (Male, Female, Unknown, Intersex/Undifferentiated),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown),
- Race (White, Black or African American, Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska Native, Multiple, Other),
- Weight (kg),
- Weight category (<50, 50 to <75, 75 to <100, ≥100 kg),
- Height (cm),
- Body mass index (BMI) (kg/m^2), calculated as 10000*weight (kg)/ height (cm)^2,
- BMI group for subjects ≥ 18 years of age (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2),
- BMI percentile group for subjects < 18 years of age based on growth charts from the Centers for Disease Control and Prevention (CDC) (Underweight: <5th percentile, Healthy or Overweight: 5th to <95th percentile, Obese: >=95th percentile),
    - Official and validated SAS programs created by CDC will be used to calculate the percentile of BMI. For more information on the CDC SAS programs, see http://www.cdc.gov/growthcharts/computer_programs.htm.

The following baseline HAE characteristics will be summarized in a separate table: age at onset of HAE symptoms (years), HAE type (Type I, Type II, Unspecified- Type I or Type II), history of laryngeal attacks, primary attack locations, number of attacks in the last 1, 3, and 12 months prior to screening, average attack duration (in days) in the last 12 months prior to screening, average severity of HAE attacks in the last 12 months prior to screening, number of attacks of different severity (mild, moderate, severe) in the last 3 months prior to screening, average 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), and run-in period HAE attack rate categories (1 to <2, 2 to <3, ≥3 attacks/4 weeks), LTP therapy use before entering the run-in period of study (yes or no) as recorded on the LTP Therapy Discontinuation eCRF, and type of LTP therapy before entering the run-in period (C1-INH, Androgens, Anti-fibrinolytics, or not on LTP).

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.

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 12.6.2) reported for that subject that lasted for ≥4 days:

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

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

5.3 Medical History

Medical history will be collected at the Screening Visit and will be coded using MedDRA Version 22.1 or newer.

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

All medical history will be presented in subject listings for FAS.

5.4 Prior Therapies, Procedures and Medication

Prior medications will be coded using the World Health Organization Drug Dictionary dated (WHO-DD) 01 Sep 2019 or later. Prior therapies and procedures will be coded using MedDRA Version 22.1 or newer.

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

Partial date imputation for medications is described in Section 12.6.2.

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

5.5 Concomitant Therapies, Procedures and Medications

Concomitant medications will be coded using the WHO Drug Dictionary dated 01 Sep 2019 or later. Concomitant therapies and procedures will be coded using MedDRA Version 22.1 or newer.

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

Any medication/therapy/procedure with a start date after the end of the treatment period will not be considered a concomitant medication/therapy/procedure. Partial date imputation for medications is described in Section 12.6.2.

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

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

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

Concomitant medications/therapies/procedures will be summarized for Treatment Period A (Day 0 through Day 182), Treatment Period B (Day 183 through Day 364), and overall for the entire Treatment Period (Day 0 through Day 364).

Detailed definition of these analysis periods is given in Section 12.3.1. Both start date and stop date will be used to determine the analysis period of concomitant medications/therapies. If a

medication/therapy has a start date and time prior to the start date and time of an analysis period and continuing after the start date and time of that analysis period or with a start date and time between the start date and time and the stop date and time of the analysis period inclusively, then this medication/therapy will be included in the summary of that analysis period. A medication/therapy can be included in the summary of multiple analysis periods.

For summaries by analysis period, the number of subjects reaching that analysis period will be presented and will be used as denominator for percentage calculation.

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

5.6 Study Drug Administration and Injection Report

Self-administration of IP is only allowed in Treatment Period B, and is defined as administration by the subject or their parent/caregiver at the investigational site or in an offsite location.

Self-administration will be permitted after a subject (and/or their parent/caregiver) has received appropriate training by the investigator or designee and has demonstrated their understanding of self-administration. The subject is required to return to the site for visits as outlined in the schedule of events Appendix 1

Table . At these on-site visits, the subject (or parent/caregiver) may continue to self-administer IP or may opt to have IP administered by study personnel or healthcare provider.

An injection report will be completed by the subject (or parent/caregiver) following each dose of IP, according to the assessment schedule in Appendix 1 Schedule of Activities Table and

Table . The injection
report will collect information on the subject's experience with SC injection of IP.

The number and percentage of subjects who performed study drug administration via study staff administration in-clinic, self-administration in-clinic (including "Self-Administration in the Study Clinic under Supervision by Study Staff" and "Parent/Caregiver Administration in the Study Clinic under Supervision by Study Staff"), or self-administration at home (including "Self-Administration at Home or Other outside Clinic" and "Parent/Caregiver Administration at Home or Other Outside Clinic"), as well as the total number of injections in each category and in each category by study visit, will be tabulated for the FAS.

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

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

5.7 Exposure to Investigational Product (IP)

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

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

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

Descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum) will be presented for time on treatment and total dose received. In addition, time on treatment will be summarized by category (<1 Month, 1 –< 3 Months, 3 –< 6 Months, >= 6 Months) for Treatment Period A and Treatment Period B, and by category (<1 Month, 1 -< 3 Months, 3 -< 6 Months, 6 -< 9 Months, 9 -< 12 Months, >= 12 Months) for the overall treatment period.

A listing of dose frequency modifications will be provided.

5.8 Measurements of Treatment Compliance

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

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

The number of planned doses is the number of doses planned to be administered up to study completion or early termination, i.e., the number of records entered using the study drug administration CRF regardless of whether the study drug was indicated to be administered or not excluding the records with answer “Attack free >= 26 weeks” checked as reason for not administering study drug.

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

5.9 Protocol Deviations

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

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

Protocol deviations will be summarized by deviation type and severity for the FAS. All protocol deviations will be included in a subject listing for the screened set. In particular, protocol deviations identified as related to the impact of COVID-19 will be flagged in the subject listings.

6. EFFICACY ANALYSES

No statistical hypothesis testing will be performed. The totality of results across all efficacy endpoints will be the measure of overall treatment benefit, with the primary goal of demonstrating consistency across the endpoints, especially the primary efficacy endpoint, with the pivotal overseas study (DX-2930-03).

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

For all efficacy analyses, unique HAE attacks, as defined in Section 12.4.1, will be used.

Handling of missing start or end date and time for HAE attacks is described in Section 12.6.1.

6.1 Analyses of Primary Efficacy Endpoint

The primary efficacy endpoint is the achievement of attack-free status for the efficacy evaluation period of Day 0 through Day 182 (Detailed definition of this period is given in Section 12.3.1).

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 of Day 0 through Day 182 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.

6.1.1 Sensitivity Analyses of Primary Efficacy Endpoint

The primary analysis will be repeated using all subject-reported HAE attacks instead of limiting the analysis to those attacks that were investigator-confirmed.

6.2 Analyses of Other Efficacy Endpoints

Other efficacy endpoints will be evaluated for the following 4 efficacy evaluation periods:

- Day 0 (after study drug administration) through Day 182 (the end of Treatment Period A)
- Day 0 (after study drug administration) through Day 364 (the end of Treatment Period B)
- Presumed steady-state period from Day 70 through Day 182
- Presumed steady-state period from Day 70 through Day 364

Detailed definition of these periods is given in Section 12.3.1. 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.

6.2.1 Number of investigator-confirmed HAE attacks during each of the efficacy evaluation periods

The total number of investigator-confirmed HAE attacks reported during each efficacy evaluation period and subject-time in months that each subject contributed to each efficacy evaluation period will be summarized.

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

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

The investigator-confirmed NNA per 4 weeks during run-in period and each of the efficacy evaluation periods will be expressed as a monthly (4 weeks, i.e., 28 days) HAE attack rate for each subject. In what follows, for conciseness, HAE attack rate refers to NNA per 4 weeks.

The baseline investigator-confirmed HAE attack rate is defined as the run-in period investigator-confirmed HAE attack rate, and will be calculated as number of investigator-confirmed 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. The run-in period is defined in more details in Section 12.3.1.

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

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

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.

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 (defined as 28 days) will be summarized by study month (per 28-day interval). The summary will include descriptive statistics for run-in period investigator-confirmed attack rate, as well as monthly treatment period investigator-confirmed attack rates, monthly change from baseline, and monthly percent change from baseline. Investigator-confirmed HAE attacks will be grouped into 28-day intervals using

the start date of the HAE attack. In particular, if a HAE attack starts during an interval and is ongoing at the start of the next interval, that HAE attack will be counted only once for the interval during which it started. The first study drug administration date and time in this study will be used as the start of the first interval and end of the interval will be the first study drug administration date and time in this study plus 28 days. Each successive interval will start the last day of the prior interval plus 1 day (24 hours) and end 28 days later.

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

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

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

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

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

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

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

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

6.2.2 Time to First HAE Attack

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.

Subjects who do not experience any attacks during the efficacy evaluation period will be censored at the date and time of the end of the period, i.e., visit date of Day 182 visit and time of

23:59. Subjects who discontinue the study during the efficacy evaluation period prior to experiencing their first on-study investigator-confirmed HAE attack will be censored at the date of study discontinuation and time of 23:59.

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

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

A sample SAS code for KM estimates and KM plots is provided in Appendix 2.

6.2.3 Characteristics of Investigator-confirmed Hereditary Angioedema 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.

6.2.3.1 Subject Level HAE Attack Characteristics

6.2.3.1.1 HAE Attack Duration

For each subject, the mean duration of all investigator-confirmed HAE attacks will be calculated in hours and summarized. See Section 12.4.1 for details on handling HAE attack duration and Section 12.6.1 for handling of missing date/time of HAE attacks. If a HAE attack starts during an efficacy evaluation period and ends after the end of that period, the end date/time will still be used to calculate the duration of the HAE attack.

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).

6.2.3.1.2 HAE Attack Severity

For each subject, the mean and maximum severity (based on HAARP) of all investigator-confirmed HAE attacks will be summarized for each efficacy evaluation period. See Section 12.4.1 for details on handling HAE attack severity.

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. The mean attack severity will be summarized for all subjects as well as only subjects with HAE attacks.

The number and percentage of subjects will be tabulated by maximum attack severity (no attacks, mild, moderate, and severe).

6.2.3.2 Event Level HAE Attack Characteristics

6.2.3.2.1 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 12.4.1 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.

6.2.3.2.2 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 (icatibant, plasma-derived C1-INH, and other) as reported in the HAE Acute Attack CRF.

See Section 12.4.1 for details on handling HAE attack rescue medication use.

6.2.3.2.3 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 12.4.1 for details on handling HAE attack supportive treatment use.

6.2.4 Achievement of at Least a 50%, 70% and 90% Reduction in the Investigator-confirmed NNA per 4 weeks Relative to the Run-in Period

There will be three classes of responders based on pre-specified percentage reduction in the investigator-confirmed NNA per 4 weeks (i.e., monthly investigator-confirmed HAE attack rate defined in Section 6.2.1) from the run-in period: 50% or more reduction, 70% or more reduction, and 90% or more 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 three predefined thresholds will be summarized for each efficacy evaluation period. The three classes of responders are nested within each other and not mutually exclusive.

6.2.5 Achievement of an Efficacy Evaluation Period NNA per 4 weeks <1.0, <0.75, <0.50, and <0.25

There will be four classes of responders based on pre-specified investigator-confirmed NNA per 4 weeks (i.e., monthly investigator-confirmed HAE attack rate defined in Section 6.2.1) for each of the efficacy evaluation periods: <1.0 per 4 weeks, <0.75 per 4 weeks, <0.50 per 4 weeks, and <0.25 per 4 weeks.

The 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.

6.2.6 Achievement of Attack-free Status for Each of the Efficacy Evaluation Period of Day 0 Through Day 364, Day 70 Through Day 182, and Day 70 Through Day 364

The definition of attack free is given in Section 6.1.

The number and percentage of subjects achieving attack-free for the efficacy evaluation period of Day 0 through Day 364, Day 70 through Day 182 and Day 70 through Day 364 will be summarized. A two-sided 95% CI for the proportion of subjects achieving attack-free will be derived using the exact method.

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.

6.2.7 Achievement of Attack-free Status for Monthly Increments through Day 364 (i.e., Month 1, Month 2, Month 3, etc.)

The definition of attack free is given in Section 6.1.

The number and percentage of subjects achieving attack-free status for the study month (Month 1, Month 2, Month3, etc) through Day 364 will be summarized. A two-sided 95% CI for the proportion of subjects achieving attack-free will be derived using the exact method.

A subject is considered as attack free during a study month if the subject has no investigator-confirmed HAE attacks during that study month. For subjects who discontinue the study during a study month, 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.

6.2.8 Achievement of Attack-free Status by interval (1 month, 2 months, 3 months, …, until the Day 182 Visit, 7 months, 8 months, …, until the Day 364 visit)

The definition of attack free is given in Section 6.1.

The number and percentage of subjects achieving attack-free status will be summarized for the following intervals: 1 month (i.e., Day 0 to Day 28 visit date minus one day), 2 months (Day 0 to Day 56 visit date minus one day), 3 months (i.e., Day 0 to Day 84 visit date minus one day), …, Day 0 through Day 182 (as defined in Section 12.3.1), 7 months (Day 0 to Day 196 visit date minus one day), 8 months (Day 0 to Day 224 visit date minus one day), …, Day 0 through Day 364 (as defined in Section 12.3.1). A two-sided 95% CI for the proportion of subjects achieving attack-free will be derived using the exact method.

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

For the first interim analysis, only the following intervals will be presented: 1 month, 3 months and Day 0 through Day 182.

6.2.9 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.

6.2.10 Sensitivity Analyses of Other Secondary Efficacy Endpoints

All secondary efficacy analyses will be repeated using all subject-reported HAE attacks instead of limiting the analysis to those attacks that were investigator-confirmed.

6.3 Multiplicity Adjustment

Not applicable; no hypothesis testing is planned.

7. SAFETY ANALYSIS

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

The definition of baseline is provided in Section 12.2.

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

7.1 Adverse Events (AE)

AEs will be coded using MedDRA Version 22.1 or newer.

Treatment-emergent AEs (TEAEs) are defined as AEs with onset at the time of or following the first exposure to lanadelumab in this study, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. For AEs with partial onset times, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date as to when the AE occurred relative to study drug administration, then the AE will be classified as treatment-emergent. Partial date imputation for AE is described in Section 12.6.3.

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

Related AEs are AEs classified as related to study drug by the investigator. Missing relationship to study drug imputation is described in Section 12.6.5.

Severe AEs are AEs classified as severe (grade 3) or life threatening (grade 4) by the investigator. Missing severity imputation is described in Section 12.6.4.

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

- Non-HAE attack reported AEs will include the subset of AEs identified in EDC as not a reported HAE attack. Essentially, this will be all AEs excluding HAE attack reported events.
- HAE reported AEs will include the subset of AEs identified in EDC as a reported HAE attack. Note that this includes investigator-confirmed HAE attacks; all investigator-confirmed HAE attacks will be coded to the PT of angioedema.

For AE summaries, AEs will be classified to one of two analysis periods:

- 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 364 visit). Treatment Period AEs will be further summarized for Treatment Period A (Day 0 through Day 182), Treatment Period B (Day 183 through Day 364), and overall for the entire Treatment Period (Day 0 through Day 364).
- 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 364 visit).

Detailed definition of these analysis periods is given in Section 12.3.1. An AE will be counted for a specific analysis period only if that AE started during that period. For AE summaries by analysis period, the number of subjects reaching that analysis period will be presented and will be used as denominator for percentage calculation.

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

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, related severe AEs, and investigator-reported AESI for each analysis period and follow-up period AEs. 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 serious AEs 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 investigator-reported AESIs will be produced.

7.1.1 Adverse Events of Special Interest (AESI)

AESI for this study are hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events). The preferred terms from MedDRA 22.1 or newer Standardized MedDRA Queries (SMQ) will be used to identify an SMQ-defined AESI. Table 2 shows the SMQs used to identify AESI of hypersensitivity, hypercoagulable, and bleeding.

Table 2. SMQ Used to Identify AESI

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

The number and percentage of subjects with any AESI, any related AESI, any serious AESI, any related serious AESI, any severe AESI, and any related severe AESI, as well as the total number of events for each category will be summarized 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.

7.1.2 Injection Site Reaction AEs

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

The number and percentage of subjects with any ISR AE, any related ISR AE, any serious ISR AE, any related serious ISR AE, any severe ISR AE, and any related severe ISR AE, as well as the total number of events for each category will be summarized 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 each analysis 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 each analysis period.

The number and percentage of subjects with an ISR AE will be summarized by SOC, PT and maximum severity for each analysis 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 each analysis period. Descriptive statistics (n, mean, SD, minimum, median, and maximum) will be presented to describe the ISR duration (hours). ISR duration will also be summarized by category (0-0.5 hour, >0.5 - 1 hour, >1 – 12 hour, >12 – 24 hour, <= 1 Day - Unclear, > 1 Day: >1-14 Days, >14 Days).

A listing of ISR AEs will be provided.

7.1.2.1 Duration of Injection Site Reaction AEs

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

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

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

7.2 Clinical Laboratory Data

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

Clinical laboratory parameters to be evaluated include the following:

Hematology	Hemoglobin, hematocrit, red blood cells (RBC), white blood cells (WBC) count total and differential - neutrophils, lymphocytes, monocytes, eosinophils, basophils, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), absolute platelet count.
Chemistry	Albumin, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin (total and direct), blood urea nitrogen (BUN), calcium, carbon dioxide (CO_2), chloride, creatinine, creatine phosphokinase (CPK), glucose, phosphate, magnesium, potassium, sodium, total protein.
Coagulation	Prothrombin time, activated partial thromboplastin time (aPTT), international normalized ratio (INR)
Urinalysis	Bilirubin, glucose, ketones, blood, nitrite, potential hydrogen (pH), protein, specific gravity, microscopy (if indicated by macroscopic findings).
Virology	Hepatitis B Surface Antigen (HbsAg); Hepatitis C Virus (HCV); Human Immunodeficiency Virus (HIV)

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

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

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

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

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 12.6.6. However, the actual values as reported in the database will be presented in data listings.

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

Among chemistry parameters, additional analyses in Table 3 will be conducted on liver function tests for the Full Analysis Set using the highest pre-treatment and highest overall 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 ALT, AST will be summarized for all pre-treatment measurements and overall 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 and overall treatment period and follow-up period measurements. Additionally, for the Full Analysis Set, a shift table summarizing the shift in categories from highest pre-treatment measurements to the highest overall treatment period and follow-up period measurements will be created for the liver function tests including ALT, AST and BILI.

Table 3. 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	-

7.3 Vital Signs

The following vital signs will be measured:

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

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

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

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

7.4 Electrocardiogram (ECG)

The following ECG variables will be measured:

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

ECG overall assessments will be classified according to clinical significance 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. 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.

7.5 Other Safety Data

7.5.1 Biomarker Test

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

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.

7.5.2 Pregnancy Test

Pregnancy test results will be listed by study visit.

7.5.3 Physical Examination

Physical examination will be listed by study visit.

8. PHARMACOKINETIC ANALYSIS

All summaries and analyses of the pharmacokinetic data will be based on the PK Set defined in Section 4.4.

8.1 Drug Concentration

The plasma concentrations of lanadelumab will be summarized for the protocol scheduled sampling visit:

- Treatment Period A: Visit 1, Visit 5, Visit 8, Visit 11, Visit 14.
- Treatment Period B: Visit 20, Visit 26 (for lanadelumab 300mg q4wks subjects) / Visit 27 (for lanadelumab 300mg q2wks subjects), Visit 28 (EOS/ ET).

8.2 Statistical Analysis of Pharmacokinetic Data

No formal statistical hypothesis will be tested.

The plasma lanadelumab concentration data 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 sampling visit.

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

8.3 Handling Below Limit of Quantitation (BLQ) Values

For PK data, the plasma concentration below the lower limit of quantitation (LLOQ) will be set to zero.

The BLQ plasma concentrations will not be imputed in the subject data listings.

9. PHARMACODYNAMIC ANALYSIS

All summaries and analyses of the pharmacokinetic data will be based on the PD Set defined in Section 4.5.

9.1 Pharmacodynamic Data

No formal statistical hypothesis will be tested.

The plasma kallikrein activity will be measured by cHMWK level (i.e., plasma concentrations of cHMWK).

cHMWK levels will be summarized for the protocol scheduled sampling visit:

- Treatment Period A: Visit 1, Visit 5, Visit 8, Visit 11, Visit 14.
- Treatment Period B: Visit 20, Visit 26 (for lanadelumab 300mg q4wks subjects) / Visit 27 (for lanadelumab 300mg q2wks subjects), Visit 28 (EOS/ET).

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 sampling visit.

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

10. OTHER ANALYSES

Subgroup analyses, health-related quality of life analyses and immunogenicity analyses are planned for this study.

10.1 Subgroup Analyses

10.1.1 Subgroup Analyses for the First Interim Analysis

For the first interim analysis, subgroup analyses are planned for the primary efficacy endpoint, some secondary efficacy endpoints and safety endpoints which are listed below in Table . The subgroups used will be:

- Subjects who completed/discontinued in Treatment Period A
- Subjects ongoing in Treatment Period A

Listings will include whether or not a subject is ongoing in Treatment Period A, discontinued, or completed Treatment Period A. The demographic table and baseline HAE characteristics table will also be presented by the subgroups defined above.

Table 4. Subgroup Analyses for the First Interim Analysis

Efficacy and Safety Endpoints	Subgroup Analysis
Achievement of Investigator-confirmed HAE Attack-Free Status During the Efficacy Evaluation Period of Day 0 to Day 182	X
Achievement of Subject Reported HAE Attack-Free Status During the Efficacy Evaluation Period Day 0 to Day 182	X
Number of Investigator-Confirmed HAE Attacks During the Efficacy Evaluation Periods Day 0 to Day 182 and Day 70 to Day 182	X
Number of Investigator-Confirmed HAE Attacks Requiring Acute Treatment During the Efficacy Evaluation Periods Day 0 to Day 182 and Day 70 to Day 182	X
Number of Moderate or Severe Investigator-Confirmed HAE Attacks During the Efficacy Evaluation Periods Day 0 to Day 182 and Day 70 to Day 182	X
Number of Investigator-Confirmed High-Morbidity HAE Attacks During the Efficacy Evaluation Periods Day 0 to Day 182 and Day 70 to Day 182	X

Subject Level Characteristics of Investigator-Confirmed HAE Attacks During the Efficacy Evaluation Periods Day 0 to Day 182 and Day 70 to Day 182	X
Event Level Characteristics of Investigator-Confirmed HAE Attacks During the Efficacy Evaluation Periods Day 0 to Day 182 and Day 70 to Day 182	X
Investigator-Confirmed HAE Attack Rate Reduction Relative to the Run-in Period by Responder Threshold During the Efficacy Evaluation Periods Day 0 to Day 182 and Day 70 to Day 182	X
Investigator-Confirmed HAE Attack Rate by Responder Threshold During the Efficacy Evaluation Periods Day 0 to Day 182 and Day 70 to Day 182	X
Achievement of Investigator-confirmed HAE Attack-free Status During the Efficacy Evaluation Period of Day 70 to Day 182	X
Achievement of Investigator-confirmed HAE Attack-free Status per Study Month	X
Achievement of Investigator-confirmed HAE Attack-free Status for the Interval of 1 Month, 3 Months or Until the Day 182 Visit	X
Percentage of Investigator-Confirmed HAE Attack-Free Days During the Efficacy Evaluation Period of Day 70 to Day 182	X
Overall Treatment-emergent Non-HAE Attack Reported Adverse Events During Treatment Period A	X
Treatment-emergent Non-HAE Attack Reported Adverse Events by System Organ Class, Preferred Term During Treatment Period A	X
Related Treatment-emergent Non-HAE Attack Reported Adverse Events by System Organ Class, Preferred Term During Treatment Period A	X
Severe Treatment-emergent Non-HAE Attack Reported Adverse Events by System Organ Class, Preferred Term During Treatment Period A	X

Serious Treatment-emergent Non-HAE Attack Reported Adverse Events by System Organ Class, Preferred Term During Treatment Period A	X
Investigational Product Exposure During Treatment Period A	X

10.1.2 Subgroup Analyses for the Second Interim Analysis and Final Analysis

For the second interim analysis and the final analysis, the following two dosing regimen periods will be investigated for the subgroup of subjects who had a dose frequency modification from 300 mg q2wks to 300 mg q4wks, as recorded on the Dose Frequency Modification eCRF. These dosing regimen periods will be applied to the efficacy parameters listed below and AEs only:

- Q2W dosing period: Any period during which a subject receives q2wks regimen, i.e., all intervals of time defined as:

  First interval:

  [date/time of first exposure to study drug, start date/time of q4wks regimen minus 1 minute]

  Subsequent intervals, if any:

  [start date/time of next q2wks regimen, start date/time of next q4wks regimen minus 1 minute] if there is another modification to q4wks regimen or

  [start date/time of next q2wks regimen, date of Day 364 visit at 23:59] otherwise.

- Q4W dosing period: Any period during which a subject receives q4wks regimen, i.e., all intervals of time defined as:

  [start date/time of q4wks regimen, start date/time of next q2wks regimen minus 1 minute] if there is another modification to q2wks regimen or

  [start date/time of q4wks regimen, date of Day 364 visit at 23:59] otherwise.

Start date/time of q2wks or q4wks regimen is defined as the date/time of the dose received prior to the date captured in the field “Initial date study drug was administered under modified dosing frequency" of eCRF corresponding to new dose regimen of 300 mg q2wks or q4wks, respectively.

Listings will present the following information separately for q2wks and q4wks dosing periods for subjects who had a dose frequency modification from q2wks to q4wks:

- Number of days on treatment, treatment compliance, number and rate of investigator-confirmed HAE attacks, HAE attacks requiring acute treatment, moderate or severe HAE attacks, high morbidity HAE attacks, maximum severity HAE attacks and the achievement of at least a 50%, 70% and 90% reduction in HAE attack rate relative to the run-in period.

Similarly, for subjects who had a dose frequency modification from q2wks to q4wks, adverse events will be flagged as starting either during the Q2W or Q4W dosing period. This categorization of adverse events will only occur in the analysis datasets.

10.2 Health-related Quality of Life Analyses

Health-related quality of life will be assessed using the angioedema quality of life (AE-QoL) questionnaire (Weller et al., 2012), at the study visits specified in Error! Reference source not found. **Table and**

Table .

The AE-QoL consists of 17 disease-specific quality-of-life items, each of the 17 items has a five-point response scale ranging from 0 (Never) to 4 (Very Often). The questionnaire is scored to produce a total score and four domain scores (functioning [item 1 – 4]. fatigue/mood [item 6 – 10], fear/shame [item 12 – 17], and nutrition [item 5, 11]). Raw domain scores (mean of the item scores within each domain) and raw total score (mean of all item scores) will be rescaled using linear transformations into final percentage scores ranging 0 to 100, based on the maximum possible score.

The AE-QoL domain scores and total score will be calculated by using the following formula:

(Sum of all completed items) / (maximum sum of all possible items) * 100.

The minimal and highest possible domain and total scores are 0 and 100, respectively. Only answered items are included in the computation. An AE-QoL domain score should not be calculated if more than one item is left unanswered in that domain. The AE-QoL total score should not be calculated if more than 25% of items (>4 items) are left unanswered.

- Computation of AE-QoL Total Score

  Example 1: All items were completed (maximum possible sum: 68 points)

  Sum of all 17 completed items: 41 points.

  Total score = 100*(41/68) = 60 (out of a possible 100 points)

  Example 2: 2 items were not completed (maximum possible sum: 60 points).

  Sum of all 15 completed items: 41 points.

  Total score = 100*(41/60) = 68 (out of a possible 100 points)

- Computation of Domain Scores (Example: Fears/Shame)

  Example: Sum of all 6 completed items: 14 points

  Maximum possible sum: 24 points

  Domain Score = 100*(14/24) = 58 (out of a possible 100 points)

The AE-QoL total score and domain scores will be summarized using descriptive statistics by study visit.

Change in total scores and 4 domain scores from baseline (Day 0) to Day 182 and Day 364 will be summarized.

The AE-QoL questionnaire responses will be listed for each subject by study visit.

10.3 Immunogenicity Analyses

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

Antibody testing is a 3-step process. If a sample tests ADA negative for the screening test, no further testing will be done; if a sample tests ADA positive for the screening test, confirmatory test will be done. ADA result is defined as positive if both the screening test result and confirmatory test result are positive; negative if either the screening test result or confirmatory test result is negative; otherwise, the ADA result is considered not evaluable.

If ADA result is positive, ADA titer result will be derived, and neutralizing ADA testing will be done. Neutralizing ADA results that is neither reactive nor non-reactive is defined as not evaluable.

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.

10.3.1 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 that period 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 6.2.1.

10.3.2 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.

10.3.3 Analyses of Immunogenicity/Pharmacodynamic Relationships

cHMWK 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.

11. INTERIM ANALYSIS/ DATA MONITORING COMMITTEE

Interim analyses of study data will be undertaken as described below. No adaptive design or data monitoring committee is planned for this study.

Two formal interim data analyses to support the Japanese New Drug Application (JNDA) submission will be completed. Both will summarize efficacy, safety, PK, HRQoL, PD, and immunogenicity of treatment with lanadelumab in Japanese subjects with HAE. The first interim analysis will be conducted when the first 6 subjects enrolled in the study have reached Day 182 or discontinued in Treatment Period A (26 weeks of treatment); enabling comparison to the DX-2930-03 pivotal overseas study data. The second interim analysis will be done when the first 4 subjects enrolled in the study have reached Day 364 or discontinued. An interim clinical study report summarizing data will be prepared for both analyses.

For the first interim analysis, the data for the first six enrolled subjects will be cleaned up to Day 182 and up to Day 98 for the following subjects. The tables, figures, and listings will include only data that has been cleaned for this interim analysis. It follows that only the following analysis periods will be presented for the first interim analysis (detailed definition of each period is provided in Section 12.3.1:

- The efficacy evaluation period of Day 0 through Day 182
- The efficacy evaluation period of Day 70 through Day 182
- Treatment period A for AEs and concomitant medications/therapies/procedures

12. DATA HANDLING CONVENTIONS

12.1 General Data Reporting Conventions

Outputs will be presented according to Shire TFLs Library V9.0.

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

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

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

BMI and AE-QoL domain/total scores will be rounded to 1 decimal place and normalized number of HAE attacks will be rounded to 2 decimal places for reporting.

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

12.2 Definition of Baseline

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

For efficacy analyses, refer to run-in period attack rate defined in Section 6.2.1.

12.3 Definition of Visit Windows

Although there is a visit window of ± 3 days around the expected visit date, nominal visits will be used for the per-visit analyses. Therefore, no windowing of visits by study day will be done for data obtained at the scheduled visits.

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

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

Study day = assessment date – first dosing date + 1

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

Study day = assessment date – first dosing date

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

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

The efficacy evaluation period of Day 0 through Day 364 is defined as the interval of time:

[*date/time of first exposure to study drug*, *date of Day 364 visit at 23:59*]

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

[*date of Day 70 visit at 0:00*, *date of Day 182 visit at 23:59*]

The efficacy evaluation period of Day 70 through Day 364 is defined as the interval of time:

[*date of Day 70 visit at 0:00*, *date of Day 364 visit at 23:59*]

The treatment period for AEs is defined as the interval of time:

[*date/time of first exposure to study drug*, *date of Day 364 visit at 23:59*]

Treatment period A for AEs and concomitant medications/therapies/procedures is defined as the interval of time:

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

Treatment period B for AEs and concomitant medications/therapies/procedures is defined as the interval of time:

[*date of Day 182 visit +1 day at 0:00*, *date of Day 364 visit at 23:59*]

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

[*date of Day 364 visit + 1 day at 0:00*, *date of last study contact at 23:59*]

12.4 Derived Efficacy Endpoints

12.4.1 Unique HAE Attacks

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

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

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

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

The imputation rules for partial start or end date and time for HAE attacks date/time is described in Section 12.6.1.

12.5 Repeated or Unscheduled assessments of Safety Parameters

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

12.6 Handling of Missing, Unused, and Spurious Data

All subjects in the analysis sets defined in Section 4 will be included in the associated analyses.

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

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

12.6.1 Missing Start or End Date and Time for HAE Attacks

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

In general, missing start date/time and end date/time will be imputed as described in Section 12.6.3. However, the following rules will be applied for the attacks satisfying the corresponding conditions, in order to conservatively classify the attacks as separate, distinct attacks with at least 24 hours in-between:

- For HAE attacks with a missing start time and a non-missing start date one calendar day after the end date of the previous attack, the start time will be imputed using the end time of the previous HAE attack to ensure there are 24 hours in between the two attacks.
- For HAE attacks with a missing start time and a non-missing end date/time within 24 hours from the end date/time of the previous attack, the attack should be considered as one attack with the previous attack (see Section 12.4.1 for details on combining HAE attacks)
- For HAE attacks with missing end time and a non-missing end date one calendar day before the start date of the next attack, the end time will be imputed as the start time of the next HAE attack to ensure there are 24 hours in between the two attacks.
- For HAE attacks with missing end time and a non-missing end date more than one calendar day before the start date of the next attack, the end time will be imputed as 23:59.
- 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 12.4.1 for details on combining HAE attacks)

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

- If the event is not indicated as ongoing, the stop date and time will be imputed as start date and time + 48 hours or 24 hours before the start date and time of the next attack, whichever is earlier.

- If the event is indicated as ongoing, the stop date and time will be imputed as the earliest of the following two date and time:
    - Start date and time + 48 hours or study completion date and the stop time of 23:59, whichever is later.
    - 24 hours before the start date and time of the next attack.

12.6.2 Missing Date/Time Information for Prior or Concomitant Medications/Therapies/Procedures

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

12.6.2.1 Incomplete Start Date/Time

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

12.6.2.1.1 Missing time

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

12.6.2.1.2 Missing Day and Month

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

12.6.2.1.3 Missing Month only

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

12.6.2.1.4 Missing Day only

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

12.6.2.2 Incomplete Stop Date/Time

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

12.6.2.2.1 Missing time

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

12.6.2.2.2 Missing Day and Month

31 December will be assigned to the missing fields

12.6.2.2.3 Missing Month only

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

12.6.2.2.4 Missing Day only

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

12.6.3 Missing Date/Time Information for Adverse Events

For AEs with partial start date/time, non-missing date/time parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date/time parts as to when the AE occurred relative to study drug administration, e.g. AE start year and month are the same as the year and month of the first dose of IP, then the AE will be classified as treatment-emergent.

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

12.6.3.1 Incomplete Start Date/Time

Follow the same rules as in Section 12.6.2.1.

12.6.3.2 Incomplete Stop Date/Time

Not applicable.

12.6.4 Missing Severity assessment for Adverse Events

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

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

12.6.5 Missing Relationship to IP for Adverse Events

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

12.6.6 Character Values of Clinical Laboratory Variables

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

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

13. ANALYSIS SOFTWARE

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

14. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

14.1 Achievement of Attack-free Status by interval

It is stated in Section 9.6 of protocol that "Subjects who discontinued during a time period are considered as non-responders for that time period.". However, subjects who discontinue the interval will not be counted as non-responders and will have their attack-free status evaluated at the time they discontinue.

15. REFERENCES

Weller, K., Groffik, A., Magerl, M., Tohme, N., Martus, P., Krause, K., Metz, M., Staubach, P.and Maurer, M. 2012. "Development and construct validation of the angioedema quality of life questionnaire." *Allergy* 67: 1289-98.

Appendix 1 Schedule of Activities

Table 6. Study Activity Schedule - Screening, Run-in and Treatment Period A

Procedures	Screening	Run-in Period[a]	Treatment Period A[b]													See protocol section below for details
			Visit 1 Day 0	Visit 2 Day 14	Visit 3 Day 28	Visit 4 Day 42	Visit 5 Day 56	Visit 6 Day 70	Visit 7 Day 84	Visit 8 Day 98	Visit 9 Day 112	Visit 10 Day 126	Visit 11 Day 140	Visit 12 Day 154	Visit 13 Day 168	Visit 14 Day 182	
Informed consent	X																Section 8.2.1
Eligibility review	X		X[m]														Section 8.2.2
Prior/current medications, therapies, and procedures	X	X	X[n]														Section 6.6
LTP washout[c]	X																Section 8.1.1.2
Lanadelumab 300 mg			X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.2.3
Site check-in[d]			*Between scheduled study visits*														
Demographic and medical history	X																Section 8.2.3
C1-INH, C1q, and C4 testing[e]	X																Section 8.2.6.4
Pregnancy test (females)[f]	X		X													X	Section 8.2.5.6
Vital signs[g]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.5.4
Physical examination	X		X		X		X			X			X			X	Section 8.2.5.1
Height and weight	X																Section 8.2.5.1
12-lead ECG	X		X				X						X			X	Section 8.2.5.7
Clinical laboratory testing[h]	X		X		X		X			X			X			X	Section 8.2.5.5
Serologies: HBsAg, HCV, and HIV	X																Section 8.2.5.5

Procedures	Screening	Run-in Period[a]	Treatment Period A[b]													See protocol section below for details
			Visit 1 Day 0	Visit 2 Day 14	Visit 3 Day 28	Visit 4 Day 42	Visit 5 Day 56	Visit 6 Day 70	Visit 7 Day 84	Visit 8 Day 98	Visit 9 Day 112	Visit 10 Day 126	Visit 11 Day 140	Visit 12 Day 154	Visit 13 Day 168	Visit 14 Day 182	
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.6
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.5.2
HAE attack data[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.4.1
Quality of life assessments[j]			X		X		X			X		X		X		X	Section 8.2.6.5
PK blood sample[k]			X				X			X			X			X	Section 8.2.6.1
PD blood sample[k]			X				X			X			X			X	Section 8.2.6.2
Plasma anti-drug antibody testing[k]			X				X			X			X			X	Section 8.2.6.3
Injection Report[l]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.6.8

BP=blood pressure; C1-INH=C1 inhibitor; ECG=electrocardiogram; EOS=End of Study; ET=Early Termination; HAE=hereditary angioedema; HAARP=HAE Attack Assessment and Reporting Procedures; HbsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HR=heart rate; LTP=long-term prophylaxis; IMP=investigational medicinal product; PD=pharmacodynamic; PK=pharmacokinetic; RR=resting rate

[a] Subjects will undergo a run-in period to determine their baseline HAE 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-week run-in period may exit the run-in period early and proceed to Treatment Period A. The run-in period may be extended to 8 weeks if the minimum baseline attack rate is not achieved in the first 4 weeks of the run-in period. Subjects who have their run-in extended must complete the full 8-week run-in period and must have at least 2 investigator-confirmed attacks during this time to be eligible to enter Treatment Period A. Subjects who do not meet the minimum attack rate during run-in or were otherwise determined to be ineligible due to screening assessments will be considered a screen fail.

[b] Treatment period visits will have a ±3 day window, with 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 who are receiving LTP 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 will 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 has successfully completed the 2-week washout period before they may enter the run-in period.

[d] Site personnel will contact the subject once between scheduled site visits (or approximately 7 days after last contact with subject) to solicit for any attacks not already reported by the subject (see also footnote i) and to collect information on AEs and concomitant medications. The preferred method of site contact is a telephone call; however, alternate methods of contact may be considered as site policies permit.

Procedures	Screening	Run-in Period[a]	Treatment Period A[b] Visit 1 Day 0	Visit 2 Day 14	Visit 3 Day 28	Visit 4 Day 42	Visit 5 Day 56	Visit 6 Day 70	Visit 7 Day 84	Visit 8 Day 98	Visit 9 Day 112	Visit 10 Day 126	Visit 11 Day 140	Visit 12 Day 154	Visit 13 Day 168	Visit 14 Day 182	See protocol section below for details

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

[f] Pregnancy testing is required for all female subjects; the test will be urine-based on Day 0 and may be serum-or urine-based at other visits.

[g] There will be a ±15 minute window for all vital signs. At study visits in which IMP will be administered, vital signs including sitting or supine BP, HR, body temperature, and RR, are to be obtained prior to dosing, 1 hour after dosing, and 2 hours after dosing for the first 4 doses with the ability to eliminate the 2-hour vitals for the remaining doses based on the discretion of the investigator and the absence of safety signals.

[h] Clinical laboratory testing will include hematology, coagulation, serum chemistry, and urinalysis.

[i] Historical attack information will be collected at screening. During the study the subjects (or their parents/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, in accordance with HAARP. 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.

[j] Quality of life data will be obtained using the Angioedema Quality of Life Questionnaire (AE-QoL).

[k] Blood samples for testing PK, PD and formation of antibodies to lanadelumab will be obtained predose (ie, within 2 hours prior to dosing).

[l] Collect the injection reports assessing the subject's experience with SC lanadelumab administration. An injection report must be completed by the subject after each dose of lanadelumab.

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

[n] Includes medications, therapies, and procedures administered/occurring prior to the first dose of lanadelumab

Note: In the event a subject prematurely discontinues from treatment and/or the study, EOS/ET procedures will be performed as soon as possible (see Table 2).
Note: Investigators are to report all SAEs to Shire Drug Safety 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.

Table 7. Study Activity Schedule - Treatment Period B and Follow-up Period

Procedures	Treatment Period B[a] *Grey-shaded columns indicate option for self-administration at the site or an offsite location* [i]													Visit 28 Day 378/ 392[o] (EOS/ ET)	See protocol section below for details
	Visit 15 Day 196	Visit 16 Day 210[n]	Visit 17 Day 224	Visit 18 Day 238[n]	Visit 19 Day 252[n]	Visit 20 Day 266	Visit 21 Day 280[n]	Visit 22 Day 294[n]	Visit 23 Day 308	Visit 24 Day 322[n]	Visit 25 Day 336[n]	Visit 26 Day 350	Visit 27 Day 364		
Lanadelumab 300 mg q2wks[c]	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 6.2.3
Lanadelumab 300 mg q4wks[c]		X		X		X		X		X		X			Section 6.2.3
Site check-in[b]			*Between scheduled study visits*												
Pregnancy test (females)[d]														X	Section 8.2.5.6
Vital signs[e]			X			X			X			X	X	X	Section 8.2.5.4
Physical examination			X			X			X			X	X	X	Section 8.2.5.1
12-lead ECG														X	Section 8.2.5.7
Clinical laboratory testing[f]			X			X			X			X	X	X	Section 8.2.5.5
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.6
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.5.2
HAE attack data[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.4.1
Quality of life assessments[h]						X							X	X	Section 8.2.6.5
PK blood sample[k]						X						X[j]	X[j]	X	Section 8.2.6.1
PD blood sample[k]						X						X[j]	X[j]	X	Section 8.2.6.2.
Plasma anti-drug antibody testing[k]						X						X[j]	X[j]	X	Section 8.2.6.3
Injection Report[l]			X			X			X			X	X		Section 8.2.6.8
Discharge from the study[m]														X	NA

Procedures	Treatment Period B[a] *Grey-shaded columns indicate option for self-administration at the site or an offsite location [i]*													Visit 28 Day 378/ 392[o] (EOS/ ET)	See protocol section below for details
	Visit 15 Day 196	Visit 16 Day 210[n]	Visit 17 Day 224	Visit 18 Day 238[n]	Visit 19 Day 252[n]	Visit 20 Day 266	Visit 21 Day 280[n]	Visit 22 Day 294[n]	Visit 23 Day 308	Visit 24 Day 322[n]	Visit 25 Day 336[n]	Visit 26 Day 350	Visit 27 Day 364		

BP=blood pressure; C1-INH=C1 inhibitor; ECG=electrocardiogram; EOS=End of Study; ET=Early Termination; HAE=hereditary angioedema; HAARP=HAE Attack Assessment and Reporting Procedures; HR=heart rate; IMP=investigational medicinal product; LTP=long-term prophylaxis; NA=not applicable; PD=pharmacodynamic; PK=pharmacokinetic; RR=resting rate

[a] Treatment period visits will have a ±3 day window, with 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.

[b] Site personnel will contact the subject once between scheduled site visits (or approximately 7 days after last contact with subject) to solicit for any attacks not already reported by the subject and to collect information on AEs and concomitant medications. The preferred method of site contact is a telephone call; however, alternate methods of contact may be considered as site policies permit. If a site check-in was performed (see footnote n), then this site contact will not be required.

[c] In Treatment Period B, a subject may continue to receive lanadelumab 300 mg q2wks or, if the subject has been well-controlled (attack free) for 26 consecutive weeks with lanadelumab treatment, the subject may switch to a dose of 300 mg q4wks at the discretion of the investigator and following approval by the sponsor's medical monitor. The first dose on the q4wks regimen must occur at an even-numbered visit (eg, Visit 16, 18, 20).

[d] Pregnency testing is required for all female subjects, and may be serum-or urine-based.

[e] There will be a ±15 minute window for all vital signs. At study visits in which IMP will be administered, vital signs including sitting or supine BP, HR, body temperature, and RR, are to be obtained prior to dosing, 1 hour after dosing, and 2 hours after dosing with the ability to eliminate the 2 hour vitals for the remaining doses based on the discretion of the investigator and the absence of safety signals.

[f] Clinical laboratory testing includes hematology, coagulation, serum chemistry, and urinalysis.

[g] During the study the subjects (or their parents/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, in accordance with HAARP. If a site check was not performed (see footnote n), site personnel will contact the subject once between study visits (or approximately 7 days after last contact with the subject) in order to solicit for any attack that may have occurred. The preferred method for site contact is a telephone call; however, alternate methods of contact may be considered as site policies permit. 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.

[h] Quality of life data will be obtained using the Angioedema Quality of Life Questionnaire (AE-QoL).

[i] Subjects (or their parent/caregiver) are allowed to initiate self-administration under the investigator supervision.

[j] For subjects who switch to q4wks dosing and are receiving lanadelumab at even-numbered study visits (eg, Visits 16, 18, 20), the PK, PD, and ADA assessments scheduled for Visit 27 will instead be performed at Visit 26.

[k] Blood samples for testing PK, PD and formation of antibodies to lanadelumab will be obtained predose (ie, within 2 hours prior to dosing) with the exception of the EOS/ET visit.

[l] Collect the injection reports assessing the subject's experience with SC lanadelumab administration. An injection report must be completed by the subject after each dose of lanadelumab.

[m] Subjects that elect to rollover to Study TAK-743-5007 will return on Day 378 to complete EOS assessments and will be discharged from this study. All other subjects will continue the study as originally planned and will be discharged from the study on Day 392 following completion of all EOS / ET visit procedures.

Procedures	Treatment Period B[a] *Grey-shaded columns indicate option for self-administration at the site or an offsite location [i]*													Visit 28 Day 378/ 392[o] (EOS/ ET)	See protocol section below for details
	Visit 15 Day 196	Visit 16 Day 210[n]	Visit 17 Day 224	Visit 18 Day 238[n]	Visit 19 Day 252[n]	Visit 20 Day 266	Visit 21 Day 280[n]	Visit 22 Day 294[n]	Visit 23 Day 308	Visit 24 Day 322[n]	Visit 25 Day 336[n]	Visit 26 Day 350	Visit 27 Day 364		

[n] This study visit may be conducted via a site check-in if a subject is self-administering lanadelumab or a subject is receiving lanadelumab q4wks and the visit is a non-dosing visit for the subject. Site personnel will perform a site check-in within 3 days after the scheduled study visit to ensure that self-administration of lanadelumab has occurred as scheduled (if applicable) and to collect AEs and concomitant medications, and solicit for any attacks not already reported by the subject. The preferred method for site check-in is a telephone call; however, alternate methods of contact may be considered as site policies permit.

[o] Day 378 will serve as the EOS Visit for subjects participating in Study TAK-743-5007. All other subjects will complete the EOS assessments on Day 392.

Note: In the event a subject prematurely discontinues from treatment and/or the study, EOS/ET procedures will be performed as soon as possible.
Note: Investigators are to report all SAEs to Shire Drug Safety 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.

Appendix 2 Sample SAS code

Sample SAS Code for Time to Event Analysis

The analysis of time to first HAE attack (see Section 6.2.2) is based on the KM method. First HAE attack is the event of interest. The following SAS code is proposed for analyses of time to first HAE attack.

Consider the subject level dataset HAEDATA which contains the variables HAETIME and STATUS. HAETIME is the time from first IP administration to the first investigator-confirmed HAE attack or censored time. STATUS=1 if the subject is censored and STATUS=0 if investigator-confirmed HAE attack happens before the date and time of the end of the period. Details of censoring is provided in Section 6.2.2.

PROC LIFETEST can be used as follows to obtain the KM plot.

```
ods graphics on;
ods output Quartiles=Quarts CENSOREDSUMMARY=Summary;
proc lifetest data=HAEDATA method=km plots=survival;
   time HAETIME*STATUS(1);
run;
```

Dataset QUARTS contains KM estimates of the 25th, 50th (median), and 75th percentiles with associated two-sided 95% CI.

Dataset SUMMARY contains the number of events of interest, number and percentage of censored observations in Variable FAILED, CENSORED and PCTCENS, respectively.