CLINICAL STUDY PROTOCOL

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

Protocol Version and Date:

Amendment 2: 22 Jun 2021

PROTOCOL: SHP643-301

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
SHORT TITLE:	Safety, Pharmacokinetics, and Pharmacodynamics Study of Lanadelumab to Prevent Hereditary Angioedema (HAE) Attacks in Pediatric Subjects 2 to <12 Years of Age
STUDY PHASE:	Phase 3
DRUG:	Lanadelumab; TAK-743 (formerly SHP643, DX-2930)
IND NUMBER:	116647
EUDRACT NUMBER:	2018-002093-42
SPONSOR:	Dyax Corp. (a wholly-owned, indirect subsidiary of Shire plc) (Shire plc, a wholly-owned subsidiary of Takeda) 300 Shire Way, Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	Multicenter study
PROTOCOL HISTORY:	Original Protocol: 06 May 2019 Amendment 1.0: 12 Aug 2019 Amendment 1.1 (Germany): 15 Oct 2019 Amendment 1.2 (Germany): 5 Dec 2019 Amendment 2.0: 22 June 2021

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

[redacted]

Investigator's Acknowledgement

I have read this protocol for Study SHP643-301.

Title: 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

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

A summary of the changes incorporated into Amendment 2.0 is provided in the table below. Any minor revisions in grammar, spelling, punctuation, and format are not reflected in the summary of changes.

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2.0**	**Amendment Date** **22 June 2021**	**Global**
Description of Each Change and Rationale		**Section(s) Affected by Change**
Sponsor approval and emergency contact information has been updated to reflect the current medical monitor.		Protocol Signature Page Emergency Contact Information
Individual subject participation duration was revised to clarify that *maximum* duration for study participation is 72 weeks. Subjects receiving treatment q2wks may complete the study in 70 weeks.		Section 1.1 Synopsis Section 4.1 Overall Design
Revised follow-up period to 2-4 weeks 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).		Section 1.1 Synopsis Section 1.3 Schedule of Activities (Table 3, footnotes n and o) Section 4.1 Overall Design Section 8.1.4 Follow-up Period
The interim analysis summarizing data up to Treatment Period A has been removed as it is no longer planned.		Section 1.2 Schema (Figure 1) Section 9.2 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee
EOS/ET visit in footnote "a" was incorrectly written as Day 292. This has been corrected to Day 392.		Section 1.3 Schedule of Activities (Table 3)
Text regarding Study DX-2930-04 as "ongoing" has been removed as this study has been completed.		Section 2.5 Product Background and Clinical Information Section 2.7 Benefit/Risk Assessment
Revised for clarity and to align with language in Amendment 1.2 (Germany).		Section 7.5.2 Individual Stopping Rules
Severity categorization for AEs was revised to clarify a portion of the protocol template language that is incongruous with program data collection and analysis procedures in the previous HAE clinical studies.		Appendix 3.3

See Appendix 8 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the "Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol" within 24 hours to the Shire Global Drug Safety Department. The fax number and e-mail address are provided on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO) using the details below.

PPD Pharmacovigilance Group Fax: [redacted]

For protocol- or safety-related questions or concerns <u>during normal business hours</u> (09:00 to 17:00 EST), the investigator must contact the Shire medical monitor:

[redacted], MD, PhD

Mobile: [redacted]

For protocol- or safety-related questions or concerns <u>outside of normal business hours</u>, the investigator must contact the Shire medical monitor:

[redacted], MD, PhD

Mobile: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Shire within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis.

A product quality complaint includes any instances where there is an allegation or report relating to Shire licensed or investigational products, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that a product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product quality complaints include, but are not limited to, the following:

Unit issues	• Capsule fill empty or overage • Bottle/vial fill shortage or overage • Capsule/tablet damaged/broken • Syringe/vial cracked/broken	• Syringe leakage • Missing components • Product discoloration • Device malfunction
Labeling	• Label missing • Leaflet or Instructions For Use (IFU) missing • Label illegible	• Incomplete, inaccurate, or misleading labeling • Lot number or serial number missing
Packaging	• Damaged packaging (e.g., secondary, primary, bag/pouch) • Tampered seals • Inadequate or faulty closure	• Missing components within package
Foreign material	• Contaminated product • Particulate in bottle/vial • Particulate in packaging	

Please report the product quality complaint using the "Product Complaint Data Collection Form" via the email address:

[redacted]

Telephone number (provided for reference if needed):

Shire, Lexington, MA (USA)

[redacted]

For instructions on reporting AEs related to product complaints, see Appendix 3.4.

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol number: SHP643-301	**Drug:** Lanadelumab
Title of the study: 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	
Short title: Safety, Pharmacokinetics, and Pharmacodynamics Study of Lanadelumab to Prevent Hereditary Angioedema (HAE) Attacks in Pediatric Subjects 2 to <12 Years of Age	
Number of subjects (total and per treatment arm): At least 20 male or female subjects with HAE Type I or II, 2 to <12 years of age, will be enrolled (signed informed consent form and met eligibility criteria), including at least 5 subjects in each age cohort of 2 to <9 years and 9 to <12 years. A minimum of 15 subjects must complete 1 year (52 weeks) of treatment on the study.	
Investigator(s): This is a multicenter study.	
Site(s) and Region(s): Approximately 18 sites in North America (United States, Canada) and Europe (Germany, Spain, Hungary) will participate.	
Study period (planned): June 2019 to October 2021	**Clinical phase:** 3
Objectives: **Primary:** 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. **Secondary:** 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]	

Rationale:

An unmet medical need for effective, safe, and convenient treatment options exist among children (2 to <12 years of age) with HAE. The unpredictable nature of HAE attacks in children results in significant decrements in vocational and school achievement, which impact the overall quality of life. Prophylactic treatment with lanadelumab may be beneficial for children based on demonstrated efficacy, safety, and tolerability in adults and adolescents with the reduced treatment burden of a low volume, infrequent, subcutaneous (SC) administration. The similarity of pathophysiology and clinical symptoms for HAE attacks between adults and children suggest the involvement of plasma kallikrein and bradykinin in both groups of patients. Lanadelumab is expected to provide significant benefit to young children suffering from HAE.

Investigational product, dose, and mode of administration:

The proposed dose regimens 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 on the date of informed consent, and subjects will remain in the same age category throughout the study.

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

Subjects in the 6 to <12 years age group who have been well controlled (eg, attack free) for 26 weeks with lanadelumab treatment in this study may switch to a dose of 150 mg q4wks during Treatment Period B at the investigator's discretion 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 drug product is a sterile, preservative-free, ready-to-use solution with a lanadelumab concentration of 150 mg/mL provided in a single-use 2 mL glass vial (150 mg/1 mL). For use in children less than 12 years, the full 1 mL (150 mg) dose will be withdrawn from the vial and administered to the subject.

Lanadelumab is formulated as liquid for injection and is intended for SC administration in the abdomen, thigh, or upper arm. Administration of lanadelumab by a subject (aged 6 years or older) or parent/caregiver (hereafter referred to as self-administration) is allowed after the subject (aged 6 years or older) or parent/caregiver has received appropriate training by the investigator or designee and their understanding is confirmed. Subjects (aged 6 years or older) or parents/caregivers may initiate self-administration after the subject has received the first 2 doses of lanadelumab at the study site and may continue to self-administer all subsequent doses. Note: Subjects less than 6 years of age must have a parent/caregiver self-administer lanadelumab. Self-administration of lanadelumab by the subject is only permitted for those aged 6 years or older and who have demonstrated the necessary skills for self-treatment, as assessed the investigator.

Methodology:

This study 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 1 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. 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.

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.

An individual subject's maximum duration of participation from screening through the completion of safety follow-up visit will be approximately 72 weeks (see below for duration of each study period).

Inclusion and Exclusion Criteria:

Inclusion Criteria:

The subject will not be considered eligible for the study without meeting all of the criteria below.

1. Be a child (male or female) 2 to <12 years of age at the time of signing the informed consent form (screening).
2. Documented diagnosis of HAE (Type I or II) based upon both of the following:
   - Documented clinical history consistent with HAE (SC or mucosal, nonpruritic swelling episodes without accompanying urticaria);
   - Diagnostic testing results obtained during screening from a sponsor-approved central laboratory that confirm C1 esterase inhibitor (C1-INH) functional level <40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. With prior sponsor approval, subjects may be retested during the baseline observation period if results are incongruent with clinical history or believed by the investigator to be confounded by recent C1 inhibitor use.
3. A historical baseline HAE attack rate of at least 1 attack per 3 months. **Note**: In addition, subjects who experience ≥1.0 angioedema attacks per three months during the 12-week baseline observation period and who remain eligible per the inclusion criteria will enter the lanadelumab treatment period.
4. Agree to adhere to the protocol-defined schedule of treatments, assessments, and procedures.
5. Have a parent(s)/legal guardian who is informed of the nature of the study and can provide written informed consent for the child to participate in the study before any study-specific procedures are performed (with assent from the child when appropriate).
6. Females of childbearing potential must agree to be abstinent or agree to comply with the applicable contraceptive requirements of this protocol through the duration of the study from screening through 70 days after the final study visit.

Exclusion Criteria:

The subject will be excluded from the study if any of the following exclusion criteria are met.

1. Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema (AAE), HAE with normal C1-INH, idiopathic angioedema, or recurrent angioedema associated with urticaria.
2. Dosing with an investigational drug or exposure to an investigational device within 4 weeks prior to screening.
3. Be pregnant or breastfeeding.

4. Have initiated androgen treatment (eg, stanozolol, danazol, oxandrolone, methyltestosterone, and testosterone) within 2 weeks prior to entering the observation period.
5. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
6. Have any active infectious illness or fever defined as an oral temperature >38°C (100.4°F), tympanic >38.5°C (101.3°F), axillary >38°C (100.4°F), or rectal/core >38.5°C (101.3°F) within 24 hours prior to the first dose of study drug in Treatment Period A.
7. Have any HAE attack that is not resolved prior to the first dose of study drug in Treatment Period A.
8. Have any of the following liver function test abnormalities: alanine aminotransferase (ALT) >3x upper limit of normal, or aspartate aminotransferase (AST) >3x upper limit of normal, or total bilirubin >2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome).
9. Have any condition (any surgical or medical condition) that, in the opinion of the investigator or sponsor, may compromise their safety or compliance, preclude the successful conduct of the study, or interfere with interpretation of the results (eg, significant pre-existing illness or other major comorbidity that the investigator considers may confound the interpretation of study results).
10. Subject has a known hypersensitivity to the investigational product or its components.

Maximum duration of subject participation in the study:

- Planned duration of screening period: up to 4 weeks.
    - Planned duration of enrollment period: up to 4 weeks, including the screening period and baseline observation period. An enrolled subject will have met the inclusion/exclusion criteria to participate in the trial and will have signed an informed consent form.
- Planned duration of baseline observation period: up to 12 weeks. The baseline observation period will be at least 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.
- Planned duration of treatment period: 52 weeks
- Planned duration of follow-up period: 2 or 4 weeks (depending on the treatment schedule)

Statistical analysis:

Primary Analyses

Safety

Assessment of safety is a primary endpoint for the study. The safety measures will 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.

Pharmacokinetics

Assessment of PK is a primary endpoint for the study. 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

Secondary Analyses

Clinical Outcomes

Clinical outcome measures are secondary endpoints for the study. Clinical outcome measures will be 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.

Pharmacodynamics

The following PD measure is the secondary endpoint for the study:

- Plasma kallikrein activity (as measured by cHMWK level).

[redacted]

Immunogenicity

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]

[redacted]

Sample Size

The sample size for the proposed 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 (including at least 5 subjects in each age group of 2 to <9 years of age and 9 to <12 years of age) 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 study inclusion criteria (Caballero, 2013), this number is considered a reasonable target at study initiation with respect to the ability to enroll eligible subjects.

Statistical Methodology

Clinical Outcomes

The analysis of clinical outcomes will be conducted using the Safety Analysis Set, which is defined as all subjects who received any study drug. Data will be summarized by dose group and overall during each treatment period, partitioned by dose regimen for subjects with dose modifications. This study is not designed for statistical hypothesis testing, and given the small sample size and the primary study objective (PK and safety), only descriptive analysis will be done, and the following will apply:

- 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. The baseline is defined as the last non-missing value prior to initial dose of study drug.
- 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 estimates. Summaries will include median time and quartiles, if estimable, and corresponding 95% confidence intervals.

Safety

Safety endpoints will be analyzed based on the Safety Analysis Set, which is defined as all subjects who received any study drug. Data will be summarized by dose group and treatment period, partitioned by dose regimen for subjects with dose modifications.

- 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).

- Only treatment emergent AEs (TEAEs) will be analyzed. The number and percentage of subjects reporting any TEAEs, SAEs, and TEAEs related to the investigational product, TEAEs leading to withdrawal, severe TEAEs and absolute count of events will be summarized by treatment group, overall and by preferred term and system organ class.
- All AEs (TEAEs and non-TEAEs) will be provided in the AE subject listing. All safety data, including derived data, will be presented in subject data listings.
- Clinical laboratory tests and vital signs will be summarized by treatment group and visit. Potentially clinically important findings will also be summarized or listed

[redacted]

Pharmacokinetics/Pharmacodynamics

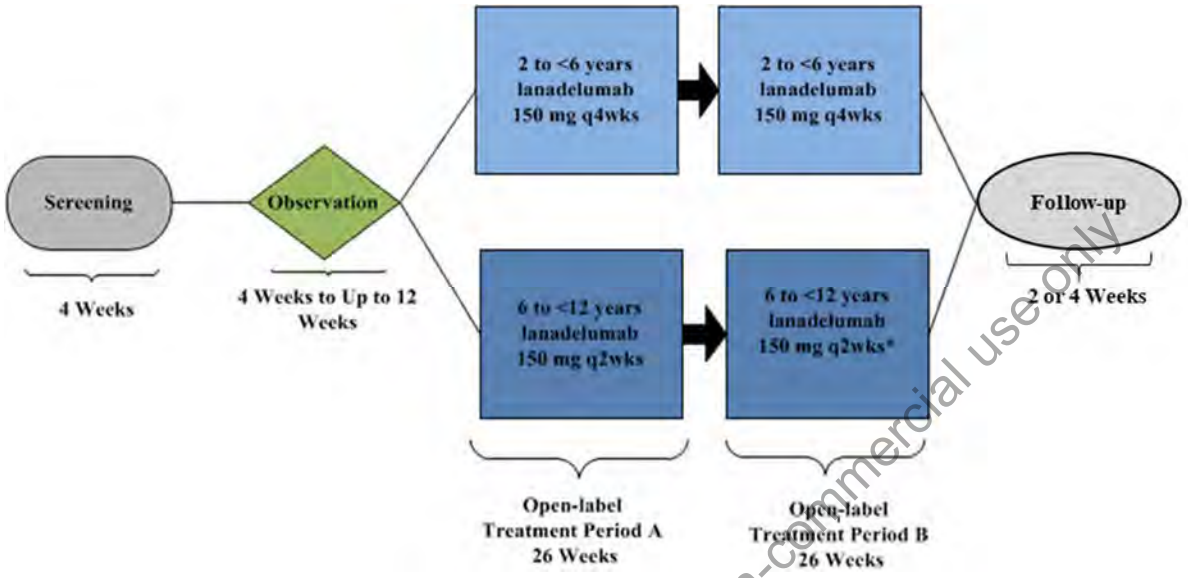
A descriptive summary analysis will be performed for plasma concentrations of lanadelumab, as appropriate, using nominal time points.

A descriptive summary analysis will be performed for cHMWK levels, [redacted], as appropriate, using nominal time points.

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 statistical analysis plan will support the population PK and PD analysis and the analysis results will be reported separately.

1.2 Schema

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.

1.3 Schedule of Activities

Table 1 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
[redacted]			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

Table 1 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	

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.

Table 2 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
SC administration survey[g]												X														X	Section 8.2.6.8

Table 2 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**	
[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.

Table 2 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**	

[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.

[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.

Table 3 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	

Table 3 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	
Lanadelumab administration (2 to <6 years old)		X				X				X				X				X				X				X					Table 7
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

Table 3 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**	
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
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=pharmacokinetic; 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

Table 3 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	

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.

2. INTRODUCTION

2.1 Disease Etiology and Pathophysiology

Hereditary angioedema (HAE) is a serious, severely debilitating, and life-threatening condition caused by mutations in the C1 inhibitor (also known as C1 esterase inhibitor [C1-INH]) *SERPING1* gene (Tosi, 1998), leading to the heterozygous deficiency (Type I HAE) or dysfunction (Type II HAE) of C1-INH plasma protein (Zuraw et al., 2013) and results in a dysregulated plasma kallikrein-kinin pathway. Dysregulated pKal is recognized as the key pathophysiologic defect responsible for the development of angioedema attacks in patients with HAE (Zuraw and Christiansen, 2016). The critical components of the plasma kallikrein-kinin pathway (or contact system) consists of 3 essential proteins: coagulation factor XII (Hageman factor), prekallikrein (Fletcher factor), and high molecular weight kininogen (HMWK, Fitzgerald factor). Factor XII autoactivation initiates a cascade of events leading to pKal generation from prekallikrein (Figure 2). Plasma kallikrein, in turn, acts on HMWK to generate cleaved HMWK (cHMWK) and release bradykinin, a potent vasodilator. Bradykinin binds to the B2 receptor on endothelial cells, causing vascular permeability and resultant tissue edema recognized as swelling (Leeb-Lundberg et al., 2005). Normal levels of C1 inhibitor regulate the activity of pKal as well as a variety of other proteases, including C1r, C1s, factor XIa, and factor XIIa. In patients with Types I and II HAE, C1-INH levels are insufficient for the regulation of pKal activity, which leads to pathologic levels of bradykinin and results in bradykinin-mediated angioedema (Davis, 2005).

HAE manifests clinically as unpredictable, intermittent attacks of subcutaneous (SC) or submucosal edema of the face, upper airway (larynx), gastrointestinal tract, limbs and/or genitalia (Zuraw, 2008; Zuraw et al., 2013). Frequency of recurrences varies between patients and within the same patient. Swelling may last up to 5 or more days; patients can range from asymptomatic to suffering 3 attacks per week. Mortality related to upper airway attacks is significant at 30% and is considerably higher (almost 3-fold to 9-fold) in patients who remain undiagnosed (Bork et al., 2012). Triggers of angioedema attacks in patients with HAE can include stress, physical trauma, medical or dental procedures, and estrogen exposure, although most attacks appear to occur spontaneously (Bork, 2014a; Bork, 2014b).

HAE affects all ethnic populations, adults and children, and both genders (Nzeako et al., 2001). Symptoms often begin in childhood and typically worsen during puberty. The unpredictability of attacks results in significant decrements in vocational and school achievement (Caballero et al., 2014). Additionally, due to the chronic, recurrent nature of HAE attacks and the ever present risk of death from asphyxiation, HAE considerably affects patient quality of life (Caballero et al., 2014; Fouche et al., 2014a; Lumry et al., 2014; Fouche et al., 2014b).

There is no evidence that there are significant differences in HAE etiology and pathophysiology based on age and, overall, clinical aspects of pediatric and adult HAE are quite similar. However, frequency and severity of attacks are variable amongst individuals, and some differences have been noticed between pediatric and adult populations. Children appear to have *less frequent* and *less severe* symptoms than adults or adolescents and life-threatening attacks are less common in the pediatric population than in adults (Read et al., 2014).

Although the genetic defect (*SERPING1* gene mutation) of HAE Type I and II is present at birth, symptoms are uncommon during neonatal age or infancy. The symptoms may occur at any age, but usually begin in childhood or adolescence (World Allergy Organization [WAO]/European Academy of Allergy and Clinical Immunology [EAACI] guidelines-2017 revision and update; (Maurer et al., 2018).

Several studies examined the natural history of HAE in children. Reported median age of first symptom onset varies in the literature. While these studies have been based on small sample sizes, they demonstrate the rarity of HAE symptoms among children younger than 6 years of age. It has been acknowledged that while angioedema episodes may occur at any age, they usually begin between 5 and 11 years of age (Farkas, 2010). Per the WAO/EAACI guidelines revised in 2017, the median age of symptom onset is approximately 12 years of age. Subcutaneous edema is the most common earliest symptom. However, abdominal symptoms may be unrecognized and often misdiagnosed in infants with Type 1 or II HAE. Asphyxia may ensue rapidly in children, and earliest occurrence was described in one 4-week old boy (Maurer et al., 2018). *Erythema marginatum* as a prodromal sign is more frequent in the pediatric population. The frequency and severity of symptoms may increase during puberty and adolescence (Maurer et al., 2018), possibly because endocrine factors seem to have a great impact on the manifestation of the disease (Frank et al., 1976). Bork et al. reported that 90% of patients had symptom onset before age 20 (Bork et al., 2006a). Very few cases of HAE attacks have been reported in children younger than 3 years of age (Bygum et al., 2011; El-Hachem et al., 2005; Nanda et al., 2015; Roche et al., 2005).

2.2 Disease Diagnosis in the Pediatric Population

Diagnosis of HAE is difficult, particularly challenging in children, and often delayed. It is often misdiagnosed or diagnosed several years after the initial attack because of its rarity and the potential lack of family history due to spontaneous mutations (Agostoni and Cicardi, 1992; Roche et al., 2005). With autosomal dominant inheritance, the offspring of a patient with HAE I or II stands a 50% chance of inheriting the disease. Therefore, it is important to establish the diagnosis as early as possible (WAO/EAACI guidelines-2017 revision and update; Maurer et al., 2018). As HAE shares similar symptoms with "allergic" conditions, misdiagnosis is frequent. Delay is often reduced when patients present family history of swelling (Read et al., 2014). The WAO guidelines recommend testing children from HAE-affected families as soon as possible and all offspring of an affected parent be tested (Maurer et al., 2018).

Some of the reasons that could explain the difficulty in diagnosing HAE are detailed as follows:

- Normal reference ranges for C1-INH concentrations and activity have not been established for children under 1 year of age (Gompels et al., 2005b; Gompels et al., 2005a).
- Testing for C1-INH level and activity conducted prior to 1 year of age should be repeated after age 1 (Bowen et al., 2008) because the complement and kallikrein/kinin systems do not reach adult maturity levels until later (from 6 to 36 months; Davis et al., 1979; Nielsen et al., 1994).

- The prevalence of patients who have symptoms of HAE, and especially HAE attacks, is extremely low in the pediatric population under 6 years of age, as median age for first symptom onset reported from large studies is generally higher than 6 years of age (Bork et al., 2006a; Bygum et al., 2011; Farkas, 2010; Roche et al., 2005).
- In many cases there is a lack of family history that would otherwise have aided in diagnosis of the disease.
- Up to 25% of HAE cases are due to new or spontaneous mutations (Agostoni and Cicardi, 1992; Zuraw, 2008; Pappalardo et al., 2000).
- Abdominal attacks are particularly difficult to diagnose in children and can be confused with acute abdominal emergencies and other abdominal events, such as appendicitis or intussusception (Agostoni and Cicardi, 1992).

Patients who present with HAE symptoms need laboratory tests to confirm HAE diagnosis. Measurements of C1-INH antigen (protein), C1-INH functional (activity) level, and C4 level are advisable in all children with angioedema without urticaria (WAO/EAACI guideline for the management of HAE- 2017 revision and update; Maurer et al., 2018). In practice, it is common to test C1-INH function levels initially, establishing HAE directly, in order to avoid, for example, problematic repeated blood draws in children.

2.3 Epidemiology in the Pediatric Population

Hereditary angioedema is an orphan disorder and its exact prevalence is unknown, but current estimates range from 1 per 10,000 to 1 per 50,000 persons (Bygum, 2009; Goring et al., 1998; Lei et al., 2011; Lumry, 2013; Nordenfelt et al., 2014; Roche et al., 2005). Although genetically present at birth, the disease may be clinically observable only many years later. In addition, variability of presentation and difficulty in diagnosis of the disease often lead to delayed recognition of the disorder. This, in turn, translates to difficulty in estimating the prevalence of symptomatic HAE, especially in the pediatric population, with any degree of certainty.

Attempts to estimate the prevalence of HAE attacks in pediatric patients can be made from case series and case reports of adult patients who report the age at which they first had symptoms or severe attacks. It is acknowledged that age of onset may be biased because the accuracy is wholly dependent upon the patient's recollection. Patients tend to remember their attacks of severe laryngeal edema more readily than their intestinal, skin or extremity edema episodes (Bork et al., 2006a; Bork et al., 2006b)

Epidemiological studies of HAE that provide information on pediatric patients report that this population includes approximately 10% to 28% of the total HAE patient population, although some of these pediatric patients were asymptomatic at the time of the report (Agostoni et al., 2004; Bygum, 2009; Farkas et al., 2002; Jolles et al., 2014; Nordenfelt et al., 2014; Stray-Pedersen et al., 2017). For example, based on the available information, it can be estimated that pediatric patients in the United States represent approximately 22.8% of the overall HAE patient population. This corresponds to a prevalence of 0.24 per 10,000 persons <18 years of age, or an estimated 1766 to 1798 pediatric patients

(diagnosed and undiagnosed) with HAE in the United States. Similarly, if we examine the pediatric population ≤12 years of age in the United States, then we have an estimated 1268-1286 patients (diagnosed and undiagnosed) with HAE, thus translating to an HAE prevalence of 0.24 per 10,000 persons ≤12 years of age in the United States. Based on the available information, it can be estimated that pediatric patients represent approximately 20% of the overall HAE patient population, which would correspond to <5,124 total pediatric patients in the European Union based on the overall prevalence of less than 0.5 per 10,000 persons (ie, <25,619 total HAE patients in the European Union, plus Iceland, Liechtenstein, and Norway, based on overall European population of 512,384,164 inhabitants on 01 Jan 2014 [EUROSTAT, 2015]) identified in the orphan drug designation in the EU for lanadelumab (EU/3/15/1551). Overall, the prevalence of patients who have HAE attacks is extremely low in the pediatric population under 6 years of age, as the median age for first symptom onset reported from large studies is generally higher than 6 years of age (Bork et al., 2006a; Bygum et al., 2011; Farkas, 2010; Roche et al., 2005).

2.4 Indication and Current Treatment Options

Management of HAE has evolved over the last 10 years from underdiagnosed disability and higher risk of death from asphyxiation if undiagnosed, towards self-administration and independence from inpatient treatment. Effective management of HAE, including optimization of therapy, may reduce the clinical burden and have an overall favorable impact on the quality of life for individual HAE patients and their families (Banerji, 2013; Caballero et al., 2014). HAE International treatment guidelines state that the goal of prophylactic treatment is to reduce the frequency and severity of attacks and thus to increase patients' quality of life (Cicardi et al., 2012; Craig et al., 2012b). Current prophylactic options for HAE have improved the lives of HAE patients, but have significant limitations (Longhurst, 2017). The treatment guidelines recommend C1-INH or attenuated androgens as the standard of care over antifibrinolytic agents (Cicardi et al., 2012; Craig et al., 2012b). The most recent WAO & EAACI guidelines recommend C1-INH as first-line long-term prophylactic therapy (androgens as second-line). Antifibrinolytics are not recommended due to the lack of efficacy in long-term prophylaxis (LTP) (Maurer et al., 2018). Given the serious morbidity and mortality associated with HAE, including a 50% lifetime chance of experiencing a life-threatening laryngeal attack (Bork et al., 2003; Bork et al., 2006a), improved prophylactic treatments are needed for patients with HAE.

A patient with HAE, regardless of age, is a candidate for a prophylactic regimen if a number of criteria are met which may include: events in life that are associated with increased disease activity, attack frequency or severity, history of laryngeal attacks, impact on quality of life including work and school performance, proximity to emergency care, physiological or psychological stress, etc. (Craig et al., 2009; Maurer et al., 2018). Like adults, children with HAE can suffer from recurrent and debilitating attacks. Symptoms may present very early in childhood, and upper airway angioedema has been reported in patients with HAE as young as the age of 3 years (Bork et al., 2003), and an earliest occurrence described in one 4-week old boy (Maurer et al., 2018). There is an unmet medical need for safe, effective and convenient prophylactic therapies for children <12 years of age with HAE (Craig et al., 2012a). Treatments available for adult HAE patients have been evaluated in a limited number of children

(Frank et al., 2016). In the European Union (EU), few treatments are approved for use in pediatric patients under the age of 12 years: Firazyr (icatibant) for acute attacks in only; Berinert (C1 esterase inhibitor [human]) for acute attacks and pre-procedure prevention for patients under 12 years of age, and Cinryze (C1 esterase inhibitor [human]), for acute treatment and pre-procedure prevention for patients at 2-17 years of age and for prevention of attacks for patients at 6-17 years of age with intravenous (IV) administration twice a week. In the United States, IV Berinert is available for acute treatment for children under the age of 12, and Cinryze has recently been approved for routine prophylaxis for children 6 to <12 years of age with IV administration twice a week. An unmet medical need still exists, especially for an effective and more convenient (eg, no venous access required or less frequent administration) prophylactic treatment for HAE in children <12 years of age.

Lanadelumab, a first-in-class monoclonal antibody inhibitor of active plasma kallikrein, may provide significant benefit to patients across age ranges, based on the results of a 26-week prevention study in adolescents and adults with HAE. Lanadelumab has a convenient dosing schedule with a recommended starting dose of 300 mg every 2 weeks (q2wks) and a dosing interval of every 4 weeks (q4wks) if the patient is well controlled or stably attack free (eg, for more than 6 months) in adolescent and adults; a similar a convenient dosing interval of q2wks or q4wks has been proposed for the pediatric population in this study as well. In addition, lanadelumab has a favorable route of administration (SC) and demonstrated efficacy in preventing HAE attacks, achieving a high proportion of patients being attack free while improving health related quality of life (HRQoL).

The targeted indication of lanadelumab (SHP643, DX-2930) is for prophylaxis to prevent attacks of HAE in patients aged 12 years and older.

Refer to the latest version of the lanadelumab investigator's brochure [IB] for details.

2.5 Product Background and Clinical Information

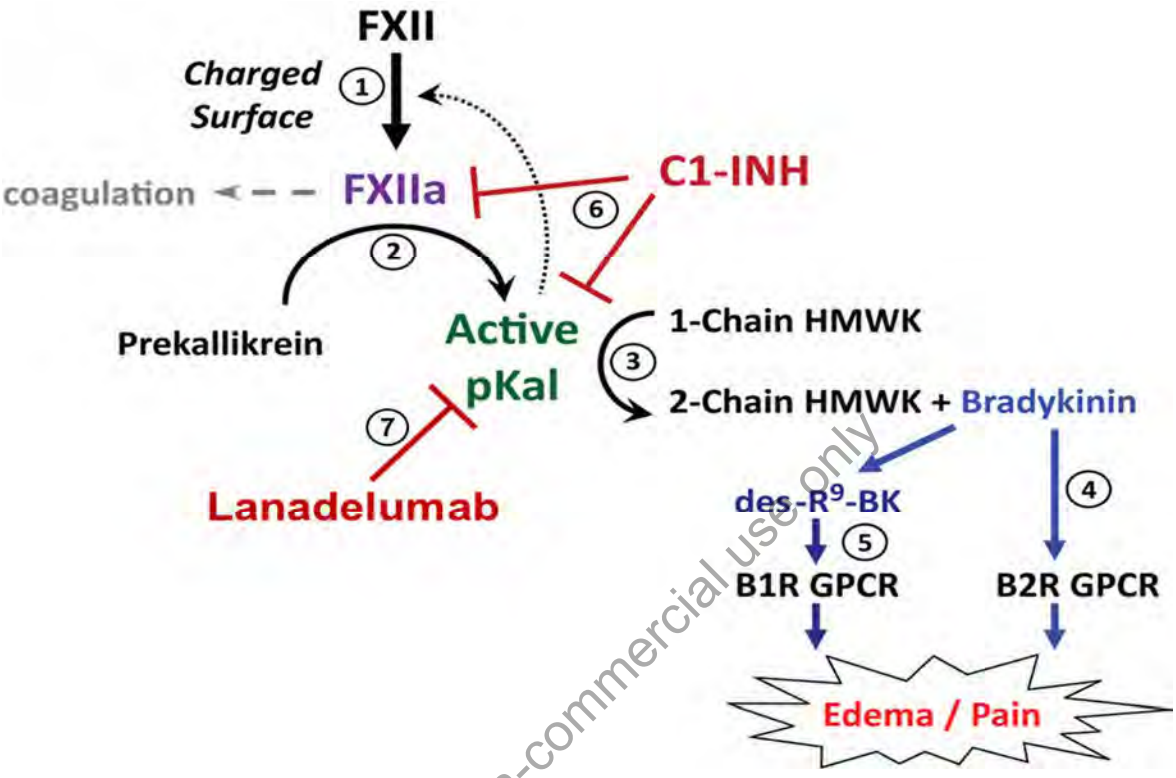
2.5.1 Drug Information

Mechanism of Action

Lanadelumab is a fully human, immunoglobulin G1 (IgG1) kappa light chain monoclonal antibody expressed in Chinese hamster ovary (CHO) cells. It is a potent (inhibition constant=125 pM) and specific inhibitor of active plasma kallikrein (pKal) activity that binds both soluble and membrane-bound forms of the enzyme (Kenniston et al., 2014). Lanadelumab was designed to specifically bind active pKal as opposed to prekallikrein, the zymogen form of the enzyme mainly present in plasma. This specificity of lanadelumab for active pKal indicates that the main form of the antibody in the circulation is free to inhibit the excess amount of pKal generated during an attack enabling near normal levels of enzyme activity prior to reversible inhibition by the antibody. Nonclinical data demonstrates that the specific inhibition of pKal by lanadelumab prevents the release of bradykinin from HMWK. Inhibition of bradykinin generation prevents the vascular leak and swelling during an angioedema attack initiated when bradykinin binds to the B2 receptor (Figure 1). The pharmacokinetic (PK) properties of lanadelumab offer the potential for a long-acting and sustained therapeutic effect (administration

q2wks or q4wks) through the control of pKal activity, limiting both contact system activation as well as the generation of bradykinin in patients with HAE.

Figure 2 Lanadelumab Specifically Inhibits Plasma Kallikrein (pKal)



The kallikrein-kinin system (KKS or contact system) is initiated by the autoactivation of the Factor XII zymogen to XIIa following contact with a negatively charged surface (1), leading to the conversion of prekallikrein to active pKal (2), which cleaves HWMK to generate cleaved HMWK (2-chain or cleaved HMWK) and bradykinin (3). In addition, pKal will activate more FXII (dotted arrow) and FXIIa can initiate coagulation via the intrinsic pathway (dashed arrow). Bradykinin binds and activates the bradykinin B2 receptor (4) and following plasma exoprotease generation of des-Arg9 bradykinin (5), the bradykinin B1 receptor. The KKS is dysregulated in HAE patients that are deficient in C1-INH (6), an endogenous inhibitor of active pKal and FXIIa. Lanadelumab (7) is a potent and specific, fully human antibody inhibitor of pKal engineered to restore normalized pKal regulation in HAE due to C1-INH through the lack of binding to prekallikrein, which is expected to permit low levels of pKal activity prior to being reversibly inhibited (Adapted from Kenniston et al., 2014).

Dosage Form

The drug product is a sterile, preservative-free, ready-to-use solution with a lanadelumab concentration of 150 mg/mL provided in a single-use 2 mL glass vial (150 mg/1 mL).

For use in children less than 12 years, the same formulation and presentation used for adolescents and adults aged 12 years and above are planned. The proposed presentation is a solution in vial (150 mg/mL) where the full 1 mL (150 mg) dose will be withdrawn from the vial and administered to the subject.

Route of Administration

Lanadelumab is formulated as a liquid for injection and is intended for SC administration in the abdomen, thigh, or upper arm.

2.5.2 Nonclinical Studies with Lanadelumab

The completed nonclinical safety studies evaluating SC administration of lanadelumab for up to 6 months in cynomolgus monkeys adequately support the pediatric patient population ages ≥2 to <12 years (refer to the latest version of the lanadelumab IB).

The nonclinical program conducted to date indicated no safety signal or toxicity with SC administered lanadelumab at doses of up to and including the highest tested dose (50 mg/kg, once weekly) for 6 months in cynomolgus monkeys. At the no-observed-adverse-effect-level (NOAEL) in the 6-month cynomolgus monkey study, exposure margins based on maximum observed concentration (C_{max}) occurring at t_{max} and area under the drug concentration-time curve (AUC) were approximately 22- and 23-fold higher, respectively, than those observed at the clinical dosage of 300 mg q2wks (Study DX-2930-03).

The battery of genotoxicity studies routinely conducted for pharmaceuticals is not applicable to biotechnology-derived pharmaceuticals and therefore was not conducted. Carcinogenicity studies were not conducted. A weight-of-evidence approach indicates a low risk for carcinogenicity in humans as lanadelumab is a fully human immunoglobulin molecule that does not target any hormonal or cell proliferation pathways; the pharmacologic mechanism of action does not pose an increased risk for carcinogenicity, nor is there evidence from any of the preclinical studies for an increased risk of hyperplasia, preneoplasia, or neoplastic lesions.

Nonclinical juvenile toxicology studies were not performed. However, the range of ages of cynomolgus monkeys used in the completed repeat-dose toxicity studies correspond to juvenile/adolescents to adults in human (Baldrick, 2010; Morford et al., 2011). Furthermore, no effects on development parameters were noted in an enhanced pre-and post-natal development (ePPND) study conducted in cynomolgus monkeys. In the ePPND study in pregnant cynomolgus monkeys administered once weekly SC doses, there were no lanadelumab-related effects on pregnancy and parturition or embryo-fetal development. In the infants maintained for 3 months post-partum, exposure to lanadelumab was dose-proportional to maternal dose and no lanadelumab-related defects on survival, growth, and/or postnatal development were noted. It is expected that the exposure of infants to lanadelumab during the fetal period and during the first 3 to 6 months of postnatal life covers many critical periods relevant to human development (Martin and Weinbauer, 2010). Since no specific target organ toxicity or toxicity relevant for developing organ systems was observed in cynomolgus monkeys administered lanadelumab, no additional nonclinical studies are planned to support the administration of lanadelumab in the pediatric population in clinical trials.

2.5.3 Clinical Studies with Lanadelumab

The proposed indication of lanadelumab for routine prophylaxis to prevent attacks of HAE in patients 12 years and older is primarily supported by the efficacy results from a double-blind, placebo-controlled Phase 3 study (DX-2930-03). Supportive data, including durability of

response and long-term safety, are provided from the open-label, Phase 3 study (DX-2930-04) and the proof of concept, Phase 1b, multiple ascending dose study (DX-2930-02). Prior to evaluating lanadelumab in subjects with HAE, a randomized, double-blind, placebo-controlled, Phase 1a, single ascending dose study evaluated the safety, tolerability, and PK of a single dose of lanadelumab in healthy adult subjects (DX-2930-01). Refer to the latest version of the lanadelumab IB for more details on the outcome from these 4 clinical studies.

Clinical study DX-2930-01 evaluated the safety, tolerability, and PK of a single dose of lanadelumab (0.1, 0.3, 1.0, or 3.0 mg/kg) in healthy subjects. The data demonstrated that lanadelumab was well tolerated by healthy subjects up to doses of 3.0 mg/kg without evidence of dose-limiting toxicity. The PK profile demonstrated linear, dose-dependent exposure with a mean half-life of approximately 17 to 21 days across dose groups. The exposure was dose proportional and the half-life was consistent across the dose groups.

Clinical study DX-2930-02 evaluated the safety, tolerability, and PK of 2 doses of lanadelumab (30, 100, 300, or 400 mg) separated by 14 days in HAE subjects and demonstrated that lanadelumab was well tolerated following 2 doses up to 400 mg. There were no deaths, serious adverse events (SAEs), discontinuations due to an adverse event (AE), or safety signals following lanadelumab treatment. One SAE of pneumonia was reported in a placebo-treated subject. Two subjects treated with lanadelumab tested positive for anti-drug antibodies (ADAs), which were not classified as neutralizing. The PK profile of lanadelumab is consistent and predictable, with a half-life of approximately 14 days in HAE subjects. Pharmacodynamic (PD) activity of lanadelumab was associated with plasma drug levels. Doses of 300 and 400 mg suppressed pKal activity and reduced kininogen cleavage to the levels observed in healthy subjects. In a prespecified efficacy analysis, a statistically significant finding of HAE attack prevention by lanadelumab was observed. Specifically, in comparison to placebo, attack rate was reduced by 100% and 88% in the 300 and 400 mg lanadelumab treatment groups, respectively. The effects on HAE attacks were associated with drug exposure. Safety results from the multiple-ascending dose study in HAE patients, in conjunction with results from the single-ascending dose study in healthy subjects and the current nonclinical data package, supported the continued clinical development of lanadelumab in patients with HAE.

Lanadelumab clinical development program has 2 Phase 3 clinical studies in adolescent (≥12 to <18 years old) and adult subjects with documented diagnosis of Type I or Type II HAE: the pivotal, double-blind Study DX-2930-03 and the open-label extension Study DX-2930-04.

Study DX-2930-03 (HELP Study™) was a multicenter, randomized, double-blind, placebo-controlled, parallel group efficacy and safety study to evaluate lanadelumab for LTP against acute attacks of HAE. Adolescent and adult patients with Type I or Type II HAE who experienced at least 1 attack per 4 weeks during the run-in period were included in this study. Based on PD bioactivity, PK, safety, and efficacy of lanadelumab from the Phase 1 clinical studies and nonclinical studies, the dosing regimens identified for this study were: 300 mg q2wks, 300 mg q4wks, and 150 mg q4wks. The 3 proposed dose-regimen combinations provide a 6-fold range of steady-state trough concentrations and leverage both the biomarker and efficacy data generated in study DX-2930-02. Evaluation of the lanadelumab plasma concentrations at the

time of attacks reported by lanadelumab-treated subjects in DX-2930-02 suggested that the 3 planned dosing regimens would provide a meaningful range of clinical response.

The primary objective of the study was to evaluate the efficacy of lanadelumab in preventing HAE attacks. The secondary objective was evaluation of the safety of repeated SC administration of lanadelumab. Each subject underwent a treatment period consisting of 13 doses of blinded investigational medicinal product (IMP) for a period of 26 weeks from the date of the first dose on Day 0 through 2 weeks after the final dose (for the 150 mg q4wks and 300 mg q4wks regimens, every second dose was placebo). Over the 26-week treatment period, all 3 lanadelumab dose regimens, 150 mg q4wks, 300 mg q4wks, and 300 mg q2wks, resulted in a highly statistically significant percentage reduction in the least squares mean investigator-confirmed HAE attack rate compared with placebo of 76%, 73%, and 87% (adjusted $p<0.001$), respectively, for the primary endpoint. During the estimated steady-state 16-week period (Day 70 through Day 182), the percentage reduction in the mean monthly HAE attack rates for lanadelumab-treated subjects compared with placebo was 78% in the 150 mg q4wks arm, 81% in the 300 mg q4wks arm, and 91% in the 300 mg q2wks arm. Furthermore, all 3 lanadelumab regimens demonstrated highly statistically significant attack rate reductions compared with placebo for all secondary efficacy analyses (adjusted $p<.001$ for all comparisons): attacks requiring acute treatment (74% to 87%), moderate or severe attacks (70% to 83%), and attacks from Day 14 through Day 182 (75% to 89%). The mean reduction in HAE attack rate was consistently higher across the lanadelumab treatment arms compared with placebo regardless of the baseline history of LTP therapy, laryngeal attacks, or attack rate during the run-in period. Notably, the magnitude of the treatment effect was consistently the largest across all endpoints in the lanadelumab 300 mg q2wks treatment arm compared with the lanadelumab q4wks arms. Lanadelumab treatment resulted in a high proportion of subjects being attack free during the 26-week treatment period and it is notable that once steady state was achieved, especially for the 300 mg q2wks group, 77% of subjects were attack free for 16 weeks. The evidence of prevention of HAE attacks was indicated by sustained decreased frequency of attacks, decreased severity of attacks, reduced need for rescue medication (acute treatment), and improved health-related quality of life (HRQoL) based on angioedema quality of life (AE-QoL) scores. Lower cleaved high molecular weight kininogen (cHMWK) levels corresponded with higher lanadelumab plasma concentrations and lower investigator-confirmed HAE attack rate (attacks/month/4 weeks), thus corroborating the outcome of the primary efficacy analysis. Lanadelumab was generally well tolerated over the 26-week treatment period; no treatment-related SAEs or deaths were reported. No discernible dose-response pattern or dose-related toxicity was observed for any related treatment-emergent AE (TEAE). Two subjects (1 lanadelumab treated and 1 placebo) discontinued the study due to a TEAE. The overall incidence of ADA in the pivotal study was 11.9% in lanadelumab-treated subjects and 4.9% in placebo-treated subjects. No subject discontinued treatment due to the presence of ADA. All ADA-positive samples were of low titer (range: 20-1280), and a few (3.2%; 2 subjects in lanadelumab 150 mg q4wks treatment arm) tested positive for antibodies classified as neutralizing. The development of ADA including neutralizing antibodies did not appear to impact PK, PD, efficacy, or safety profiles.

Study DX-2930-04 (HELP Study Extension™) was an open-label, long-term safety and efficacy extension study of DX-2930-03 to evaluate the IMP, lanadelumab, in preventing acute angioedema attacks in patients with Type I or Type II HAE.

The open-label extension study DX-2930-04 has been completed. The study enrolled 212 total subjects, including 109 who rolled over from DX-2930-03 and 103 nonrollover subjects. At the time of the interim analysis based on the data cutoff date of 31 August 2018, the safety profile in this study was consistent with the pivotal Study DX-2930-03 and previous interim analysis (data cutoff date of 01 Sep 2017) for the global marketing license or authorization applications for lanadelumab. No treatment-related SAEs or deaths were reported. Treatment-emergent AEs for most subjects were mild or moderate in severity with few reported severe events considered related to lanadelumab treatment. Lanadelumab 300 mg q2wks remained highly effective during this extension study for rollover and nonrollover subjects. Efficacy was maintained and shown to be durable with over 12 months of lanadelumab exposure across Study DX-2930-03 and Study DX-2930-04 for rollover subjects. Improved HRQoL based on AE-QoL scores were observed for rollover and nonrollover subjects.

In addition, a Phase 1 clinical study, SHP643-101, evaluated the PK properties and the safety of lanadelumab administered as a single subcutaneous dose of 300 mg in healthy male and female adult volunteer subjects of Japanese descent and matched non-Hispanic, Caucasian healthy male and female volunteer subjects. The data indicated that the peak and systemic exposure to lanadelumab (C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$) in healthy Japanese subjects was similar to that observed in healthy Caucasian subjects. Lanadelumab was generally safe and well tolerated by both ethnic groups.

2.5.4 Adolescent Clinical Trial Experience

The Phase 3 clinical studies for lanadelumab, pivotal Study DX-2930-03 and the open-label extension Study DX-2930-04, evaluated the adult and adolescent population; inclusion of adolescents in these studies was justified based on the similarity of the pathophysiology and clinical presentation of HAE in adults and adolescents, as well as by the lack of any safety signal identified in nonclinical and clinical studies to date. As of the data cut for the global marketing license or authorization application for lanadelumab, 23 unique adolescent subjects across the 2 Phase 3 studies received a total of 413 doses of lanadelumab, most of which were 300 mg.

Both Phase 3 studies demonstrated superior efficacy compared to placebo or baseline and well tolerated safety profiles in both adolescent and adult populations. In the pivotal Study DX2930-03, although the number of adolescent subjects was low (150 mg q4wks=1; 300 mg q4wks=3; 300 mg q2wks=2, placebo = 4), overall, a lower mean (SD) HAE attack rate during the treatment period was observed in the 6 lanadelumab-treated pediatric subjects (0.254 [0.284]) compared to the mean (SD) HAE attack rate in the 4 placebo-treated pediatric subjects (0.917 [0.992]), and the results were consistent with the results observed in the well represented age groups ≥18 to <40 and ≥40 to <65 years. A similar observation was made for <18 years of age (N=8) in the rollover population in Study DX2930-04 and for the nonrollover subjects who were <18 years of age (N=13). All pediatric subjects had >50% reduction in HAE attack rate relative to the run-in period or the pretreatment baseline.

Lanadelumab was generally well-tolerated by subjects across the clinical development program. The pediatric study in patients with HAE, <12 years of age, is being initiated after the completion of the 26-week long pivotal Phase 3 study and a mean (SD) duration of exposure of 19.98 (4.942) months with a maximum of 26.1 months of data from the Phase 3 long-term safety clinical study in patients with HAE, including adolescents (Study DX-2930-04 Interim Analysis 2 data cutoff on 31 August 2018).

In the 23 unique adolescent subjects who participated across Phase 3 Studies DX-2930-03 and DX-2930-04, no relevant differences between the TEAE profile for pediatric subjects and that reported for adult subjects were identified. The most frequently reported treatment-related TEAE was injection site pain. No adolescent subjects had reported investigator-confirmed AESIs in Study DX-2930-03 or at the time of the interim analysis data cut of 31 August 2018 in Study DX-2930-04. One adolescent subject in the lanadelumab treatment arms in Study DX-2930-03 had 1 unrelated severe, serious TEAE of catheter site infection. As of the data cut of 31 August 2018, one rollover adolescent subject in Study DX-2930-04 had 1 unrelated severe, serious TEAE of suicidal ideation. There were no deaths or discontinuations in adolescent subjects due to TEAEs during the treatment period in the pivotal Phase 3 study or its open-label extension study.

No safety signals were identified in terms of clinical laboratory hematology or coagulation, laboratory test abnormalities, vital signs, physical examination or ECGs. Overall, the safety and tolerability of lanadelumab were similar in the pediatric population (12 to <18 years old) and adults (≥18 years old).

Based on analyses of PK parameters for adolescents and adults in Phase 3 studies, no influence of age was apparent on clearance (CL/F) of lanadelumab after correcting for body weight. Based on the evaluation of PK, efficacy and safety, no dosing regimen adjustment has been recommended for adolescents (12 to < 18 years). Refer to the latest lanadelumab investigator's brochure.

2.6 Study Rationale

No safety signal has been identified in nonclinical and clinical studies of lanadelumab, to date, which supports the administration of lanadelumab in the pediatric population ≥2 to <12 years of age in the proposed clinical study.

A significant unmet medical need for effective and safe treatment options exist among children (2 to <12 years of age) with HAE (see Section 2.4 for current treatment options). Like adults, children with HAE can experience recurrent, debilitating, and life-threatening upper airway attacks. The unpredictable nature of HAE attacks in children results in significant decrements in vocational and school achievement, which impact the overall quality of life (Caballero et al., 2014). Prophylactic treatment with lanadelumab may be beneficial for children based on demonstrated efficacy, safety, and tolerability in adults and adolescents with the reduced treatment burden of a low volume, infrequent, SC administration.

Proteins in the complement and the plasma kallikrein-kinin systems reach adult maturity levels at 6 to 36 months of age, the occurrence of which may precede or coincide with the early onset of

symptoms in patients with HAE (Davis et al., 1979; Nielsen et al., 1994; Bork, 2013). The similarity of pathophysiology and clinical symptoms for HAE attacks between adults and children suggest the involvement of plasma kallikrein and bradykinin in both groups of patients, with similar treatment recommendations (Maurer et al., 2018; Sabharwal and Craig, 2017; Kuhlen and Banerji, 2015). The specificity of lanadelumab was engineered to maintain basal plasma kallikrein activity, as observed in the Phase 3 studies (DX-2930-03 and DX-2930-04) using the PD biomarker cHMWK, which approximated or slightly exceeded that of healthy controls (Banerji et al., 2017). Thus, lanadelumab should provide significant benefit to young children suffering from HAE.

2.7 Benefit/Risk Assessment

Clinical studies with lanadelumab demonstrated the improved efficacy and safety for routine prophylaxis to prevent and control symptoms of HAE in patients 12 years and older (Section 2.5.3 and Section 2.5.4; refer to the latest version of the lanadelumab IB).

From a benefit/risk perspective, lanadelumab was generally well tolerated by subjects with HAE across the clinical program and has not shown safety limitations. There were no deaths and few subjects withdrew due to TEAEs. There were no discontinuations of treatment due to TEAEs in adolescent subjects in any of the Phase 3 studies (until the interim data cut of 01 Sep 2017).

In the pivotal study (DX-2930-03), lanadelumab was generally well tolerated over the 26-week treatment period. No discernible dose-response pattern or dose-dependent or limiting toxicity was observed for any related TEAEs. The safety profile in the Phase 3 open-label study (DX-2930-04) was consistent with the pivotal study. Across both Phase 3 studies, changes in hematology, coagulation, and chemistry laboratory parameters over time were small and no clinically relevant trends were observed, especially in adolescent subjects. Overall, there were no clinically meaningful changes in vital signs and physical findings. No subject receiving treatment with lanadelumab had an abnormal, clinically significant ECG result.

Across both Phase 3 studies, 5.0% of lanadelumab-treated subjects reported SAEs, and none of them were related to lanadelumab treatment. There was no discernible pattern or commonality to the events reported as SAEs. One adolescent subject randomized to 300 mg q2wks treatment arm in pivotal Study DX-2930-03 had a serious, severe TEAE of catheter site infection that required hospitalization 138 days after the first dose of the investigational product. No action was taken with the investigational product due to the SAE. Treatment for the SAE included acetaminophen, vancomycin, ibuprofen, and piperacillin/tazobactam and removal of the catheter. The event was not considered related to the investigational product and resolved after a duration of 3 days. The subject completed the study and enrolled in the extension study (DX-2930-04). No serious or severe TEAEs were reported in the adolescent population until the interim data cut of 01 Sep 2017 for the open-label extension Study DX-2930-04.

In Study DX-2930-03, most frequently reported TEAEs in lanadelumab treated adolescent subjects were in the following system organ class (SOC): general disorders and administration site conditions (4 subjects, 66.7%), infections and infestations (3 subjects, 50.0%), and skin and SC tissue disorders (3 subjects, 50.0%). In Study DX-2930-04, the most frequently reported

TEAEs in lanadelumab treated pediatric subjects were in the following SOCs: infections and infestations (11 subjects, 52.4%), general disorders and administration site conditions (9 subjects, 42.9%), gastrointestinal disorders (5 subjects, 23.8%), and nervous system disorders (2 subjects, 9.5%). Overall, 3 lanadelumab treated adolescent subjects (50.0%) had a total of 13 treatment related non-HAE TEAEs, all of which were in the SOC of general disorders and administration site conditions in Study DX-2930-03. The most common preferred term (PT) was injection site pain (3 subjects, 50.0%). Similarly, in Study DX-2930-04, overall, 9 adolescent subjects (42.9%) had a total of 65 treatment related TEAEs. Treatment emergent AEs were most frequently reported in the SOC of general disorders and administration site conditions (8 subjects, 38.1%). The most frequently reported treatment related TEAE was injection site pain (8 subjects, 38.1%). All other treatment related TEAEs occurred in only 1 subject each.

Prespecified identified risks associated with the use of lanadelumab or other monoclonal antibodies include injection site reactions (ISRs) (identified risk) and hypersensitivity (important identified risk).

The most frequently reported non-HAE TEAEs in the overall lanadelumab-treated population were ISRs. Most (90.8%) ISRs were considered related to treatment and were mild or moderate in intensity. No subject reported an ISR that was serious, severe, or that resulted in discontinuation of treatment. The majority (66.4%) of ISRs were ≤0.5 hour duration, with 89.2% of all ISR AEs ≤1 day duration. Analyses of TEAEs by duration of exposure showed no evidence of dose-limiting toxicity, repetitive events, or late-emergent safety concerns (eg, more serious events or AESIs) with longer term exposure.

An important identified risk was hypersensitivity. Hypersensitivity reactions were prespecified AESIs due to the theoretical risk associated with monoclonal antibodies, including anaphylactoid events or anaphylaxis. The incidence of hypersensitivity was low (1.8%) in lanadelumab-treated population and there were no events of anaphylaxis observed in both phase 3 studies. It was at the investigator's discretion the PT used to report the AESI AEs. Few investigator-defined AESIs were reported in the pivotal study: 1 subject in the 300 mg q2wks arm had 2 related events reported as hypersensitivity reactions (1 mild and 1 moderate in severity), which included symptoms of tingling, itchiness, and discomfort of the tongue, dry cough, and mild headache and 3 lanadelumab-treated subjects from 1 clinical site (1 in each dosing arm) had a total of 5 related events (all mild in severity) that were investigator-defined AESI, with the PTs of ISR, erythema, or induration (all "delayed or recall ISR" according to the principal investigator). No anaphylaxis or anaphylactoid events were reported and none of the subjects with these AESIs developed ADAs. No investigator-defined AESI of hypersensitivity were reported in the placebo group.

In the open-label Phase 3 extension study (DX-2930-04), 7 investigator-reported hypersensitivity AESIs occurred in 6 subjects (4 in rollover subjects and 3 in non-rollover subjects).
Three hypersensitivity reactions and 4 ISRs in 3 subjects were classified as hypersensitivity. All of the hypersensitivity AESIs were classified as related to treatment, and 3 of the subjects discontinued (hypersensitivity reactions [rash at site of injection and slight swelling under the eyes; edema, wheals and joint pain] and ISR papules). One AESI of hypersensitivity was classified as related and severe because it coincided with an HAE attack and ongoing disease.

However, no anaphylaxis and no anaphylactoid reactions were observed and none of the subjects with these AESIs developed ADAs.

Besides hypersensitivity, disordered coagulation (bleeding events or hypercoagulable events potentially associated with the mechanism of action of lanadelumab, an active plasma kallikrein inhibitor) was a prespecified AESI. One adult subject in Study DX-2930-03 diagnosed with gastroesophageal reflux had an investigator-reported AESI, 1 mild event of microcytic anemia, although screening hemoglobin and hematocrit were below the normal range and there was no actual event of "bleeding" reported. Two subjects had 4 investigator-reported AESIs of vaginal bleeding in Study DX-2930-04 (1 subject had uncontrolled hypothyroidism and the other subject had comorbidity of uterine adenomyosis). None of these 4 events were related to lanadelumab treatments or required dosing interruption.

No adolescent subject across both Phase 3 studies had any investigator-reported AESI of hypersensitivity, or AESIs with PT of ISRs, or disordered coagulation, until the interim analysis data cut on 01 Sep 2017.

An important potential risk associated with the use of lanadelumab or other monoclonal antibodies includes immunogenicity. The overall incidence of ADA in the pivotal study was 11.9% in lanadelumab-treated subjects and 4.9% in placebo-treated subjects. Pre-existing ADA of low titer was observed in 3 lanadelumab-treated subjects and 1 placebo-treated subject at baseline. No subject discontinued treatment due to the presence of ADA. All ADA-positive samples were of low titer (range: 20-1280), and 2/84 or 2.4% lanadelumab-treated subjects tested positive for antibodies classified as neutralizing. The overall prevalence of ADAs in treated subjects in Study DX-2930-04 was 9.0% (19 of 212 subjects), which included 12 rollover and 7 non-rollover subjects. Six subjects developed ADAs classified as neutralizing. All titers were low (between 20 and 320). Formation of ADAs or neutralizing antibodies had no observable effect on the PK, PD, efficacy or safety profiles.

In Study DX-2930-03, one 12-year-old adolescent subject in lanadelumab 300 mg q4wks treatment arm was positive for transient, low titer non-neutralizing ADA with no apparent clinical consequence. This subject rolled over to Study DX-2930-04 and was positive for low titer (titer =80) ADA classified as neutralizing with no apparent clinical consequence. Another 13-year old adolescent rollover subject previously treated with placebo was positive for transient low titer (titer=80) non-neutralizing ADA in Study DX-2930-04 with no apparent clinical consequence.

Overall, the safety and tolerability of lanadelumab are similar in adolescent population 12-17 years old and adults (≥18 years old). Although the number of adolescent subjects aged ≥12 to <18 years was small (N=23) across pivotal Phase 3 study and its open-label extension), no relevant differences between the TEAE profile for adolescent subjects and that reported for adult subjects were identified.

In summary, the known biology of the drug target, does not identify any particular safety risks for the pediatric population. Safety signals have not emerged from all available clinical and nonclinical data to date for systemically administered lanadelumab. The proposed pediatric study

is being initiated after completion of one 26-week long pivotal study and after obtaining 16 months of safety data from the long-term safety study patients with HAE, including adolescents 12 to 17 years of age. This development program has thus enabled the safety of chronic lanadelumab therapy to be characterized first in this broader population before exposing children younger than 12 years old to lanadelumab. Frequent safety assessments will be conducted throughout this pediatric study (see Schedule of Activities, Table 2 and Table 3).

Always refer to the latest version of the lanadelumab IB for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, pharmacokinetics, efficacy, and safety of lanadelumab.

2.8 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, 1996; ICH E6 R2, 2016), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives (2001/20/EC; 2005/28/EC), and applicable national and local regulatory requirements.

The responsibilities of the study sponsor and investigator(s) are described fully in Appendix 1.

3. OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

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

3.1.2 Secondary Objectives

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 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]

3.2 Study Endpoints

A list of endpoints which support the study objectives are tabulated below. A detailed description of endpoints and the planned statistical analysis are provided in Section 9.

Table 4 Objectives and Endpoints

Objective	Endpoint(s)
Primary	
1. To evaluate the **safety** of lanadelumab in children (2 to <12 years of age) with HAE.	**Measures of safety include:** • Adverse events including SAEs and AESI. • Clinical laboratory testing (hematology, clinical chemistry, coagulation) • Vital signs including blood pressure, heart rate, body temperature, and respiratory rate.
2. To evaluate the **pharmacokinetics** (**PK)** of lanadelumab in children (2 to <12 years of age) with HAE.	**Measures of PK 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: o $C_{max,ss}$: Maximum observed concentration at steady state o $C_{avg,ss}$: Average concentration over dosing interval at steady state o $C_{trough,ss}$: Predose concentration at steady state o t_{max}: Time to reach C_{max} in plasma o $AUC_{tau,ss}$: Area under the concentration-time curve over the dosing interval at steady state o $t_{½}$: Terminal half-life o CL/F: Apparent clearance o V/F: Apparent volume of distribution
Secondary	
1. 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.	Clinical outcome measures are secondary endpoints for the study. 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: • 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.

Table 4 Objectives and Endpoints

Objective	Endpoint(s)
	• 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
2. To characterize the **pharmacodynamics (PD)** of lanadelumab in children (2 to <12 years of age) with HAE	• Plasma kallikrein activity (as measured by cHMWK level).
3. 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.	• Measured by presence or absence of neutralizing or non-neutralizing anti-drug antibody in plasma
[redacted]	[redacted]

AESI=adverse event of special interest; [redacted]; cHMWK=cleaved high molecular weight kininogen; HAE=hereditary angioedema; SAE=serious adverse event; [redacted]

4. STUDY DESIGN

4.1 Overall Design

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 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

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.

Section 4.3 provides justification for the dosing regimen proposed for this study. See the following for more details:

- Section 2.5.1 for the route of administration for the study
- Section 2.6 for the rationale for this study

- Section 4.2 for the discussion around the study design
- Section 6.2.3 for dosing frequency and timing
- Appendix 5 for HAE attack collection
- Section 8.2.6.7 for administration of lanadelumab by a subject (aged 6 years or older) or parent/caregiver (hereafter referred to as self-administration)

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 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 2.

4.2 Scientific Rationale for Study Design

At this time no safety signal has been identified in nonclinical (see Section 2.5.2) and clinical studies of lanadelumab, including 26-week long repeat-dose treatment in Phase 3 clinical studies with adolescent and adults subjects with HAE (see Section 2.5.3 and Section 2.5.4), which supports the administration of lanadelumab in the pediatric population 2 to <12 years of age in this open-label, uncontrolled Phase 3 study. Study SHP643-301 aims to provide knowledge on the safety, PK, PD and clinical outcomes of lanadelumab for prevention of attacks in children aged 2 to <12 years with Type I or Type II HAE.

Hereditary angioedema is usually diagnosed in the first or second decade of age as disease symptoms appear. While occasional severe attacks have been reported, children overall have less severe symptoms than adults or adolescents (Bork et al., 2006a; Bygum et al., 2011). The severity of HAE increases at puberty (Bork et al., 2006a; Bygum et al., 2011; Farkas, 2010; Roche et al., 2005; Gompels et al., 2005b).

As mentioned in Section 2.3 (epidemiology in pediatric population), the prevalence of patients who experience HAE attacks is extremely low in the pediatric population under 6 years of age; the mean age for first symptom onset reported from large studies is 6 to 12 years of age (Bork et al., 2006a; Bygum et al., 2011; Farkas, 2010; Roche et al., 2005). The low prevalence of HAE symptoms in children younger than 6 years of age also leads to particularly difficult diagnosis of this pathology and corresponds to an extremely small potentially treatable

population. Long-term prophylactic treatment is seldom necessary for the pediatric population under the age of 6 years old because frequent HAE symptoms are rare before this age (Farkas, 2010; Jolles et al., 2014; MacGinnitie, 2014), and international treatment guidelines currently recommend that on-demand therapy for attacks in children is preferable, as opposed to LTP, unless the patient has frequent, severe attacks that disrupt education and family life (Craig et al., 2012b; Farkas, 2010; Farkas et al., 2007). Therefore, although enrollment will be open to children 2 to <12 years of age, the target enrollment is at least 5 subjects in the 2 to <9 year age group and at least 5 subjects in the 9 to <12 year age group.

Definitive diagnosis of HAE in patients under the age of 2 years is difficult given clinical and unreliable diagnostic challenges. Serum levels of complement system components, including C4 and C1-INH, which form the basis for the diagnosis of HAE, do not stabilize until up to 3 years of age (Davis et al., 1979; Roach et al., 1981). The proportion of patients under 2 years of age who manifest symptoms and have a confirmed diagnosis of HAE requiring treatment for HAE attacks is not known and it is difficult to estimate. However, it is likely to be a very small subpopulation. Giving prophylactic treatments to patients for whom a diagnosis of HAE is not properly confirmed would result in exposing this younger population to suboptimal prophylactic therapy. Therefore, patients <2 years of age are not planned to be included in this pediatric study.

For this pediatric study, PK/PD modelling and simulations were employed to inform pediatric lanadelumab dosing regimens in 2 to <12 years old, using an aggregate of available data from clinical studies of lanadelumab in adults and adolescents (see Section 2.5.3 and Section 2.5.4). As characterized by modeling and simulation, lanadelumab exposure, as seen with other monoclonal antibodies, is associated with body weight. A weight-adjusted modeling approach for dose selection is reasonable and has been conducted. Currently available safety and nonclinical toxicity data support a wide safety margin for dosing. See Section 4.3 for further details on the rationale for the planned pediatric dosing regimens.

Extrapolation of efficacy data from adults to pediatrics is reasonable, given that there are no known differences in the clinical presentation (other than a lower frequency and severity of attacks in pre-adolescent children) or differences in underlying pathophysiology for HAE between the two populations. PK and PD data from the Phase 1b study (DX-2930-02), together with additional data from the 26-week long Phase 3 studies (DX-2930-03 and DX-2930-04 [interim analysis data]), provide a robust dataset against which the PK and PD data obtained from the pediatric study will be assessed in extrapolating efficacy. The extrapolation may be supplemented by clinical outcomes data from this pediatric study if subjects have sufficiently high baseline attack frequencies, which will provide additional supportive clinical efficacy. This study applies the endpoint measures similar to those used in the Phase 3 studies in adults and adolescents.

Initial feasibility evaluations, together with the well-recognized rarity of disease (particularly in pre-adolescent patients who have less frequent and less severe attacks), indicate that the number of subjects who may realistically enroll in this study will be low. Broadening the range of attack rate frequency in the entry criteria will be helpful towards recruiting subjects for the study. The proposed enrollment number will be sufficient to facilitate meaningful PK assessment, efficacy

extrapolation and long-term safety evaluation (duration of subject participation exceeds 12 months, including a 52-week long treatment period).

In summary, this open-label, uncontrolled, study aims to provide knowledge on the safety, PK, PD and clinical outcomes of lanadelumab for prevention of attacks in children aged 2 to <12 years with HAE.

4.3 Justification for Dose

Based on the population PK modeling and simulation using the previously established population PK model, the similarity of etiology of HAE between adult, adolescent, and pediatric subjects with HAE, and body weight distribution information on the related age groups, the proposed dose regimens for pediatric subjects 2 to <12 years are:

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

The above-proposed lanadelumab dose regimens for pediatric subjects are expected to provide similar exposure to lanadelumab 300 mg q2wks, the recommended dose regimen in the lanadelumab prescribing information for adults and adolescents with HAE based on the results of the pivotal Phase 3 HELP Study® (Study DX-2930-03). The Phase 3 clinical studies for lanadelumab, pivotal Study DX-2930-03 and open-label extension Study DX-2930-04, evaluated the adult and adolescent population; inclusion of adolescents in these studies was justified based on the similarity of the pathophysiology and clinical presentation of HAE in adults and adolescents (Bork et al., 2003; Farkas, 2010; Bennett and Craig, 2015; Zuraw, 2008) which was confirmed in the clinical trial, as well as the lack of any safety signal identified in nonclinical and clinical studies to date. In the two Phase 3 studies, DX-2930-03 and DX-2930-04, PK, PD, and exposure-response data were available in a total of 6 and 21 adolescents (including rollovers from Study DX-2930-03), respectively. Overall, the efficacy and safety profile of lanadelumab in adolescents was similar to that in adults. Based on post-hoc analyses of PK parameters for adolescents (12 to <18 years, N=21) and adults (18 to 65 years, N=180) in Study DX-2930-04 for up to 1 year of treatment, no influence of age was CL/F of lanadelumab after correcting for body weight. Based on mean estimated PK parameters, as expected, an approximately 37% higher exposure (area under the concentration-time curve over the dosing interval at steady state [$AUC_{tau,ss}$]) in adolescents than adults (18 to 65 years), was observed. Based on the evaluation of PK, efficacy, and safety, no dosing regimen adjustment has been recommended for adolescents (12 to <18 years).

The dose regimens proposed for children 6 to <12 years old and 2 to <6 years old are based on population PK modeling and simulation using the final population PK model, and similarity of etiology of HAE between adult, adolescent and pediatric subjects with HAE (Farkas, 2010; Bennett and Craig, 2015). Using the final population PK model and the Centers for Disease Control and Prevention information on the body weight distribution, the exposure to lanadelumab in these age groups (N=1000 per age group; body weight range: 8.99 to 76.1 kg) have been simulated and estimated. The results show that the proposed fixed-dose regimen of lanadelumab 150 mg q2wks for children 6 to <12 years of age and lanadelumab 150 mg q4wks

for children 2 to <6 years of age (see Table 5 and Table 6) are expected to provide similar exposure to lanadelumab 300 mg q2wks observed in adults and adolescents, the fixed-dose regimen which demonstrated the optimal benefit-risk profile in Phase 3 studies. Hence, these simulation results are expected to support the fixed-dose regimens proposed to be tested in pediatric subjects 2 to <12 years. Notably, lanadelumab 300 mg q2wks provides exposure approximately above the maximal inhibitory concentration (IC_{90}) of cHMWK, $EAUC_{90}$ for clinical response in the majority of subjects across a large range of body weight (46.8-150 kg), and the safety profile supports lanadelumab 300 mg q2wks as the recommended fixed-dose regimen, including adolescent population. Meanwhile, understanding the need for clinicians to individualize therapy, including an opportunity for flexible dosing regimen, and thus, extending the dosing interval beyond every 2 weeks, to every four weeks, represents a [redacted] benefit for patients and would be considered if the subjects are well controlled (eg, attack free for 26 weeks) on the recommended dose.

Table 5 Lanadelumab Exposure in Virtual Pediatric Patients (6 to <12 years, 150 mg q2wks) Relative to Patients with HAE ≥12 years (300 mg q2wks)

Age Group	Descriptive Statistics	$AUC_{0\text{-}2week,ss}$ (µg•day/mL)	$C_{avg,ss}$ (ng/mL)	$C_{max,ss}$ (ng/mL)	$C_{min,ss}$ (ng/mL)	CL/F (L/h)	V_c/F (L)	$t_{1/2}$ (h)
6-<12 years 150 mg q2wks	n	1416	1416	1416	1416	1416	1416	1416
	Mean (SD)	505 (130)	36100 (9310)	40400 (10200)	29600 (7950)	0.0132 (0.00356)	7.68 (1.65)	408 (20.8)
	CV%	25.8	25.8	25.3	26.9	26.9	21.5	5.11
	Median	499	35600	39900	29200	0.0125	7.38	409
	Min	233	16600	18900	13200	0.0066	4.42	352
	Max	944	67400	74500	56600	0.0268	13.6	463
≥12 years 300 mg q2wks	n	211	211	211	211	211	211	211
	Mean (SD)	474 (166)	33800 (11800)	38700 (13500)	26900 (9530)	0.0292 (0.0112)	14.4 (4.09)	354 (45.1)
	CV%	34.9	34.9	34.9	35.4	38.5	28.4	12.7
	Median	469	33400	38000	26800	0.0261	13.3	349
	Min	121	8670	10400	7590	0.0123	7.52	247
	Max	1050	74800	84900	60500	0.0822	31.3	507
Ratio 6-<12 years versus ≥12 years	Median	1.06	**1.07**	**1.05**	**1.09**	0.479	0.553	1.17
	Min	0.496	**0.497**	**0.498**	**0.491**	0.253	0.331	1.01
	Max	2.01	**2.02**	**1.96**	**2.11**	1.03	1.02	1.33

$AUC_{0\text{-}2week,ss}$=area under the curve over 2 weeks at steady state; $C_{ave,ss}$=average concentrations at steady state; CL/F=apparent clearance; $C_{max,ss}$=maximum observed concentration at steady state; $C_{min,ss}$=minimum observed concentration at steady state; $t_{1/2}$=terminal elimination half-life; V_c/F=apparent volume of distribution

Note: Descriptive statistics for ratios were derived by dividing individual PK parameters in children by the median value in patients with HAE ≥12 years.

Table 6 Lanadelumab Exposure in Virtual Pediatric Patients (2 to <6 years, 150 mg q4wks) Relative to Patients with HAE ≥12 years (300 mg q2wks)

Age Group	Descriptive Statistics	$AUC_{0\text{-}4\ week,ss}$ (µg•day/mL)	$C_{avg,ss}$ (ng/mL)	$C_{max,ss}$ (ng/mL)	$C_{min,ss}$ (ng/mL)	CL/F (L/h)	V_c/F (L)	$t_{1/2}$ (h)
2-<6 years 150 mg q4wks	n	584	584	584	584	584	584	584
	Mean (SD)	969 (186)	34600 (6660)	45600 (8320)	22000 (4650)	0.00668 (0.00130)	4.44 (0.692)	464 (17.4)
	CV%	19.2	19.2	18.3	21.1	19.4	15.6	3.75
	Median	958	34200	45100	21700	0.00651	4.36	465
	Min	535	19100	26000	11400	0.00400	2.95	415
	Max	1560	55600	71600	36900	0.0117	6.98	511
≥12 years 300 mg q2wks	n	211	211	211	211	211	211	211
	Mean (SD)	949 (331)	33800 (11800)	38700 (13500)	26900 (9530)	0.0292 (0.0112)	14.4 (4.09)	354 (45.1)
	CV%	34.9	34.9	34.9	35.4	38.5	28.4	12.7
	Median	937	33400	38000	26800	0.0261	13.3	349
	Min	242	8670	10400	7590	0.0123	7.52	247
	Max	2100	74800	84900	60500	0.0822	31.3	507
Ratio 2-<6 years/≥12 years	Median	1.02	**1.02**	**1.19**	**0.810**	0.249	0.327	1.33
	Min	0.57	**0.571**	**0.682**	**0.426**	0.153	0.221	1.19
	Max	1.66	**1.66**	**1.88**	**1.38**	0.447	0.523	1.46

$AUC_{0\text{-}4week,\ ss}$=area under the curve over 4 weeks at steady state; $C_{avg,\ ss}$=average concentrations at steady state; CL/F=apparent clearance; $C_{max,\ ss}$=maximum observed concentration at steady state; $C_{min,\ ss}$=minimum observed concentration at steady state; $t_{1/2}$=terminal elimination half-life; V_c/F=apparent volume of distribution

Note: Descriptive statistics for ratios were derived by dividing individual PK parameters in children by the median value in patients with HAE ≥12 years.

4.4 Duration of Subject Participation and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 72 weeks. Individual subject participation from screening through the completion of safety follow-up visit will include: up to 4-week screening period, up to 12- week baseline observation period, 52-week treatment period, and a 2 or 4-week post-treatment safety follow-up visit. The study will be completed in approximately 72 weeks.

The Study Completion Date is defined as the date on which the last subject in the study completes the final protocol-defined assessment(s). This includes the follow-up visit or contact, whichever is later (refer to Section 8.1.4 for the defined follow-up period for this protocol).

The Study Completion Date is used to ascertain timing for study results posting and reporting.

4.5 Sites and Regions

This is a multicenter study. Approximately 18 sites in North America (United States, Canada) and Europe (Germany, Spain, Hungary) will participate.

5. STUDY POPULATION

At least 20 pediatric subjects (male or female) age 2 to <12 years of age with HAE Type I or II are planned to be enrolled and treated with lanadelumab, including at least 5 subjects in each age group of 2 to <9 years and 9 to <12 years. Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed. Inclusion and exclusion criteria for enrolling subjects in this study are presented in Section 5.1 and Section 5.2, respectively.

5.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

1. Be a child (male or female) 2 to <12 years of age at the time of screening.
2. Documented diagnosis of HAE (Type I or II) based upon both of the following:
   - Documented clinical history consistent with HAE (SC or mucosal, nonpruritic swelling episodes without accompanying urticaria);
   - Diagnostic testing results obtained during screening from a sponsor-approved central laboratory that confirm C1-INH functional level <40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. With prior sponsor approval, subjects may be retested during the baseline observation period if results are incongruent with clinical history or believed by the investigator to be confounded by recent C1 inhibitor use.
3. A historical baseline HAE attack rate of at least 1 attack per 3 months. **Note**: In addition, subjects who experience ≥1.0 angioedema attacks per three months during the 12-week baseline observation period and who remain eligible per the inclusion criteria will enter the lanadelumab treatment period.
4. Agree to adhere to the protocol-defined schedule of treatments, assessments, and procedures.
5. Have a parent(s)/legal guardian who is informed of the nature of the study and can provide written informed consent for the child to participate in the study before any study-specific procedures are performed (with assent from the child when appropriate).
6. Females of childbearing potential must agree to be abstinent or agree to comply with the applicable contraceptive requirements of this protocol through the duration of the study from screening through 70 days after the final study visit.

5.2 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met.

1. Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema (AAE), HAE with normal C1-INH, idiopathic angioedema, or recurrent angioedema associated with urticaria.
2. Dosing with an investigational drug or exposure to an investigational device within 4 weeks prior to screening.
3. Be pregnant or breastfeeding.
4. Have initiated androgen treatment (eg, stanozolol, danazol, oxandrolone, methyltestosterone, and testosterone) within 2 weeks prior to entering the observation period.
5. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
6. Have any active infectious illness or fever defined as an oral temperature >38°C (100.4°F), tympanic >38.5°C (101.3°F), axillary >38°C (100.4°F), or rectal/core >38.5°C (101.3°F) within 24 hours prior to the first dose of study drug in Treatment Period A.
7. Have any HAE attack that is not resolved prior to the first dose of study drug in Treatment Period A.
8. Have any of the following liver function test abnormalities: alanine aminotransferase (ALT) >3x upper limit of normal (ULN), or aspartate aminotransferase (AST) >3x ULN, or total bilirubin >2x ULN (unless the bilirubin elevation is a result of Gilbert's syndrome).
9. Have any condition (any surgical or medical condition) that, in the opinion of the investigator or sponsor, may compromise their safety or compliance, preclude the successful conduct of the study, or interfere with interpretation of the results (eg, significant pre-existing illness or other major comorbidity that the investigator considers may confound the interpretation of study results).
10. Subject has a known hypersensitivity to the investigational product or its components.

5.3 Restrictions

5.3.1 Medical Interventions

Medical interventions deemed necessary by the investigator for the health and well-being of the subjects will not be excluded during this study.

5.3.2 Fluid and Food Intake

There are no restrictions on fluid and food intake. Subjects may continue their usual dietary regimens.

5.3.3 Activity

There are no activity restrictions. Subjects may continue their usual activity regimens.

5.4 Reproductive Potential

A study of lanadelumab in cynomolgus monkeys does not indicate effects on embryo-fetal development (see the latest version of lanadelumab IB). Lanadelumab has not been studied in pregnant women, and there are limited data from its use in pregnant women. However, a risk to the pregnant woman or developing fetus cannot be excluded. Therefore, a decision should be made whether to initiate or discontinue treatment with lanadelumab, taking into account the risk/benefit of therapy.

No evidence of testicular toxicity or adverse effects on male fertility or teratogenicity transferable to a fetus/embryo from animal studies were observed (see the latest version of lanadelumab IB).

5.4.1 Female Contraception

Female subjects should be either:

- Premenarchal and either Tanner stage 1 or less than age 9 years, or
- Females of childbearing potential with a negative urine beta-human chorionic gonadotropin (β-hCG) pregnancy test prior to first dose on Study Day 0 (Visit 1). Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Sexually active females of childbearing potential should use a medically acceptable form of contraception. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period and for 70 days following the last dose of investigational product. If used, hormonal contraceptives should be administered according to the package insert. Any female of childbearing potential who is not currently sexually active must agree to use acceptable contraception, as defined below, if she becomes sexually active during the study and for 70 days following the last dose of investigational product.

Acceptable methods of contraception include the following:

- Intrauterine devices (IUD, all types) or intrauterine hormone releasing systems (IUS) plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Progestin-only contraceptive associated with inhibition of ovulation (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the screening visit, plus condoms. Note: If subject becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

Note: estrogen-containing medications with systemic absorption are not allowed in the study.

5.4.2 Male Contraception

The study population includes male children <12 years of age. Therefore, male contraception is not required in this study.

6. STUDY INTERVENTION

6.1 Investigational Product

6.1.1 Identity of Investigational Product

The investigational product is lanadelumab, which will be provided as solution in a vial (150 mg/mL) where the full 1 mL (150 mg) dose will be withdrawn from the vial and administered to the subject. Additional information regarding the dosage forms is provided in the latest version of the lanadelumab IB or the medication guide.

6.1.2 Blinding the Treatment Assignment

Not applicable. This is an open-label study.

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

An Interactive Response Technology (IRT) vendor will be used for this study to manage packaged IMP supply, IMP shipments, receipt of IMP at clinical sites, assignment of IMP to subjects, expiry tracking, IMP returns, and IMP accountability.

6.2.2 Allocation of Subjects to Treatment

This is an open-label study. Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a study), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The Medication Identification Number (MedID) represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined. Individual subject treatment is automatically assigned by the IRT.

6.2.3 Dosing

Lanadelumab injection will be administered SC in the abdomen, thigh, or upper arm.

The lanadelumab dose regimens are:

- 150 mg q2wks for subjects 6 to <12 years old; a total of 27 doses over the 52-week treatment period, and
- 150 mg q4wks for subjects 2 to <6 years old; a total of 14 doses over 52-week treatment period.

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.

Modification of these dosing regimens may be considered for subjects in one or both age groups following an interim PK analysis, and modification of the dosing regimen for individual subjects may be considered based on a benefit-risk assessment; refer to Section 6.2.5 for details.

The presentation is a solution in vial (150 mg/mL) where the full 1 mL (150 mg) dose will be withdrawn and administered to the subject.

Table 7 presents the frequency and timing of dose administration.

Table 7 Treatment Period Dosing Schedule

Lanadelumab 150 mg every 2 weeks[a] (for subjects 6 to <12 years)[b]		**Lanadelumab 150 mg every 4 weeks (for subjects 2 to <6 years)[b]**	
Dose Number	**Study Visit/Study Day/Study Week**	**Dose Number**	**Study Visit/Study Day/Study Week**
Treatment Period A			
1	Visit 1/Day 0/Week 0	1	Visit 1/Day 0/Week 0
2	Visit 3/Day 14/Week 2		
3	Visit 4/Day 28/Week 4	2	Visit 4/Day 28/Week 4
4	Visit 6/Day 42/Week 6		
5	Visit 8/Day 56/Week 8	3	Visit 8/Day 56/Week 8
6	Visit 10/Day 70/Week 10		
7	Visit 12/Day 84/Week 12	4	Visit 12/Day 84/Week 12
8	Visit 14/Day 98/Week 14		
9	Visit 16/Day 112/Week 16	5	Visit 16/Day 112/Week 16
10	Visit 18/Day 126/Week 18		
11	Visit 20/Day 140/Week 20	6	Visit 20/Day 140/Week 20
12	Visit 22/Day 154/Week 22		
13	Visit 24/Day 168/Week 24	7	Visit 24/Day 168/Week 24
14	Visit 26/Day 182/Week 26		
Treatment Period B			
15	Visit 28/Day 196/Week 28	8	Visit 28/Day 196/Week 28
16	Visit 30/Day 210/Week 30		
17	Visit 32/Day 224/Week 32	9	Visit 32/Day 224/Week 32
18	Visit 34/Day 238/Week 34		
19	Visit 36/Day 252/Week 36	10	Visit 36/Day 252/Week 36
20	Visit 38/Day 266/Week 38		
21	Visit 40/Day 280/Week 40	11	Visit 40/Day 280/Week 40

Table 7 Treatment Period Dosing Schedule

Lanadelumab 150 mg every 2 weeks[a] (for subjects 6 to <12 years)[b]		Lanadelumab 150 mg every 4 weeks (for subjects 2 to <6 years)[b]	
Dose Number	**Study Visit/Study Day/Study Week**	**Dose Number**	**Study Visit/Study Day/Study Week**
22	Visit 42/Day 294/Week 42		
23	Visit 44/Day 308/Week 44	12	Visit 44/Day 308/Week 44
24	Visit 46/Day 322/Week 46		
25	Visit 48/Day 336/Week 48	13	Visit 48/Day 336/Week 48
26	Visit 50/Day 350/Week 50		
27	Visit 52/Day 364/Week 52	14	Visit 52/Day 364/Week 52

[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.

6.2.4 Unblinding the Treatment Assignment

Not applicable. This is an open-label study.

6.2.5 Dose Modification

The decision to continue with the proposed dose regimen or proceed with another dose regimen (either an increase or a decrease in the dose and/or dosing frequency) will be made by the sponsor's study team after 5 subjects receive at least 5 doses of lanadelumab, and an interim PK analysis is conducted to evaluate the dose regimens using available data.

An individual subject's dose frequency may also 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. Other modifications may be considered at the discretion of the investigator in consultation with the sponsor's medical monitor.

6.3 Labeling, Packaging, Storage, and Handling of Investigational Product

6.3.1 Packaging and Labeling

The open-label lanadelumab will be supplied by the sponsor and pre-packaged in a study kit for the study. Each study kit will contain 1 vial of investigational product. Both the vial and carton (kit) will be appropriately labeled according to local regulations and bear the unique study drug kit number. The investigative site will provide ancillary supplies including syringes, needles, and

alcohol wipes to subjects. The site has the option of using needles of a different gauge to aid subject comfort with each SC injection.

Detailed instructions on preparation and administration of investigational product will be provided to the clinical sites in a Pharmacy Manual.

Subjects (aged 6 years or older) or parents/caregivers who elect to self-administer investigational product, where permitted per protocol (see Section 8.2.6.7), will be provided the following supplies as applicable:

- 1 dose supply of investigational product
- Ancillary supplies, and a container for sharps disposal
- Subject accountability form to record investigational product administration details

All used and unused vials should be returned to the study kit cartons/boxes and transported to the site for drug accountability. Written instructions on lanadelumab handling and self-administration procedures will be provided to the trained subject (aged 6 years or older) or parent/caregiver prior to initiating self-administration. Refer to the Pharmacy Manual for additional details on lanadelumab and its administration.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

Labels containing study information and pack identification are applied to the investigational product(s) container.

All investigational product is labeled with a minimum of the following: protocol number, MedID number, lot number, expiry date, dosage form, directions for use, storage conditions, the sponsor's name, address, and telephone number, the statements “For clinical trial use only” and "Keep out of sight and reach of children". Any additional labeling requirements for participating countries will also be included on the label.

Space is allocated on the label so that the site representative can record the site number and subject number.

Additional labels may not be added without the sponsor’s prior full agreement.

6.3.2 Storage and Handling

Lanadelumab should be stored in a refrigerator at 2 to 8°C (36–46°F). Vials should be removed from refrigeration and allowed to get to room temperature before administration. Do not freeze. The vial should be protected from light in the original carton. Refer to the latest version of the IB for current stability data.

Before use, each vial of study drug should be inspected for appearance. Any vial containing visible particles or discoloration should not be used (any such issues should be reported to the

sponsor as per the instructions on the Product Quality Complaints page of this protocol). Avoid shaking or vigorous agitation of the vial.

Any unused contents of a vial of study medication should be discarded in accordance with local requirements for investigational materials. Intact vials of study medication that are not used during the course of the clinical study should be returned according to direction from the sponsor.

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject number on the investigational product vial/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering and dispensing investigational product (for dosing by site personnel and self-administration, respectively). Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer/dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered/dispensed medication will be documented in the subject's source and/or other investigational product record. The investigator is responsible for ensuring the retrieval of all study supplies from subjects**.** Due to the health/safety concerns with returning the investigational product container, the investigator must request that subjects keep the empty investigational product packaging after use and return it to the site for drug accountability purposes.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

With the written agreement of the sponsor, at the end of the study all unused stock, subject-returned investigational product, and empty/used investigational product packaging may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor. Destruction of investigational product must be in accordance with local, state, and national laws.

If the sponsor has not provided written agreement for destruction at the site or a local facility then, at the end of the study or as instructed by the sponsor, all unused stock, subject-returned investigational product, and empty/used investigational product packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational product being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated CRO). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Validated electronic return systems (ie, IRT) do not require a shipment form. Returned investigational product must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

Subjects must be instructed to bring unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed at the

container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (vials) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

6.6 Prior and Concomitant Therapy

All non-study treatment including but not limited to all prescriptions, over-the counter medications, herbal treatments, vitamins and supplements, behavioral treatment, non-pharmacological treatments and procedures (such as psychotherapy, surgical, diagnostic, or dental), as appropriate, received within 28 days (4 weeks) prior to the screening visit (or PK equivalent of 5 half-lives, whichever is longer) and through the final study contact (including protocol-defined follow-up period) must be recorded in the subject's source document following informed consent.

6.6.1 Prior Treatment

Prior treatment includes all non-study treatments received within 28 days (4 weeks) prior to screening visit (or PK equivalent of 5 half-lives, whichever is longer) up to the date of first dose of investigational product.

6.6.2 Concomitant Treatment

Concomitant treatment refers to all non-study treatments taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive.

Parents or caregivers should record in the subject's diary any medications taken by the subject for the management of HAE attacks during the baseline observation period and during the treatment period.

6.6.3 Permitted Treatment

The following concomitant therapies are allowed during the study:

- Therapies for co-existing conditions, including those for acute attacks of HAE, are permitted if not excluded during the study (see Section 6.6.4). Acute HAE attacks during the study will be managed in accord with the investigator's usual care of their patients, including use of individualized acute therapy that the investigator deems as medically appropriate. Use of C1-INH will be permitted as an acute attack therapy but not as LTP. Administration of lanadelumab and study procedures will continue without alteration to the protocol-specified study schedule, even if the subject has symptoms of an HAE attack the day of lanadelumab administration and/or receives treatment for an HAE attack. The administration of lanadelumab can also be re-scheduled as long as the minimum and maximum timeframe between doses are met based on subject preference or physician discretion.

- The use of short-term prophylactic treatment for HAE will be permitted if medically indicated. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or antifibrinolytics used to avoid angioedema complications from medically indicated procedures.
- Therapies to treat any AEs the subject experienced during the study will be permitted.

6.6.4 Prohibited Treatment

Use of the following treatments will not be permitted during the study:

- Long-term prophylaxis for HAE (eg, use of C1-INH for LTP, attenuated androgens, or antifibrinolytics) from the time that LTP is discontinued prior to the baseline observation period and during the study.
- Angiotensin-converting enzyme (ACE) inhibitors within 4 weeks prior to screening and during the study.
- Estrogen-containing medications with systemic absorption within 4 weeks prior to screening and during the study.
- Use of androgens (eg, stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) for non-HAE related medical conditions or for HAE, from discontinuation of these androgens at least 2 weeks prior to entering the observation period and throughout the study.
- Any other investigational drug or device.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

Subjects who prematurely discontinue investigational product, regardless of the reason, should undergo the end of study (EOS) visit procedures specified for Study Day 392 (Visit 56) whenever possible (see Section 8.1.4). Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for discontinuation of investigational product, date of discontinuation of the investigational product, and the total amount of investigational product administered must be recorded in the source documents.

Subjects who prematurely discontinue investigational product will not be replaced.

7.2 Reasons for Discontinuation

The reason for discontinuation (from treatment and/or the study) must be determined by the investigator and recorded in the subject's source document: subject's medical record and on the case report form (CRF). If a subject is discontinued for more than 1 reason, each reason should be documented in the source and the most clinically relevant reason should be indicated.

Reasons for discontinuation of study include, but are not limited to:

- Withdrawal of consent (by a parent or both parents/legal guardian for pediatric subjects)
- Adverse event (must specify on the CRF)
- Protocol deviation (eg, lack of compliance, use of experimental drug)
- Pregnancy
- Sponsor decision (must specify on the CRF)
- Investigator decision (must specify on the CRF)
- Death
- Lost to follow-up
- Lack of efficacy
- Other (must specify on the CRF)

7.3 Withdrawal from the Study

A subject may withdraw from the study at any time and for any reason without prejudice to his/her future medical care by the physician or at the institution, or may be withdrawn at any time at the discretion of the investigator or sponsor (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject with the medical monitor when possible.

7.4 Subjects "Lost to Follow-up" Prior to the Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject who is lost to follow-up at any time point prior to the last scheduled contact (office visit or site contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that the subject return to the site for final safety evaluations and return any unused investigational product.

7.5 Stopping Rules

7.5.1 Study Level Stopping Rules

Study data, including SAEs and AESI (as defined in Section 8.2.5.6), will be monitored regularly throughout the duration of the study. If any potential safety signal is identified as a result of monitoring in this study, the sponsor may take actions as deemed appropriate, including suspending dosing in the study, while the potential risk is evaluated and a course of action has been determined.

7.5.2 Individual Stopping Rules

Dosing for any individual subject will be discontinued if the subject experiences a lanadelumab-related SAE (or a lanadelumab-related, clinically-significant, non-serious AE) that, in the assessment of the investigator, warrants discontinuation from further dosing for that subject's well-being. The investigator has the ability to contact and consult with the medical monitor on such matters. Subjects who prematurely discontinue investigational product should undergo the EOS visit procedures specified for Study Day 392 (Visit 56) (see Section 8.1.4), unless they request to be immediately discontinued from the study without additional assessments.

7.5.3 Follow-Up for Subjects Meeting Stopping Criteria

Subjects that develop either an SAE or other toxicity considered clinically relevant (AE, laboratory, physical examination, or vital sign finding) will be carefully monitored until resolution, which may include the following:

- Additional clinical laboratory tests and/or other clinical investigations
- Additional visits or extended duration of follow-up
- Obtaining a specialist consultation

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Study Periods

Refer to Table 1, Table 2, and Table 3 for the schedule of study activities. Study assessments are detailed in Section 8.2.

8.1.1 Screening Period (up to 4 weeks)

Informed consent must be obtained before any study specific procedures are performed.

As indicated in Table 1, following procedures and assessments are to be performed during Screening:

- Informed consent
- Demographics, medical history, and HAE history
- Prior/current medications, therapies and procedures
- Vital signs including blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR)
- Complete physical examination, including documentation of height and weight.
- Tanner staging (for female subjects who are premenarchal and ≥9 years of age; see Section 5.4.1).
- Clinical laboratory testing including hematology, coagulation, and serum chemistry
- Functional C1-INH, C4, and C1q testing
- Virology testing for Hepatitis B surface antigen (HbsAg), Hepatitis C Virus (HCV), and Human Immunodeficiency Virus (HIV)
- Adverse events collection; pre-existing signs and symptoms

At the in-clinic visit of the screening period, the subject and their parent/caregiver should be given an HAE Attack Diary.

A subject should complete all screening procedures within 4 weeks. Eligibility review may be conducted by the site as screening data become available. A final eligibility review will be conducted prior to Day 0, after a subject has completed all screening procedures and all results are available.

A screen failure is a subject who has given informed consent and failed to meet all inclusion criteria and/or has met at least 1 of the exclusion criteria and has not been administered investigational product(s). Once a subject has been designated as a screen failure, the subject may be rescreened at the discretion of the investigator and following discussion with the sponsor medical monitor.

Subjects who complete all screening procedures and are determined to be eligible for the study may enter the baseline observation period (Section 8.1.2). After confirming a subject's eligibility, the site will contact the subject and their parent/caregiver to (a) notify them of study eligibility; (b) instruct the subject to discontinue long-term prophylactic therapy (if applicable) prior to entering the baseline observation period; and (c) instruct the subject or parent/caregiver to begin the daily diary of angioedema symptoms and attack monitoring (Appendix 5) on the first day of the baseline observation period.

8.1.2 Baseline Observation Period (up to 12 weeks)

As indicated in Table 1, eligible subjects will undergo a baseline observation period of up to 12 weeks to determine the baseline HAE attack rate. Subjects who were receiving LTP during the screening period must discontinue LTP prior to entering the baseline observation period.

During the baseline observation period, the following information will be collected on an ongoing basis, via parent/caregiver reporting in a daily diary and via site contacts at Weeks 2, 4, 6, 8, 10, and 12 (Note: The preferred method of site contact is a telephone call; however, an alternate method of contact may be considered as site policies permit):

- Daily diary of angioedema symptoms and attack monitoring (Appendix 5) (Note: Parent/caregivers must also report details of an attack to the study site within 72 hours of the onset of an HAE attack. [redacted].)
- Prior and current medications, therapies and procedures
- Adverse events collection, including SAEs and AESIs

Subjects who report more than 2 HAE attacks (as confirmed by the investigator in consultation with the sponsor's medical monitor) within the first 2 weeks may exit the baseline observation period after 2 weeks. All other subjects must stay in the baseline observation period for at least 4 weeks. Subjects who report at least 1 investigator-confirmed attack within the first 4 weeks may exit the baseline observation period after 4 weeks.

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.

8.1.3 Treatment Period

Refer to Table 7 for the dosing schedule in the treatment period.

8.1.3.1 Study Visit 1; Study Day 0

Visit 1 on Day 0 will be a scheduled on-site visit. The following procedures and assessments are to be performed on Day 0 prior to the first dose administration:

- Confirmation of eligibility criteria
- Vital signs, including body temperature, HR, BP and RR

- Complete physical examination (including body weight and height)
- Clinical laboratory testing including hematology, serum chemistry, and coagulation
- Pregnancy testing (urine) will be performed on females who have reached menarche
- Pharmacokinetic baseline sample collection
- Pharmacodynamic (cHMWK, [redacted]) baseline sample collection
- Baseline plasma ADA sample collection
- [redacted]
- Prior therapies, medications, and procedures
- Diary of angioedema symptoms and attacks (Appendix 5) (Note: Parent/caregivers must also report details of an attack to the study site within 72 hours of the onset of an HAE attack. [redacted]
- Adverse events collection, including SAEs and AESIs

As specified in Table 2, after lanadelumab administration (q2wks or q4wks; see Table 7), the following post treatment procedures and assessments will be performed:

- Lanadelumab injection report
- Vital signs including body temperature, HR, BP and RR 30 minutes post-dose
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

8.1.3.2 Study Visit 2-Visit 52; Study Day 4- Study Day 364

As indicated in Table 2 and Table 3 the following procedures and assessments are to be performed prior to the dose administration, as specified for a visit/study day during the treatment period:

- Vital signs including body temperature, HR, BP and RR
- Physical examination (including body weight)
- Clinical laboratory testing, including hematology, serum chemistry, and coagulation
- Pregnancy testing (urine or serum) will be performed on females who have reached menarche
- Pharmacokinetic predose sample collection
- Pharmacodynamic (cHMWK, [redacted]) predose sample collection
- Plasma ADA predose sample collection

- [redacted]
- Daily diary of angioedema symptoms and attacks (Appendix 5) (Note: Parent/caregivers must also report details of an attack to the study site within 72 hours of the onset of an HAE attack. [redacted]
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

As specified in Table 2 and Table 3, after lanadelumab administration (q2wks or q4wks; see Table 7), the following post treatment procedures and assessments will be performed:

- Lanadelumab injection report
- SC administration survey
- Vital signs including body temperature, HR, BP and RR 30 minutes post-dose
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

On-site visits will be scheduled at Visits 1, 2, 3, 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48, 52, and 56 (shaded columns in Table 2 and Table 3).

Site check-in calls will occur throughout the treatment period as specified in Table 2 and Table 3. If a subject does not have a scheduled on-site visit on study days specified in these tables, 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.

8.1.3.3 Final Treatment Visit (Study Visit 52; Study Day 364)

As indicated in Table 3, completion of treatment or last dose administration will occur on Day 364 or Visit 52 of the study. This will be a scheduled on-site visit. The following procedures or assessments will be performed prior to dose administration:

- Vital signs including body temperature, HR, BP and RR
- Physical examination (including body weight)
- Clinical laboratory testing, including hematology, serum chemistry, and coagulation
- Pregnancy testing (urine or serum) will be performed on females who have reached menarche

- Pharmacokinetic predose sample collection
- Pharmacodynamic (cHMWK, [redacted]) predose sample collection
- Plasma ADA predose sample collection
- [redacted]
- Diary of angioedema symptoms and attacks (Appendix 5) (Note: Parent/caregivers must also report details of an attack to the study site within 72 hours of the onset of an HAE attack. [redacted]
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

As specified in Table 3, after lanadelumab administration the following post treatment procedures and assessments will be performed:

- Lanadelumab injection report
- SC administration survey
- Vital signs including body temperature, HR, BP, and RR 30 minutes post dose
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

8.1.4 Follow-up Period

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 will occur on Study Day 378 (Visit 54). The preferred method of site check-in is a telephone call; however, an alternate method of contact may be considered as site policies permit. At the end of the 4-week follow-up period there will be a scheduled on-site EOS visit on Study Day 392 (Visit 56) to query for SAEs and AEs, and concomitant treatments. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Appendix 3.2). In addition, the following assessments and procedures will be performed:

- Vital signs including body temperature, HR, BP and RR
- Physical examination (including body weight)
- Clinical laboratory testing, including hematology, serum chemistry, and coagulation
- Pregnancy testing (urine or serum) will be performed on females who have reached menarche

- Pharmacokinetic sample collection
- Pharmacodynamic (cHMWK, [redacted]) sample collection
- Plasma ADA sample collection
- [redacted]
- Daily diary of angioedema symptoms and attacks (Appendix 5) (Note: Parent/caregivers must also report details of an attack to the study site within 72 hours of the onset of an HAE attack.)

8.1.5 Early Termination

All procedures and assessments scheduled for the EOS visit will be followed for the early termination (ET) visit (see Table 3).

8.1.6 Additional Care of Subjects after the Study

No aftercare is planned for this study.

8.2 Study Assessments

Please refer to the Study Schedule of Activities in Table 1, Table 2, and Table 3.

8.2.1 Informed Consent

Informed Consent (parent/caregiver) and Assent (child) forms must be approved for use by the reviewing institutional review board (IRB), research ethics board (REB) or independent ethics committee (IEC). Informed consent must be obtained for all subjects participating in the study prior to performing any study-related activities. Assent will also be obtained from each subject, where required in accordance with IRB/REB/IEC and local regulations, prior to performing any study-related activities. Subjects and their parent(s)/caregiver(s) may withdraw consent at any time. Participation in the study may be terminated at any time without the parent/caregiver's consent or child's assent as determined by the investigator.

8.2.2 Eligibility Review

The investigator or qualified site personnel will confirm that all Inclusion and Exclusion Criteria have been met as described in Section 5.1 and Section 5.2, respectively.

8.2.3 Demographic and Other Baseline Characteristics

Subject demographic information including gender, age, and race will be collected prior to the subject receiving the first dose of investigational product.

8.2.3.1 Medical and Medication History

Medical and medication history will be collected during screening and recorded in the subject's source documents.

8.2.4 Clinical Outcomes

8.2.4.1 Collection of Hereditary Angioedema Attacks

HAE attack information will be solicited by site personnel during scheduled study visits and site check-ins, as shown in Table 1, Table 2, and Table 3. In addition, study subjects (or parent/caregivers, in the event the subject is <18 years old or is incapacitated) will be instructed to report details of the HAE attack to the study site within 72 hours of the onset of the attack.

The collection, reporting and assessment of HAE attacks in this study will be done in accordance with the HAE Attack Assessment and Reporting Procedures (HAARP) provided in Appendix 5 of this protocol. Site personnel will be trained on HAARP prior to screening subjects at their site.

A high morbidity HAE attack is defined as any 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.

8.2.4.2 Management of Acute Hereditary Angioedema Attacks

As mentioned in Section 4.1, acute HAE attacks during the study are to be managed in accord with the investigator's usual care of their patients, including use of acute attack therapies that the investigator deems as medically appropriate. Use of C1-INH will be permitted as an acute attack therapy but not as LTP.

Administration of the investigational product and study procedures will continue without alteration to the protocol specified study schedule, even if the subject receives any treatment for an HAE attack.

8.2.5 Safety

8.2.5.1 Physical Examination

A physical examination (including body weight) will be performed by the investigator or his/her qualified designee according to the Study Schedule of Activities (Table 1, Table 2, and Table 3). The date and time of each examination will be recorded on the source documents and electronic CRF (eCRF). Adverse events emerging from any physical examination will be recorded on the source document and eCRF.

The physical examination will be performed in accordance with standards at the site. The physical examination will include, at a minimum, assessments of the body systems listed below:

- Weight
- General appearance
- Ears, nose, and throat
- Head and Neck
- Ophthalmological
- Respiratory

- Cardiovascular
- Abdomen
- Neurological
- Extremities
- Dermatological
- Lymphatic

In addition, height will be measured at the screening visit and Day 1 only.

The screening physical examination will also include Tanner staging for premenarchal female subjects who are ≥9 years of age. For such subjects, Tanner staging may also be performed during other physical examination assessments at the discretion of the investigator if clinically indicated.

Abnormalities identified at the screening visit and at subsequent study visits will be recorded in the subject's source documents.

8.2.5.2 Vital Signs

Vital signs will be assessed by the investigator or his/her qualified designee according to the Study Schedule of Activities in Table 1, Table 2, and Table 3. Routine vital sign assessments will be taken with the subject in the sitting or supine position after 5 minutes at rest and will include body temperature, HR, BP, and RR. Blood pressure should be determined using the same arm and the same equipment, and the same position for each assessment throughout the study.

During the study, additional vital signs measurements will be performed if clinically indicated.

Vital signs performed on dosing days should be obtained prior (within 60 minutes) to the start of the injection and 30 minutes (±15 minutes) after completion of the injection of study drug. Every effort should be made to measure and record vital signs prior to any blood sample collection.

The investigator will assess whether a change from baseline (predose, Visit 1/Day 0) in vital signs may be deemed clinically significant and whether the change should be considered and recorded as an AE.

8.2.5.3 Pregnancy Test

For all females who have reached menarche, pregnancy testing (β-hCG) will be performed at the time points specified in Schedule of Activities in Table 2 and Table 3; if pregnancy is suspected; or on withdrawal (early termination visit) of the subject from the study. Pregnancy testing at Day 0 will be urine-based. All other pregnancy testing in this study may be urine or serum based.

8.2.5.4 Clinical Laboratory Tests for Safety Assessments

A complete list of clinical laboratory tests to be performed to assess general safety parameters is provided in Appendix 2.

All clinical laboratory tests will be performed according to the laboratory's standard procedures, using established and validated methods. Reference ranges will be supplied by the laboratory and used to assess the results for clinical significance and out-of-range changes which may be associated with, or constitute, an AE. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

All safety laboratory assessments will be performed at a central laboratory. The clinical laboratory values will be reported to the investigator who will review them for clinical significance and consideration of abnormal values as potential AEs.

8.2.5.5 Adverse Events

Each subject will be monitored for the occurrence of AEs, including SAEs and AESIs, from signing of the informed consent form through the final follow-up visit:

- Subjects will be questioned and/or examined by the investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.
- The clinical outcomes endpoint, HAE attacks, will also be captured as AEs in this study (see details below).
- Subjects having treatment-emergent AEs (TEAEs) will be monitored until resolution with relevant clinical assessments and laboratory tests, as determined by the investigator. AEs, actions taken as a result of AEs, and follow-up results must be recorded in the eCRF as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.
- For any SAEs or AEs that require the subject to be discontinued from dosing, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s). Subjects who discontinue treatment will complete EOS visit procedures as described in Section 7.1.

All AEs, regardless of seriousness, severity, or causal relationship to study drug, will be recorded on the AE page of the eCRF (see exception below for HAE attack AEs). Any AE meeting criteria for an SAE, as defined in Appendix 3, must also be reported to the sponsor using the SAE Reporting Form within 24 hours of the site becoming aware of the event. All AESIs, as defined in Section 8.2.5.6, must also be reported to the sponsor using the same timelines as described for SAE reporting.

Further information on AE definitions, collection time frame, assessment of causality and severity, and safety reporting is provided in Appendix 3, Appendix 3.2, and Appendix 3.3, Appendix 3.4, respectively. Information on SAE collection time frame, onset/resolution dates,

and SAEs with a fatal outcome is presented in Appendix 3.5, Appendix 3.6, and Appendix 3.7, respectively.

The clinical outcomes endpoint, HAE attacks, will also be captured as AEs in this study. To avoid complicating the interpretation of safety, 2 mutually exclusive subgroups of AEs will be defined based on whether the AE is (or is not) identified in the eCRF as a subject-reported HAE attack:

- Non-HAE attack AEs will include the subset of AEs that are not identified in the eCRF as a subject-reported HAE attack. Essentially, this will be AEs excluding the subject-reported HAE attack events. **These non-HAE attack AEs will be reported on the AE page of the eCRF.** The severity of these AEs will be assessed according to the Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Table (Appendix 6).
- HAE attack AEs will include the subset of AEs identified in the eCRF as a subject-reported HAE attack. This will include, but will not be limited to, investigator-confirmed HAE attacks. **These HAE attack AEs will be reported on the designated angioedema attack page of the eCRF.** Severity of the HAE attack will be assessed in accordance with HAARP (Appendix 5), which includes an assessment using HAARP criteria and an assessment using DMID criteria.

For all SAEs that are reported as HAE attacks, the investigator will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. For all non-serious AEs that are reported as HAE attacks, the investigator will review the event within 7 days of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. If necessary for the evaluation, the investigator or designee may contact the subject for additional information. Any subject-reported attack not confirmed by the investigator must have an alternate AE diagnosis recorded. All subject-reported and investigator-confirmed HAE attacks will be recorded in the eCRF. Note: Hereditary angioedema is the indication for treatment and should be considered expected as the events are considered disease related (progression of underlying disease) and not subject to expedited reporting.

Emergency department visits for HAE attacks and HAE attacks resulting in hospital admissions will be captured in the eCRF.

8.2.5.6 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) will be captured and monitored during this study. **Investigators will report all AESI to the sponsor, regardless of causality, using the same timelines as described for SAE reporting.** The following describe the AESI and the criteria for reporting AESI.

Hypersensitivity Reactions

As hypersensitivity reactions have been observed for monoclonal antibodies as a class, these events are considered AESI for this study. Investigators will report all diagnoses, or signs and

symptoms when diagnoses cannot be determined, that are consistent with hypersensitivity reactions, regardless of causality, within 24 hours from the time of study drug administration. Investigators will report hypersensitivity reactions that occur after 24 hours, only if the reactions are suspected to be related to study drug.

Events of Disordered Coagulation

Bleeding AESI

Although activated partial thromboplastin time (aPTT) prolongation due to plasma kallikrein inhibition is an artifactual in vitro phenomenon, as a precautionary measure in evaluating the safety of lanadelumab, bleeding events will be reported as AESI for this study. Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with a clinical event of bleeding. Coagulation testing (aPTT, PT, INR) should be performed when possible, and when temporally reasonable, with any reports of bleeding or for clinical conditions possibly indicative of bleeding.

Hypercoagulable AESI

Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with a thrombotic or embolic etiology.

8.2.6 Other

8.2.6.1 Clinical Pharmacology

Blood samples for the measurement of plasma lanadelumab concentration will be obtained at the study days specified in Table 2 and Table 3. Samples should be obtained at pre-dose (ie, within 2 hours prior to dosing), with the exception of Day 4, Day 14 (for q4wks dose regimen only), and Day 182, when the samples may be collected at any time of the scheduled day. [redacted]

8.2.6.2 Pharmacodynamics

Blood samples for the measurement of cHMWK, [redacted] will be obtained at the study days specified in Table 2 and Table 3. Samples should be obtained at pre-dose (ie, within 2 hours prior to dosing), with the exception of Day 4, Day 14 (for q4wks dose regimen only), and Day 182, when the samples may be collected at any time of the scheduled day. [redacted]

8.2.6.3 Immunogenicity (Anti-drug Antibody Testing)

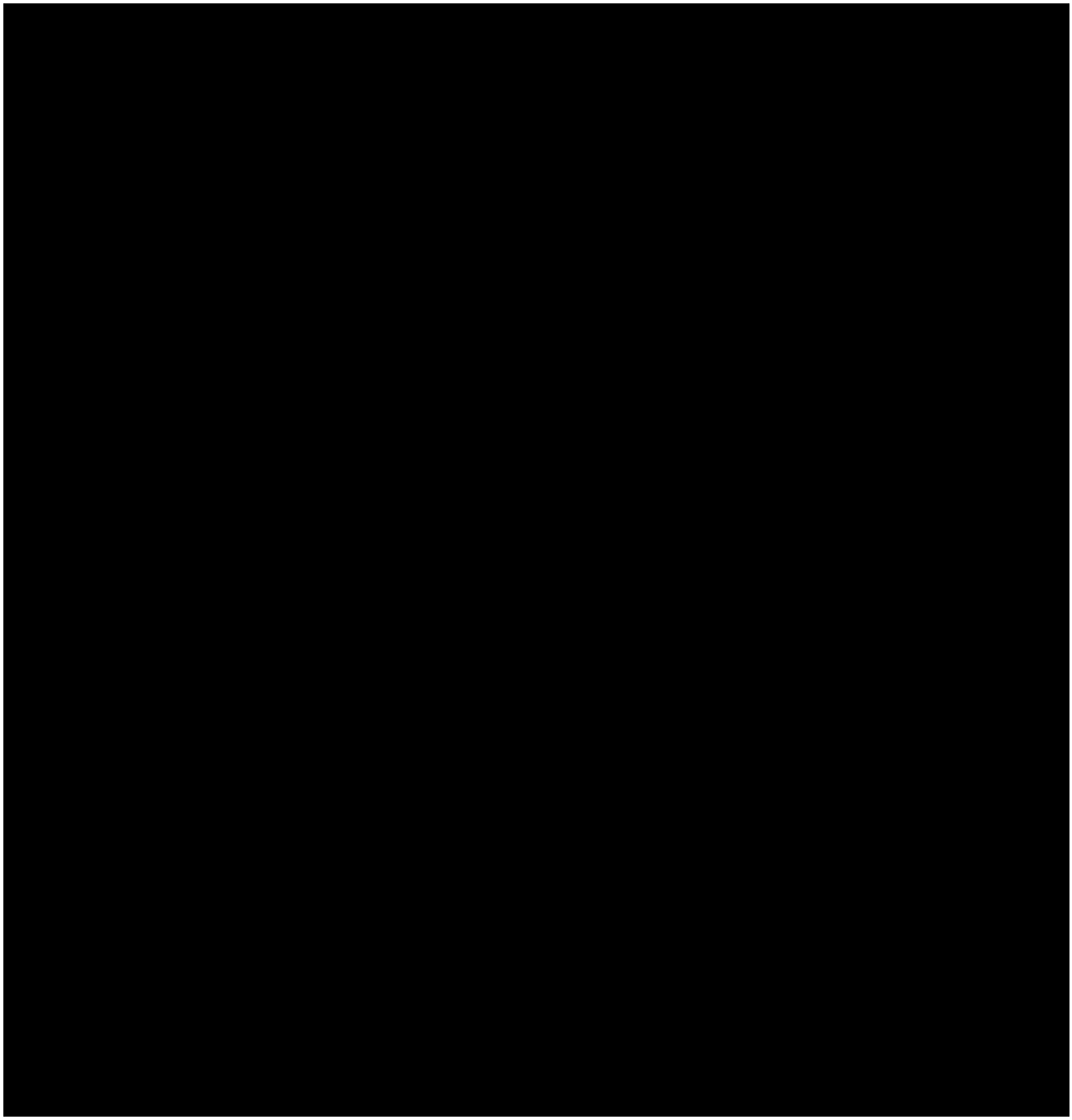
Immunogenicity will be measured based on the presence or absence of neutralizing or non-neutralizing ADA in plasma. Blood samples will be collected at the study days specified in Table 2 and Table 3. Samples should be obtained at pre-dose (ie, within 2 hours prior to dosing), with the exception of Day 4, Day 14 (for q4wks dose regimen only), and Day 182, when the samples may be collected at any time of the scheduled day. [redacted]

8.2.6.4 Biomarkers

Diagnostic Biomarkers (C1-INH, C1q, and C4)

One blood sample will be obtained at the screening visit for evaluation of C1-INH, C4, and C1q to confirm a diagnosis of HAE. Results of a C1-INH functional assay are required for eligibility assessment in all subjects. Results of the C4 assay are required for eligibility in subjects with a C1-INH level of 40-50%. With prior sponsor approval, subjects may be retested for C1-INH or C4 if results are incongruent with clinical history or believed by the investigator to be confounded by recent LTP use. Note: Because C1-INH therapy may alter the laboratory results of C1-INH functional assay, the investigator's discretion in collaboration with medical monitor is advised for proper documentation of eligibility.

[redacted]



8.2.6.6 Healthcare Resource Utilization

Not applicable.

8.2.6.7 Self-administration of Lanadelumab

Self-administration of lanadelumab is defined as administration by a subject (aged 6 years or older) or parent/caregiver, either at the clinic or in an offsite location. Self-administration of lanadelumab by the subject is **only** permitted for those aged 6 years or older who have demonstrated the necessary skills for self-treatment, as assessed the investigator. Subjects less than 6 years of age must have a parent/caregiver self-administer lanadelumab in this study.

Self-administration by the subject (aged 6 years or older) or parent/caregiver is allowed after the subject (aged 6 years or older) or parent/caregiver has received appropriate training by the investigator or designee and their understanding is confirmed. The subject (aged 6 years or older) or parent/caregiver may initiate self-administration in an offsite setting after the subject has received the first 2 doses of lanadelumab at the study site (administered by study personnel or health care provider) and may continue to self-administer all subsequent doses. The subject is required to return to the clinic for visits as outlined in the schedule of events. At these in-clinic visits, the subject (aged 6 years or older) or parent/caregiver may opt to continue to self-administer lanadelumab or opt for administration by study personnel or health care provider.

The investigator or designee will train subjects (aged 6 years or older) or parents/caregivers who elect to self-administer lanadelumab on the following:

- The parent/caregiver's transportation of investigational product using a sponsor-provided cooler, and the recommended storage conditions of investigational product when stored at an offsite location.
- Maintenance of accurate records regarding each administration of investigational product including supply identification (ie, lot/kit number), date and time of injection, injection site location, infusion time, and if applicable, any reason the self-administration could not be completed as instructed.
- Retention of all used and unused vials of investigational product for drug accountability purposes.
- Additional information, as provided in the Pharmacy Manual.

Site check-in will occur throughout the treatment period as specified in Table 2 and Table 3. If a subject does not have a scheduled on-site visit on study days specified in these tables, 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.

8.2.6.8 Injection Report and Subcutaneous Administration Survey

An Injection Report will be completed by the subject (aged 6 years or older) or subject's parent/caregiver following each dose of lanadelumab, according to the assessment schedule in Table 2 and Table 3. The Injection Report will collect information on the subject's experience with SC injection of lanadelumab. Study personnel will document the subject's responses in the subjects' medical record and eCRF.

A Subcutaneous Administration Survey will be completed by the subject (aged 6 years or older) or subject's parent/caregiver approximately every 3 months, according to the assessment schedule in Table 2 and Table 3. This survey collects information on the subject's experience with self-administration (for subjects aged 6 years or older) or self-administration by the parent/caregiver (if applicable) and with SC injection of lanadelumab. Subjects who have previously received LTP with C1-INH products via IV administration will be asked to indicate the preferred route for medication administration. Study personnel will document subject's responses in the subjects' medical record and eCRF.

8.2.7 Volume of Blood to Be Drawn from Each Subject

Laboratory testing will be performed according to the Study Activities Schedule (Table 1, Table 2, and Table 3).

Laboratory testing includes general safety parameters (hematology, serum chemistry, and coagulation), serology, pregnancy tests, [redacted] C1q assay, PK samples, PD samples, and plasma ADA testing. All laboratory tests will be performed using established and validated methods.

When multiple sample collection types are performed at the same assessment time point, the samples will be drawn in the following order (depending on what sample types are to be collected at that time point): laboratory safety samples (hematology, coagulation, serum chemistry), [redacted], C1q, PK, anti-drug antibodies, PD. [redacted] Subjects will be in a seated or supine position during blood collection.

As shown in Table 8, during this study it is expected that approximately 175 mL of blood will be drawn from all subjects, regardless of age or gender. Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 175 mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined. Please refer to the Laboratory Manual for more information.

Table 8 Volume of Blood to Be Drawn from Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic samples[a]		2.5	15	37.5
Pharmacodynamic (cHMWK, [redacted]) samples		2.7	15	40.5
HBsAg, HIV, HCV (virology)		6	1	6
C1-INH, C4, C1q at screening		5	1	5
Anti-drug antibody testing samples		2.5	10	25
Safety	Clinical Chemistry	1	13	13
	Coagulation	2.7	13	35.1
	Hematology	1	13	13
Total		23.4	81[b]	**175.1**

C1-INH=C1 esterase inhibitor; cHMWK=cleaved high molecular weight kininogen; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PK=pharmacokinetic.
[a] The first 0.25 mL will be discarded if a catheter is used, after which, withdraw 2.25 mL and dispense into the appropriate tube for PK sampling. A total of 2.5 mL of blood drawn has been used in determination of sample volume.
[b] This represents the total number of samples collected during the study. The number of samples drawn at any given study visit is expected to range from 3 to 7.

8.2.8 Blood Sample Collection, Storage, and Shipping

Blood samples for laboratory assessments will be collected at the site by a trained site staff designated and/or approved by the study investigator. Details for the collection, processing, storage and shipment of samples for all laboratory determinations will be provided in the Laboratory Manual. Biological material will be stored and secured in a manner that assures that unauthorized access is prohibited and the samples are not lost, allowed to deteriorate, or accidentally or illegally destroyed.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the clinical outcomes and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

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

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC 27513).

9.2 Planned Interim Analysis, Adaptive Design, and Data Monitoring 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.

9.3 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.

9.4 Statistical Analysis Set(s)

Safety Analysis Set is defined as all subjects who receive any study drug.

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

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

9.5 Analysis Set Description and Exposure

9.5.1 Subject Disposition

The numbers of subjects treated with study drug, completed the study, and discontinued prematurely by reason will be summarized for each analysis population.

9.5.2 Demographics and Other Baseline Characteristics

Baseline and demographic variables will be summarized for each analysis population.

9.5.3 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by SOC and PT for each analysis population.

9.5.4 Treatment Exposure and Compliance

Treatment compliance and the extent of exposure to study drug 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 for each analysis population.

9.5.5 Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization-Drug Dictionary. The number and percentage of subjects with prior or concomitant medications will be summarized by therapeutic class and PT for each analysis population. A separate, similar table will be provided for the subset of concomitant medications classified as rescue medications.

9.6 Clinical Outcome Analyses

The clinical outcomes analysis is a secondary study objective and will be conducted using the Safety Analysis Set. Data will be summarized by dose group and overall during each treatment period, partitioned by dose regimen for subjects with dose modifications. This study is not designed for statistical hypothesis testing, and given the small sample size and the primary study objective (PK and safety), only descriptive analysis will be done, and the following will apply:

- 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. The baseline is defined as the last non-missing value prior to initial dose of study drug.

- 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 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])

9.6.1 Primary Clinical Outcome Endpoint

Clinical outcome measures are secondary endpoints for the study.

9.6.2 Secondary Clinical Outcome Endpoints

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.

9.6.2.1 Normalized Number of Investigator-confirmed Hereditary Angioedema 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 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.

The baseline investigator-confirmed HAE attack rate will be calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the observation period divided by the number of days the subject contributed to the observation 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. 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 Day 0 for each subject.

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. The date of the first exposure to study drug in this study will be used as the start of the first interval and end of the interval will be the date of first exposure to study drug in this study plus 28 days. Each successive interval will start the last day of the prior interval plus 1 day and end 28 days later.

Similar summary tables 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

9.6.2.2 Time to First Attack

The time to the first investigator-confirmed HAE attack (days) for each efficacy evaluation period will be calculated from the date and time of the first dose of lanadelumab for that efficacy evaluation period to the date and time of the first investigator-confirmed HAE attack after the first open-label dose for that efficacy evaluation period. Subjects who do not experience any attacks during the efficacy evaluation period will be censored at the date and time of the end of the period. 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 using the Kaplan-Meier method.

9.6.2.3 Characteristics of Investigator-confirmed Hereditary Angioedema Attacks

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 (<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 and summarized. The number and percentage of subjects will be tabulated by maximum attack severity (no attacks, 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 (ecallantide, icatibant, nano-filtered C1-INH, plasma-derived C1-INH, recombinant C1-INH, fresh frozen plasma, and other) as reported in the AE CRF.

9.6.2.4 Achievement of Attack-free Status

The number and percentage of subjects that are attack-free 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.

[redacted]

9.7 Safety Analyses

Safety endpoints will be analyzed based on the Safety Analysis Set. Data will be summarized by dose group and treatment period, partitioned by dose regimen for subjects with dose modifications.

- 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).

9.7.1 Adverse Events

Adverse events will be coded using the MedDRA coding dictionary.

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.

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 Day 0 through Day 364 visit). Treatment Period AEs will be further summarized for Treatment Period A (Day 0 through Day 182), Treatment Period B (Day 183 through Day 364), and overall for the entire Treatment Period (Day 0 through Day 364).
- Follow-up Period AEs will include all AEs starting at or after the subject's last visit date of the treatment period in this study (AEs starting after the Day 364 visit).

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

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized by SOC, and PT for each analysis period. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, related severe AEs, and investigator-reported AESI for treatment period and follow-up period AEs.

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized by PT for treatment period AEs only. This tabulation will be repeated for related AEs and serious AEs for treatment period AEs.

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

Adverse events of special interest for this study are hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events). Standardized MedDRA Queries (SMQ) for each AESI will be performed using the study data. The number an percentage of subjects with an AESI, as well as the total number of AESIs, will be summarized by SOC and PT for each analysis period. Separate summary tables will be created for each AESI and for those events with the SMQs classified as related, serious, related serious, severe, and related severe. A listing detailing the PT within the SMQ will be provided.

9.7.2 Laboratory Test Results

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

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

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

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 visit to identify any trends.

9.7.3 Vital Signs

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. All vital sign data will be presented in subject listings.

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

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

9.8 Other Analyses

[redacted]

9.8.2 Pharmacokinetic/Pharmacodynamic Analyses

A descriptive summary analysis will be performed for plasma concentrations of lanadelumab, as appropriate, using nominal time points.

A descriptive summary analysis will be performed for cHMWK levels, [redacted], as appropriate, using nominal time points.

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.

9.8.3 Immunogenicity Analyses

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 by study visit and overall.

9.9 Statistical/Analytic Considerations

9.9.1 Multiplicity Adjustment

No adjustment for multiple comparisons will be performed. Any statistical testing will be considered exploratory.

9.9.2 Handling of Missing Data

All available data will be included in the analysis. No imputation of missing data will be performed except for the handling of partial or missing AE start dates as described in Section 9.7.1.

9.9.3 Multicenter Studies

Data from all study sites that participate in this protocol will be combined so that an adequate number of subjects will be available for analyses.

9.9.4 Subgroup Analyses

Subgroup analyses are planned for the number of investigator-confirmed HAE attacks during the efficacy evaluation period and AEs using the Safety Analysis Set.

The following subgroups will be used:

- Age Group: (2 to <9 (years), 9 to <12 (years))

9.10 Sensitivity Analyses

The following sensitivity analysis will be performed on the number of investigator-confirmed HAE attacks during each efficacy evaluation period for the Safety Analysis Set to evaluate the robustness of the results. Data summaries will parallel those described for the number of investigator-confirmed HAE attacks during each efficacy evaluation period.

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

To evaluate the impact of treatment discontinuation on the achievement of attack-free status for each efficacy evaluation period, 2 sensitivity analyses will be conducted. The first will be based only on the subset of subjects that complete the 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.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

APPENDIX 1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Appendix 1.1 Regulatory and Ethical Considerations

This study is conducted in accordance with current applicable regulations including ICH E6, EU Directive 2001/20/EC, and all updates, as well as local ethical and legal requirements.

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

Appendix 1.2 Sponsor's Responsibilities

Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, current ICH GCP Guidelines, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO, as necessary.

Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

The timing for study registration and results summary posting must be in accordance with applicable local and national requirements.

Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

Appendix 1.3 Investigator's Responsibilities

Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator will be appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

Protocol Adherence and Investigator Agreement

The investigator and any sub-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

Documentation and Retention of Records

Case Report Forms

Case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

The final, clean CRFs with subject data must be approved (signed-off in EDC) by the investigator prior to database lock

Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diary cards, and original clinical laboratory reports.

All key data must be recorded in the subject's source documents.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

Appendix 1.4 Data Management Considerations

Data Collection

The investigators' authorized site personnel must enter into the CRF the information required by the study protocol, according to the CRF Completion Guidelines or similar. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting.

Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

Appendix 1.5 Ethical Considerations

Informed Consent

It is the responsibility of the investigator to obtain written informed consent (and assent, where applicable) from all study subjects prior to any study-related procedures including screening assessments. All consent (and assent) documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent (and assent) documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

Within the source documents, site personnel should document instruction of and understanding by the parent/legally authorized representative/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

The principal investigator provides the sponsor with a copy of the consent form (and assent form, where applicable) that was reviewed by the IRB/EC and received their favorable

opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement. Investigational product supplies will not be released until the sponsor has received written IRB/EC approval.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue. If required by local law, substantial amendments to the protocol must also be approved by the appropriate regulatory agency prior to implementation.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol at least annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. This can be the responsibility of the sponsor or investigator for sites within the EU; or for multicenter studies, the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs as required by IRB/EC procedures.

Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in

addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market lanadelumab; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities. Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected, if permitted under local laws governing privacy.

The results of studies containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth, where allowed per local law, may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

Study Results/Publication Policy

The term "Publication" shall mean any paper, article, manuscript, report, poster, internet posting, presentation slides, abstract, outline, video, instructional material, presentation (in the form of a written summary), or other public disclosure of the study results, in printed, electronic, oral, or other form. The parties understand and agree that participation in the study may involve a commitment to publish the data from all sites participating in the study in a cooperative publication with other investigators prior to publication or oral presentations of the study results on an individual basis. The site agrees not to publish or present the site's study results until such time as either the aggregate multi-site study results are published in a cooperative publication or for a period of one (1) year after termination or completion of the study at all participating sites, whichever shall first occur. After that time, the site may publish the site's study results in scientific journals or present the study results at symposia or other professional meetings in accordance with the following provisions:

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

At least sixty (60) days prior to submitting an abstract, manuscript, or other document for publication, a copy of the proposed publication will be provided to the sponsor by the site for review. Upon the sponsor's request, the site agrees to remove any and all confidential information (expressly excluding study results) identified in the publication and to delay such submission or presentation for an additional sixty (60) day period in order to allow the sponsor time to file any patent application(s). All publications of the study results shall appropriately

reference the multi-site study publication, if any, or the fact that the study results are a subset of data resulting from a larger multi-site study.

Shire is committed to transparent dissemination of all scientific, technical and medical manuscripts generated from Shire-supported research. Therefore, after January 1, 2018, Shire will require the submission of all Shire-supported research manuscripts to journals that offer public availability via Open Access (including publisher platforms/repositories and self-archiving). Open Access refers to the free at point of entry, online availability of published research output with, where available, rights of re-use according to an End User License.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals. Participation as an investigator does not confer any rights to authorship of publications.

APPENDIX 2 CLINICAL LABORATORY TESTS

The following clinical laboratory assessments will be performed as mentioned in Section 8.2.5.4:

Chemistry

- Albumin
- Alkaline phosphatase
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Bilirubin (total and direct)
- Blood urea nitrogen (BUN)
- Calcium
- Carbon dioxide (CO_2)
- Chloride
- Creatinine
- Creatine phosphokinase (CPK)
- Glucose
- Phosphate
- Magnesium
- Potassium
- Sodium
- Total protein
- Uric acid

Hematology

- Hemoglobin
- Hematocrit
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Absolute platelet count

Coagulation

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

Virology (at screening only)

Hepatitis B Surface Antigen (HbsAg); Hepatitis C Virus (HCV); Human Immunodeficiency Virus (HIV)

See Section 8.2.7 for volume of blood to be drawn.

APPENDIX 3 ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Appendix 3.1 Adverse Event Definitions

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this investigational product or medicinal product. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not causality is suspected (ICH Guidance E2A 1995).

Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as any event emerging or manifesting at or after the initiation of treatment with an investigational product or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the investigational product or medicinal product.

Serious Adverse Event

A serious adverse event (SAE) is any untoward clinical manifestation of signs, symptoms or outcomes (whether considered related to investigational product or not and at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of hospitalization. Note: Hospitalizations that are the result of elective or previously scheduled investigations procedures or surgery for pre-existing conditions and have not worsened after initiation of treatment should not be classified as SAEs.
- For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Results in a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include:

- Bronchospasm associated with anaphylaxis requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.
- Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

Unexpected Adverse Event

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the latest version of the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the latest version of the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any suspected adverse reaction to study treatment (ie, including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Symptoms of the Disease under Study

As discussed in Section 8.2.5.5 of this protocol, HAE attacks will be captured as AEs in this study and will be evaluated in accordance with HAARP (Appendix 5).

Clinical Laboratory and Other Safety Assessment

A change in the value of a clinical laboratory or vital sign measure can represent an AE if the change is clinically relevant or if, during administration of investigational product, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further warning of an already clinically

significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the investigational product, and the range of variation of the respective parameter within its reference range, should also be considered.

In general, laboratory abnormalities are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. A clinically significant laboratory abnormality that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to lanadelumab interruption or discontinuation, will be considered an AE.

When laboratory abnormalities are considered to be AEs, the severity of these AEs will be assessed according to the DMID Pediatric Toxicity Table (Appendix 6).

Where discrepancies in the upper limit of normal (ULN) and lower limit of normal (LLN) of laboratory ranges occur between those included in the DMID tables and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade. Clinical significance of individual laboratory AEs will be determined by the investigator with input from the medical monitor as needed.

The following is an exception to defining clinically significant, abnormal laboratory values as AEs:

- aPTT prolongation in the absence of any associated bleeding or other evidence of clinical relevance will not be considered a clinically significant laboratory abnormality or AE. In the appropriate physiologic setting, such as IV heparin therapy, aPTT can be used to monitor bleeding risk. However, as noted in the investigators brochure, aPTT prolongation due to plasma kallikrein inhibition is an artifactual in vitro phenomenon. Although plasma kallikrein drives fibrin formation in the aPTT assay, plasma kallikrein-driven coagulation does not appear to have hemostatic or other physiologically important functions in vivo. It is well documented that, in humans, deficiency of factor XII or prekallikrein (and thus plasma kallikrein) is not associated with abnormal bleeding, either spontaneous or during surgical procedures (Renne and Gruber, 2012). Despite the lack of clinical effect, deficiency of either protein is associated with marked prolongation of the aPTT.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel) or vital sign values which were not present at the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of the subject, whether a change in a clinical laboratory value or vital sign parameter is clinically significant and represents an AE.

Appendix 3.2 Collection of Adverse Events

All AEs/SAEs are collected from the time the informed consent document is signed until the defined follow-up period stated in Section 8.1.4. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered.

All AEs/SAEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to baseline), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained.

Appendix 3.3 Assessment of Adverse Events

Severity Categorization

The severity of AEs must be recorded during the course of the event. If the subject experiences a change in the severity of an AE, the event should be captured once with the maximum severity recorded. Worsening medical conditions, signs or symptoms present prior to initiation of investigational product, must be recorded as new AEs.

For example, if a subject reports mild intermittent dyspepsia prior to initiation of dosing with the investigational product, and the dyspepsia becomes severe and more frequent after first dose a new AE of severe dyspepsia (with the appropriate date of onset) should be documented in the source.

In this study, the severity of all AEs will be assessed according to the DMID Pediatric Toxicity Table (Appendix 6). HAE attacks are also captured as AEs in this study; HAE attacks assessed as described in HAARP (Appendix 5), which includes an assessment using HAARP criteria and an assessment using DMID criteria.

For abnormalities not specifically found in the Toxicity Tables, the following general scale will be used to estimate grade of severity:

- GRADE 1 (Mild): Transient or mild discomfort; no medical intervention/therapy required
- GRADE 2 (Moderate): Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
- GRADE 3 (Severe): Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
- GRADE 4 (Life-threatening): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source.

The following additional guidance may be helpful:

The causal relationship between lanadelumab and the AE will be assessed using one of the following categories:

Not Related: Factors consistent with an assessment of Not Related include:

- Temporal relationship is lacking (eg, the event did not occur within a reasonable time frame following administration of lanadelumab); or
- Other causative factors more likely explain the event (eg, a pre-existing condition, other concomitant treatments).

Related: Factors consistent with an assessment of Related include:

- A positive temporal relationship (eg, the event occurred within a reasonable time frame following administration of lanadelumab); or
- The AE is more likely explained by administration of lanadelumab than by another cause (ie, the AE shows a pattern consistent with previous knowledge of lanadelumab or the class of lanadelumab).

Outcome Categorization

The outcome of AEs must be documented in the source during the course of the study. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved

- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

If applicable, action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF.

Appendix 3.4 Safety Reporting

Reference Safety Information

The RSI for this study is the lanadelumab latest investigator's brochure, which the sponsor has provided under separate cover to all investigators.

Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the CRO within 24 hours of becoming aware of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Appendix 3.9) unless they result in an SAE.

The investigator must complete, sign, and date the Shire "Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol", verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested), and fax or e-mail the form to the Shire Global Drug Safety Department. A copy of the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol.

Appendix 3.5 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to investigational product) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 8.1.4 and must be reported to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the reported first becoming aware of the event.

Appendix 3.6 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the

event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms reported by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

The investigator is required to follow SAEs until resolution regardless of whether the subjects are still participating in the study. SAE resolution is defined as:

- Resolved with or without residual effects.
- A return to baseline for a pre-existing condition.
- Laboratory values have returned to baseline or stabilized.
- The investigator does not expect any further improvement or worsening of the event.
- Fatal outcome (see Appendix 3.7)—if an autopsy is performed; the autopsy report is requested to be provided to the sponsor as soon as it is available.

Appendix 3.7 Fatal Outcome

Any SAE that results in the subject's death (eg, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of withdrawn should not be selected solely as a result of the subject's death.

Appendix 3.8 Pregnancy

All pregnancies are reported from the time informed consent is signed until the defined follow-up period stated in Section 8.1.4.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Global Drug Safety Department using the Clinical Study Pregnancy Report Form.

A copy of the Clinical Study Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days and 1 year post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form as well as the Clinical Study Pregnancy Report Form. The test date of the first positive serum/urine β-hCG test or ultrasound result will determine the pregnancy onset date.

Appendix 3.9 Abuse, Misuse, Overdose and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Appendix 3.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- Abuse – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- Misuse – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- Overdose – Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed dose
- Medication Error – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally authorized representative/caregiver.

Appendix 3.10 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm, these do not constitute de facto deviation from the protocol. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may implement urgent safety measures to protect study subjects from immediate hazard to their health or safety. The measures should implement immediately and does not require prior authorization from the sponsor. In the event(s) of an apparent direct hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, and within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible EC(s) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

Appendix 3.11 Regulatory Agency, Institutional Review Board, Ethics Committee and Site Reporting

The sponsor and the clinical CRO are responsible for notifying the relevant regulatory authorities of related, unexpected SAEs. The clinical CRO is responsible for notifying the relevant US and Canada central and local IRBs and EU central ECs of related, unexpected SAEs.

In addition, the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP643 program.

The investigator is responsible for notifying the local IRB/EC of SAEs or significant safety findings that occur at his or her site as required by IRB/EC procedures (see Appendix 1.5).

APPENDIX 5 HEREDITARY ANGIOEDEMA ATTACK ASSESSMENT AND REPORTING PROCEDURES (HAARP)

HAE ATTACK ASSESSMENT AND REPORTING PROCEDURES (HAARP)

Title: HAE Attack Assessment and Reporting Procedures (HAARP)

Product Name: TAK743 / SHP643, lanadelumab (formerly DX-2930)

Sponsor:

Dyax Corp. (a wholly-owned, indirect subsidiary of Shire plc) (Shire plc, a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited)
300 Shire Way, Lexington, MA 02421 USA

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LIST OF ABBREVIATIONS

AE	adverse event
eCRF	electronic case report form
HAARP	HAE Attack Assessment and Reporting Procedures
HAE	hereditary angioedema
SAE	serious adverse event

1. PURPOSE

This document applies to clinical trials that involve investigator adjudication/assessment of angioedema attacks. The purpose of this document is to provide a definition of a hereditary angioedema (HAE) attack and to define a standardized set of procedures for the subject (or parent/caregiver) reporting and investigator assessment of events reported by subjects to determine whether those events meet the criteria of an angioedema attack as defined in this document.

2. DEFINITION OF AN ATTACK

To be confirmed as an HAE attack, the event must have symptoms or signs consistent with an attack in at least 1 of the following locations:

- Peripheral angioedema: cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region
- Abdominal angioedema: abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea
- Laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx

Despite the presence of these symptoms, the investigator may still determine clinically that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an angioedema attack (eg, urticaria), the reported event persists well beyond the typical time course of an attack (eg, >7 days), or there is a likely alternate etiology for the event (eg, the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

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

Attacks that progress from 1 body site (physical location on the body) to another will be considered a single attack. Attacks that begin to regress and then worsen before complete resolution will be considered 1 attack.

Attack resolution is defined as when the subject no longer has symptoms of the attack.

Prodromal symptoms by themselves are not considered an attack.

Subject (or parent/caregiver) report of use of acute HAE attack treatment for an attack by itself is not confirmation that an attack met HAE attack criteria.

3. REPORTING AND ASSESSMENT OF ATTACK DATA

At screening for applicable clinical trials, subject HAE attack history will be collected by the site for entry into the clinical database. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant location(s), average duration, acute attack therapy use, and history of long-term prophylaxis.

During the relevant study periods, as defined in the applicable study protocol, subjects (or parents/caregivers) will be instructed to contact the site within 72 hours of the start of symptoms of an attack. In the situation that a subject (or parent/caregiver) is incapacitated and is unable to contact the site, another family member or other individual with detailed knowledge of the event can provide the information.

Site personnel will review the information provided by the subject (or parent/caregiver) and solicit additional information as necessary to document the attack. Information will be documented in the HAE Attack Source Worksheet by the site and will be considered source for the study.

A designated individual at the site (the collector) will contact the subject (or parent/caregiver) on a regular basis as defined in the study protocol, regardless of whether or not the subject has reported any attacks, in order to solicit for any attacks that may have occurred but were not reported or updates to previously reported attacks. In addition, during each study visit, site personnel will solicit for any new attack information that was not provided through previous contact with the subject (or parent/caregiver).

The investigator or designee (the assessor) will review the attack information and evaluate if the event represents a confirmed HAE attack. If necessary for the evaluation, the investigator or designee may contact the subject (or parent/caregiver) to receive additional information.

3.1 Subject (or Parent/Caregiver) Reported Symptoms

Subjects (or parents/caregivers) will use the sponsor-provided Daily HAE Attack Diary. Diaries will include a daily response documenting whether or not the subject experienced an HAE attack. On days a subject experiences an attack, additional information will be captured in the HAE Attack Worksheet that is part of the diary. Subjects (or parents/caregivers) will contact the study site as soon as possible, but no later than 72 hours (3 full days) after the first symptoms appear, to report the information. The study site will utilize the sponsor-provided HAE Attack Source Worksheet to document the reported attack.

3.1.1 Attack Information

The following information should be provided by the subject (or parent/caregiver) at the time they are reporting an attack to the site:

- Date and time symptoms of an attack were first experienced
- Description of symptoms experienced, including triggers and location(s)

- Impact on activity and whether any assistance or medical intervention was required, including hospitalizations or emergency department visits
- Any medications used to treat the attack, including both acute therapies and other medications.
- If the attack resolved, date and time the subject was no longer experiencing symptoms
- Any other pertinent information related to the attack

Subjects (or parents/caregivers) do not have to wait for their symptoms to completely resolve to report an attack. Information about ongoing symptoms can be obtained by the site during the check-in call and/or at a scheduled study visit. Subjects (or parents/caregivers) should not withhold or delay any treatment that would normally be received by the subject to treat their attack in order to contact the site.

3.1.2 Worsening Symptoms

The site may request the subject call them back if they experience worsening symptoms and/or new symptoms for a reported attack. Otherwise, the new information will be captured during the next check-in call or scheduled study visit. Subjects (or parents/caregivers) may contact the site on their own to provide information about any worsening symptoms.

3.1.3 Subject Training

During screening, site personnel will train subjects (and/or parents/caregivers) on identifying symptoms of an attack, the requirements for reporting attacks, and the information they will be expected to provide. The subject (or parent/caregiver) will confirm their understanding of what is required of them for reporting attacks to the site. Sites will assess the subject's (or parent's/caregiver's) compliance with the reporting requirements throughout the study and may retrain the subject (or parent/caregiver) if necessary in order to maintain the integrity of the data provided to the site.

3.1.4 Reporting Multiple Attacks

If a subject experiences symptoms that he/she attributes to more than 1 unique attack, the subject (or parent/caregiver) may report this as multiple attacks to the site. Based on the definition of an attack, it will be the determination of the investigator or designee as to whether events reported as being separate are confirmed as separate attacks or not.

3.1.5 Subject (or Parent/Caregiver) Contact with Sites

Site personnel will establish a recommended method and time window for each subject (or parent/caregiver) to contact the site to report any symptoms of an attack. Sites will establish a primary contact person and, if possible, a back-up person, with contact information. Back-up plans, including call backs and/or use of back-up contacts, should be established in case the subject (or parent/caregiver) is unable to reach someone at the site.

3.2 Site Contact with the Subject

Sites will establish a recommended day and time window for check-in calls between study visits, as outlined in the study protocol. The date and time for check-ins can be modified based on when

the last contact with the subject (or parent/caregiver) was made. When the site is contacted by a subject (or parent/caregiver) reporting symptoms of an attack. The site should make sure they have the ability to record the information provided in a complete and accurate way. Back-up plans should be established in case the subject (or parent/caregiver) misses a call from the site. A study schedule for each subject's on-site visits will be provided to the subject (or parent/caregiver) by the site.

3.2.1 Review, Documenting, and Assessing a Reported Attack

During contact with the subject (or parent/caregiver), whether initiated by the subject (or parent/caregiver) or at a regular check-in, site personnel should ask the subject (or parent/caregiver) to provide them information about new or ongoing HAE attacks experienced by the subject.

The site will try to obtain all information necessary to document the attack completely. Missing information may impact the assessment of an attack and should be avoided whenever possible.

Complete and accurate documentation of each reported attack is important to making an investigator assessment of the attack. The site should document the following information about each attack reported by the subject (or parent/caregiver):

- Date and time of contact with the subject (or parent/caregiver)
- Date and time the subject first experienced symptoms
- Description of symptoms experienced, including location(s)
- Description of any HAE attack triggers
- Impact on daily activity and whether any assistance was required
- If the attack has resolved or is ongoing. If the attack has resolved, the date and time the subject was no longer experiencing any symptoms of the attack.
- Names and dates and times of any medications used to treat the attack including HAE acute therapy or other non-HAE treatments.
- If hospitalization occurred
- If a trip to the emergency department occurred

Additional probing questions about what the subject experienced to determine:

- If the subject only experienced prodromal symptoms
- If the subject experienced anything different than their typical attack
- If there were any possible alternative etiologies of the symptoms. For example, a viral gastroenteritis outbreak in the household could explain abdominal symptoms

The overall severity of the subject's attack will be determined by the site using the following definitions (per HAARP):

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

The site will also document the date and time of investigator or designee review, the official designation of the event as an attack or not, and if applicable, the reason why an event is not considered an attack.

All reported attacks will be entered by site personnel into the electronic case report form (eCRF).

3.2.2 Site Training

Site personnel responsible for collecting attack information about subject HAE attacks will need to pass a "collector" training assessment covering the following:

- Definition of an HAE attack
- Requirements of subjects (or parents/caretakers) for reporting attacks
- Reporting worsening symptoms and multiple attacks
- Information to be collected from subjects (or parents/caregivers) as well as the additional probing questions to gather context for the attack information provided
- Assessment of attack severity
- Entry of the attack data into the eCRF
- Reporting HAE attacks as adverse events
- Requirements for investigator assessment of attacks

Trainings will be conducted prior to sites screening subjects. Trainings will be documented in the Trial Master File. Investigators and designees will be trained on these procedures as well and must pass an "assessor" training in order to officially assess attacks for this study.

All responsible persons involved in assessing attacks must be listed on FDA Form 1572 or regulatory equivalent document as applicable.

3.3 Hereditary Angioedema Attacks as Adverse Events

At the time of each contact, including scheduled study visits, site personnel will ask if the subject experienced any adverse events (AEs) or changes to the medications they are taking.

All AEs, regardless of seriousness, severity, or causal relationship to study drug, will be recorded in the eCRF.

Any AE reported to the site meeting criteria for a serious adverse event (SAE) must be reported to the sponsor using the SAE Reporting Form within 24 hours of the site staff becoming aware of the event. Sites should also complete the appropriate AE form in the electronic data capture system as well. For all SAEs that are reported as HAE attacks, the principal investigator or physician designee will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack.

For all non-serious AEs that are reported as HAE attacks, the principal investigator or physician designee will review the event within 7 days of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. If necessary for the evaluation, the

investigator or designee may contact the subject for additional information. Any subject-reported attack not confirmed by the investigator must have an alternate AE diagnosis recorded in the source documents and eCRF. All subject-reported and investigator-confirmed HAE attacks will also be recorded in the source documents and eCRF.

Hereditary angioedema attacks will be captured as AEs; however, all HAE attacks will be recorded on the designated angioedema attack page of the eCRF and **not** on the AE page of the eCRF.

4. INVESTIGATOR ATTACK ASSESSMENT

The principal investigator for a study site may identify a physician designee to assess patient angioedema symptom information and make attack determinations. Sites should be limited to 2 individuals responsible for assessing attacks, one of them being the principal investigator.

Assessors must be experienced with HAE and familiar with the study subject's disease history.

The assessor must review the relevant, subject-reported information and determine whether the event meets the criteria of an angioedema attack or not. If needed, the assessor can contact the subject (and/or parent/caregiver) to clarify information or ask for any additional detail. The determination will be documented in the source documents, along with the date and time the determination was made. Any angioedema event reported by the subject (and/or parent/caregiver) deemed not an angioedema acute attack by the investigator must be accompanied by an explanation and alternative diagnosis assigned by the assessor.

When reviewing subject information, the assessor will follow the definitions of an attack as outlined in these procedures and, taking all available information about the event into consideration, will determine if it is a confirmed attack. The assessment of the attack is the investigator or designee's own, and not the opinion of the subject (or parent/caregiver) or any other site personnel. Assessors may consult with one another about a particular subject's attack but only 1 assessor makes the documented determination. It is possible for both the principal investigator and physician designee to assess different attacks for the same subject.

APPENDIX 6 NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES (US NATIONAL INSTITUTES OF HEALTH; NATIONAL INSTITUTE OF ALLERGY AND INFECTION DISEASES)

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

Note: The following toxicity table is a DRAFT and designed to provide general guidance on parameters for monitoring safety in clinical trials. This toxicity table is not comprehensive and should not be applied directly to all trials.

When selecting a toxicity table, the following are some of the items that must be taken into consideration:

- The population being studied
  - Does the clinical trial evaluate healthy subjects, subjects with a particular disease or condition?
- The stage of test article development
  - Is the clinical trial a Phase I (is it for the fisrt time in human subjects?) , II, III or IV?
- The type of test article
  - Does the clinical trial evaluate a drug, device, vaccine or other biologic agent?
- The prior human and preclinical experience with the test article
  - Are there any specific findings that require adjustment of the toxicity table?
  - Has it been approved for this indication in adult population?

Single site clinical trials evaluating healthy subjects should conform to the laboratory normal values at the single site. Multi-center clinical trials should reconcile among their laboratory normal values when evaluating a healthy volunteer population.

Please confer with the DMID protocol team and DMID's Office of Clinical Research Affairs when selecting or developing a toxicity table for a DMID-sponsored trial.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
GRADE 5	**Death**	

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Selected Values for children less than or equal to 3 months of age – does not apply for preterm infants)

For all parameters not listed on this table, please refer to the DMID Toxicity Table for children > 3 months of age.

HEMATOLOGY				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin				
1-7 days old	13.0-14.0 gm/dL	12.0-12.9 gm/dL	<12 gm/dL	Cardiac Failure secondary to Anemia
8-21 days old	12.0-13.0 gm/dL	10.0-11.9 gm/dL	<10.0 gm/dL	Cardiac Failure secondary to Anemia
22-35 days old	9.5-10.5 gm/dL	8.0-9.4 gm/dL	<8.0 gm/dL	Cardiac Failure secondary to Anemia
36-60 days old	8.5-9.4 gm/dL	7.0-8.4 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
61-90 days old	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
Abs Neutrophil Ct				
1 day old	5000-7000/mm^3	3000-4999/mm^3	1500-2999/mm^3	<1500/mm^3
2-6 days old	1750-2500/mm^3	1250-1749/mm^3	750-1249/mm^3	<750/mm^3
7-60 days old	1200-1800/mm^3	900-1199/mm^3	500-899/mm^3	<500/mm^3
61-90 days old	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3
Bilirubin (Fractionated bilirubin test must be preformed when total bilirubin is elevated)				
<7 days old	.	20-25mg/dL	26-30 mg/dL	>30 mg/dL
7-60 days old	1.1-1.9xN	2.0-2.9Xn	3.0-7.5xN	>7.5xN
61-90 days old	1.1-1.9xN	2.0-2.9xN	3.0-7.5xN	>7.5xN

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Selected Values for children less than or equal to 3 months of age)

HEMATOLOGY (continued)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Creatinine				
<7 days old	1.0-1.7 mg/dL	1.8-2.4 mg/dL	2.5-3.0 mg/dL	>3.0 mg/dL
7-60 days old	0.5-0.9 mg/dL	1.0-1.4 mg/dL	1.5-2.0 mg/dL	>2.0 mg/dL
61-90 days old	0.6-0.8 mg/dL	0.9-1.1 mg/dL	1.2-1.5 mg/dL	>1.5 mg/dL
Cr Clearance				
<7 days old	35-40 ml/min	30-34 ml/min	25-29 ml/min	<25 ml/min
7-60 days old	45-50 ml/min	40-44 ml/min	35-39 ml/min	<35 ml/min
61-90 days old	60-75 ml/min	50-59 ml/min	35-49 ml/min	<35 ml/min
Hypocalcemia				
<7 days old	6.5–6.9 mEq/L	6.0-6.4 mEq/L	5.5-5.9 mEq/L	<5.5 mEq/L
7-60 days old	7.6-8.0 mEq/L	7.0-7.5 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
61-90 days old	7.8-8.4 mEq/L	7.0-7.7 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
Hypercalcemia				
<7 days old	12.0-12.4 mEq/L	12.5-12.9 mEq/L	13.0-13.5 mEq/L	>13.5 mEq/L
7-60 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L
61-90 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

LOCAL REACTIONS				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Induration	< 10mm	10-25 mm	26-50mm	>50mm
Erythema	< 10mm	10-25 mm	26-50mm	>50mm
Edema	< 10mm	10-25 mm	26-50mm	>50mm
Rash at Injection Site	< 10mm	10-25 mm	26-50mm	>50mm
Pruritus	Slight itching at injection site	Moderate itching at injection extremity	Itching at injection extremity and other sites	Itching over entire body

HEMATOLOGY				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin for children greater than months and less than 2 years of age	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to anemia
Hemoglobin for children greater that 2 years of age	10-10.9 gm/dL	7.0-9.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to anemia
Absolute Neutrophil Count	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3
Platelets	-------	50,000-75,000/mm^3	25,000-49,999/mm^3	<25,000/mm^3
Prothrombin Time (PT)	1.1-1.2 x ULN	1.3 -1.5 x ULN	1.6 -3.0 x ULN	>3.0 x ULN
Partial Thromboplastin Time (PTT)	1.1-1.6 x ULN	1.7-2.3 x ULN	2.4 -3.0 x ULN	>3.0 x ULN

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

GASTROINTESTINAL				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Bilirubin (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Bilirubin (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Pancreatic Amylase	1.1-1.4 x ULN	1.5-1.9 x ULN	2.0-3.0 x ULN	>3.0 x ULN
Uric Acid	7.5-9.9mg/dL	10-12.4 mg/dL	12.5-15.0 mg/dL	>15.0 mg/dL
CPK	See Neuromuscular Toxicity			
Appetite	----------	Decreased appetite	Appetite very decreased, no solid food taken	No solid or liquid taken
Abdominal Pain	Mild	Moderate- No Treatment Needed	Moderate- Treatment Needed	Severe- Hospitalized for treatment
Diarrhea	Slight change in consistency and/or frequency of stools	Liquid stools	Liquid stools greater that 4x the amount or number normal for this child	Liquid stools greater than 8x the amount or number normal for this child

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

GASTROINTESTINAL (continued)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Constipation	Slight change in the consistency/frequency of stool	Hard, dry stools with a change in frequency	Abdominal pain	Distention and Vomiting
Nausea	Mild	Moderate-Decreased oral intake	Severe-Little oral intake	Unable to ingest food or fluid for more than 24 hours
Vomiting	1 episode/day	2-3 episodes per day	4-6 episodes per day	Greater than 6 episodes per day or Intractable Vomiting

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

ELECTROLYTES				
	GRADE 1	GRADE 2	GRADE 3	GRADE 4
CREATININE				
3 Months -2 Years of age	0.6-0.8 x ULN	0.9-1.1 x ULN	1.2-1.5 x ULN	>1.5 x ULN
2 Years- 12 Years of age	0.7-1.0 x ULN	1.1-1.6 x ULN	1.7-2.0 x ULN	>2.0 x ULN
Greater than 12 Years of age	1.0-1.7 x ULN	1.8-2.4 x ULN	2.5-3.5 x ULN	>3.5 x ULN

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

ELECTROLYTES				
	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Hypernatremia		<145-149 mEq/L	150-155 mEq/L	>155 mEq/L or abnormal sodium AND mental status changes
Hyponatremia		130-135 mEq/L	129-124 mEq/L	<124 mEq/L or abnormal sodium AND mental status changes
Hyperkalemia	5.0-5.9 mEq/L	6.0-6.4 mEq/L	6.5-7.0 mEq/L	>7.0 mEq/L or abnormal potassium AND cardiac arrhythamia
Hypokalemia	3.0-3-5 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L	<2.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypercalcemia	10.5-11.2mg/dL	11.3-11.9 mg/dL	12.0-12.9 mg/dL	>13.0 mg/dL
Hypocalcemia	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.0-6.9 mg/dL	<6.0 mg/dL
Hypomagnesemia	1.2-1.4 mEq/L	0.9-1.1 mEq/L	0.6-0.8 mEq/L	<0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia
Hypoglycemia	55-65 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose AND mental status changes
Hyperglycemia	116-159 mg/dL	160-249 mg/dL	250-400 mg/dL	>400 mg/dL or ketoacidosis
Proteinuria	Tr-1+ or <150 mg/day	2+ or 150-499 mg/day	3+ or 500-1000 mg/day	4+ or Nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25	Microscopic >25		Gross hematuria

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

	cells/hpf	cells/hpf		

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

CENTRAL NERVOUS SYSTEM (CNS)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Generalized CNS Symptoms			Dizziness	Hypotonic, hyporesponsive episodes; Seizures; Apnea/Bradycardia; Inconsolable crying > 3 hrs;
Headache	Mild	Moderate, Responds to non-narcotic analgesia	Moderate to Severe, Responds to narcotic analgesia	Intractable
Level of Activity		Slightly irritable OR slightly subdued	Very irritable OR Lethargic	Inconsolable OR Obtunded
Visual		Blurriness, diplopia, or horizontal nystagmus of < 1 hour duration, with spontaneous resolution	More than 1 episode of Grade 2 symptoms per week, or an episode of Grade 2 symptoms lasting more than 1 hour with spontaneous resolution by 4 hours or vertical nystagmus	Decrease in visual acuity, visual field deficit, or oculogyric crisis
Myelopathy		None	None	Myelopathic/spinal cord symptoms, such as: pyramidal tract weakness and disinhibition, sensory level, loss of proprioception, bladder/bowel dysfunction

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

PERIPHERAL NERVOUS SYSTEM				
PARAMETER	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Neuropathy/ Lower Motor Neuropathy		Mild transient Paresthesia only	Persistent or progressive paresthesias, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss	Onset of significant weakness, decrease or loss of DTRs, sensory loss in "stocking glove" distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness.
Myopathy or Neuromuscular Junction Impairment	Normal or mild (<2 x ULN) CPK elevation	Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/- mild CPK elevation (<2 x ULN)	Proximal muscle weakness and/or atrophy affecting motor function +/- CPK elevation; or severe myalgias with CPK >2 x ULN;	Onset of myasthenia-like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

OTHER				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Allergy	Pruritus without Rash	Pruritic Rash	Mild Urticaria	Severe Urticaria Anaphylaxis, Angioedema
Drug Fever (Rectal)	.	38.5-40C 101.3 – 104.0F	Greater than 40.0C Greater than 104.0F	Sustained Fever: Equal or greater than 40C (104.0F) for longer than 5 days
Cutaneous	Localized rash	Diffuse maculopapular Rash	Generalized urticaria	Stevens-Johnson Syndrome or Erythema multiforme
Stomatitis	Mild discomfort	Painful, difficulty swallowing, but able to eat and drink	Painful: unable to swallow solids	Painful: unable to swallow liquids; requires IV fluids
Clinical symptoms *not otherwise specified* in this table	No therapy; monitor condition	May require minimal intervention and monitoring	Requires medical care and possible hospitalization	Requires active medical intervention, hospitalization, or hospice care
Laboratory values *not otherwise specified* in this table	Abnormal, but requiring no immediate intervention; follow	Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug	Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug	Life-threatening severity; Requires immediate evaluation, treatment, and usually hospitalization; Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism that study drug

APPENDIX 7 ABBREVIATIONS

AAE	acquired angioedema
ACE	angiotensin-converting enzyme
ADA	Anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AE-QoL	angioedema quality of life
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}2week,ss}$	area under the concentration-time curve over 2 weeks at steady state
$AUC_{0\text{-}4week,ss}$	area under the concentration-time curve over 4 weeks at steady state
$AUC_{tau,ss}$	area under the concentration-time curve over the dosing interval at steady state
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
$C_{avg,\ ss}$	average concentration over dosing interval at steady-state
C1-INH	C1 esterase inhibitor
CFR	Code of Federal Regulations
cHMWK	cleaved high molecular weight kininogen
CHO	Chinese hamster ovary
CL/F	apparent clearance
C_{max}	maximum observed concentration
$C_{max,ss}$	maximum observed concentration at steady state
$C_{min,ss}$	minimum observed concentration at steady state
$C_{trough,ss}$	predose concentration at steady state
CRF	case report form
EAACI	European Academy of Allergy and Clinical Immunology
$EAUC_{90}$	Area under the concentration-time curve at 90% maximal effect

eCRF	electronic case report form
EOS	end of study
ET	early termination
EU	European Union
EUDRA	European Union Drug Regulatory Authorities
EUDRACT	European Union clinical trials database
FDA	Food and Drug Administration
FIM	Family Impact Module
GCP	Good Clinical Practice
HAARP	HAE Attack Assessment and Reporting Procedures
HAE	hereditary angioedema
HIV	human immunodeficiency virus
HMWK	high molecular weight kininogen
HR	heart rate
HRQoL	Health-related quality of life
IC_{90}	90% inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IgG1	immunoglobulin G1
IMP	investigational medical product
IND	Investigational New Drug
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ISR	injection site reaction
IV	intravenous(ly)
LLN	lower limit of normal
LTP	long-term prophylaxis
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCID	minimal clinically important difference

MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NA	not applicable
NOAEL	no-observed-adverse-effect-level
PD	pharmacodynamics(s)
[redacted]	[redacted]
PK	pharmacokinetic(s)
pKal	plasma kallikrein
PT	preferred term
q2wks	every 2 weeks
q4wks	every 4 weeks
RBC	red blood cell
RR	respiratory rate
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SC	subcutaneous(ly)
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
$t_{1/2}$	terminal elimination half life
t_{max}	time to reach maximum observed plasma concentration
UK	United Kingdom
ULN	upper limit of normal
US(A)	United States
[redacted]	[redacted]
WAO	World Allergy Organization
WBC	white blood cell
V/F or V_c/F	apparent volume of distribution

APPENDIX 8 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	06 May 2019	Global
Amendment 1	12 Aug 2019	Global
Amendment 1.1	15 Oct 2019	Germany
Amendment 1.2	5 Dec 2019	Germany
Amendment 2.0	22 Jun 2021	Global