STATISTICAL ANALYSIS PLAN

NCT Number: NCT04070326

Study Title: SPRING STUDY: An Open-Label, Multicenter, Phase 3 Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Lanadelumab for Prevention Against Acute Attacks of Hereditary Angioedema (HAE) in Pediatric Subjects 2 to <12 Years of Age

Study Number: SHP643-301

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Shire is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

Statistical Analysis Plan

for

Full Analysis

Lanadelumab

Phase 3

SPRING STUDY: An Open-Label, Multicenter, Phase 3 Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Lanadelumab for Prevention Against Acute Attacks of Hereditary Angioedema (HAE) in Pediatric Subjects 2 to <12 Years of Age

Protocol Identifier: SHP643-301

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Confidentiality Statement

VERSION HISTORY

Version	Issue Date	Summary of Changes
1.0	May 26, 2021	New Document
2.0	Sep 27, 2021	1) Updated based on PA 2: a) Individual subject participation duration was revised to clarify that maximum duration for study participation is 72 weeks in Section 3.1. Subjects receiving treatment q2wks may complete the study in 70 weeks. b) Revised follow-up period to 2-4 weeks in Section 3.1 as follow-up period depends on the treatment schedule. Subjects receiving treatment q2wks will have a 2 week follow-up period (EOS Visit at Day 378); subjects receiving treatment q4wks will have a 4-week follow-up period (EOS Visit at Day 392). c) The text about the interim analysis summarizing data up to Treatment Period A has been removed from Section 3.1 and Sec 11 as it is no longer planned. d) EOS/ET visit in footnote "a" was incorrectly written as Day 292. This has been corrected to Day 392 in Appendix 1, Schedule of Activities. e) Removed the text in Section 14 as the PA 2 has addressed the previous changes. 2) Updated section 7.1 for all AEs summaries that summarized by SOC and PT, will be presented by the dose regimen the subject actually received and separated to Treatment Period A, Treatment Period B, overall treatment period, and Follow-up period.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	Body Mass Index
C1-INH	C1 esterase inhibitor
cHMWK	cleaved high molecular weight kininogen
CRF	case report form
eCRF	electronic case report form
FIM	Family Impact Module
HAARP	HAE Attack Assessment and Reporting Procedures
HAE	hereditary angioedema
[redacted]	[redacted]
IP	study drug
IcEv	intercurrent event
IMP	investigational medicinal product
ISR	Injection Site Reaction
KM	Kaplan-Meier
LLN	lower limit of normal
LOE	lack of efficacy
LTP	long-term prophylaxis
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic(s)
[redacted]	[redacted]
PK	pharmacokinetic(s)
PT	preferred term
PY	patient-year
Q2WKS	every 2 weeks

Abbreviation	Definition
Q4WKS	every 4 weeks
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SMQ	standardized MedDRA® query
SOC	system organ class
SY	subject-year
ULN	upper limit of normal
[redacted]	[redacted]
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of safety, pharmacokinetic (PK)/pharmacodynamic (PD), clinical outcomes, [redacted] and immunogenicity as described in the study protocol amendment version 1.0 dated 12 Aug 2019. Specifications for tables, figures, and listings are contained in a separate document. This SAP contains detailed information to aid in the implementation of the statistical analysis of the study data for use in the clinical study report (CSR) and publication.

2. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of the study is to evaluate the safety and pharmacokinetics (PK) of lanadelumab in children (2 to <12 years of age) with HAE.

2.1.2 Secondary Objective(s)

The secondary objectives of the study are:

- To evaluate the clinical activity/outcomes (hereafter referred to as clinical outcomes) of lanadelumab in preventing HAE attacks in children (2 to <12 years of age) with HAE.
- To characterize the pharmacodynamics (PD) of lanadelumab in children (2 to <12 years of age) with HAE.
- To assess the immunogenicity of chronically administered lanadelumab and its effect on PK, PD, clinical outcomes, and safety in children (2 to <12 years of age) with HAE.

[redacted]

2.2 Estimands

The types of intercurrent events are described in Table 1. The primary and secondary estimands are described in Table 2. The treatment conditions are always "Treatment with Lanadelumab (150 mg s.c. q2wks for subjects 6 to <12 years old and q4wks for subjects 2 to <6 years old)".

Table 1 Intercurrent Event Types

Label	Intercurrent Event Type
IcEv1 (IMP-related Discontinue)	Discontinuation of IMP due to a reason linked to the IMP (lack of efficacy or treatment related treatment-emergent AE or tolerability issue)
IcEv2 (IMP-unrelated Discontinue)	Discontinuation of IMP due to a reason not linked to IMP such as an unrelated intercurrent illness, logistical reason (e.g. COVID19 lock-down, personal circumstances)
IcEv3 (IMP Interruption)	Interruption in dosing (delayed dose)
IcEv4 (Meds)	Use of rescue medications (ecallantide, icatibant, nano-filtered C1-INH, plasma-derived, C1-INH, recombinant C1-INH, fresh frozen plasma)

Table 2 List of Estimands

			Attributes		
Estimand	**Definition**	**A: Population**	**B: Variable (or endpoint)**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Primary	Proportion of pediatric patients with HAE who would develop treatment-emergent AE (including each AESI [hypersensitivity reactions, hypercoagulability events and bleeding events] and all serious events) if exposed to Lanadelumab.	Pediatric patients (aged 2 to <6, 6 to <12 and overall) with HAE	Occurrence of treatment-emergent AEs following first Lanadelumab dose	IcEv1 (IMP-related Discontinue): While on Treatment: Count subjects with treatment-emergent AEs IcEv2 (IMP-unrelated Discontinue): While on Treatment: Count subjects with treatment-emergent AEs IcEv3 (IMP Interruption): Treatment Policy (ignoring the interruption) IcEv4 (Meds): Treatment Policy: AEs are included regardless of the use of other medications	Number and proportion of patients who experience treatment-emergent AEs
Primary	Average number of treatment-emergent AEs per patient year (including each AESI [hypersensitivity reactions, hypercoagulability events and	Pediatric patients (aged 2 to <6, 6 to <12 and overall) with HAE	Number of treatment-emergent AEs while on treatment.	IcEv1 (IMP-related Discontinue): While on Treatment: Count treatment-emergent AEs IcEv2 (IMP-unrelated Discontinue): While on	Number of treatment-emergent AEs, normalized by exposure time

	bleeding events] and all serious events).			Treatment: Count treatment-emergent AEs IcEv3 (IMP Interruption): Treatment Policy (ignoring the interruption) IcEv4 (Meds): Treatment Policy: AEs are included regardless of the use of other medications	(patient year) over all patients
Secondary	Normalized number of investigator-confirmed HAE attacks per 4 weeks, while on treatment	Pediatric patients (aged 2 to <6, 6 to <12 and overall) with HAE	Number of investigator-confirmed HAE attacks	IcEv1 (IMP-related Discontinue): While on treatment: Count attacks through end of Treatment Period B IcEv2 (IMP-unrelated Discontinue): While on treatment: Count attacks through end of Treatment Period B IcEv3 (IMP Interruption): Treatment policy (ignoring the interruption) IcEv4 (Meds): Treatment policy: Attacks are included regardless of the use of other medications	Normalized number of investigator-confirmed HAE attack per 4 weeks during Treatment Period and comparison to normalized number of investigator-confirmed HAE attack per 4 weeks during baseline observation period.

Notes: For ease of reading, the endpoints in the estimand definitions are italicized.
Generally, the treatment policy strategy implies the analysis ignores the occurrence of the IcEv, and is selected to estimate what is expected to occur under the same conditions as those of the trial.
Abbreviations: FU=follow-up; IcEv=intercurrent event; IMP=investigational medical product.

2.3 Endpoints

2.3.1 Primary Endpoint(s)

The primary endpoint for this study is safety and PK.

The safety measures include:

- Adverse events (AEs) including serious adverse events (SAEs) and adverse events of special interest (AESI).
- Clinical laboratory testing (hematology, clinical chemistry, coagulation)
- Vital signs including blood pressure, heart rate, body temperature, and respiratory rate.

The PK endpoints include:

- Plasma concentrations of lanadelumab over the treatment period.
- PK parameters in plasma, by age group, will be estimated by a population modelling and simulation approach and reported separately:
  - $C_{max,ss}$: Maximum observed concentration at steady state
  - $C_{avg,ss}$: Average concentration over dosing interval at steady state
  - $C_{trough,ss}$: Predose concentration at steady state
  - t_{max}: Time to reach C_{max} in plasma
  - $AUC_{tau,ss}$: Area under the concentration-time curve over the dosing interval at steady state
  - $t_{½}$: Terminal half-life
  - CL/F: Apparent clearance
  - V/F: Apparent volume of distribution

2.3.2 Secondary Endpoint(s)

Clinical outcome measures are secondary endpoints for the study.

Clinical outcome measures are based on 5 efficacy evaluation periods: the overall treatment period (Day 0 through Day 364), Treatment Period A (Day 0 through Day 182), Treatment Period B (Day 183 through Day 364), an overall presumed steady state period (Day 70 through Day 364), and the presumed steady state period for Treatment Period A (Day 70 through Day 182).

The primary clinical outcome endpoint will be the normalized number of investigator-confirmed HAE attacks for the overall treatment period.

The other clinical outcome endpoints are as follows:

- Normalized number of investigator-confirmed HAE attacks for each efficacy evaluation period other than the overall treatment period.
- Time to the first attack, ie, duration that a subject is attack-free until their first attack for each efficacy evaluation period.
- Normalized number of investigator-confirmed HAE attacks requiring acute therapy use for each efficacy evaluation period.
- Normalized number of moderate or severe investigator-confirmed HAE attacks for each efficacy evaluation period.
- Normalized number of high morbidity investigator-confirmed HAE attacks for each efficacy evaluation period.
- Characteristics of investigator-confirmed HAE attacks for each efficacy evaluation period, including duration, severity, attack location, and rescue medication use.
- Achievement of attack-free status for each efficacy evaluation period.

The other secondary endpoints are as follows:

- PD measurements: Plasma kallikrein activity (as measured by cHMWK level).
- Immunogenicity as measured by presence or absence of neutralizing or non-neutralizing anti-drug antibody (ADA) in plasma is a secondary endpoint for the study.

[redacted]

3. STUDY DESIGN

3.1 General Description

This is an open-label, multicenter study to evaluate the safety, PK, and PD of Lanadelumab for prevention against acute attacks of hereditary angioedema (HAE) in pediatric subjects 2 to <12 years of age.

Study SHP643-301 targets to enroll at least 20 pediatric subjects (2 to <12 years of age; at least 5 subjects in each age group of 2 to <9 years of age and 9 to <12 years of age) to ensure that a minimum of 15 subjects complete 1 year (52 weeks) of treatment on the study. All subjects must have a diagnosis of HAE (Type I or II) with a history of ≥1.0 angioedema attacks per 3 months (12 weeks).

Subjects meeting all eligibility criteria will be enrolled and enter the observation period for up to 12 weeks; all subjects must discontinue long-term prophylaxis (LTP) before entering the observation period. The attack rate in the observation period will serve as the baseline for the study. Subjects who experience ≥1.0 angioedema attacks per 3 months during the 12-week baseline observation period and who remain eligible per study criteria will enter the lanadelumab treatment period for 52 weeks. Subjects must stay in the observation period for a minimum of 4 weeks except for those subjects who report more than 2 HAE attacks (confirmed by the investigator and agreed with the sponsor's medical monitor) within the first 2 weeks of the observation period. Subjects may exit the observation period after reporting one investigator-confirmed attack after 4 weeks in the observation period; subjects will then enter the treatment period.

The 52-week treatment period will comprise a 26-week Treatment Period A and a 26-week Treatment Period B. Subjects who complete Treatment Period A will immediately continue into Treatment Period B.

The proposed dose regimens for pediatric subjects 2 to <12 years are shown below, and are based on population PK modeling and simulation, the similarity of etiology of HAE between adult, adolescent, and pediatric subjects with HAE, and body weight distribution information on the related age groups. Dosing regimen will be determined based on a subject's age at the date of informed consent, and subjects will remain in the same age category throughout the study.

- 6 to <12 years: lanadelumab 150 mg q2wks
- 2 to <6 years: lanadelumab 150 mg q4wks

Dose group is defined based on the planned dose regimen:

- "lanadelumab 150 mg every 2 weeks" consistents of subjects with planned dosing regimen of lanadelumab 150 mg q2wks
- "lanadelumab 150 mg every 4 weeks" consistents of subjects with planned dosing regimen of lanadelumab 150 mg q4wks

Subjects 6 to <12 years will receive lanadelumab 150 mg q2wks in Treatment Period A and may remain on the same dose regimen in Treatment B or, if the subject has been well controlled (eg, attack free) for 26 weeks with lanadelumab treatment in this study, the subject may switch to a dose of 150 mg q4wks at the discretion of the investigator and following approval by the sponsor's medical monitor. Subjects 2 to <6 years will receive lanadelumab 150 mg q4wks in both Treatment Period A and Treatment Period B.

The justification for the dosing regimen proposed for this study is in Section 4.3 of the protocol. The dose modification is in section 6.2.5 of the protocol.

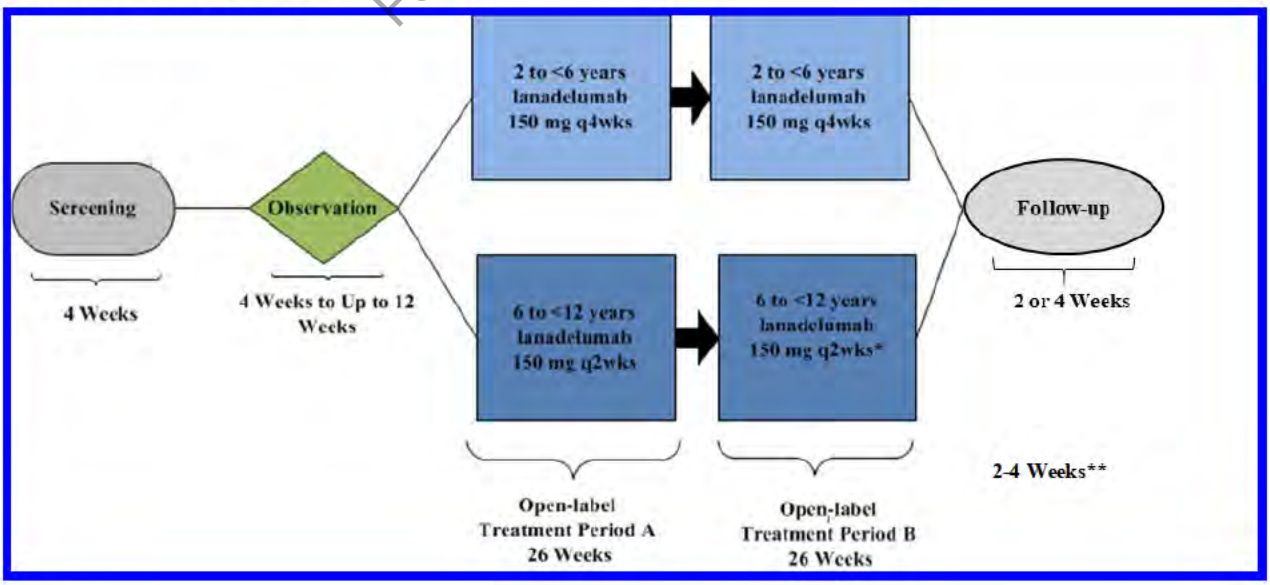
After completion of the second 26-week treatment period (Treatment Period B), subjects will be followed for an additional 2 or 4 weeks (depending on the treatment schedule).

Acute HAE attacks during the treatment period will be managed in accordance with the investigator's usual care of their patients, including use of individualized acute therapy that the investigator deems medically appropriate. C1-INH will be permitted as an acute attack therapy but not as a long-term prophylactic therapy during the study.

After 5 subjects receive at least 5 doses of lanadelumab, an interim PK analysis will be conducted to evaluate the proposed dose regimens using available data for this study (see protocol Section 6.2.5).

An individual subject's maximum duration of participation from screening through the completion of safety follow-up visit will be approximately 72 weeks (up to 4-week screening visit, up to 12-week baseline observation period, 52-week treatment period, and a 2 or 4-week post-treatment safety follow-up visit). An overview of the study design is provided in Figure 1.

Figure 1. Study Design



*An individual subject's dose frequency may be modified based on a benefit-risk assessment and recommendation from the treating physician. Consultation with and approval by the sponsor's medical monitor is required. For example, subjects 6 to <12 years of age may administer lanadelumab 150 mg q4wks in Treatment Period B at the investigator's discretion and sponsor's medical monitor approval, if they are well controlled (eg, attack free) for 26 weeks with lanadelumab treatment in this study.

**The follow-up period for this protocol is 14 to 28 days (2-4 weeks). For subjects receiving treatment q2wks, the follow-up period is 2 weeks. At the end of the 2-week follow-up period, a scheduled on-site EOS visit will be on Study Day 378 (Visit 54) to query for SAEs and AEs, concomitant treatments, and perform the assessments and procedures described for the EOS assessment (there is no site check-in call). For subjects receiving treatment q4wks, the follow-up period is 4 weeks, a site check-in call will occur on Study Day 378 (Visit 54).

3.2 Randomization

Not applicable. This is an open-label study and randomization is not conducted.

3.3 Blinding

Not applicable. This is an open-label study.

3.4 Sample Size and Power Considerations

The sample size for this pediatric study is driven by feasibility considerations as enrollment of pediatric patients 2 to <12 years old is expected to be difficult. Statistical analyses will be descriptive in nature. The primary emphasis will be to assess the safety and PK of lanadelumab in this age group, but also to generate data on clinical outcomes if subjects have sufficient baseline attack frequency for evaluation. At least 20 subjects will be enrolled to ensure a minimum of 15 subjects complete 1 year (52 weeks) of treatment on the study. Given the limited number of pediatric subjects with HAE who will fall within this age category and have a history of angioedema attacks appropriate to meet the study inclusion criteria (Caballero, 2013), this number is considered a reasonable target at study initiation with respect to the ability to enroll eligible subjects.

4. STATISTICAL ANALYSIS SETS

4.1 Screened Set

The Screened Set will consist of all subjects who have signed informed consent.

4.2 Safety Analysis Set

The Safety Analysis Set will consist of all subjects who receive any study drug.

4.3 Pharmacokinetic Set

The Pharmacokinetic (PK) Set is defined as all subjects in the Safety Analysis Set who have at least 1 evaluable post dose PK concentration value.

4.4 Pharmacodynamic Set

The Pharmacodynamic (PD) Set is defined as all subjects in the Safety Analysis Set who have at least 1 evaluable post dose PD value.

5. STUDY SUBJECTS

All summary for treatment compliance and exposure will be conducted according to the actual dose regimen received. Other summary for disposition, protocol deviation, demographic and baseline characteristics, medical history, prior and concomitant medication will be conducted according to the dose regimen assigned at Visit 1 Day 0.

5.1 Disposition of Subjects

A listing of all screen failures (i.e., subjects who were screened but not enrolled) will be presented along with reasons for screen fail and details of any AEs. The listing will include the first screening data for re-screened subjects.

The number of subjects who were included in each defined analysis set (i.e., Screened, Safety) will be summarized by dose group and overall, except for the Screened Set, which will be summarized only overall.

The number and percentage of subjects who completed 3 months, completed treatment period A, completed treatment period B, completed the study and prematurely discontinued the study will be presented by dose group and overall for the Safety Analysis Set. Reasons for premature discontinuation as recorded on the termination page of the eCRF will be summarized (number and percentage) by dose group and overall for the Safety Analysis Set. All subjects who prematurely discontinued the study will be listed by discontinuation reason for Safety Analysis Set.

5.2 Protocol Deviations

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.

Summary tables of protocol deviations by dose group and overall will be provided for the Safety Analysis Set. All protocol deviations will be included in a subject listing. A separate listing will list the deviations for inclusion/exclusion criteria. The protocol deviations related to COVID-19 will be listed separately for the Safety Analysis Set.

5.3 Demographic and Other Baseline Characteristics

Baseline and demographic variables will be descriptively summarized by dose group and overall for the Safety Analysis Set, the PK set and the PD set.

The baseline and demographic characteristics will be summarized in the following order in the tables:

- Age (years)
- Age group 1 (2 to <6 years and 6 to <12 years)

  Age group 2 (2 to <9 years and 9 to <12 years)
- Sex
- Ethnicity
- Race
- Race group (White, Other)
- Geographic region (US, Canada, Europe)
- Weight (kg)
- Weight percentile group (Underweight: <5th percentile, Healthy or Overweight: 5th – <95th percentile, Obese: ≥ 95th percentile)
- Height (cm)
- BMI (kg/m^2)
- BMI percentile group (Underweight: <5th percentile, Healthy or Overweight: 5th – <95th percentile, Obese: ≥ 95th percentile)
- Prior long-term prophylactic (LTP) treatment (Yes or No)
- LTP therapy use (C1-INH, Androgens, Anti-fibrinolytics, or not on LTP)
- Type of LTP therapy (C1-INH, Oral Therapy, C1-INH and Oral Therapy, not on LTP)

Age will be calculated as the date of birth minus the date of informed consent + 1 day with 1 decimal place. If date of birth is partial date, age recorded on the CRF page will be used.

The LTP therapy use and type of LTP therapy are defined in Appendix 4.

Height and weight will be used to calculate BMI using the formula below:

$$BMI = \text{weight [kg]} / (\text{height [m]})^2$$

A SAS program for the 2000 CDC Growth Charts will be used to derive the BMI percentiles and weight percentiles (Kuczmarski, R. J. et al. 2000 CDC Growth Charts).

A separate table will be created for HAE attack history and will include:

- Age at onset of angioedema symptoms
- HAE type (Type I, Type II, Unspecified-Type I or Type II)
- History of laryngeal attack
- Primary attack locations
- Number of attacks in the last 1, 3, and 12 months
- Average severity of HAE attacks in the last 12 months
- Severity of HAE attacks in the last 3 months
- Average duration of HAE attacks in the last 3 and 12 months
- Baseline HAE attack rate (attacks during baseline observation period) (refer to Section 6.2.1 for a definition of the baseline HAE attack rate).
- Baseline HAE attack rate group (>0 to <1, 1 to <2, 2 to <3, ≥3 attacks/month)

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

5.4 Medical History

Medical history will be collected at the Screening Visit and will be coded using MedDRA Version 22.0 or newer. A listing will be provided using the Safety Analysis Set.

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

5.5 Prior and Concomitant Medication

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary dated March 2019 or newer.

Prior medication is defined as any medication with the start date prior to the date of the first dose of study drug.

Concomitant medication is defined as any medication with a start date prior to the date of the first dose of study drug and continuing after the first dose of study drug or with a start date from the date of the first dose of study drug until end of study, inclusive.

Rescue medication is defined as any medication identified by the investigator as given for an HAE attack.

For medications with partial onset times, non-missing date parts will be used to determine whether the medication is concomitant or prior medication. If a determination cannot be made using the non-missing date parts as to when the medication occurred relative to study drug administration, then the medication will be classified as concomitant.

The number and percentage of subjects with prior or concomitant medications excluding rescue medications will be summarized by therapeutic class and preferred term by dose group and overall for each analysis population. Therapeutic class will be based on the Therapeutic Subgroup corresponding to level 2 of the Anatomic Therapeutic Chemical (ATC) classification system. Tabulations will be presented sorted by therapeutic class in alphabetical order and by PT within each therapeutic class by descending frequency in the overall group. A separate, similar table will be provided for the subset of prior or concomitant medications classified as rescue medications for each analysis population. Concomitant medications will be summarized by Treatment Period A, Treatment Period B, and Overall Study Period (including follow-up period).

Prior and concomitant therapies/procedures will be coded using MedDRA Version 22.0 or newer. The number and percentage of subjects with prior or concomitant therapies/procedures will be summarized per system organ class and preferred term by the dose regimen assigned at Visit 1 Day 0 and overall for each analysis population.

All medications/therapies/procedures will be presented in subject listings for the Safety Analysis Set.

5.6 Treatment Exposure and Compliance

All planned study drug administrations will be recorded in the eCRF, including whether the injection was given by parent/caregiver at home, parent/caregiver administered in clinic, study staff in clinic, self-administered in clinic, or self-administered at home; whether a full, partial, or no dose was given; date and time of dose; and location of the injection.

The number of planned doses is the number of doses a subject is scheduled to receive based on the actual dosing regimen. Treatment compliance will be described by the percentage of planned doses received by the subject, total number of doses received by the subject, and the number and percentage of subjects that received at least 80% of planned doses, summarized by actual dose regimen and overall during the treatment period A, treatment period B and overall treatment period for each analysis population.

For each actual dose regimen and overall, exposure to the study treatment will be summarized using total dose (mg) received by the subject, time on study, and total patient-years during Treatment Period A, Treatment Period B and overall treatment period for each analysis population. Exposure will be calculated and summarized by actual dose regimen.

Treatment Exposure for Subjects with No Dose Modifications

Treatment exposure intervals and formulas of time on study (month) are presented below in Table 3 for subjects with no dose modifications. These formulas can be applied to subjects assigned to either dose group.

Table 3 Treatment Exposure Intervals for Subjects with No Dose Modifications

Treatment Period	Treatment Exposure	
	Interval	Formula of Time on Study (month)
A	[first dose date, date of Visit 26 Day 182]	*(date of Visit 26 Day 182 – first dose date + 1)/28 days*
B	[date of Visit 26 Day 182 + 1, last date of the treatment period*]	*(last date* of the treatment period* - *(date of Visit 26 Day 182 + 1) + 1)/28 days*
Overall	[first dose date, last date of the treatment period*]	*(last date* of the treatment period*- *first dose date + 1)/28 days*

*The last date of the treatment period is defined as the earliest of the date of early study discontinuation or the end date of the treatment period.

Treatment Exposure for Subjects with Dose Modifications

Dose modifications were allowed during Treatment Period B as mentioned in section 6.2.5 of the protocol.

Subjects Assigned to 150 mg every 2 weeks

Treatment exposure intervals and formulas of time on study (month) for the actual 150 mg every 2 weeks regimen and actual 150 mg every 4 weeks regimen are detailed in Table 4 and Table 5, respectively, for subjects assigned to the 150 mg every 2 weeks dosing regimen with dose modification once.

These subjects are assigned to the 150 mg every 2 weeks dosing regimen in Treatment Period A, but have their dose regimen modified to 150 mg every 4 weeks during Treatment B. Table 4 details the exposure interval and formula for the actual time on the 150 mg every 2 weeks regimen. Table 5 details the exposure interval and formula for the actual time on the 150 mg every 4 weeks regimen.

Table 4 Actual Treatment is 150 mg every 2 weeks

Treatment Period	Treatment Exposure for Actual 150 mg every 2 weeks Regimen	
	Interval	Time on Regimen (months)
A	[first dose date, date of Visit 26 Day 182]	*(date of Visit 26 Day 182 – first dose date + 1)/28 days*
B	[date of Visit 26 Day 182 + 1, date of first q4wk dose - 1]	*((date of first q4wk dose -1) - (date of Visit 26 Day 182 + 1) + 1)/28 days*
Overall	[first dose date, date of first q4wk dose - 1]	*((date of first q4wk dose -1) - first dose date + 1)/28 days*

Table 5 Actual Treatment is 150 mg every 4 weeks

Treatment Period	Treatment Exposure for Actual 150 mg every 4 weeks Regimen	
	Interval	Time on Regimen (month)

A	NA	*NA*
B	[date of first q4wk dose, last date of the treatment period*]	*(last date of the treatment period* - date of first q4wk dose + 1)/28 days*
Overall	[date of first q4wk dose, last date of the treatment period*]	*(last date of the treatment period*- date of first q4wk dose + 1)/28 days*

*The last date of the treatment period is defined as the earliest of the date of early study discontinuation or the end date of the treatment period.

Subjects Assigned to 150 mg every 4 weeks

Treatment exposure intervals and formulas of time on study (month) for the actual 150 mg every 4 weeks regimen and 150 mg every 2 weeks regimen are detailed in Table 6 and Table 7, respectively, for subjects assigned to the 150 mg every 4 weeks dosing regimen with dose modification once.

These subjects are assigned to the 150 mg every 4 weeks dosing regimen in Treatment Period A, but have their dose regimen modified to 150 mg every 2 weeks during Treatment B. Table 6 details the exposure interval and formula for the actual time on the 150 mg every 4 weeks regimen. Table 7 details the exposure interval and formula for the actual time on the 150 mg every 2 weeks regimen.

Table 6 Actual Treatment is 150 mg every 4 weeks

Treatment Period	Treatment Exposure for Actual 150 mg every 4 weeks Regimen	
	Interval	Time on Regimen (month)
A	[first dose date, date of Visit 26 Day 182]	*(date of Visit 26 Day 182 – first dose date + 1)/28 days*
B	[date of Visit 26 Day 182 + 1, date of first q2wk dose - 1]	*((date of first q2wk dose - 1) - (date of Visit 26 Day 182 + 1) + 1)/28 days*
Overall	[first dose date, date of first q2wk dose - 1]	*((date of first q2wk dose - 1) - first dose date + 1)/28 days*

Table 7 Actual Treatment is 150 mg every 2 weeks

Treatment Period	Treatment Exposure for Actual 150 mg every 2 weeks Regimen	
	Interval	Time on Regimen (month)
A	NA	*NA*
B	[date of first q2wk dose, last date of the treatment period*]	*(last date of the treatment period* - date of first q2wk dose + 1)/28 days*
Overall	[date of first q2wk dose, last date of the treatment period*]	*(last date of the treatment period*- date of first q2wk dose + 1)/28 days*

*The last date of the treatment period is defined as the earliest of the date of early study discontinuation or the end date of the treatment period.

In general, for subjects who had dose modifications in Treatment Period B, assuming only one modification occurred during the study, the interval of time on the planned treatment assignment in Treatment Period B and overall treatment period is defined as [start date of treatment period, start date of modified dosing regimen – 1 day] and the interval of time on the modified dosing regimen is [start date of modified dosing regimen, last date of the treatment period].

However, if there are subsequent dose modifications in Treatment Period B, the intervals of time on the 1st modified dosing regimen in Treatment Period B and overall treatment period are defined as [start date of 1st modified dosing regimen, start date of subsequent modified dosing regimen – 1 day]. Furthermore, the intervals of time on the subsequent dose modifications in Treatment Period B and overall treatment period is defined as [start date of subsequent modified dosing regimen, last date of the treatment period]. Treatment exposure for a dose regimen will be summed across a subject to represent the total exposure time a subject experienced for each dose regimen.

The duration of participation will be categorized by <1 month, 1-<3 months, 3-<7 months, and ≥7 months during Treatment Period A and Treatment Period B, and it will be categorized by <1 month, 1-<3 months, 3-<6 months, 6-<13 months, and ≥13 months during overall treatment period for each analysis population. Summaries will also be provided by dose group of the total number of doses received, percentage of injections that were given by parent/caregiver at home, parent/caregiver administered in clinic, study staff in clinic, self-administered in clinic, or self-administered at home during Treatment Period A, Treatment Period B and overall treatment period for each analysis population.

A listing of study administrations will be created by subject number and giving the date and time of dose administration using the Safety Analysis Set.

6. CLINICAL OUTCOME (EFFICACY) ANALYSES

All clinical outcome analyses will be based on the Safety Analysis Set. Data will be summarized by the dose regimen the subject actually received (refer to Appendix 5) and overall during each treatment period except where otherwise indicated.

- Continuous clinical outcome endpoints (eg, HAE attack rates) will be analyzed using descriptive statistics including number of subjects, mean, standard deviation (SD), median, minimum, and maximum. Whenever appropriate, clinical outcome endpoints will be summarized for the observation period, each efficacy evaluation period, and each efficacy evaluation period change from observation period by treatment.

- Categorical clinical outcome endpoints (eg, attack severity) will be summarized by the number of subjects in each category and the percentage of subjects out of the total in the respective analysis set.

- Time-to-event endpoint (eg, time to the first HAE attack) will be analyzed using Kaplan-Meier (KM) estimates. Summaries will include median time and quartiles, if estimable, and corresponding 95% confidence intervals.

Clinical outcome endpoints will be evaluated for each of the following 5 efficacy evaluation periods:

- Overall treatment period (Day 0 [after study drug administration] through Day 364 [Week 52])
- Treatment Period A (Day 0 [after study drug administration] through Day 182 [Week 26])
- Treatment Period B (Day 183 through Day 364 [Week 52])
- Overall presumed steady state period (Day 70 [Week 10] through Day 364 [Week 52])
- Presumed steady state period for Treatment Period A (Day 70 [Week 10] through Day 182 [Week 26])

6.1 Analyses of Primary Clinical Outcome Endpoint(s)

The primary objective for this study is safety and PK. All clinical outcome endpoints are secondary endpoints.

6.2 Analyses of Secondary Clinical Outcome Endpoint(s)

The secondary endpoints are as follows:

- Normalized number of investigator-confirmed HAE attacks for each efficacy evaluation period.
- Time to the first attack, i.e. duration that a subject is attack-free until their first attack for each efficacy evaluation period.
- Normalized number of investigator-confirmed HAE attacks requiring acute therapy use for each efficacy evaluation period.
- Normalized number of moderate or severe investigator-confirmed HAE attacks for each efficacy evaluation period.
- Normalized number of high morbidity investigator-confirmed HAE attacks for each efficacy evaluation period.
- Characteristics of investigator-confirmed HAE attacks for each efficacy evaluation period, including duration, severity, attack location, and rescue medication use.
- Achievement of attack-free status for each efficacy evaluation period.

6.2.1 Normalized Number of Investigator-confirmed HAE Attacks

The normalized number of investigator-confirmed HAE attacks during each efficacy evaluation period will be expressed as a monthly HAE attack rate and will be analyzed using the Safety Analysis Set.

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

The normalized investigator-confirmed HAE attack rate during each efficacy evaluation period will be calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the efficacy evaluation period divided by the number of days the subject contributed to the efficacy evaluation period multiplied by 28 days. The total number of attacks as well as the subject-time in months, where a month is defined as 28 days, will also be presented.

For subject's with dose modifications, the attack rate is calculated as the number of investigator-confirmed attacks occurring during the actual dosing regimen divided by the number of days on the actual dosing regimen multiplied by 28 days. In the total column, the HAE attack rage will be calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the efficacy evaluation period divided by the number of days the subject contributed to the efficacy evaluation period multiplied by 28 days.

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

The number of investigator-confirmed HAE attacks per month will be summarized by month (per 28-day interval) for the Safety Analysis Set. The summary will include descriptive statistics for baseline investigator-confirmed attack rate, as well as monthly investigator-confirmed attack rates, monthly change from baseline, and monthly percent change from baseline for each efficacy evaluation period. Investigator-confirmed HAE attacks will be grouped into 28-day intervals using the start date of the HAE attack. For the overall treatment period and Treatment Period A, the date of the first exposure to study drug in this study will be used as the start of the first interval. For Treatment Period B, the (visit date of Visit 26 Day 182 + 1 day) will be used as the start of the first interval. For the presumed steady state period and presumed steady state period for Treatment Period A, the Day 70 will be used as the start of the first interval. The end of the interval will be the start of the interval plus 27 days. Each successive interval will start the last day of the prior interval plus 1 day and end 28 days later, refer to Table 8.

Figures will be created for the Safety Analysis Set by plotting the on-study investigator-confirmed HAE attacks reported during each efficacy evaluation period relative to Visit 1 Day 0

for each subject in Safety Analysis Set. Figures will be presented by the dose regimen assigned at Visit Day 0.

All HAE attacks will be presented in a listing.

Table 8. Defining Treatment Months

Efficacy Evaluation Period	Month	Study Day (Study Schedule in Appendix 1)
Overall Treatment Period	1	0-27
	2	28-55
	3	56-83
	4	84-111
	5	112-139
	6	140-167
	7	168-195
	8	196-223
	9	224-251
	10	252-279
	11	280-307
	12	308-335
	13	336-363
	14	364- visit date of Visit 52 Day 364
Treatment Period A	1	0-27
	2	28-55
	3	56-83
	4	84-111
	5	112-139
	6	140-167
	7	168- visit date of Visit 26 Day 182
Treatment Period B	1	(visit date of Visit 26 Day 182+1) - (visit date of Visit 26 Day 182+28)
	2	(visit date of Visit 26 Day 182+29) - (visit date of Visit 26 Day 182+56)

Efficacy Evaluation Period	Month	Study Day (Study Schedule in Appendix 1)
	3	(visit date of Visit 26 Day 182+57) - (visit date of Visit 26 Day 182+84)
	4	(visit date of Visit 26 Day 182+59) - (visit date of Visit 26 Day 182+112)
	5	(visit date of Visit 26 Day 182+113) - (visit date of Visit 26 Day 182+140)
	6	(visit date of Visit 26 Day 182+141) - (visit date of Visit 26 Day 182+168)
	7	(visit date of Visit 26 Day 182+169) - visit date of Visit 52 Day 364
Overall Presumed Steady State Period	1	70-97
	2	98-125
	3	126-153
	4	154-181
	5	182-209
	6	210-237
	7	238-265
	8	266-293
	9	294-321
	10	322-349
	11	350- visit date of Visit 52 Day 364
Presumed Steady State Period for Treatment Period A	1	70-97
	2	98-125
	3	126-153
	4	154-181
	5	182- visit date of Visit 26 Day 182

Similar summary tables for each efficacy evaluation period will be presented for the following clinical outcome measures for the Safety Analysis Set:

- Normalized number of investigator-confirmed HAE attacks requiring acute treatment

- Normalized number of moderate or severe investigator-confirmed HAE attacks
- Normalized number of high-morbidity investigator-confirmed HAE attacks

A high morbidity investigator-confirmed HAE attack is defined as any investigator-confirmed attack that has at least one 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.

A subject level listing will be presented to list the HAE attack rate for each efficacy evaluation period. A separate listing will be presented for subjects who have dose regimen changes.

6.2.2 Time to First Attack

The time to the first investigator-confirmed HAE attack (days) for each efficacy evaluation period will be calculated from the start date and time of that efficacy evaluation period to the date and time of the first investigator-confirmed HAE attack after the start date and time of that efficacy evaluation period. Time to first attack analyses will be presented by dose group (dose regimen the subject assigned at Visit 1 Day 0).

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. 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 and time of study discontinuation.

Time to the first investigator-confirmed HAE attack will be summarized for each efficacy evaluation period using the Kaplan-Meier (KM) method by the dose regimen assigned at Visit Day 0. The KM plots will be produced for the Safety Analysis Set. Each subject's censoring status and time to event will be provided in a subject level efficacy listing.

6.2.3 Characteristics of Investigator-confirmed HAE

Characteristics of investigator-confirmed HAE attacks will be summarized for 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.

Subject level HAE attack characteristics:

- HAE Attack Duration: For each subject, the mean duration of all investigator-confirmed HAE attacks will be calculated in hours and summarized. The subject-level average attack duration will be categorized into 12-hour intervals and tabulated by category (No attacks, >0-<12 hours, 12-24 hours, >24-48 hours, and >48 hours).
- HAE Attack Severity: For each subject, the mean and maximum severity of all investigator-confirmed HAE attacks will be calculated using a numerical rating (refer to Appendix 2) and summarized. The number and percentage of subjects will be tabulated by maximum attack severity (no attack, mild, moderate, and severe).

Event level HAE attack characteristics:

- HAE Attack Location: The number and percentage of subjects with attacks, as well as the total number of attacks, will be tabulated by the primary attack location (peripheral, abdominal, and laryngeal) as determined by the investigator. 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.

- Rescue Medication Use: The number and percentage of subjects with rescue medication use for an HAE attack, as well as the number of rescue medications, will be tabulated by rescue medication by type (no use, ecallantide, icatibant, nano-filtered C1-INH, plasma-derived C1-INH, recombinant C1-INH, and fresh frozen plasma) as reported in the AE CRF.

- Supportive Medication Use: The number and percentage of subjects with supportive medication use for an HAE attack, as well as the number of supportive medications, will be tabulated by rescue medication by type (no use, IV fluids, pain medication, oxygen, anti-emetic, and other) as reported in the AE CRF.

6.2.4 Achievement of Attack-free Status

The number and percentage of subjects that are attack-free of investigational-confirmed HAE will be summarized for each efficacy evaluation period. For subjects that discontinue treatment during the efficacy evaluation period, only the period of time for which the subject was on treatment will be used to evaluate attack-free status for that efficacy evaluation period. Subjects who discontinued treatment during the efficacy evaluation period but are attack-free for the time observed, will be counted as attack-free in the analysis.

A subject level listing will be presented to list the subject level HAE characteristics and Attack-free days for each efficacy evaluation period. A separate listing will be presented for subjects who have dose regimen changes.

6.2.5 Sensitivity Analyses

The following sensitivity analysis will be performed to evaluate the robustness of the results.

The analysis of normalized investigator-confirmed HAE attack rate during each efficacy evaluation will be repeated using all subject-reported HAE attacks. The baseline all HAE attack rate, as well as HAE attack rate, change from baseline, and percent change from baseline using all subject-reported HAE attacks for each efficacy evaluation period will be summarized for the Safety Analysis Set.

Two sensitivity analyses will be conducted to evaluate the impact of treatment discontinuation on the achievement of attack-free status for each efficacy evaluation period. The first will be based only on the subset of subjects that complete each efficacy evaluation period. The second will include all subjects in the analysis set, but attribute subjects that discontinue treatment during the efficacy evaluation period as not attack-free.

6.3 Subgroup Analyses

Subgroup analyses are planned for the number of investigator-confirmed HAE attacks during each efficacy evaluation period using the Safety Analysis Set. The same subgroup will be used for the overall AE summary table and summary table by SOC and PT (all treatment-emergent AEs, related Treatment-emergent AEs and severe Treatment-emergent AEs) on non-HAE attack reported AEs using the Safety Analysis Set.

The following subgroups will be used:

- Age group 1 (2 to <6 years and 6 to <12 years)

  Age group 2 (2 to <9 years and 9 to <12 years)
- Sex
- Race group (White, Other)
- Geographic region (US, Canada, Europe)
- Weight percentile group (Underweight, Healthy or Overweight, Obese)
- BMI percentile group (Underweight, Healthy or Overweight, Obese)
- Baseline HAE attack rate group (>0 to <1, 1 to <2, 2 to <3, ≥3 attacks/month)
- Type of LTP therapy (C1-INH, Oral Therapy, C1-INH and Oral Therapy, not on LTP)
- HAE Type (Type I, Type II, Unspecified-Type I or Type II)
- History of laryngeal HAE attack (history of laryngeal attack, no history of laryngeal attack)

7. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Analysis Set. Safety variables include AEs, clinical laboratory variables and vital signs. For each safety variable, the last value collected before the first dose of study drug will be used as baseline for all analyses of that safety variable. The safety variables will be summarized in the tables and all available data will be shown in the listings.

The safety analyses for AEs will be conducted according to the dose regimen the subject actually received (refer to Appendix 5) and overall. The safety analyses for other safety variables will be conducted according to the dose group (dose regimen the subject assigned at Visit 1 Day 0) and overall.

- Continuous endpoints (eg, change in laboratory parameters) will be summarized using number of subjects (n), mean, SD, median, minimum value, and maximum value. As appropriate, raw (actual) values, changes from baseline, and percent changes from baseline will be summarized overall and at each scheduled time point.

- Categorical endpoints (eg, presence or absence of an outcome measure) will be summarized using counts and percentages. Summaries will include but are not limited to number and percentage of subjects with an outcome measure and laboratory shift tables (categorical change from baseline).

7.1 Adverse Events

Adverse events will be coded using MedDRA Version 22.0 or newer.

Treatment-emergent AEs 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.

The analyses described in this section will be based on treatment-emergent AEs; plainly referred to as AEs in this section for brevity.

Related AEs are AEs classified as related to study drug by the investigator. Severe AEs are AEs classified as severe (grade 3) or life threatening (grade 4) by the investigator using DMID criteria.

For this analysis, 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 Visit 1 Day 0 through Visit 52 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 Visit 52 Day 364).

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

be summarized in the overall summary table. The total patient-years will be included in the overall summary table. The overall summary table will be repeated by HAE attack reported AEs, non-HAE attack reported AEs and investigator-reported AESI.

The number and percentage of subjects with an AE, as well as the total number of AEs and the rate of number of AEs by total patient-years will be summarized by SOC, and PT. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, related severe AEs, and investigator-reported AESI. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the total column of the Safety Analysis Set. This summary table will be separated by HAE attack reported AEs and non-HAE attack reported AEs.

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized by PT on non-HAE attack reported AEs. This tabulation will be repeated for related non-HAE attack reported AEs and serious non-HAE attack reported AEs.

All AEs summaries that summarized by SOC, and PT will be presented by the dose regimen the subject actually received (Refer to Appendix 5) and separated to Treatment Period A, Treatment Period B, overall treatment period, and Follow-up period. All other AEs summaries will be presented by the dose regimen the subject actually received (Refer to Appendix 5) and separated to Treatment Period A, Treatment Period B and overall study period. The overall study period will include Follow-up period AEs.

All AEs will be provided in subject listings. In addition, subject listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs, related AEs, severe AEs, and AESI will be produced. All follow-up period AEs will be provided in a separate listing.

7.1.1 SMQ-defined Adverse Events of Special Interest (AESI)

Adverse events of special interest for this study are hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events). Investigators are required to document any potential AESI AEs on the CRF page. In addition to investigator-reported AESI, standardized MedDRA Queries (SMQ) for each AESI category will be performed using the study data. The preferred terms from MedDRA 22.0 or newer version SMQ will be used to identify an SMQ-defined AESI, refer to Table 9.

For each dose regimen the subject actually received, the number and percentage of subjects with an AESI, as well as the total number of AESIs and the rate of number of AEs by total patient-years will be summarized by SOC and PT. This tabulation will be created for each AESI and for those events with the SMQs 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 in the total column of the Safety Analysis Set.

Listings detailing the PT within the SMQ will be provided.

Table 9. SMQs 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)

7.1.2 Injection Site Reaction (ISR) Adverse Events

Injection site reaction (ISR) AEs are AEs with the preferred terms (PT) starting with "Injection site", "Application site", or "Administration site".

The number and percentage of subjects with any ISR AE, any related ISR AE, any severe ISR AE, any related severe ISR AE, any ISR SAE, and any related ISR SAE, as well as the total number of events for each category, will be summarized. The number of deaths due to an ISR AE, hospitalization due to an ISR AE, and study discontinuation due to an ISR AE will be summarized. The total patient-years will be included in the overall summary table.

The number and percentage of subjects with an ISR AE, as well as the total number of ISR AEs and the rate of number of AEs by total patient-years will be summarized by dose regimen the subject actually received, SOC and PT. The separate table will be created for ISR AEs by dose regimen the subject actually received, SOC, PT and maximum severity. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the total column of the Safety Analysis Set.

The number of injections, number of injection site reactions, and the percent of injections with ISR AEs will be summarized by the administration type of the injection and location of the injection. The duration of ISR AEs overall and by PT will be summarized numerically (summary statistics) and categorically (0 - 0.5 hour, >0.5 - 1 hour, >1- 12 hours, >12 – 24 hours, ≤1 day – unclear, >1 – 14 days, and >14 days). Definition of the duration of ISR is provided in Appendix 6.

A listing of ISR AEs will be provided.

7.2 Clinical Laboratory Data

Descriptive statistics for clinical laboratory values (in conventional units) and changes from baseline at each scheduled study visit, combined all scheduled study visits, combined all unscheduled visits, and combined all visits including both scheduled and unscheduled visits will be presented by dose group and overall for the following clinical laboratory variables in the Safety Analysis Set. If more than one laboratory result is reported per scheduled study visit per

parameter, the last non-missing result will be selected for analysis. The non-standard laboratory results will be converted to numeric values using the rules shown in Table 11. Baseline is defined as the last non-missing value prior to the first exposure to lanadelumab.

Hematology	Hemoglobin, hematocrit, red blood cells (RBC) count, absolute platelet count, white blood cell count – total and differential (WBC), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH), and mean corpuscular volume (MCV).
Chemistry	Albumin, alkaline phosphatase, alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), bilirubin (total and direct), blood urea nitrogen (BUN), calcium, carbon dioxide (CO2), chloride, creatinine, creatine phosphokinase (CPK), glucose, phosphate, magnesium, potassium, sodium, total protein, uric acid.
Coagulation	Prothrombin time, activated partial thromboplastin time (aPTT), international normalized ratio (INR).

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. See Appendix 3 for details on handling clinical significance attribution for laboratory values. The number of subjects with a non-missing result, and the number and percentage of subjects with a clinically significant result below the lower limit of normal (LLN), clinically non-significant result below the LLN, within the normal range, clinically non-significant result above the upper limit of normal (ULN), and clinically significant result above 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. In the event of a tie, the earlier measurement will be used.

Categorical laboratory test results 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.

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 visits to identify any trends. All laboratory data will be provided in subject listings by panel type.

7.2.1 Additional Laboratory Analyses

For the Safety Analysis Set, additional analyses will be conducted on liver function tests and selected hematology, chemistry and coagulation tests using the highest pre-treatment and highest treatment period measurements. The number and percentage of subjects with highest results falling into the categories of < LLN, normal, >1-<3 x ULN, 3-5 x ULN, and > 5 x ULN on the liver function tests for ALT and AST will be summarized for all pre-treatment measurements,

treatment period A measurements, treatment period B assessments, and overall study period assessments which include follow-up assessments. ALP will be summarized by the number and percentage of subjects with highest results fall into the categories of ≤ 3 x ULN and > 3 x ULN for all pre-treatment measurements, treatment period A measurements, treatment period B assessments, and overall study period assessments. Total bilirubin will be summarized by the number and percentage of subjects with highest results fall into the categories of ≤ 2 x ULN and > 2 x ULN for all pre-treatment measurements, treatment period A measurements, treatment period B assessments, and overall study period assessments. This table will be repeated for hematology, chemistry, and coagulation using the categories defined in Table 10.

Additionally, for the Safety Analysis Set, a shift table summarizing the shift in categories from highest pre-treatment measurements to the highest treatment period A measurements, treatment period B assessments, and overall study period assessments will be created for the liver function tests including ALT, AST, ALP and total bilirubin. For ALT and AST, the categories are < LLN, normal, >1-<3 x ULN, 3-5 x ULN, and > 5 x ULN; for ALP, the categories are ≤ 3 x ULN and > 3 x ULN; for total bilirubin, the categories are ≤ 2.0 x ULN and > 2.0 x ULN. Also, for the Safety Analysis Set, shift tables will be repeated for hematology, chemistry, and coagulation using the categories defined in Table 10.

Additional laboratory parameters may be evaluated as identified by the study physician.

Table 10. Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	Criteria Categories				
Liver Function Tests					
ALT (U/L)	< LLN	Normal	>1-<3 x ULN	3-5 x ULN	>5 x ULN
AST (U/L)	< LLN	Normal	>1-<3 x ULN	3-5 x ULN	>5 x ULN
ALP (U/L)	≤3.0 x ULN	>3.0 x ULN	-	-	-
Total Bilirubin (mg/dL)	≤2.0 x ULN	>2.0 x ULN	-	-	-
Chemistry					
Albumin (g/dL)	Low (<0.6 x LLN)	Normal (≥0.6 x LLN)	-	-	-
Creatinine (mg/dL)	Normal (≤1.5 x ULN)	High (>1.5 x ULN)	-	-	-
Glucose (mg/dL)	Low (<0.6 x LLN)	Normal (0.6 x LLN - 3.5 x ULN)	High (>3.5 x ULN)	-	-
Potassium (mEq/L)	Low (<0.85 x LLN)	Normal (0.85 x LLN - 1.2 x ULN)	High (>1.2 x ULN)	-	-
Urea Nitrogen (mg/dL)	Normal (≤3.0 x ULN)	High (>3.0 x ULN)	-	-	-
Hematology					
Eosinophils/Leukocytes	Normal (≤4.0 x ULN)	High (>4.0 x ULN)	-	-	-
Hematocrit	Low (<0.6 x LLN)	Normal (0.6 x LLN - 1.3 x ULN)	High (>1.3 x ULN)	-	-
Hemoglobin (g/dL)	Low (< 0.6 x LLN)	Normal (0.6 x LLN - 1.3 x ULN)	High (>1.3 x ULN)	-	-
Leukocytes (10^3/uL)	Low (<0.5 x LLN)	Normal (0.5 x LLN – 2.0 x ULN)	High (>2.0 x ULN)	-	-
Neutrophils (10^3/uL)	Low (<0.5 x LLN)	Normal (≥0.5 x LLN)	-	-	-
Platelets (10^3/uL)	Low (<0.4 x LLN)	Normal (0.4 x LLN – 2.0 x ULN)	High (>2.0 x ULN)	-	-
Coagulation					

Activated Partial Thromboplastin Time (sec)	≤ 1.5 x ULN	> 1.5 x ULN	-	-	-
Prothrombin Intl. Normalized Ratio	≤ 2 x ULN	> 2 x ULN	-	-	-
Prothrombin Time (sec)	≤ 1.5 x ULN	> 1.5 x ULN	-	-	-

7.3 Vital Signs

Vital signs will be summarized by dose group and overall using the Safety Analysis Set including body temperature, heart rate, blood pressure, and respiratory rate. 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.

Baseline is defined as the last non-missing value prior to the first exposure to lanadelumab.

Actual values and changes from baseline in vital signs will be summarized by study visit and study time point (within 60 minutes pre-dose and 30 minutes (± 15 minutes) post-dose).

All vital sign data will be presented in subject listings.

8. PHARMACOKINETIC/ PHARMACODYNAMIC ANALYSIS

A descriptive summary analysis will be performed for plasma concentrations of lanadelumab, as appropriate, using nominal time points in the PK Set. A listing of plasma concentrations of lanadelumab will be provided.

A descriptive summary analysis will be performed for plasma kallikrein activity (cHMWK levels), [redacted], as appropriate, using nominal time points in the PD Set. A listing of cHMWK levels, [redacted] will be provided.

The PK and PD properties of lanadelumab (including PK parameters, cHMWK, [redacted], and [redacted] as appropriate) will be evaluated by a population modeling and a simulation approach using data from this study and from all other studies in the lanadelumab clinical development program. A separate clinical pharmacology SAP will support the population PK and PD analysis and the analysis results will be reported separately.

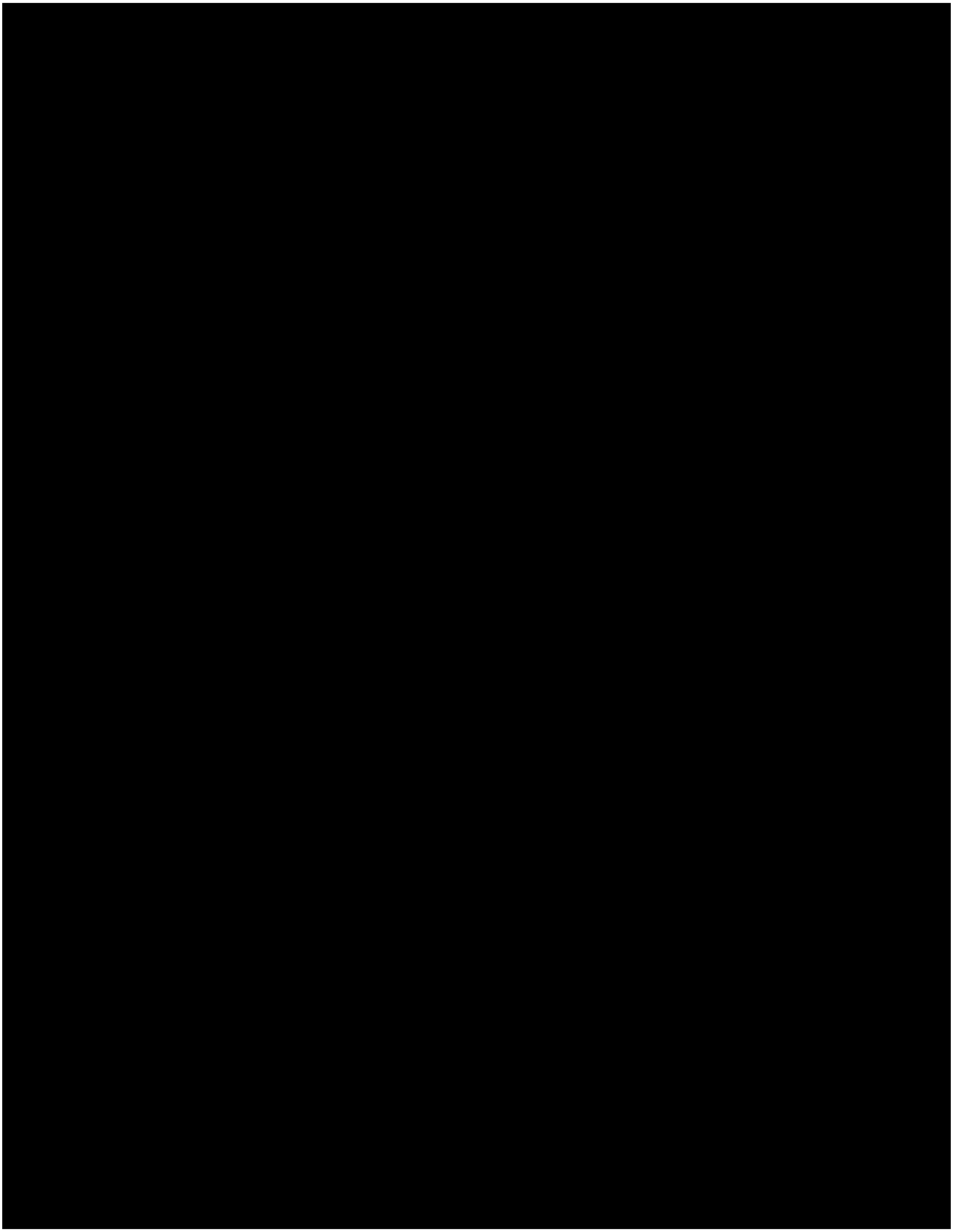
9. IMMUNOGENICITY DATA

Immunogenicity will be evaluated based on the number and percentage of subjects with positive ADAs and whether they were neutralizing or non-neutralizing. Data will be summarized at each scheduled study visit, overall Treatment Period A, overall Treatment Period B, and overall study period (including follow-up period) by dose group and overall using the Safety Analysis Set.

All immunogenicity data will be provided in subject listings for the Safety Analysis Set.

10. OTHER ANALYSES

[redacted]



[redacted]

10.1.4 Coronavirus Pandemic

COVID-19 pandemic since 2019 poses risks to the safety of subjects enrolled in clinical trials, and may impact the availability and interpretability of data from those trials. The protocol deviations related to COVID-19 as reported in the protocol deviation log will be listed for the Safety Analysis Set. The study disruptions related to COVID-19 as reported on the visit eCRF page will be listed for the Safety Analysis Set.

10.2 Healthcare Resource Utilization

Not applicable.

11. INTERIM ANALYSIS/ DATA MONITORING (REVIEW) COMMITTEE

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

After 5 subjects receive at least 5 doses of lanadelumab, an interim PK analysis will be conducted to evaluate the proposed dose regimens using available data for this study. The details of the analysis will be described in a separate document.

A separate clinical pharmacology SAP will support the population PK and PD analysis and the analysis results will be reported separately.

12. DATA HANDLING CONVENTIONS

12.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, minimum, maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in respective analysis set.

Unless specified otherwise, min/max will be presented to the same decimal places as the raw data. Percentage, mean and median will be presented to 1 more decimal places than the raw data. Standard deviation and standard error will be presented to 2 more decimal places than the raw data.

BMI should be rounded to 1 decimal place for reporting.

[redacted]

Averaged lab and vital sign results should be rounded to 1 decimal place for reporting.

12.2 Definition of Baseline

Baseline HAE attack rate for all efficacy analyses is defined as the monthly HAE attacks during baseline observation period.

For safety variables and immunogenicity variables, the last value collected before the first dose of study drug will be used as baseline.

[redacted]

12.3 Definition of Visit Windows

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

12.4 Derived Efficacy Endpoints

Refer to Section 6.2 and Appendix 1 for derivation instructions of efficacy endpoints.

12.5 Repeated or Unscheduled assessments of Safety Parameters

If a subject has repeated assessments before the start of study drug, then the results from the final assessment made prior to the start of study drug will be used as baseline. If end of study

assessments are repeated or unscheduled, the last post-baseline assessment will be used as the end of study assessment for generating descriptive statistics. If a subject has unscheduled assessments between the start of investigational product in the treatment period and the end of study visit, the assessments of unscheduled visits will be excluded in the table summary unless specified. However, all assessments will be presented in the data listings.

12.6 Handling of Missing, Unused, and Spurious Data

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 study drug 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 Date of Last Dose of Study drug

When the date of the last dose of study drug is missing for a subject in the Safety Analysis Set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last non-missing dose date of study drug will be used in the calculation of treatment duration.

12.6.2 Missing Date 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 and/or stop date will be imputed. When the start date/time and the stop date/time are both incomplete for a subject, the start date/time will be imputed 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 dose of study drug (before or after imputation), then the time of first dose of study drug 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 study drug, then the day and month of the date of the first dose of study drug will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the date of the first dose of study drug, then December 31 will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the date of the first dose of study drug, 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 study drug, then the day of the date of the first dose of study drug will be assigned to the missing day

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

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

12.6.2.2 Incomplete Stop Date/Time

Not applicable.

12.6.3 Missing Date 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 study drug, then the AE will be classified as treatment-emergent. Refer to Section 7.1.

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

12.6.3.1.1 Incomplete Start Date/Time

Follow the same rule as in section 12.6.2.1.

12.6.3.1.2 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 study drug, 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 study drug, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

12.6.5 Missing Relationship to Study drug for Adverse Events

If the relationship to study drug is missing for an AE starting on or after the date of the first dose of study drug, a causality of "Related" will be assigned. The imputed values for relationship to study drug 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

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. The appropriately determined coded value will be used in the statistical analysis. However, the actual values as reported in the database will be presented in data listings.

Table 11. Examples for Coding of Special Character Values for Clinical Laboratory Variables

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

12.7 Handling Below Quantitation Limit (BQL) Values

For PK analysis, the plasma concentration below the lower limit of quantitation (LLOQ) will be imputed to zero in the table. The BQL plasma concentrations will not be imputed in the data listings.

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

The following change to the analysis specified in Protocol Amendment 2 dated 22 Jun 2021 (final version 1.0 dated 06 May 2019, Amendment 1 dated 12 Aug 2019) has been made:

- The SAP added the definition of Screened Set.

15. REFERENCES

[redacted]

Caballero, T. 2013. Angio-oedema due to hereditary C1 inhibitor deficiency in children. *Allergol Immunopathol (Madr)*, 41, 45-53.

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Kuczmarski, R. J. et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11, 1–190 (2002). https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

[redacted]

16. APPENDIX

Appendix 1 Schedule of Activities

Schedule of Activities- Screening and Baseline Observation Period

Procedures	Screening[a] (up to 4 weeks)	End of Screening Site Contact[a]	BASELINE OBSERVATION PERIOD (by week; up to 12 weeks)[b]											See protocol section below for details
			1	2	3	4	5	6	7	8	9	10	11	12
Informed consent (written permission and assent)	X													Section 8.2.1
Demographics, medical history, and HAE history	X													Section 8.2.3
Eligibility review	X													Section 8.1.1
Discontinue long-term prophylactic therapy[a]		X												Section 8.1.1
Telephone contact[c]				X		X		X		X		X		X	
Vital signs[d]	X													Section 8.2.5.2
Physical examination[e]	X													Section 8.2.5.1
Tanner staging[f]	X													Section 8.2.5.1
Hematology, serum chemistry, and coagulation tests	X													Section 8.2.5.4
Virology testing: HBsAg, HCV, and HIV (serologies)[g]	X													Section 8.2.5.4
C1-INH, C1q, and C4 testing[h]	X													Section 8.2.6.4
EQ-5D-Y			Within 24 hours after the onset of symptoms of an HAE attack, if applicable											Section 8.2.6.5
HAE attack data (subject HAE attack diary and site monitoring)[i]			X----------X											Appendix 5
Prior/current medications, therapies, and procedures[j]	X		X----------X											Section 6.6
Adverse events/serious adverse events	X		X----------X											Section 8.2.5.5, Section 8.2.5.6

C1-INH=C1 esterase inhibitor; HAE=hereditary angioedema; HbsAg = Hepatitis B Surface Antigen; HCV=Hepatitis C Virus; HIV=Human Immunodeficiency Virus

[a] Subjects should complete all screening procedures within 4 weeks. After confirming that a subject meets all eligibility criteria, the site will contact the subject and parent/caregiver to notify them of study eligibility. The site will instruct that the subject must discontinue long-term prophylactic therapy (if applicable) prior to the baseline observation period and begin the HAE attack diary on the first day of the baseline observation period.

[b] Subjects must stay in the observation period for at least 4 weeks except for those subjects who report more than 2 HAE attacks within the first 2 weeks that are confirmed by the investigator and agreed with the sponsor's medical monitor. Subjects may exit the observation period after reporting 1 investigator confirmed attack after 4 weeks in the observation period; subjects will then enter the treatment period.

[c] Study personnel will contact the parent/caregiver on Weeks 2, 4, 6, 8, 10, and 12 to discuss study compliance (ie, completion of the diary) and to evaluate the subject's HAE attacks and other adverse events that may have occurred since the last contact. The preferred method of site contact is a telephone call; however, an alternate method of contact may be considered as site policies permit. Site contacts will be documented in the source notes at the clinical site.

[d] Vital signs, including sitting or supine blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR).

[e] Complete physical examination, including height and body weight. Tanner staging may also be required for premenarchal female subjects (see footnote f).

[f] Tanner staging will be required at screening for female subjects who are premenarchal and ≥9 years of age, to confirm that contraception is not required during the study (Section 5.4.1).

[g] HIV (Inno-Lia) and hepatitis (hepatitis B surface antigen, hepatitis C antibody) will be tested only at the screening visit.

[h] C1-INH, C1q, and C4 testing is required at screening from the sponsor-approved central laboratory.

[i] During the baseline observation period, parents/caregivers will use a diary to daily record the subject's symptoms or occurrences of HAE attacks, and any medications taken for the management of these attacks. HAE attacks will be monitored daily and recorded as they occur. Parents/caregivers will also be instructed to notify and report details of an attack to the study site within 72 hours of the onset of an HAE attack, in accordance with HAARP (Appendix 5).

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

Schedule of Activities- Treatment Period A (Day 0 [Week 1] to Day 182 [Week 26])

Treatment Period
Shaded columns: scheduled on-site visits
Non-Shaded columns: potential subject-elected offsite activity

Study Week	1-2		3-4		5-8				9-12				13-16				17-20				21-24				25-26		See Protocol Section below for details
Study Visit (± 4 days)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	
Study Day	0	4	14	28	35	42	49	56	63	70	77	84	91	98	105	112	119	126	133	140	147	154	161	168	175	182	
Confirmation of eligibility	X																										Section 8.2.2
Prior/current medications, therapies, and procedures	X																										Section 6.6
Vital signs[a]	X		X	X				X				X				X				X				X			Section 8.2.5.2
Physical examination[b]	X		X	X				X				X				X				X				X			Section 8.2.5.1
Hematology, serum chemistry, and coagulation tests	X			X				X				X				X				X				X			Section 8.2.5.4
Pregnancy testing[c]	X							X								X								X			Section 8.2.5.3
Plasma PK sample[d]	X	X	X	X				X				X				X				X				X		X	Section 8.2.6.1
Plasma PD (cHMWK) sample[d]	X	X	X	X				X				X				X				X				X		X	Section 8.2.6.2
Plasma PD ([redacted]) sample[d]	X			X				X				X				X				X				X		X	Section 8.2.6.2
Plasma anti-drug antibody sample[d]	X			X								X								X						X	Section 8.2.6.3
Lanadelumab administration (6 to <12 years old)	X		X	X		X		X		X		X		X		X		X		X		X		X		X	Table 7
Lanadelumab administration (2 to <6 years old)	X			X				X				X				X				X				X			Table 7
Site check-in call[e]						X				X				X				X				X			X		
Injection report (6 to <12 years)[f]	X		X	X		X		X		X		X		X		X		X		X		X		X		X	Section 8.2.6.8
Injection report (2 to <6 years old)[f]	X			X				X				X				X				X				X			Section 8.2.6.8

Schedule of Activities- Treatment Period A (Day 0 [Week 1] to Day 182 [Week 26])

Treatment Period
Shaded columns: scheduled on-site visits
Non-Shaded columns: potential subject-elected offsite activity

Study Week	1-2		3-4		5-8				9-12				13-16				17-20				21-24				25-26		See Protocol Section below for details
Study Visit (± 4 days)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	
Study Day	0	4	14	28	35	42	49	56	63	70	77	84	91	98	105	112	119	126	133	140	147	154	161	168	175	182	
SC administration survey[g]												X														X	Section 8.2.6.8
[redacted]	X			X				X				X				X				X				X		X	Section 8.2.6.5
[redacted]	X																									X	Section 8.2.6.5
[redacted]	X	Within 24 hours after the onset of symptoms of an HAE attack, if applicable																								X	Section 8.2.6.5
HAE attack data (subject HAE attack diary and site monitoring)[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Appendix 5
Concomitant therapies, medications, procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.6
Adverse events/serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.5.5, Section 8.2.5.6

[redacted]; ; HAE=hereditary angioedema; PD=pharmacodynamic; [redacted]; PK=pharmacokinetic; SC=subcutaneous

Note: Permissible assessment window during treatment period and follow-up period: Study Visit Day ±4 days

[a] Vital signs, including sitting or supine blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR), will be measured using standard methods at each study site. On dosing days, vital signs will be obtained prior (within 60 minutes) to the injection of lanadelumab and 30 minutes (± 15 minutes) after completion of the injection of lanadelumab. Additional vital signs measurements will be performed if clinically indicated.

[b] Complete physical examination, including body weight (and height at Day 1 only). Additional physical examination will be targeted based on reporting of adverse events; symptom-oriented physical examinations other than protocol-specified examinations will be performed when clinically indicated in accordance with standard at the site. For premenarchal female subjects, the physical examination may also include Tanner staging at the discretion of the investigator, if clinically indicated.

[c] Pregnancy testing will be performed for females who have reached menarche. Tests performed on Day 0 must be urine-based to confirm eligibility prior to first dose. Tests performed at the indicated visits after Day 0 may be serum or urine-based.

[d] Blood samples for testing PK, PD and formation of antibodies to lanadelumab will be obtained predose. **Note:** On Study Days 4, 14 (for q4wks dose regimen), and 182, PK and PD samples can be collected at any time of the day. All sample collection and dosing time should be accurately recorded in the eCRF (as date, hours, and minutes). [redacted]

[e] If a subject does not have a scheduled on-site visit on the indicated study day, site personnel will perform a site check-in (within 3 days of the study day) to collect AEs and concomitant medications, to ensure all HAE attacks have been appropriately documented and, if applicable, to ensure that self-administration of lanadelumab (by the subject [aged 6 years or older] or parent/caregiver) has occurred as scheduled. The preferred method of site check-in is a telephone call; however, an alternate method of contact may be considered as site policies permit.

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

[g] The subject's parent/caregiver will complete the SC Administration survey at the indicated visits.

[h] [redacted]

[i] During the treatment and follow-up period, parents/caregivers will use a diary to daily record the subject's symptoms or occurrences of HAE attacks, and any medications taken for the management of these attacks. HAE attacks will be monitored daily and recorded as they occur. Parents/caregivers will also be instructed to notify and report details of an attack to the study site within 72 hours of the onset of an HAE attack, in accordance with HAARP (Appendix 5). Any parent/caregiver-reported attack not confirmed by the investigator must have an alternate AE diagnosis reported.

Schedule of Activities- Treatment Period B (Day 183 [Week 27] through Day 364 [Week 52]) and Follow-up Period

	Treatment Period Shaded columns: scheduled on-site visits Non-Shaded columns: potential subject-elected offsite activity																									Follow-up Period				
Study Week	**27-28**		**29-32**				**33-36**				**37-40**				**41-44**				**45-48**				**49-52**				**53-56**				
Study Visit (± 4 days)	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**52 [a]**	**53**	**54**	**55**	**56 EOS/ ET[n]**	**See Protocol Section below for details**
Study Day	**189**	**196**	**203**	**210**	**217**	**224**	**231**	**238**	**245**	**252**	**259**	**266**	**273**	**280**	**287**	**294**	**301**	**308**	**315**	**322**	**329**	**336**	**343**	**350**	**357**	**364 [a]**	**371**	**378**	**385**	**392**	
Vital signs[b]		X				X				X				X				X				X				X				X	Section 8.2.5.2
Physical examination[c]		X				X				X				X				X				X				X				X	Section 8.2.5.1
Hematology, serum chemistry, and coagulation tests[d]		X								X								X							X				X	Section 8.2.5.4
Pregnancy testing[e]						X								X								X								X	Section 8.2.5.3
Plasma PK sample[f]		X								X								X								X				X	Section 8.2.6.1
Plasma PD (cHMWK) sample[f]		X								X								X								X				X	Section 8.2.6.2
Plasma PD ([redacted]) sample[f]		X								X								X								X				X	Section 8.2.6.2
Plasma anti-drug antibody sample[f]		X								X								X								X				X	Section 8.2.6.3
Lanadelumab administration (6 to <12 years old)		X		X[l]		X		X[l]		X		X[l]		X		X[l]		X		X[l]		X		X[l]		X					Table 7
Lanadelumab administration (2 to <6 years old)		X				X				X				X				X				X				X					Table 7

Schedule of Activities- Treatment Period B (Day 183 [Week 27] through Day 364 [Week 52]) and Follow-up Period

	Treatment Period Shaded columns: scheduled on-site visits Non-Shaded columns: potential subject-elected offsite activity																														Follow-up Period				
Study Week	**27-28**		**29-32**				**33-36**				**37-40**				**41-44**				**45-48**				**49-52**				**53-56**				
Study Visit (± 4 days)	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**52 [a]**	**53**	**54**	**55**	**56 EOS/ ET[n]**	**See Protocol Section below for details**
Study Day	**189**	**196**	**203**	**210**	**217**	**224**	**231**	**238**	**245**	**252**	**259**	**266**	**273**	**280**	**287**	**294**	**301**	**308**	**315**	**322**	**329**	**336**	**343**	**350**	**357**	**364 [a]**	**371**	**378**	**385**	**392**	
Site check-in[g]	X			X				X				X				X				X				X				X[o]			
Injection report (6 to <12 years old)[h]		X		X[l]		X		X[l]		X		X[l]		X		X[l]		X		X[l]		X		X[l]		X					Section 8.2.6.8
Injection report (2 to <6 years old)[h]		X				X				X				X				X				X				X					Section 8.2.6.8
SC administration survey[i]														X												X					Section 8.2.6.8
[redacted]		X				X				X				X				X				X				X				X	Section 8.2.6.5
																										X				X	Section 8.2.6.5
	Within 24 hours after the onset of symptoms of an HAE attack, if applicable[j]																									X				X	Section 8.2.6.5
HAE attack data (subject HAE attack diary and site monitoring)[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Appendix 5
Concomitant therapies, medications, procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.6

Schedule of Activities- Treatment Period B (Day 183 [Week 27] through Day 364 [Week 52]) and Follow-up Period

	Treatment Period Shaded columns: scheduled on-site visits Non-Shaded columns: potential subject-elected offsite activity																										Follow-up Period				
Study Week	**27-28**		**29-32**				**33-36**				**37-40**				**41-44**				**45-48**				**49-52**				**53-56**				
Study Visit (± 4 days)	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**52 [a]**	**53**	**54**	**55**	**56 EOS/ ET[n]**	**See Protocol Section below for details**
Study Day	**189**	**196**	**203**	**210**	**217**	**224**	**231**	**238**	**245**	**252**	**259**	**266**	**273**	**280**	**287**	**294**	**301**	**308**	**315**	**322**	**329**	**336**	**343**	**350**	**357**	**364 [a]**	**371**	**378**	**385**	**392**	
Adverse events/serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.5.5, Section 8.2.5.6
End of study Visit[m]																														X	Section 8.1.4

[redacted] EOS=End of Study; ET=Early Termination; HAE= hereditary angioedema; PD=pharmacodynamic; PK=pharmaco kinetic; q2wks=every 2 weeks; q4wks=every 4 weeks

Note: Permissible assessment window during treatment period and follow-up period: Study Visit Day ±4 days

[a] End of Treatment (Section 8.1.3.3) will occur on Day 364/Visit 52 for subjects who complete Treatment Period B. Subjects who prematurely discontinue study treatment should complete the End-of-Study (EOS) / Early Termination (ET) visit procedures at Day 392/Visit 56, whenever feasible (Section 8.1.4).

[b] Vital signs, including sitting or supine blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR), will be measured using standard methods at each study site. On dosing days, vital signs will be obtained prior (within 60 minutes) to the injection of lanadelumab and 30 minutes (± 15 minutes) after completion of the injection of lanadelumab. Additional vital signs measurements will be performed if clinically indicated.

[c] Complete physical examination, including body weight. Additional physical examination will be targeted based on reporting of adverse events; symptom-oriented physical examinations other than protocol-specified examinations will be performed when clinically indicated in accordance with standard at the site.

[d] Clinical laboratory testing including hematology, serum chemistry, and coagulation.

[e] Pregnancy testing will be performed on females who have reached menarche. Tests performed at the indicated visits may be serum or urine-based.

[f] Blood samples for testing PK, PD, and formation of antibodies to lanadelumab will be obtained predose. **Note:** The End of Study (EOS) PK and PD sample may be collected at any time of the day. All sample collection and dosing time should be accurately recorded in the eCRF (as date, hours, and minutes). [redacted].

[g] If a subject does not have a scheduled on-site visit on the indicated study day, site personnel will perform a site check-in (within 3 days of the study day) to collect AEs and concomitant medications, ensure all HAE attacks have been appropriately documented and, if applicable, ensure that self-administration of lanadelumab (by the subject [aged 6 years or older] or parent/caregiver) has occurred as scheduled. The preferred method of site check-in is a telephone call; however, an alternate method of contact may be considered as site policies permit.

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

[i] The subject's parent/caregiver will complete the SC Administration survey at the indicated visits.

[redacted]

[k] During the treatment and follow-up period, parents/caregivers will use a diary to daily record the subject's symptoms or occurrences of HAE attacks, and any medications taken for the management of these attacks. HAE attacks will be monitored daily and recorded as they occur. Parents/caregivers will also be instructed to notify and report details of an attack to the study site within 72 hours of the onset of an HAE attack, in accordance with HAARP (Appendix 5). Any parent/caregiver-reported attack not confirmed by the investigator must have an alternate AE diagnosis reported.

[l] An individual subject's dose frequency may be modified based on a benefit-risk assessment and recommendation from the treating physician. Consultation with and approval by the sponsor's medical monitor is required. For example, subjects 6 to <12 years of age may administer lanadelumab 150 mg q4wks in Treatment Period B at the investigator's discretion and sponsor's medical monitor approval, if they are well controlled (eg, attack free) for 26 weeks with lanadelumab treatment in this study.

[m] Subjects who terminate from the study early (ET) will undergo (if possible) all of the assessments and procedures at Day 392 (EOS) at their final study visit.

[n] The EOS visit on Study Day 392 (Visit 56) will occur only for subjects receiving treatment q4wks; the EOS visit for subjects receiving treatment q2wks will occur on Study Day 378 (Visit 54) (see Section 8.1.4)

[o] For subjects receiving treatment q4wks only.

Appendix 2 Handling of HAE Attack Data

The following rules apply to the handling of HAE attack data for efficacy analyses only. HAE attacks starting prior to the baseline observation period are not processed by these rules. For safety analyses, HAE attacks will be analyzed as reported.

Imputing Missing Start or End Date and Time for HAE Attacks

In general, missing start time will be imputed as 0:00 and missing end time will be imputed as 23:59. 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.

- For HAE attacks with missing end time and a non-missing end date one calendar day before the start date of the next attack, the end time will be imputed as the start time of the next HAE attack to ensure there are 24 hours in between the two attacks.

- For HAE attacks with a missing end time and non-missing start date/time within 24 hours from the start date/time of the next attack, the attack should be considered as one attack with the next attack.

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

- If the event is not indicated as ongoing, the end 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 end date and time will be imputed as the earlier of the following two date and time:

    - Start date and time + 48 hours or study completion date and the end time of 23:59, whichever is later.

    - 24 hours before the start date and time of the next attack.

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 end 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 end 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. 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.

In order to assign the actual dose regimen for an HAE attacks that need to be combined for efficacy analyses, the HAE attack will be combined first, then the start date/time will be used for consideration of the actual dosing regimen after the HAE attack has been combined. See Appendix 5 for the algorithm of actual dose regimen assignment.

HAE Attack Duration

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

Investigator-confirmed HAE Attacks Requiring Acute Therapy

Investigator-confirmed HAE attacks requiring acute therapy are those attacks identified as 'treated for HAE attack with acute therapy' on the CRF.

Moderate and Severe Investigator-confirmed HAE Attacks

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

HAE Attack Severity

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

- Mild: Transient or mild discomfort
- Moderate: Mild to moderate limitation in activity - some assistance needed

- Severe: Marked limitation in activity, assistance required

The average attack severity will be calculated per subject by attributing a numeric value to each severity as follows: 1=Mild, 2=Moderate, and 3=Severe. Higher values will indicate more severe attacks, while lower values will indicate less severe attacks.

Appendix 3 Clinical Significance Attributions for Laboratory Results

The EDC system design permitted attribution of clinical significance for all laboratory values, not just those that are outside of the reference range. Therefore, many data points have an attribution of clinical significance when none is expected.

The laboratory results will be programmatically classified for analysis due to the database limitation using the following algorithm:

- Lab results within the reference range will be classified as Normal.
- Lab results outside of the reference range will be classified as a) CS Low, b) NCS Low, c) NCS High, or d) CS High using a combination of the CS/NCS classification by the investigator and the Low/High classification based on the central lab reference range.

Appendix 4 Algorithm to Identify LTP Use at Baseline

The LTP (C1-INH, Androgens, or Anti-fibrinolytics) treatment a subject was on prior to study enrollment will be determined by applying the algorithm presented in Table 12 to prior medications (i.e., medications with start and stop date prior to study enrollment) reported for that subject that lasted for ≥4 days.

Table 12 LTP Prior to Study Enrollment

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

Subjects will be further classified into four LTP subgroups, based on the LTP use prior to study enrollment. Table 13 provides the algorithm to classify subjects by type of LTP use prior to study enrollment.

Table 13 LTP Subgroup

LTP	Algorithm to Identify Medications
C1-INH	Subjects who took only C1-INH as LTP
Oral Therapy	Subjects who took either androgens and/or anti-fibrinolytics as LTP
C1-INH and Oral Therapy	Subjects who took C1-INH and androgens and/or anti-fibrinolytics as LTP
Not on LTP	Subjects who didn't take any LTP medications prior to first dose of study drug

Appendix 5 Actual Dose Regimen

Dose modification is mentioned in section 6.2.5 of the protocol. A subject's dose regimen may be modified based on an interim PK analysis or a benefit-risk assessment or recommendation from the treating physician. For example, in Treatment Period B, subjects in the 6 to <12 years age group may administer lanadelumab 150 mg q4wks at the investigator's discretion and sponsor's medical monitor approval, if they are well controlled (eg., attack free) for 26 weeks with lanadelumab treatment in this study. Other modifications may be considered at the discretion of the investigator in consultation with the sponsor's medical monitor.

The actual dosing regimen is the dosing regimen the subject is on when the assessment/event occurs.

Because there were no dose modifications in Treatment Period A, efficacy/safety assessments/events will be attributed to the dose regimen assigned to the subject at Visit 1 Day 0.

For dose modifications, the start date/time of the assessment/event will be compared to the visit date/time at which the dose modification occurred to assign the assessment/event to the appropriate dose regimen. For HAE attacks that are combined for efficacy analyses, the start date/time of the combined HAE attack will be used to assign to the appropriate dose regimen.

For example, if a subject has a dose modification at Visit 28 Day 196 which reduces dosing frequency from q2wks to q4wks, then assessments/events with start date/time prior to the Visit 28 Day 196 will be attributed to the q2wks dosing regimen and assessments/events with start date/time on or after the Visit 28 Day 196 will be attributed to the q4wks dosing regimen (see schematic in Table 14). The last dose on the q2wks regimen will be considered the first dose of the q4wks regimen.

For concomitant medications, adverse events, and HAE attacks, if the start date/time of assessment/event is partially missing, the start date/time after imputation per section 12.6 will be used to assign the actual dose regimen. For other assessments/events, if the start date/time of assessment/event is partially missing, non-missing date parts will be used to determine the dose regimen. If a determination cannot be made using the non-missing date parts or the start date is missing, the actual dose regimen will be set to dose regimen the subject assigned at Visit 1 Day 0. Note, that in general, assessment dates should not be missing. It is anticipated that missing dates could arise from assessments performed on a continual basis like adverse events.

Additionally, if a subject had a dose modification on Visit 48/ Day 336 which increases the dosing frequency from q4wks to q2wks, then assessments/events with start date/time on or after the Visit 48/Day 336 will be attributed to the q2wks dosing regimen (see schematic in Table 14).

For by visit assessments such as clinical laboratory data, vital signs, PK/PD, immunogenicity, [redacted], the assessment date will be used to assign the actual dose regimen instead of date and time.

Table 14 Dose Modification Example

	Lanadelumab 150 mg Every 2 Weeks[a] (for subjects 6 to <12 years)[b]	
Treatment Period	**Dose Number**	**Study Visit/Study Day/Study Week**
A	1	Visit 1/Day 0/Week 0
	2	Visit 3/Day 14/Week 2
	3	Visit 4/Day 28/Week 4
	4	Visit 6/Day 42/Week 6
	5	Visit 8/Day 56/Week 8
	6	Visit 10/Day 70/Week 10
	7	Visit 12/Day 84/Week 12
	8	Visit 14/Day 98/Week 14
	9	Visit 16/Day 112/Week 16
	10	Visit 18/Day 126/Week 18
	11	Visit 20/Day 140/Week 20
	12	Visit 22/Day 154/Week 22
	13	Visit 24/Day 168/Week 24
	14	Visit 26/Day 182/Week 26
B	15	Visit 28/Day 196/Week 28
	16	Visit 32/Day 224/Week 32
	17	Visit 36/Day 252/Week 36
	18	Visit 40/Day 280/Week 40
	19	Visit 44/Day 308/Week 44
	20	Visit 48/Day 336/Week 48
	21	Visit 50/Day 350/Week 50
	22	Visit 52/Day 364/Week 52

Dosing Regimen: Every 2 weeks

Dose Modification

Dosing Regimen: Every 4 weeks

Dose Modification

Dosing Regimen: Every 2 weeks

[a] Subjects 6 to <12 years of age may administer lanadelumab 150 mg q4wks in Treatment Period B at the investigator's discretion and sponsor's medical monitor approval, if they are well controlled (eg, attack free) for 26 weeks with lanadelumab treatment in this study.
[b] A subject's dosing regimen will be determined based on the subject's age at enrollment (ie, date of informed consent), and subjects will remain in the same age category throughout the study.

Appendix 6 Injection Site Reaction AEs

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

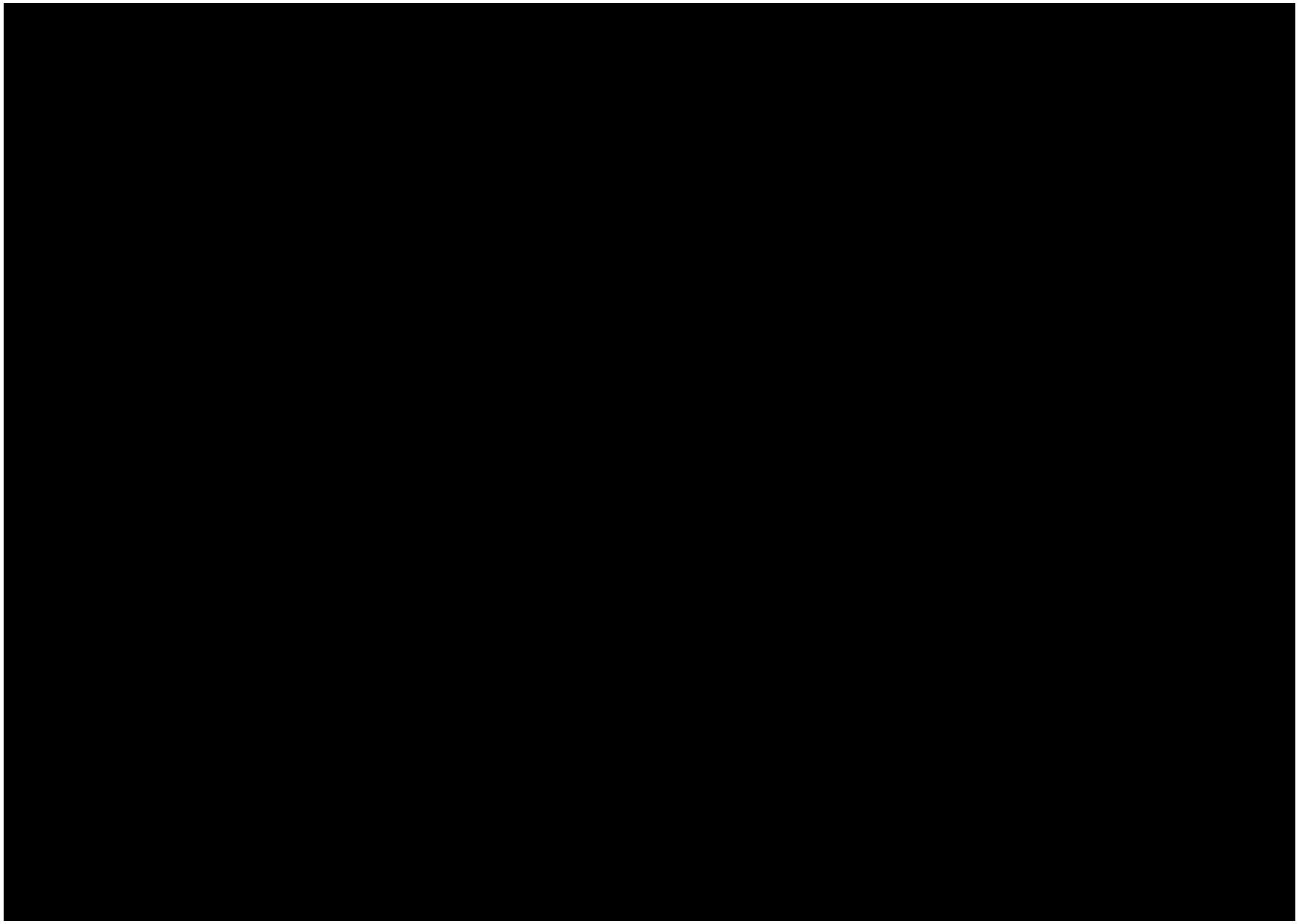
Duration of ISR AEs is calculated as "stop date/time – start date/time" for the ISR AEs with non-missing start and stop date/time.

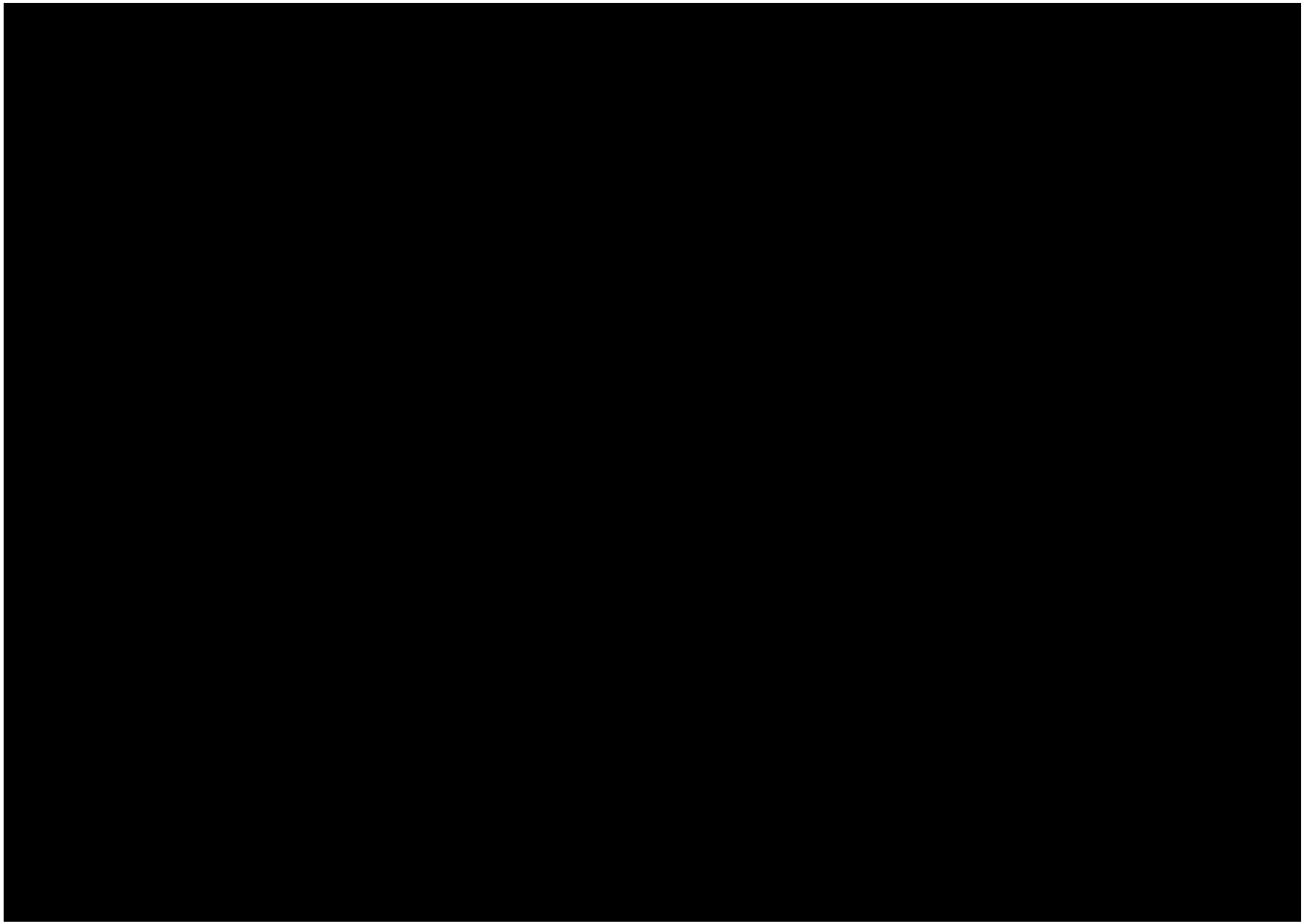
The missing start or stop date/time for ISR AEs will not be imputed. ISR AEs with missing start or stop date/time will be excluded from the summary statistics analysis and reported as number missing in the continuous analysis of ISR AE duration. For the categorical analyses on ISR AE duration, the following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

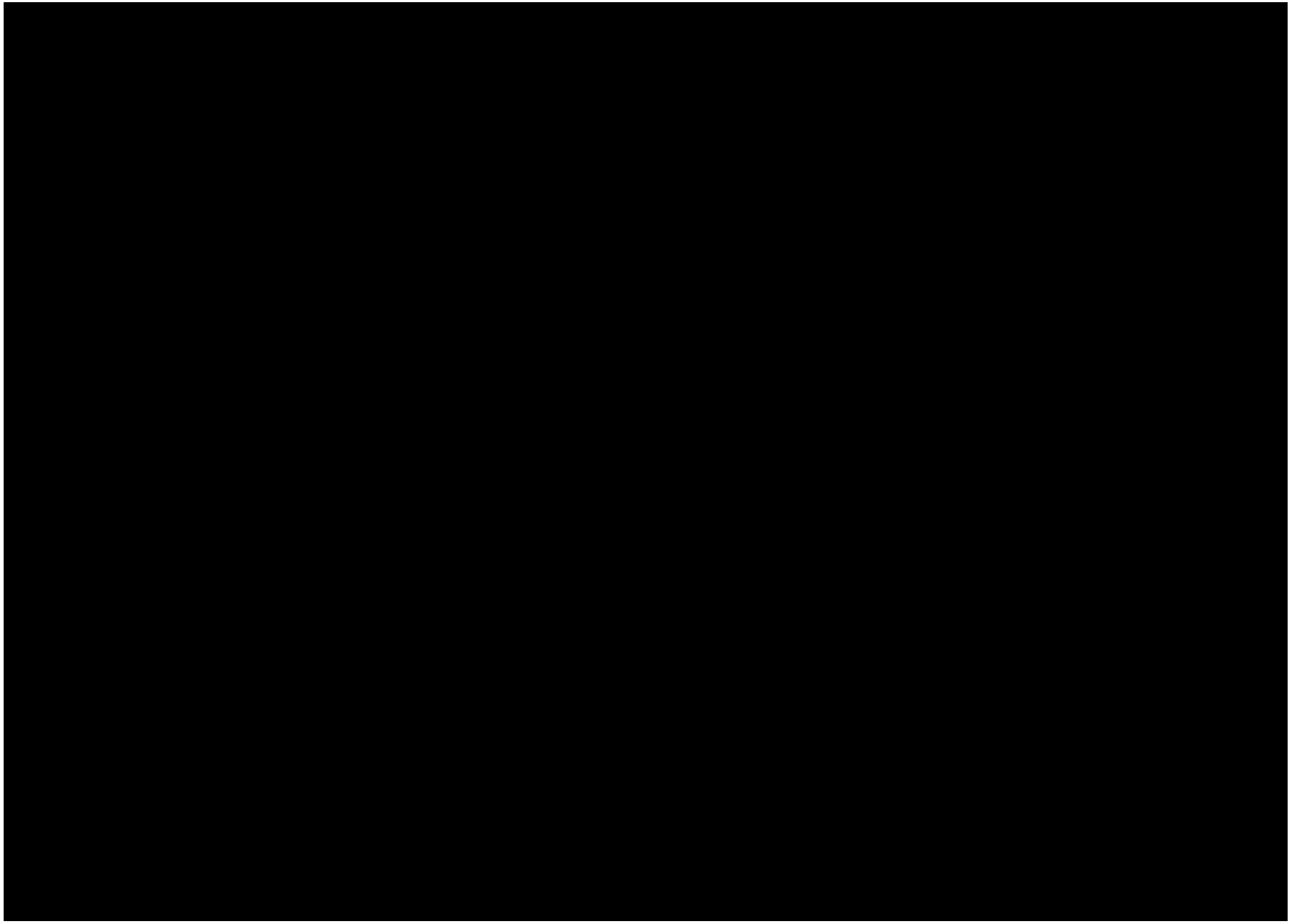
- ISR AE with non-missing start and stop date/time: duration of the AE will be calculated as 'stop date/time – start date/time' and mapped to a duration category.

- 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.







Appendix 8 List of Statistical Outputs

Table 18 List of Planned Tables

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14.1.4.4	Prior Medications (Excluding Medications taken for an HAE Attack) (Safety Set)
14.1.4.5	Prior Medications taken for an HAE Attack (Safety Set)
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Table No.	Title
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Table No.	Title
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14.2.1.1.56	Summary of Normalized Number of Investigator-Confirmed HAE Attacks by HAE Type and Treatment Group During Treatment Period A (Safety Set)
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14.2.1.1.58	Summary of Normalized Number of Investigator-Confirmed HAE Attacks by HAE Type and Treatment Group During Treatment Period B (Safety Set)
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14.2.1.2.1	Summary of Normalized Number of Investigator-Confirmed HAE Attacks Requiring Acute Treatment by Treatment Group During Treatment Period A (Safety Set)
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Table No.	Title
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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