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

NCT Number: NCT04180163

Protocol Approve Date: 05-Oct-2020

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

PROTOCOL: SHP643-302

TITLE:	A Phase 3 Multi-center, Open-label Study to Evaluate the Efficacy and Safety of Lanadelumab (SHP643) in Japanese Subjects with Hereditary Angioedema
SHORT TITLE:	Efficacy and Safety of Lanadelumab (SHP643) in Japanese Subjects with Hereditary Angioedema
STUDY PHASE:	Phase 3
DRUG:	Lanadelumab; TAK-743 (formerly SHP643, DX-2930)
IND NUMBER:	Non-IND
EUDRACT NUMBER:	Non-EUDRACT
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
PRINCIPAL/ COORDINATING INVESTIGATOR:	Multicenter study
PROTOCOL HISTORY:	Original Protocol: 03 Apr 2019 Amendment 1.0: 29 Jul 2019 Amendment 2.0: 05 Oct 2020

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature and Date:	PPD
PPD	

Investigator's Acknowledgement

I have read this protocol for Study SHP643-302.

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

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:** _____

AMENDMENT SUMMARY

Noteworthy changes to the protocol are captured in the table below including corrections for consistency. Additionally, any minor revisions in grammar, spelling, punctuation, and format are not reflected in the summary of changes.

Summary of Changes from Amendment 1 to Amendment 2:

Summary of Change(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
Revised Sponsor approval to PPD .	Protocol Signature Page
Added that subjects may elect to roll over into an expanded access study (Study TAK-743-5007). Provided clarification that subjects continuing to Study TAK-743-5007 will have their EOS visit on Day 378. All other subjects will continue the study as originally planned and have their EOS visit on Day 392. A site check-in will occur at Day 371 for subjects participating in Study TAK-743-5007.	Section 1.1 Synopsis Section 1.2 Schema Table 2 Section 4.1 Overall Design Section 8.1.3 Follow-up Period
Revised the interim analysis to include 2 interim analyses: the first analysis will be performed when the first 6 subjects enrolled in the study have reached Day 182 or discontinued in Treatment Period A (26 weeks of treatment) and the second analysis will be performed when the first 4 subjects enrolled in the study have reached Day 364 or discontinued. Two interim clinical study reports along with a final clinical study report will be prepared.	Section 1.1 Synopsis Section 1.2 Schema Section 4.1 Overall Design Section 9.2 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee
Updated interim results from Study DX-2930-04 with final results as the study is now complete. The safety profile observed from the interim analysis is consistent with the final analysis.	Section 2.4.3.4 Clinical Study DX-2930-04 Section 2.4.3.6 Adolescent Clinical

Summary of Change(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
	Trial Experience Section 2.6 Benefit/Risk Assessment
Corrected error that screening visit is also Visit 1.	Section 6.6 Prior and Concomitant Therapy
Corrected error on collection of prior treatment: prior treatments should be collected prior to *screening visit*.	Section 6.6.1 Prior Treatment
Corrected investigator-confirmed HAE attacks to state: *3 or* more than 3 investigator-confirmed HAE attacks.	Section 8.1.1.2 Run-in Period (up to 8 weeks)
Removed body weight from physical exams at Visit 26 and Visit 27.	Section 8.1.2.4 Study Visit 26 (Study Day 350) Section 8.1.2.5 Final Treatment Period Visit at Study Visit 27 (Study Day 364)
Removed pregnancy tests at Visit 26 and Visit 27.	Section 8.1.2.4 Study Visit 26 (Study Day 350) Section 8.1.2.5 Final Treatment Period Visit at Study Visit 27 (Study Day 364)
Removed the following sentence: *Overall attack rates will be estimated using a Poisson general linear model adjusting for run-in period attack rate and accounting for potential overdispersion.*	Section 9.6 Efficacy Analyses
Added *if applicable* to analysis of efficacy endpoints at 4 efficacy evaluation periods.	Section 9.6 Efficacy Analyses

Summary of Change(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
The following other efficacy endpoints were added: • Achievement of attack-free status for monthly increments through Day 364. • Achievement of attack-free intervals. The statistical methods for analyzing these other efficacy endpoints were added.	Section 9.6.2 Other Efficacy Endpoints Section 9.6.2.1 Statistical Methods Analyzing Other Efficacy Endpoints
Added language that subgroup analyses may be performed.	Section 9.9.5 Subgroup Analyses
Corrected carbon dioxide to bicarbonate.	CCI [redacted]

CCI [redacted]

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)/Shire medical monitor using the details below.

PPD

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

PPD

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

PPD

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:

PPD

PPD

PPD

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

TABLE OF CONTENTS

CCI

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol number: SHP643-302	**Drug:** Lanadelumab
Title of the study: A Phase 3 Multi-center, Open-label Study to Evaluate the Efficacy and Safety of Lanadelumab (SHP643) in Japanese Subjects with Hereditary Angioedema	
Short title: Efficacy and Safety of Lanadelumab (SHP643) in Japanese Subjects with Hereditary Angioedema	
Study phase: Phase 3	
Number of subjects (total and per treatment arm): A sufficient number of subjects will be enrolled to ensure that at least 8 subjects enter Treatment Period A, after having successfully completed the washout period (if applicable) and run-in period.	
Investigator(s): This is a multicenter study.	
Site(s) and Region(s): Up to 15 sites in Japan will participate.	
Study period (planned): Nov 2019 to Dec 2021	**Clinical phase:** 3
Objectives: The objectives of the study are: • To evaluate the efficacy of repeated subcutaneous (SC) administrations of lanadelumab in Japanese subjects with hereditary angioedema (HAE). • To evaluate the safety of repeated SC administrations of lanadelumab in Japanese subjects with HAE. • To evaluate the pharmacokinetics (PK) of repeated SC administrations of lanadelumab in Japanese subjects with HAE. • To evaluate the effect of repeated SC administrations of lanadelumab on health-related quality of life (HRQoL) in Japanese subjects with HAE. • To evaluate the pharmacodynamics (PD) of repeated SC administrations of lanadelumab in Japanese subjects with HAE. • To evaluate the immunogenicity of repeated SC administration of lanadelumab and the effect on lanadelumab PK, PD, efficacy, and safety in Japanese subjects with HAE.	

Rationale:

HAE is a long-term, debilitating, and life-threatening disease caused by mutations in the C1-inhibitor (C1-INH) gene, resulting in deficiency or dysfunction of C1-INH protein.

The United States (US) Food and Drug Administration (FDA) approved the first monoclonal antibody, lanadelumab (Takhzyro, SHP643), for the treatment of types I and II HAE in patients aged 12 years and older on 23 August 2018. Also, European Medicines Agency (EMA) approved Lanadelumab (Takhzyro, SHP643), for preventing attacks of hereditary angioedema in patients aged 12 years and over on 22 November 2018.

There are currently no approved therapies in Japan that are safe and effective for the long-term prevention of angioedema attacks in patients with Types I or II HAE. Lanadelumab is expected to fulfill this unmet medical need. The current study will bridge the global lanadelumab efficacy, safety, PK, HRQoL, PD and immunogenicity data to Japanese HAE subjects.

Investigational product, dose, and mode of administration:

Treatment will consist of SC injection of lanadelumab. A single dose regimen of 300 mg q2wks lanadelumab will be evaluated in Treatment Period A. In Treatment Period B, a subject may continue to receive lanadelumab 300 mg q2wks or, if the subject has been well-controlled (eg., attack free) for 26 consecutive weeks of lanadelumab treatment in the study, the subject may switch to a dose of 300 mg q4wks at the discretion of the investigator and following approval by the sponsor's medical monitor.

In Treatment Period A, all doses of lanadelumab will be administered by site personnel. Self-administration of lanadelumab will be permitted in Treatment Period B. All subjects (adolescent or adult) who are considered suitable candidates (ie, those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer treatment. Subjects (and/or their parent/caregiver) must complete appropriate training by the investigator or designee and understanding of the training must be confirmed by the investigator or designee. Subjects (or their parent/caregiver) are allowed to initiate self-administration under the investigator supervision; once initiated, subjects (or their parent/caregiver) may self-administer subsequent doses of lanadelumab at the investigational site or an offsite location.

The drug product is a sterile, preservative-free, ready-to-use solution of lanadelumab at a concentration of 150 mg/mL. For Treatment Period A, lanadelumab will be provided in a single-use 5 mL glass vial (2 mL fill). For all subjects, a 2 mL (300 mg) dose will be withdrawn from the vial and administered to the subject. For Treatment Period B, lanadelumab will be provided in similar single-use glass vials and may also be provided in pre-filled syringes (PFS) if available and permitted per local regulations. Lanadelumab will be administered by SC injection in the upper arm, thigh, or abdominal area. The upper arm location is not recommended for self-administration but rather as an additional injection site when administered by a parent/caregiver or healthcare provider.

Methodology:

This open-label Phase 3 study will enroll approximately 8 Japanese subjects with HAE Type I or II. Following signing of informed consent, subjects will undergo screening assessments; eligible subjects who are on long-term prophylaxis (LTP) for HAE are required to undergo a minimum 2-week washout period prior to entering the run-in period. This LTP washout period is permitted as long as the investigator determines that doing so would not place the subject in any undue safety risk, and that the subject is at least 18 years of age.

Eligible subjects who are not on LTP therapy for HAE, or who have completed the required washout period, will enroll and enter a run-in period of 4 weeks to determine their baseline attack rate. Only subjects meeting a minimum baseline attack rate of at least 1 investigator-confirmed attack per 4 weeks will be eligible for treatment. Subjects who experience 3 or more investigator-confirmed attacks before the end of the 4-week run-in period may exit the run-in period early and proceed to Treatment Period A. Subjects without at least 1 Investigator-confirmed attack after 4 weeks of run-in may have their run-in period extended for another 4 weeks. Subjects who have their run-in extended must complete the full 8-week run-in period and must have at least 2 investigator-confirmed attacks during this time to be eligible to enter Treatment Period A. Subjects who do not meet the minimum attack rate during the run-in period, or are otherwise determined to be ineligible based on screening assessments, will be considered a

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

- **Treatment Period A:**

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

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

- **Treatment Period B:**

  Subjects who enter the Treatment Period B will receive lanadelumab for an additional 26 weeks (total of 52 weeks). During these additional 26 weeks, an individual subject may remain on the same dose regimen as Treatment Period A or may consider lanadelumab 300 mg q4wks if they have been well-controlled (eg, attack free) for 26 consecutive weeks with lanadelumab treatment. The dose frequency change will be based on the investigator's discretion and approval by the sponsor's medical monitor.

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

Hereditary angioedema attacks occurring during the run-in period and study treatment periods will be treated according to the local standard of care. In case of insufficient response to the first dose, additional rescue medications will be allowed.

Individual subject participation from screening through the completion of safety follow-up visit will be approximately 68 weeks (see below for duration of each study period). Subjects participating in Study TAK-743-5007 will be discharged from this study 2-weeks early on Day 378.

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 of Japanese descent, defined as born in Japan and having Japanese parents and Japanese maternal and paternal grandparents.
2. The subject is male or female and ≥12 years of age at the time of informed consent.
3. Documented diagnosis of HAE (Type I or II) based upon all of the following:
   - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).
   - Diagnostic testing results obtained during screening that confirm HAE Type I or II: C1 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 run-in period if results are incongruent with clinical history or believed by the investigator to be confounded by recent C1 inhibitor use.
   - At least one of the following: age at reported onset of first angioedema symptoms ≤30 years, a family history consistent with HAE Type I or II, or C1q within normal range.
4. Attack rate:
   - Subjects must experience at least 1 investigator-confirmed HAE attack per 4 weeks during the run-in period to enter the lanadelumab treatment period.

5. The subject (or the subject's parent/legally authorized representative, if applicable) has provided written informed consent approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC).

   If the subject is an adult, be informed of the nature of the study and provide written informed consent before any study-specific procedures are performed.

   OR

   If the subject is a minor (ie, below the age of majority), have a parent/legally authorized representative who is informed of the nature of the study provide written informed consent (ie, permission) for the minor to participate in the study before any study-specific procedures are performed. Assent will be obtained from minor subjects.

6. Males, or nonpregnant, nonlactating females who are fertile and sexually active and who agree to be abstinent or agree to comply with the applicable contraceptive requirements of this protocol for the duration of the study, or females of nonchildbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or postmenopausal for at least 12 months.
7. Agree to adhere to the protocol-defined schedule of assessments and procedures.

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 (also known as HAE Type 3), idiopathic angioedema, or recurrent angioedema associated with urticaria.
2. Participation in a prior lanadelumab study.
3. Dosing with investigational drug or exposure to an investigational device within 4 weeks prior to entering to screening.
4. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systematic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
5. Exposure to androgens (eg, danazol, methyltestosterone, testosterone) within 2 weeks prior to entering the run-in period.
6. Use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to entering the run in period.
7. Use of short-term prophylaxis for HAE 7 days prior to entering the run-in period. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.
8. Any of the following liver function abnormalities: alanine aminotransferase (ALT) >3x upper limit of normal, or aspartate aminotransferase (AST) >3x upper limit of normal or bilirubin >2x upper limit of normal (unless the bilirubin is a result of Gilbert's syndrome).
9. Pregnancy or breast feeding.
10. Subject has any condition that in the opinion of the investigator or sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (eg, history of substance abuse, or dependence, significant pre-existing illnesses or major comorbidity the investigator considers may confound the interpretation of the study results).
11. Subject has a known hypersensitivity to the investigational drug or its components.

Maximum duration of subject participation in the study:

- Planned duration of screening period: up to 4 weeks (Note: Eligible subjects on LTP must complete a 2-week

washout prior to entering the run-in period.)

  - Planned duration of enrollment period: up to 4 weeks. An enrolled subject will have signed the informed consent form and met the inclusion criteria (and no exclusion criteria) for the screening visit.

- Planned duration of run-in period: up to 8 weeks. The run-in period will be at least 4 weeks except for those subjects who report ≥3 investigator-confirmed HAE attacks before the end of the 4 weeks. The run-in period may be extended to 8 weeks in subjects without at least 1 investigator-confirmed attack after 4 weeks.
- Planned duration of treatment period (Treatment Periods A and B): 52 weeks
- Planned duration of follow-up period: 4 weeks

Statistical analysis:

Analysis Sets

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

- Full analysis set (FAS): All subjects who received at least 1 dose of lanadelumab (investigational product). All safety, efficacy, and HRQoL analyses will be based on the FAS.
- Pharmacokinetic set (PK Set): All subjects in the FAS who have at least 1 evaluable post dose PK concentration value. All PK analyses will be based on the PK set.
- Pharmacodynamic set (PD Set): All subjects in the FAS who have at least 1 evaluable post dose PD value. All PD analyses will be based on the PD set.

Efficacy Endpoints and Analyses

Efficacy Evaluation Periods

There will be a total of 4 efficacy evaluation periods:

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

Efficacy Endpoints

The primary efficacy endpoint is achievement of attack-free status for the efficacy evaluation period of Day 0 through Day 182.

Other efficacy endpoints are:

- Number of investigator-confirmed HAE attacks during each of the efficacy evaluation periods.
- Number of investigator-confirmed HAE attacks requiring acute treatment during each of the efficacy evaluation periods.
- Number of investigator-confirmed moderate or severe HAE attacks during the each of efficacy evaluation periods.
- Maximum attack severity during each of the efficacy evaluations periods.
- Number of investigator-confirmed high-morbidity attacks during each of the efficacy evaluation periods; a high morbidity HAE attack is defined as any attack that has at least 1 of the following characteristics: severe, results in hospitalization (except hospitalization for observation <24 hours),

hemodynamically significant (systolic blood pressure <90, requires IV hydration, or associated with syncope or near syncope) or laryngeal.

- Time to first HAE attack after Day 0 for the efficacy evaluation period of Day 0 through Day 182.
- Time to first HAE attack after Day 0 for the efficacy evaluation period of Day 70 through Day 182.
- Achievement of at least a 50%, 70% and 90% reduction in the investigator-confirmed normalized number of attacks (NNA) per 4 weeks relative to the run-in period NNA for each of the efficacy evaluation periods.
- Achievement of an efficacy evaluation period NNA <1.0 per 4 weeks, <0.75 per 4 weeks, <0.50 per 4 weeks, and <0.25 per 4 weeks for each of the efficacy evaluations periods.
- Achievement of attack-free status for each of the efficacy evaluation period of Day 0 through Day 364, Day 70 through Day 182, and Day 70 through Day 364.
- Percentage of attack free days during each of the efficacy evaluation periods.

Efficacy Analyses

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

- Continuous efficacy endpoints will be summarized using number of subjects (n), mean, SD, median, minimum, and maximum. Whenever appropriate, raw (actual) values and changes from baseline will be summarized at each scheduled time point. Overall attack rates will be estimated using a Poisson general linear model adjusting for run-in period attack rate and accounting for potential overdispersion. Additionally, the attack rates will be calculated using the number of attacks divided by the duration of time for each subject for each efficacy evaluation period.
- Categorical efficacy endpoints (eg, attack severity) will be summarized in terms of the number and percentage of subjects in each category of the efficacy endpoint.
- Time-to-event endpoint (eg, time to the first HAE attack) will be summarized using Kaplan-Meier (KM) estimates. Summaries will include 25th, 50th (median), and 75% percentiles, if estimable, and the corresponding 95% confidence intervals. In addition, KM plots detailing each subject's contribution to the analysis will be provided.

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

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

The treatment period HAE attack rate percentage change from the run-in period will be calculated for each subject as the difference in attack rates, treatment period attack rate minus run-in period attack rate, divided by the run-in period attack rate. The attack rates for each period (run-in period and each efficacy evaluation period) will be calculated for each subject using the number of attacks for that period divided by the duration of time the subject spent in the period.

Safety Endpoints and Analyses

Safety Endpoints

The safety measures will include:

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

Safety Analyses

No statistical hypothesis testing will be performed.

- Continuous safety endpoints (eg, change in laboratory parameter) will be summarized using number of subjects (n), mean, standard deviation (SD), median, minimum value, and maximum value. As appropriate, raw (actual) values and 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, TEAEs related to the investigational product, TEAEs leading to withdrawal, severe TEAEs and absolute count of events will be summarized by PT and SOC.
- Clinical laboratory tests and vital signs will be summarized by visit. Potentially clinically important findings will also be summarized or listed).

Other Study Endpoints and Analyses

Pharmacokinetics and pharmacodynamics: The PK endpoints include plasma concentrations of lanadelumab. The PD endpoints include plasma kallikrein (pKal) activity as measured by cleaved high molecular weight kininogen (cHMWK) level (ie, plasma concentrations of cHMWK). No formal statistical hypothesis will be tested. Individual PK concentrations and cHMWK levels will be provided in subject data listing(s) and summarized using descriptive statistics (number of subjects, arithmetic mean, standard deviation [SD], coefficient of variation [CV%], median, minimum, maximum, geometric mean, and %CV of geometric mean). Figures of individual and mean (± SD) concentration-time profiles plasma lanadelumab will be generated. Tabular and graphical summaries will be analyzed based on the PK set and PD set, as appropriate.

Health-related quality of life (HRQoL): HRQoL will be measured by the angioedema quality of life (AE-QoL) questionnaire, which consists of 17 disease-specific quality-of-life items, to produce a total AE-QoL score and 4 domain scores (functioning, fatigue/mood, fear/shame, and nutrition). The AE-QoL total score and domain scores will be summarized using descriptive statistics by scheduled visit. Change in total AE-QoL score and 4 domain scores from baseline (Day 0) to Day 182 and Day 364 will be reported.

Immunogenicity: Immunogenicity will be measured by the presence or absence of anti-drug antibody (ADA) in plasma (neutralizing or non-neutralizing antibody in plasma). Immunogenicity data will be summarized using descriptive statistics, and the effect on lanadelumab plasma concentrations, cHMWK, and the number of

investigator-confirmed HAE attacks during the efficacy evaluation periods will be evaluated.

Interim Analysis

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

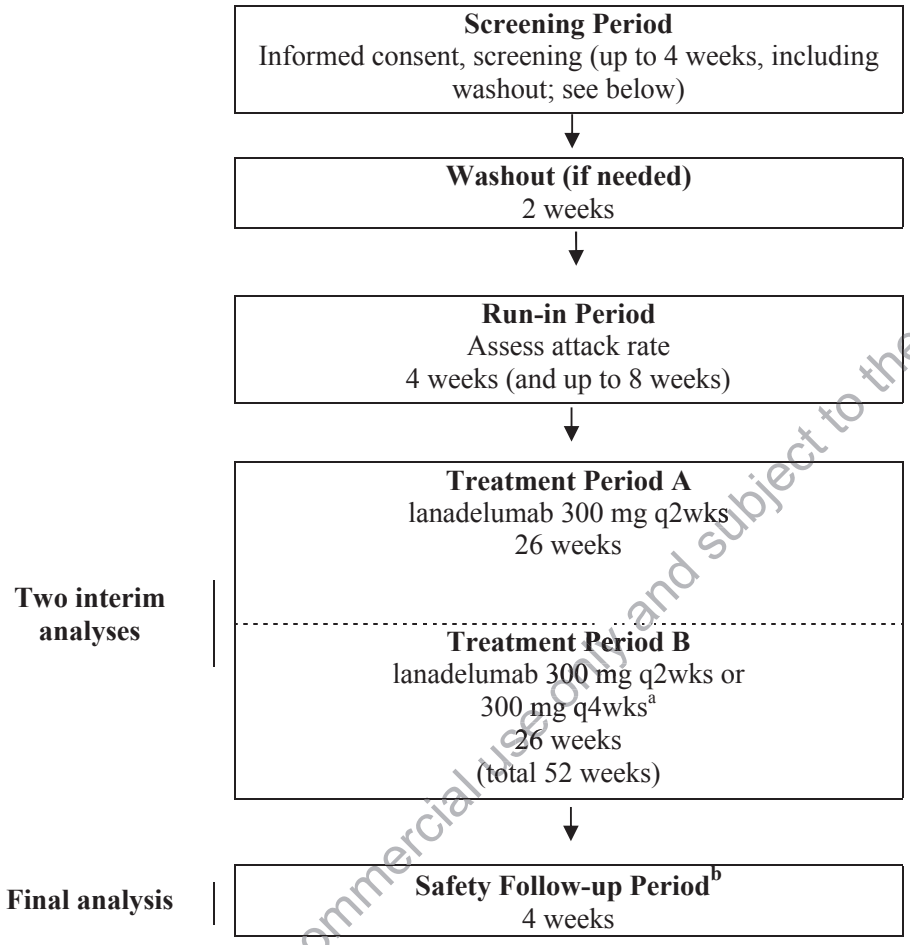
A final data analysis will summarize the efficacy, long-term safety, PK, HRQoL, PD and immunogenicity of 52 weeks of treatment with lanadelumab in Japanese subjects with HAE (Treatment Periods A and B) and additional 4 weeks follow-up and will be submitted to further support the JNDA during the review period.

Sample Size

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

1.2 Schema

Figure 1: Study Design



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

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

1.3 Schedule of Activities

Table 1: Study Activity Schedule-Screening, Run-in and Treatment Period A

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

Table 1: Study Activity Schedule-Screening, Run-in and Treatment Period A

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

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

[a] Subjects will undergo a run-in period to determine their baseline HAE attack rate. Only subjects meeting a minimum baseline attack rate of at least 1 investigator-confirmed attack per 4 weeks will be eligible for treatment. Subjects who experience 3 or more investigator-confirmed attacks before the end of the 4-week run-in period may exit the run-in period early and proceed to Treatment Period A. The run-in period may be extended to 8 weeks if the minimum baseline attack rate is not achieved in the first 4 weeks of the run-in period. Subjects who have their run-in extended must complete the full 8-week run-in period and must have at least 2 investigator-confirmed attacks during this time to be eligible to enter Treatment Period A. Subjects who do not meet the minimum attack rate during run-in or were otherwise determined to be ineligible due to screening assessments will be considered a screen fail.

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

[c] Subjects who are receiving LTP for HAE will be required to undergo a minimum 2-week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the investigator determines that doing so will not place the subject at any undue safety risk and the subject is at least 18 years of age. The investigator will confirm that the subject has successfully completed the 2-week washout period before they may enter the run-in period.

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

Table 1: Study Activity Schedule-Screening, Run-in and Treatment Period A

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

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

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

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

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

[i] Historical attack information will be collected at screening. During the study the subjects (or their parents/caregivers, in the event the subject is <18 years old or is incapacitated) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack, in accordance with HAARP. Site personnel will also contact the subject once a week or at approximately 7 days after last contact with the subject during the run-in period and once between study visits or approximately 7 days after last contact with the subject during the treatment period in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not given through prior subject contact with the site.

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

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

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

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

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

Note: In the event a subject prematurely discontinues from treatment and/or the study, EOS/ET procedures will be performed as soon as possible (see Table 2).
Note: Investigators are to report all SAEs to Shire Drug Safety through 30 days after the last dose of investigational product and SAEs considered related to investigational product >30 days after the last dose of investigational product.

Table 2: Study Activity Schedule - Treatment Period B and Follow-up Period

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

Table 2: Study Activity Schedule - Treatment Period B and Follow-up Period

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

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

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

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

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

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

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

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

[g] During the study the subjects (or their parents/caregivers, in the event the subject is <18 years old or is incapacitated) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack, in accordance with HAARP. If a site-check was not performed (see footnote n), site personnel will contact the subject once between study visits (or approximately 7 days after last contact with the subject) in order to solicit for any attack that may have occurred. The preferred method for site contact is a telephone call; however, alternate methods of contact may be considered as site policies permit. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not given through prior subject contact with the site.

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

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

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

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

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

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

Table 2: Study Activity Schedule - Treatment Period B and Follow-up Period

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

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

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

Note: In the event a subject prematurely discontinues from treatment and/or the study, EOS/ET procedures will be performed as soon as possible.
Note: Investigators are to report all SAEs to Shire Drug Safety through 30 days after the last dose of investigational product and SAEs considered related to investigational product >30 days after the last dose of investigational product.

2. INTRODUCTION

Lanadelumab (SHP643), a first-in-class monoclonal antibody inhibitor of active plasma kallikrein (pKal), has been developed lanadelumab for prevention of angioedema attacks in patients with Type I or II HAE, a rare and life-threatening disease (Section 2.1). Lanadelumab (TAKHZYRO™) has received marketing approval in the United States (23 Aug 2018), Canada (19 Sep 2018), and the European Union (22 Nov 2018) for prophylaxis to prevent attacks of HAE in patients aged 12 years and older. To date, the worldwide applications for marketing authorization of lanadelumab have been supported by 4 clinical studies, including two completed Phase 1 studies, a completed pivotal Phase 3 study in adolescent and adult subjects with HAE, and an ongoing open-label Phase 3 extension study in adolescent and adult subjects with HAE (Section 2.4.3).

Lanadelumab is expected to fulfill a medical need in Japan for long-term prophylaxis (LTP) in patients with Type I or Type II HAE (Section 2.3). The Sponsor recently completed a Phase 1 study (SHP643-101) comparing the pharmacokinetics (PK), safety, tolerability, and pharmacodynamics (PD) of a single 300 mg subcutaneous dose of lanadelumab in healthy adult Japanese subjects and matched non-Hispanic Caucasian adult subjects (Section 2.4.3.5). The current Phase 3 study (SHP643-302) will evaluate the efficacy, safety, PK, HRQoL, PD, and immunogenicity of lanadelumab in Japanese patients with Types I or II HAE and is intended to bridge the global clinical data for lanadelumab to Japanese HAE subjects. Together, these studies are intended to support the application for marketing authorization of lanadelumab in Japan.

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).

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). 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).

2.2 Epidemiology in Japanese Patients with Hereditary Angioedema

In Japan, the number of identified patients with HAE has been reported as 52 patients with type I or type II HAE (Iwamoto et al., 2012), 132 unique Japanese patients with HAE (Yamamoto et al., 2012), 171 HAE patients (Ohsawa et al., 2015), and 350 HAE patients (Ohi et al., 2017). HAE may have been historically under reported in Japan due to the medical community's lack of recognition of disease characteristics and/or misdiagnosis of symptoms given the similarity with many other more common angioedemas. Publication of the Japan HAE guidelines and other educational interventions have contributed to a recent rise in HAE diagnosis.

The genetic characteristics, pathophysiology, and clinical presentation of HAE appear to be similar between Japanese HAE patients and the overseas HAE population. Worldwide, over 400 different mutations in the SERPING1 gene have been identified. Two studies in Japanese HAE patients have shown that gene mutations are widely distributed across the C1-INH gene and conclude that the genetic characteristics of Japanese HAE patients are likely to be similar to those of HAE patients in Western populations (Yamamoto et al., 2012; Gordon et al., 1981). The pathophysiology of HAE is linked to the kallikrein-kinin pathway and is not known to differ between ethnic groups. Levels of plasma prekallikrein and high-molecular kininogen were reported to be similar in Oriental and Caucasian healthy subjects (Gordon et al., 1981), and Phase 1 studies with lanadelumab and another small molecule pKal inhibitor showed similar kallikrein activity profiles in Japanese and non-Japanese healthy subjects (Cornpropst et al., 2016; lanadelumab investigator's brochure). Data from a Phase 1 clinical study conducted by the Sponsor (SHP643-101) 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. Clinical manifestations in Japanese HAE patients are similar to those of the overseas population, consistent with the common genetic characteristics and disease pathophysiology of HAE. In the largest survey of HAE status in Japan, the onset of HAE was reported to be delayed in Japan compared to Western countries (24 years vs. 10-15 years)

(Ohsawa et al., 2015). The authors suggested that this finding was hindered by low representation of younger HAE patients in the survey (8% younger than 20 years and 5% pediatrics), and low awareness of HAE among Japanese physicians, which ultimately results in a diagnostic delay. In addition, a high incidence of laryngeal edema was observed in Japanese subjects (10%), which the authors hypothesized may be due to the lack of HAE-specific prophylactic drugs in Japan and the lack of timely recognition of HAE symptoms that would permit early administration of acute treatment to prevent the worsening of attacks.

2.3 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., 2012). These guidelines recommend C1-INH or attenuated androgens as the standard of care over anti-fibrinolytic agents (Cicardi et al., 2012; Craig et al., 2012). The most recent World Allergy Organization [WAO]/European Academy of Allergy and Clinical Immunology [EAACI] guidelines (2017 revision and update) recommend C1-INH as first-line long-term prophylactic therapy (androgens as second-line). Anti-fibrinolytics are not recommended due to the lack of efficacy in LTP (Maurer et al., 2018). 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).

Currently, there are no approved therapies in Japan that are safe and effective for the long-term prevention of angioedema attacks in patients with Types I or II HAE. The only currently approved HAE therapies in Japan are Berinert, a human plasma-derived C1-INH concentrate for intravenous (IV) administration that is indicated for the treatment of acute attack and peri-procedural (short-term) prevention of acute attacks and, more recently, Firazyr, a subcutaneous B2-receptor antagonist that is indicated for the treatment of acute attacks. The Japan HAE guidelines recommend LTP in patients with a history of laryngeal edema and/or a high frequency of attacks (ie, symptoms at least once per month and/or more than 5 days/month) (Horiuchi et al., 2012). As there are no approved therapies in Japan for the long-term prevention of angioedema attacks in patients with Types I or II HAE, the Japan HAE guidelines currently recommend off-label use of attenuated androgens (eg, danazol) and the anti-fibrinolytic tranexamic acid as first-line long-term prevention strategies.

Lanadelumab is expected to fulfill an unmet medical need in Japan for a long-term safe, effective and convenient intervention to prevent HAE attacks. Lanadelumab may provide significant benefit to Japanese HAE patients, given the demonstrated efficacy in preventing HAE attacks in

an overseas population (Section 2.4.3.3 and Section 2.4.3.4) and the similarity in genetic characteristics, pathophysiology, and clinical presentation of HAE between the overseas population and Japanese HAE patients. In the overseas population, 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 convenient dosing interval of q2wks or q4wks is being proposed for the Japanese HAE patient population in this study. In addition, lanadelumab has a favorable route of administration (SC).

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

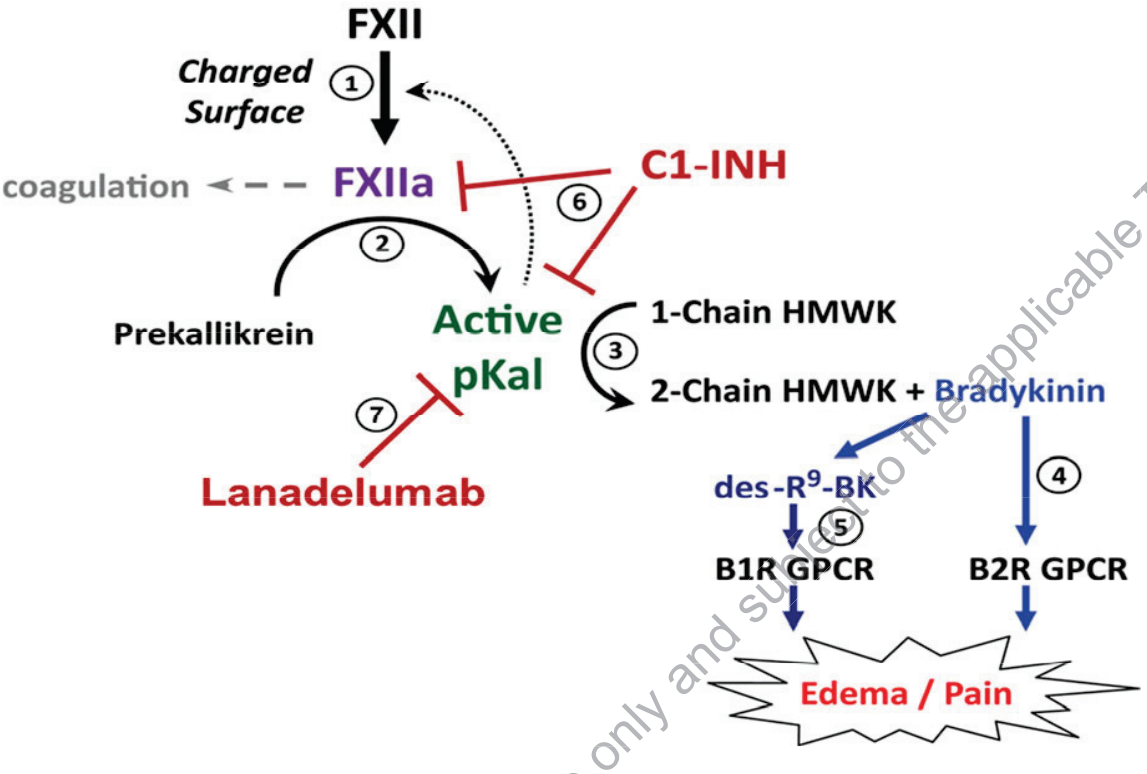
2.4 Product Background and Clinical Information

2.4.1 Drug Information

Mechanism of Action

Lanadelumab is a fully human, immunoglobulin G1 kappa light chain monoclonal antibody expressed in Chinese hamster ovary cells. It is a potent (inhibition constant=125 pM) and specific inhibitor of active 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 at a lanadelumab concentration of 150 mg/mL, provided in a single-use 5 mL glass vial (300 mg in 2 mL fill).

For Japanese patients with HAE, the same formulation and presentation used in the overseas population of adolescents and adults aged 12 years and above are planned. In this study, the proposed presentation is a solution in a vial, where 2 mL (300 mg) will be withdrawn from the vial and administered to the subject. In addition, for Treatment Period B only, the proposed presentation may include a pre-filled syringe, if available and permitted per local regulations.

Route of Administration

Lanadelumab is formulated as a liquid for injection and is intended for SC administration in the abdomen, thigh, or upper arm. The upper arm location is not recommended for

self-administration but rather as an additional injection site when administered by a parent/caregiver or healthcare provider.

2.4.2 Nonclinical Studies with Lanadelumab

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 in the 6-month cynomolgus monkey study, exposure margins based on maximum observed concentration (C_{max}) occurring at time to reach maximum observed plasma concentration (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).

Collectively, the nonclinical studies demonstrate that lanadelumab did not have adverse effects on vital functions or produce adverse target organ pathologies in rats or cynomolgus monkeys and support the safe use in patients with HAE as a prophylactic treatment by subcutaneous injection.

2.4.3 Clinical Studies with Lanadelumab

To date, the worldwide applications for marketing authorization of lanadelumab have been supported by 4 clinical studies. 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). In addition, in support of the intended application for marketing authorization of lanadelumab in Japan, the Sponsor recently completed a Phase 1 study (SHP643-101) comparing the PK, safety, tolerability, and PD of a single 300 mg subcutaneous dose of lanadelumab in healthy adult Japanese subjects and matched non-Hispanic Caucasian adult subjects. Results for all 5 clinical studies are briefly summarized below. A summary of results in adolescent patients with HAE (in Studies DX-2930-03 and DX-2930-04) is also provided below.

Refer to the latest version of the lanadelumab IB for details.

2.4.3.1 Clinical Study DX-2930-01

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 17-21 days across dose groups. The exposure was dose proportional and the half-life was consistent across the dose groups.

2.4.3.2 Clinical Study DX-2930-02

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 mg 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.

2.4.3.3 Clinical Study DX-2930-03

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 (74-87%), moderate or severe attacks (70-83%), and attacks from Day 14 through Day 182 (75-89%). 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.

2.4.3.4 Clinical Study DX-2930-04

Study DX-2930-04 (HELP Study Extension™) is 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. The safety profile of this study is 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.

2.4.3.5 Clinical Study SHP643-101

Study SHP643-101 was a Phase 1, open-label, matched-control, single dose, single-center study. Its primary objective was to evaluate the pharmacokinetic (PK) properties of lanadelumab administered as a single subcutaneous (SC) dose of 300 mg in healthy adult male and female volunteer subjects of Japanese descent and matched non-Hispanic, Caucasian healthy volunteer subjects. The secondary objective was to assess the safety and tolerability of lanadelumab administered as a single SC dose of 300 mg. The study duration was comprised of a 28-day screening period, followed by a 5-day in-house confinement treatment period, and then 8 out-patient visits up to a total of 112 days follow-up after the single dose of investigational product was administered.

A total of 32 male and female subjects between the ages of 18-55 years, inclusive, were planned to be enrolled: 16 non-Hispanic, Caucasian subjects and 16 subjects of Japanese descent.

Of the 32 subjects enrolled, all 32 subjects completed the study.

Following a single SC administration of 300 mg lanadelumab in healthy adult Japanese and matched-control healthy adult Caucasian subjects, peak exposures to lanadelumab of 21.9 µg/mL and 21.4 µg/mL (C_{max}, geometric mean estimates) were attained (tmax) at approximately 114 and 120 hours postdose (median estimates), respectively; thereafter, plasma concentrations of lanadelumab declined in a monophasic manner with a geometric mean t½ of 15.5 and 15.8 days for Japanese and Caucasian subjects, respectively.

Following single SC administration of 300 mg lanadelumab in healthy Japanese subjects, peak and overall systemic exposure to lanadelumab (C_{max}, area under the concentration-time curve from time zero to the last measurable concentration [$AUC_{0\text{-last}}$], and area under the

concentration-time curve from time zero extrapolated to infinity [$AUC_{0-\infty}$]) was similar to that observed in healthy Caucasian subjects, as determined from the 90% CIs. As is shown in Table 3, the 90% CIs of the geometric mean ratios (Japanese vs Caucasian) were contained within bioequivalence limits (0.80, 1.25).

Table 3 Statistical Analysis of Lanadelumab Plasma Pharmacokinetic Parameters Using ANOVA (Pharmacokinetic Set)

Parameter	Ethnic Group	N	n	Geometric LS Means	Ethnic Group Comparison	Ratio of Geometric LS Means	90% CI of the Ratio
C_{max} (ng/mL)	Japanese	16	16	21.91	Japanese vs Caucasian	1.0229	(0.8473, 1.2349)
	Caucasian	16	16	21.42			
$AUC_{(0\text{-last})}$ (h*ng/mL)	Japanese	16	16	510.6	Japanese vs Caucasian	0.9324	(0.8016, 1.0846)
	Caucasian	16	16	547.6			
$AUC_{(0-\infty)}$ (h*ng/mL)	Japanese	16	16	515.0	Japanese vs Caucasian	0.9318	(0.8005, 1.0846)
	Caucasian	16	16	552.7			

CI = confidence interval; CV%=coefficient of variation; LS = least squares; N = number of subjects in the PK Set, defined as all subjects in the Safety Analysis Set (all subjects dosed) who have at least 1 evaluable postdose PK concentration value; n=number of subjects with evaluable PK parameter values.

Note: An ANOVA-based analysis was performed with the ln transformed pharmacokinetic parameters as the dependent variable and ethnic group as a fixed effect independent variable.

Lanadelumab was generally safe and well tolerated by both ethnic groups when administered as a single 300 mg dose. There were no deaths, serious TEAEs, severe TEAEs, TEAEs considered related to lanadelumab, or any TEAEs leading to discontinuation of lanadelumab treatment. Overall, there were no notable differences between ethnic groups in the number of subjects who has TEAEs.

Raw means and mean changes from baseline in biochemistry, hematology, and urinalysis values at all time points were generally similar between ethnic groups, with the majority of results normal at all time points. The number of results flagged as potentially clinically important were low for biochemistry, hematology and urinalysis. None of the results were reported as TEAEs by the investigator.

Raw values and mean changes from baseline in vital signs, including pulse rate, systolic blood pressure, and diastolic blood pressure, were generally similar between ethnic groups with no clinically meaningful differences between ethnic groups.

There were no notable mean changes from baseline in ECG results. No ECG results were considered clinically significant and reported as TEAEs.

One subject in the Caucasian ethnic group had positive ADA at Day 112; the subject did not have a positive result at any previous time point during the study. The positive ADA sample was low titer and negative for neutralizing antibodies and did not impact the exposure profile.

2.4.3.6 Adolescent Clinical Trial Experience

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, 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, the 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 DX-2930-03, 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 DX-2930-04 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 33 months of data from the Phase 3 long-term safety clinical study in patients with HAE, including adolescents (Study DX-2930-04).

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 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. 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).

2.5 Study Rationale

There is an unmet medical need in Japan for a long-term safe, effective and convenient intervention to prevent HAE attacks (see Section 2.3). The current study is being conducted to bridge the global lanadelumab efficacy, safety, PK, HRQoL, PD and immunogenicity data to Japanese HAE subjects.

2.6 Benefit/Risk Assessment

Clinical studies with lanadelumab demonstrated the improved efficacy and safety for routine prophylaxis to prevent and control symptoms of HAE in an overseas population of patients 12 years and older (Section 2.4.3; 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.

In the pivotal study (DX-2930-03), 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-dependent or limiting toxicity was observed for any related TEAEs. Hypersensitivity reactions occurred in few patients and were generally mild, transient, did not lead to discontinuation and did not need further treatment. The most frequent TEAE was injection site reaction, a majority of which were generally mild, lasted <0.5 hours in duration, and did not lead to study discontinuation. The safety profile of the completed Phase 3 open-label study (DX-2930-04) is consistent with the pivotal study.

As of the data cutoff on 24 July 2020 (IB Edition 8.0), the most frequently reported AEs in the lanadelumab-treated population across Study DX-2930-03 and Study DX-2930-04 were injection site pain (53.6%), viral upper respiratory tract infection (43.2%), headache (27.7%), upper respiratory tract infection (25.9%), injection site erythema (18.2%), and injection site bruising (13.6%).

Overall, 63.6% (140/220) of lanadelumab-treated subjects reported a total of 2541 related TEAEs across Study DX-2930-03 and Study DX-2930-04. The vast majority of related TEAEs were injection site reactions (ISRs), eg: injection site pain (50.0%, 110/220), injection site erythema (17.3%, 38/220), injection site bruising (10.9%, 24/220), injection site swelling (6.4%, 14/220), and injection site pruritus (5.9%, 13/220) in ≥5.0% of lanadelumab-treated population. The most frequently occurring non-ISR related AE was headache, reported by 4.5% (10/220) of lanadelumab-treated population. Other related non-ISR AEs reported by ≥2 subjects included hypersensitivity (2.3%, 5/220), ALT increased (1.4%, 3/220), aspartate aminotransferase (AST) increased (1.4%, 3/220), dizziness, (1.4%, 3/220), dysgeusia (0.9%, 2/220), and nausea (0.9%, 2/220).

Across both Phase 3 studies, 8.6% (19/220) 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.

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.

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

In the pivotal Study DX-2930-03, 84 lanadelumab-treated subjects received 2118 injections of investigational product. Approximately half (52.4%) of the lanadelumab treated subjects experienced 398 ISRs, most of which were considered related to investigational product (98.2%) and were mild in intensity (97%), and none of which were serious or severe. No subject discontinued due to an ISR. The majority of ISRs were ≤0.5 hours duration, with over 90% of all ISRs resolving within 1 day of onset.

For Study DX-2930-04, 117 (55.2%) subjects had a total of 2287 injection site reaction TEAEs during the treatment period. These ISRs occurred across a collective 11899 doses, equivalent to a mean of 56.1 doses per subject. Most of the ISRs were related to lanadelumab (2083 of 2287 ISR TEAEs). None of the ISRs were serious or severe. Most ISRs were mild in severity (98.8% [2260 of 2287 ISR TEAEs]) and reports of moderate ISRs were infrequent; the most frequent single event, injection site pain, had a maximum severity of mild in 98 (46.2%) subjects and moderate in 2 (0.9%) subjects. The majority of ISRs (92.6%) resolved within a day, while 70.2% resolved within an hour. Similar frequencies of ISRs were reported by subjects regardless of administration type (self-administered at home, self-administered in-clinic, and study staff administration in-clinic).

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. At the time of the global marketing and authorization application, 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. Few investigator-defined AESIs were reported in the pivotal Study DX-2930-03: 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 Study DX-2930-04, there were 9 investigator-reported hypersensitivity AESIs: 4 events in rollover subjects and 5 events in nonrollover subjects. Four of the AESIs were hypersensitivity reactions (all occurring in nonrollover subjects); there were also 6 ISRs that were classified as hypersensitivity. All of the hypersensitivity AESIs were classified as related to lanadelumab. None of the events were serious. Three of the subjects discontinued due to the hypersensitivity AESIs. One of these AESIs of hypersensitivity was classified as related and severe because it coincided with an HAE attack and ongoing disease under study. However, no anaphylaxis and no anaphylactoid reactions were observed and none of the subjects with these AESIs developed ADA.

Besides hypersensitivity, disordered coagulation (bleeding events or hypercoagulable events potentially associated with the mechanism of action of lanadelumab, an active pKal 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.

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 9.9% (21/212 subjects), which included 13 rollover and 8 nonrollover subjects. A total of 6 subjects on the study developed ADAs classified as neutralizing; therefore, the prevalence of neutralizing antibody was 2.8% (6/212). Except for 1 subject at one time point, all other ADA-positive samples were consistent with the low titer range (20-1280) observed in the prior interim analysis data and in Study DX-2930-03.

Overall, the formation of ADAs or neutralizing antibodies had no observable effect on the PK, PD, efficacy or safety profiles.

In summary, safety signals have not emerged from all available clinical and nonclinical data to date for systemically administered lanadelumab. The proposed study in Japanese HAE patients is being initiated after completion of a 26-week pivotal study in an overseas population of adolescent and adult HAE patients, with further safety data available from the completed long-term safety study in this population. The Japanese HAE patients enrolled in the current study will have a similar baseline clinical presentation to the population in the pivotal overseas study, as the eligibility criteria for this study will be identical (confirm) to those of the pivotal study. Additionally, the type and frequency of safety assessments will be comparable to the pivotal overseas study (see Schedule of Activities, Table 1 and Table 2).

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.

2.7 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (Integrated Addendum to ICH E6[R1]: Guideline for Good Clinical Practice E6[R2] Current Step 4 version, 9 November 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.

CCI [redacted]

3. OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

The objectives of the study are:

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

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)
1. To evaluate the **efficacy** of repeated SC administrations of lanadelumab in Japanese subjects with HAE.	**Primary efficacy measure is:** • Achievement of attack-free status for the efficacy evaluation period of Day 0 through Day 182 **Other efficacy measures include:** • Number of investigator-confirmed HAE attacks during each of the efficacy evaluation periods. • Number of investigator-confirmed HAE attacks requiring acute treatment during each of the efficacy evaluation periods. • Number of investigator-confirmed moderate or severe HAE attacks during the each of efficacy evaluation periods. • Maximum attack severity during each of the efficacy evaluations periods. • Number of investigator-confirmed high-morbidity attacks during each of the efficacy evaluation periods; a high morbidity HAE attack is defined as any attack that has at least 1 of the following characteristics: severe, results in hospitalization (except hospitalization for observation <24 hours), hemodynamically significant (systolic blood pressure <90, requires IV hydration, or associated with syncope or near syncope) or laryngeal. • Time to first HAE attack after Day 0 for the efficacy evaluation period of Day 0 through Day 182. • Time to first HAE attack after Day 0 for the efficacy evaluation period of Day 70 through Day 182. • Achievement of at least a 50%, 70% and 90% reduction in the investigator-confirmed NNA per 4 weeks relative to the run-in period NNA for each of the efficacy evaluation periods. • Achievement of an efficacy evaluation period NNA <1.0 per 4 weeks, <0.75 per 4 weeks, <0.50 per 4 weeks, and <0.25 per 4 weeks for each of the efficacy evaluations periods. • Achievement of attack-free status for each of the efficacy evaluation period of Day 0 through Day 364, Day 70 through Day 182, and Day 70 through Day 364. • Percentage of attack free days during each of the efficacy evaluation periods.
2. To evaluate the **safety** of repeated SC administrations of lanadelumab in Japanese subjects with HAE.	• Treatment emergent adverse events (TEAEs), including adverse events of special interest (AESI) and serious adverse events (SAEs) • Clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis) • Vital signs including blood pressure (BP), heart rate (HR), body temperature, and respiratory rate • 12 lead-electrocardiogram (ECG)
3. To evaluate the PK of repeated SC administrations of lanadelumab in Japanese subjects with HAE.	• Plasma concentrations of lanadelumab

Table 4: Objectives and Endpoints

Objective	Endpoint(s)
4. To evaluate the effect of repeated SC administrations of lanadelumab on health-related quality of life (HRQoL) in Japanese subjects with HAE.	• Measured by the AE-QoL questionnaire, which consists of 17 disease-specific quality-of-life items, to produce a total AE-QoL score and 4 domain scores (functioning, fatigue/mood, fear/shame, and nutrition). Change in total and domain AE-QoL scores from baseline (Day 0) to Day 182 and Day 364 will be reported.
5. To evaluate the pharmacodynamics (PD) of repeated SC administrations of lanadelumab in Japanese subjects with HAE.	• Plasma kallikrein activity as measured by cHMWK level (ie, plasma concentrations of cHMWK).
6. To evaluate the immunogenicity of repeated SC administration of lanadelumab and the effect on lanadelumab PK, PD, efficacy, and safety in Japanese subjects with HAE.	• Measured by the presence or absence of anti-drug antibody (ADA) in plasma (neutralizing or non-neutralizing antibody in plasma).

AE-QoL= angioedema quality of life; HAE=hereditary angioedema; cHMWK=cleaved high molecular weight kininogen; IV=intravenous; NNA=normalized number of attacks

4. STUDY DESIGN

4.1 Overall Design

This open-label Phase 3 study will enroll approximately 8 Japanese subjects with HAE Type I or II. Following signing of informed consent, subjects will undergo screening assessments; eligible subjects who are on long-term prophylaxis (LTP) for HAE are required to undergo a minimum 2-week washout period prior to entering the run-in period. This LTP washout period is permitted as long as the investigator determines that doing so would not place the subject in any undue safety risk, and that the subject is at least 18 years of age.

Eligible subjects who are not on LTP therapy for HAE, or who have completed the required washout period, will enroll and enter a run-in period of 4 weeks to determine their baseline attack rate. Only subjects meeting a minimum baseline attack rate of at least 1 investigator-confirmed attack per 4 weeks will be eligible for treatment. Subjects who experience 3 or more investigator-confirmed attacks before the end of the 4-week run-in period may exit the run-in period early and proceed to Treatment Period A. Subjects without at least 1 Investigator-confirmed attack after 4 weeks of run-in may have their run-in period extended for another 4 weeks. Subjects who have their run-in extended must complete the full 8-week run-in period and must have at least 2 investigator-confirmed attacks during this time to be eligible to enter Treatment Period A. Subjects who do not meet the minimum attack rate during the run-in period, or are otherwise determined to be ineligible based on screening assessments, will be considered a screen failure and will not be allowed to enter the treatment phase of the study; they will be replaced with new HAE subjects, until at least 8 subjects have entered Treatment Period A.

- **Treatment Period A:**

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

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

- **Treatment Period B:**

  Subjects who enter the Treatment Period B will receive lanadelumab for an additional 26 weeks (total of 52 weeks). During these additional 26 weeks, an individual subject may remain on the same dose regimen as Treatment Period A or may consider lanadelumab 300 mg q4wks if they have been well-controlled (eg, attack free) for 26 consecutive weeks with lanadelumab treatment. The dose frequency change will be based on the investigator's discretion and approval by the sponsor's medical monitor.

Section 4.3 provides justification for the dosing regimen proposed for this study. All doses of lanadelumab will be administered by SC injection (Section 2.4.1). Further details on dosing and self-administration of lanadelumab are provided in Section 6.2.3 and Section 8.2.6.7, respectively.

After completion of the second 26-week treatment (Treatment B) period, subjects may roll over into an expanded access study, Study TAK-743-5007. Subjects that elect to rollover to Study

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

Hereditary angioedema attacks occurring during the run-in period and study treatment periods will be treated according to the local standard of care. In case of insufficient response to the first dose, additional rescue medications will be allowed.

Two interim clinical study reports along with a final clinical study report will be prepared. The first interim analysis will be conducted when the first 6 subjects enrolled in the study have reached Day 182 or discontinued in Treatment Period A (26 weeks of treatment); enabling comparison to the DX-2930-03 pivotal overseas study data. The second interim analysis will be done when the first 4 subjects enrolled in the study have reached Day 364 or discontinued. The final clinical study report will summarize data from all subjects for the entire study duration.

Individual subject participation from screening through the completion of safety follow-up visit will be approximately 68 weeks (up to 4-week screening visit [including a 2-week washout period, if applicable], up to 8-week run-in period, 52-week treatment period, and 4-week safety follow-up visit [Day 392]). Subjects participating in Study TAK-743-5007 will be discharged from this study 2-weeks early on Day 378. An overview of the study design scheme is provided in Figure 1. All study procedures are detailed in the schedule of assessments (Table 1 and Table 2). CCI [redacted]

4.2 Scientific Rationale for Study Design

The current study is intended to bridge the overseas clinical data to Japanese HAE subjects. Therefore, the study design for SHP643-302 is similar to that of the pivotal overseas study (DX-2930-03).

The eligibility criteria for SHP643-302 are identical to those in Study DX-2930-03 with respect to subject age, diagnosis, and clinical presentation of HAE at study entry. To further ensure the similarity in baseline clinical presentation of the respective study populations, the subjects in the current study (like those in DX-2930-03) will undergo a 2-week washout from LTP after which they will complete a run-in period of 4 weeks (up to 8 weeks) to ensure a robust evaluation of baseline attack rate, and must have a baseline attack rate of at least 1 attack per 4 weeks to be eligible to enter the treatment period.

The planned sample size of 8 subjects is driven by feasibility, given the low estimates of the prevalence of HAE in Japan (refer to Section 2.2) and the enrollment in this study of only those patients with severe HAE. In a recent survey including data collected from 94 physicians on 171 HAE patients in Japan, the percent of patients experiencing frequent attacks that would potentially qualify them for enrollment in the proposed study was less than 21% (Yamamoto et al., 2012). Of these patients with severe HAE, not all patients will have access to study sites, attrition during screening and run-in period is likely, either because HAE attacks (which do not typically present regularly) may not be experienced during the run-in period or because other eligibility criteria are not met, and not every eligible HAE patient will choose to enroll and comply with the protocol requirements.

Study SHP643-302 will be an open-label single-arm study. Unlike DX-2930-03, the current study will not include a parallel placebo control group. Prior to the conduct of the overseas Phase 3 program there were insufficient data to support the clinical use of lanadelumab in HAE; therefore, a randomized, placebo-controlled study was necessary to support the development goal of demonstrating that lanadelumab was safe and effective for the prevention of angioedema attacks in patients with HAE. Study DX-2930-03 and an ongoing overseas open-label extension study (DX-2930-04), which are the largest and longest ever conducted in HAE patients, provide compelling results that lanadelumab is both safe and effective for the prevention of angioedema attacks in Western populations, and served as the basis for multiple global submissions and initial major regulatory approvals. At this time the objective of the Japanese development program, and Study SHP643-302 specifically, is to demonstrate similar lanadelumab treatment effects in Japanese HAE patients, using the most ethical and effective approach. Therefore, SHP643-302 will administer lanadelumab at the most effective dose regimen observed in the overseas clinical development, which is also the dose assessed in the open-label extension study (300 mg q2wks) (refer to Section 4.3 for further dose justification). Given the severity of the patients' disease at enrollment and the established efficacy and safety profile of lanadelumab in the overseas population, it was considered unethical to expose the Japanese HAE subjects to 26 weeks of placebo treatment. Moreover, inclusion of a parallel placebo arm could jeopardize the reproducibility and reliability of study outcomes given that the planned sample size of 8 subjects, which is driven by feasibility, would lead to small cohorts (approximately 4 subjects), and a patient assigned to placebo might discontinue prior to completing the 26-week treatment period, leading to missing data and potentially uninterpretable results. A cross-over design with placebo, while overcoming the problem of extremely small cohorts, was not feasible due to the very long half-life of lanadelumab and would not overcome the ethical challenge of 26 weeks of placebo treatment in patients with severe HAE.

The objectives of Study SHP643-302 are identical to those of the overseas Phase 3 studies, and similar endpoints will be used to evaluate the effect of lanadelumab in Japanese HAE patients. The primary treatment period will be 26 weeks (Treatment Period A), the same duration as the pivotal overseas study. Additional data on long-term safety and efficacy will be collected during a further 26 weeks of treatment (Treatment Period B). Overall treatment benefit will be based on the totality of results across all efficacy endpoints, with the primary goal of demonstrating consistency across the endpoints (especially the primary efficacy endpoint) with the pivotal overseas study (DX-2930-03). The primary efficacy endpoint in the current study, as agreed in the Sponsor's discussions with PMDA, will be achievement of attack-free status for the efficacy evaluation period from Day 0 through Day 182 (Treatment Period A). Similar analysis methods for estimating attack rates will enable comparison across studies for the 300 mg q2wks treatment group with respect to unadjusted attack rates for the run-in period, treatment period, and treatment period change from run-in period, as well as, model-based estimates of adjusted treatment period attack rates.

Data from Treatment Period A (26 weeks) will be submitted at the Japanese New Drug Application (JNDA), enabling comparison to the DX-2930-03 pivotal overseas study data. Final study data, including Treatment Periods A and B (52 weeks) and safety follow-up (4 weeks) will be submitted to further support the JNDA during the review period.

4.3 Justification for Dose

Lanadelumab was first approved overseas on 23 August 2018 for routine prophylaxis to prevent attacks of HAE in patients 12 years and older. In all the countries where lanadelumab is currently approved, the recommended dose regimen is 300 mg q2wks. A dosing interval of 300 mg q4wks may be considered in patients who are stably attack free on treatment.

Based on the totality of efficacy, PK and PD, and safety data from the pivotal overseas study in adolescent and adult subjects with HAE (Study DX-2930-03), the 300 mg q2wks dose regimen was considered the recommended dose as it consistently demonstrated the greatest treatment effect compared with placebo and had an optimal benefit-risk profile during the 26-week treatment period. Lanadelumab treatment resulted in a high proportion of subjects being attack free on all dosing regimens evaluated (300 mg q2wks, 300 mg q4wks, and 150 mg q4wks), with the 300 mg q2wks dosing regimen having the highest percentage of subjects (44%) who were attack free for the entire 26 week treatment period, and ~77% of subjects attack free after achieving steady state.

The ongoing open-label Phase 3 HELP Study Extension™ (Study DX-2930-04) in adolescent and adult subjects with HAE demonstrated that the prevention of HAE attacks for lanadelumab 300 mg q2wks was consistent with a substantially longer treatment duration. The safety profile in this study was consistent with the pivotal Study DX-2930-03. No treatment related SAEs or deaths were reported. Treatment-emergent AEs for most subjects were mild or moderate in severity with few severe events were considered related to lanadelumab treatment. Sustained decreases in plasma levels of the pharmacodynamic biomarker, cHMWK, and significant improvements in health-related quality of life (as determined using the AE-QoL instrument; see below) in lanadelumab-treated subjects were observed in both DX-2930-03 and DX-2930-04, corroborating the efficacy outcomes.

Significant reductions of AE-QoL total and functioning scores (minimal clinically important difference [MCID] of 6 points) demonstrated significant improvement in HRQoL for subjects treated with lanadelumab in the pivotal study (DX-2930-03), and in the extension study (DX-2930-04) this effect was sustained for the subjects who rolled over from the pivotal study and a significant improvement was demonstrated for subjects who were previously treated with placebo.

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 q2wks to q4wks represents a substantial quality of life benefit for patients and could be considered if the subjects are well-controlled (eg., attack free for 26 weeks) on the recommended dose.

A recently completed Phase 1 clinical study (Study SHP643-101) evaluated the PK and safety of lanadelumab when administered as a single SC dose of 300 mg in healthy adult subjects of

Japanese descent and matched non-Hispanic, Caucasian healthy adult 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.

Therefore, based on the available data from the lanadelumab overseas clinical development program and from Study SHP643-301, the current study will evaluate a single dose regimen of 300 mg q2wks lanadelumab for the first 26 weeks of treatment (Treatment Period A). In the subsequent 26 weeks of treatment (Treatment Period B), a subject may continue to receive lanadelumab 300 mg q2wks or, if the subject has been well-controlled (attack free) for 26 consecutive weeks with lanadelumab treatment, the subject may switch to a dose of 300 mg q4wks at the discretion of the investigator and following approval by the sponsor's medical monitor.

4.4 Duration of Subject Participation and Study Completion Definition

An enrolled subject will have signed an informed consent form and met the inclusion criteria to participate in the trial (and none of the exclusion criteria).

The subject's maximum duration of participation is expected to be approximately 68 weeks, including the following: up to 4-week screening period (including a 2-week washout, if applicable), up to 8-week run-in period, 52-week treatment period, and 4-week safety follow-up visit. The study will be completed in approximately 26 months

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 8.1.3 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. Up to 15 sites in Japan will participate.

5. STUDY POPULATION

The study will enroll Japanese subjects with a confirmed diagnosis of HAE (Type I or II), 12 years of age and older. Only subjects who experience at least 1 investigator-confirmed attack per 4 weeks during the run-in period will enter the treatment period (Treatment Period A). Overall, 8 Japanese subjects with HAE are planned to enter the treatment period. All inclusion and exclusion criteria for enrolling subjects in this study are presented in Section 5.1 and Section 5.2, respectively.

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

5.1 Inclusion Criteria

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

1. Be of Japanese descent, defined as born in Japan and having Japanese parents and Japanese maternal and paternal grandparents.
2. The subject is male or female and ≥12 years of age at the time of informed consent.
3. Documented diagnosis of HAE (Type I or II) based upon all of the following:
    - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).
    - Diagnostic testing results obtained during screening that confirm HAE Type I or II: C1 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 run-in period if results are incongruent with clinical history or believed by the investigator to be confounded by recent C1 inhibitor use.
    - At least one of the following: age at reported onset of first angioedema symptoms ≤30 years, a family history consistent with HAE Type I or II, or C1q within normal range.
4. Attack rate:
    - Subjects must experience at least 1 investigator-confirmed HAE attack per 4 weeks during the run-in period to enter the lanadelumab treatment period.
5. The subject (or the subject's parent/legal authorized representative, if applicable) has provided written informed consent approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC).

If the subject is an adult, be informed of the nature of the study and provide written informed consent before any study-specific procedures are performed.

OR

If the subject is a minor (ie, below the age of majority), have a parent/legally authorized representative who is informed of the nature of the study provide written informed consent (ie, permission) for the minor to participate in the study before any study-specific procedures are performed. Assent will be obtained from minor subjects.

6. Males, or nonpregnant, nonlactating females who are fertile and sexually active and who agree to be abstinent or agree to comply with the applicable contraceptive requirements of this protocol for the duration of the study, or females of nonchildbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or postmenopausal for at least 12 months.
7. Agree to adhere to the protocol-defined schedule of assessments and procedures.

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 (also known as HAE Type 3), idiopathic angioedema, or recurrent angioedema associated with urticaria.
2. Participation in a prior lanadelumab study.
3. Dosing with investigational drug or exposure to an investigational device within 4 weeks prior to entering to screening.
4. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systematic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
5. Exposure to androgens (eg, danazol, methyltestosterone, testosterone) within 2 weeks prior to entering the run-in period.
6. Use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to entering the run in period.
7. Use of short-term prophylaxis for HAE 7 days prior to entering the run-in period. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.
8. Any of the following liver function abnormalities: alanine aminotransferase (ALT) >3x upper limit of normal, or aspartate aminotransferase (AST) >3x upper limit of normal or bilirubin >2x upper limit of normal (unless the bilirubin is a result of Gilbert's syndrome).
9. Pregnancy or breast feeding.
10. Subject has any condition that in the opinion of the investigator or sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with

interpretation of the results (eg, history of substance abuse, or dependence, significant pre-existing illnesses or major comorbidity the investigator considers may confound the interpretation of the study results).

11. Subject has a known hypersensitivity to the investigational drug 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

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.

Adult female subjects should be either:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and age ≥51 years)

- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization
- Of childbearing potential with a negative urine beta-human chorionic gonadotropin (β-hCG) pregnancy test at predose 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.
- Premenarchal with a negative urine β-hCG pregnancy test at predose on Study Day 0 (Visit 1).

Acceptable methods of contraception include the following:

- Intrauterine devices (IUD, all types) or intrauterine hormone releasing systems (IUS) plus condoms

5.4.2 Male Contraception

Males, including males who are surgically sterile (post vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from screening through 70 days after the final study visit.

6. STUDY INTERVENTION

6.1 Investigational Product

6.1.1 Identity of Investigational Product

The investigational product is lanadelumab, which will be provided as a sterile, preservative-free, ready-to-use solution at a concentration of 150 mg/mL in a single-use 5 mL glass vial (300 mg/2 mL). In addition, for Treatment Period B only, the proposed presentation may include a pre-filled syringe, if available and permitted per local regulations.

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, randomization 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 randomization number 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 upper arm location is not recommended for self-administration but rather as an additional injection site when administered by a parent/caregiver or health care provider.

The lanadelumab dose regimen for this study is 300 mg q2wks. All subjects will receive lanadelumab 300 mg q2wks throughout Treatment Period A (Visit 1 [Day 0] to Visit 14 [Day 182]), for a total of 14 doses of lanadelumab in this treatment period. All dose of lanadelumab in Treatment Period A will be administered by site personnel.

Beginning in Treatment Period B:

- Dose modification may be considered for individual subjects based on benefit-risk assessment; refer to Section 6.2.5 for details.
- Self-administration will be permitted after a subject (and/or their parent/caregiver) has received appropriate training by the investigator or designee and has demonstrated their understanding of self-administration; refer to Section 8.2.6.7 for details.

Subjects who continue to receive lanadelumab at a dose of 300 mg q2wks throughout Treatment Period B will receive a further 14 doses of lanadelumab (for a total of 28 doses in the study). Subjects who receive a dose modification to 300 mg q4wks in Treatment Period B must receive their first dose on the q4wks regimen at an even-numbered visit (eg, Visit 16, 18, 20) and will receive between 6 and 11 doses of lanadelumab, depending on the exact timing of this dose modification.

The presentation is a solution in vial (150 mg/mL) where 2 mL (300 mg) will be withdrawn from the vial and administered to the subject. In addition, for Treatment Period B only, the proposed presentation may include a PFS, if available and permitted per local regulations.

6.2.4 Unblinding the Treatment Assignment

Not applicable. This is an open-label study.

6.2.5 Dose Modification

An individual subject's dose 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 may administer lanadelumab 300 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. Subjects who receive a dose modification to 300 mg q4wks in Treatment Period B must receive their first dose on the q4wks regimen at an even-numbered visit (eg, Visit 16, 18, 20). Note: The timing of PK, PD, and ADA assessments at Visit 27 will be adjusted for subjects receiving a dose modification, as shown in the Schedule of Activities (Table 2).

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 Labeling

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, and the statements “For clinical trial use only” and "Keep out of sight and reach of children". The label will comply with Japanese GCP.

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

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label.
- Obscure the clinical study label.
- Identify the study subject by name.

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

6.3.2 Packaging

Investigational product is packaged in the following labeled containers:

- Treatment Period A: 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.
- 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 (or 1 PFS, if available and permitted per local regulations). Both the vial (or PFS) 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 (as applicable), 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 (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 (or PFS) 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 trained subjects (and their 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.

6.3.3 Storage and Handling

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 identifier on the investigational product bottle/carton labels as they are distributed.

Lanadelumab should be stored in a refrigerator at 2-8°C. 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.

Storage and handling of PFS will be similar to that described above for vials. Refer the latest version of the lanadelumab IB for details.

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 PFS) 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 prior to the screening visit (or pharmacokinetic 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.

6.6.1 Prior Treatment

Prior treatment includes all non-study treatments received within 28 days (4 weeks) (or PK equivalent of 5 half-lives, whichever is longer) prior to screening visit. Prior treatment information must be recorded in the subject's source document.

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. Concomitant treatment information must be recorded in the subject's source document.

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).
- Hereditary angioedema attacks occurring during the run-in period and study treatment periods will be treated according to the local standard of care. In case of insufficient response to the first dose, additional rescue medications will be allowed. 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 periprocedural prophylactic treatment for HAE will be permitted if medically indicated.
- Therapies to treat any AEs the subject experiences 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 anti-fibrinolytics) within 2 weeks prior to entering the run-in 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 within 2 weeks prior to entering the run-in period and during the study.
- Any other investigational drug or device.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

If investigational product is discontinued, regardless of the reason, the evaluations listed for the end of study (EOS) visit will be performed as completely as possible (see Section 8.1.3). 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 are discontinued from the study because they do not meet the minimum HAE attack rate during the run-in period, or who are otherwise determined to be ineligible based on screening assessments will be considered to be screen failures; they will be replaced with new HAE subjects until at least 8 subjects have entered Treatment Period A.

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. If a subject is discontinued for more than 1 reason, each reason should be documented in the source and the primary 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 authorized representative for adolescent subjects)
- Adverse event
- Protocol deviation (eg, lack of compliance, use of experimental drug)
- Pregnancy
- Sponsor decision
- Investigator decision
- Death
- Lost to follow-up
- Lack of efficacy
- Other (must specify on the electronic case report form [eCRF])

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 [preferably a phone call]). 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 8.2.5.3), 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 evaluations listed for the end of study (EOS) visit as completely as possible (see Section 8.1.3).

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 and Table 2 for the schedule of study activities. Study assessments are detailed in Section 8.2.

8.1.1 Screening, Washout, and Run-in Period

8.1.1.1 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 and medical history
- Collection of historical HAE attack data [redacted]
- 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.
- 12-lead ECG
- Pregnancy test (for female subjects)
- Clinical laboratory testing including hematology, serum chemistry, coagulation, and urinalysis
- 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

A subject should complete all screening procedures within 4 weeks. When all screening results are available, an eligibility review will be conducted by the site to determine if the subject meets all study eligibility criteria. (Note: As indicated in Section 8.1.1.2, a final eligibility review will be conducted prior to dosing on Day 0.)

Eligible subjects who are on LTP therapy for HAE are required to undergo a minimum 2-week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm that the subject has successfully completed the 2-week washout period before they can enter the run-in period.

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.

8.1.1.2 Run-in Period (up to 8 weeks)

Eligible subjects who are not on LTP therapy for HAE, or who have completed the required washout period, will enroll and enter a run-in period to determine their baseline attack rate. The run-in period will be 4 weeks and may be extended up to 8 weeks, as described below.

During the run-in period, the following information will be collected on an ongoing basis:

- HAE attack data (Note: Subjects must report details of an HAE attack to the study site within 72 hours of onset of the attack, in accordance with HAE Attack Assessment and Reporting Procedures (HAARP) [CCI [redacted]]).
- Prior/current medications, therapies, and procedures
- Adverse events collection, including SAEs and AESIs

Subjects who report 3 or more than 3 investigator-confirmed HAE attacks before the end of the 4-week run-in period may exit the run-in period early and proceed to the Treatment Period A. All other subjects must stay in the run-in period for at least 4 weeks. A subject who does not experience at least 1 investigator-confirmed attack after 4 weeks may have their run-in period extended for another 4 weeks (a total of 8 weeks); these subjects must complete the entire 8-week run-in period and must experience at least 2 investigator-confirmed attacks during the run-in period to be eligible for enrollment.

Subjects who experience at least 1 investigator-confirmed HAE attack per 4 weeks during the run-in period, and who remain eligible for the study based on an eligibility review conducted at Day 0, may begin treatment with lanadelumab in Treatment Period A.

8.1.2 Treatment Period

8.1.2.1 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 study eligibility
- Vital signs, including body temperature, HR, BP and RR
- Complete physical examination
- 12-lead ECG
- Clinical laboratory testing including hematology, serum chemistry, coagulation, and urinalysis

- Pregnancy test (for female subjects)
- Pharmacokinetic sample collection
- Pharmacodynamic sample collection
- Plasma ADA sample collection
- Health-related quality of life assessment (AE-QoL)
- Prior therapies, medications, and procedures
- HAE attack data [redacted].
- Adverse events collection, including SAEs and AESIs

As specified in Table 1 and Table 2, after lanadelumab administration (q2wks; Section 6.2.3), the following post treatment procedures and assessments will be performed:

- Lanadelumab injection report
- Vital signs including body temperature, HR, BP and RR at 1 hours and 2 hours post-dose
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

8.1.2.2 Study Visit 2 (Study Day 14) to Study Visit 14 (Study Day 182)

As indicated in Table 1, 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
- 12-lead ECG
- Clinical laboratory testing, including hematology, serum chemistry, coagulation, and urinalysis
- Pregnancy test (for female subjects)
- Pharmacokinetic predose sample collection
- Pharmacodynamic predose sample collection
- Plasma ADA predose sample collection
- Health-related quality of life assessments (AE-QoL)
- HAE attack data (Note: Subjects must report details of an HAE attack to the study site within 72 hours of onset of the attack, in accordance with HAARP[redacted]).
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

As specified in Table 1, after lanadelumab administration (q2wks; Section 6.2.3), the following post treatment procedures and assessments will be performed:

- Lanadelumab injection report
- Vital signs including body temperature, HR, BP and RR at 1 hours and 2 hours post-dose (see Section 8.2.5.4 regarding elimination of the 2 hour post-dose measurement).
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

All scheduled study visits from Visit 2 through Visit 14 will be on-site visits.

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

8.1.2.3 Study Visit 15 (Study Day 196) to Study Visit 25 (Study Day 336)

As indicated in Table 2, 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
- 12-lead ECG
- Clinical laboratory testing, including hematology, serum chemistry, coagulation, and urinalysis
- Pregnancy test (for female subjects)
- Pharmacokinetic predose sample collection
- Pharmacodynamic predose sample collection
- Plasma ADA predose sample collection
- Health-related quality of life assessments (AE-QoL)
- HAE attack data (Note: Subjects must report details of an HAE attack to the study site within 72 hours of onset of the attack, in accordance with HAARP CCI [redacted]).
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

As specified in Table 2, after lanadelumab administration (q2wks or q4wks; Section 6.2.3), the following post treatment procedures and assessments will be performed:

- Lanadelumab injection report
- Vital signs including body temperature, HR, BP and RR at 1 hours and 2 hours post-dose (see Section 8.2.5.4 regarding elimination of the 2 hour post-dose measurement).
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

On-site visits will be scheduled at Visits 17, 20, and 23 (non-shaded columns in Table 2).

Other study visits may be scheduled as on-site visits or, if a subject is self-administering lanadelumab where permitted per protocol (see Section 8.2.6.7) or a subject is receiving lanadelumab q4wks and the visit is a non-dosing visit for the subject, then the study visit may be completed via a site check-in, which should occur within 3 days of the nominal study day. The preferred method of site check-in is a telephone call; however, alternate methods of contact may be considered as site policies permit. During this site check-in, site personnel will ensure that self-administration of lanadelumab has occurred as scheduled (if applicable) and will solicit for any HAE attacks not already reported by the subject and collect information on AEs and concomitant medications. If a site check-in is performed within 3 days after a scheduled visit, it is not necessary to also have a site contact at 7 days after last contact with the subject as described below.

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

8.1.2.4 Study Visit 26 (Study Day 350)

Note: The procedures and assessments at Visit 26 will differ depending on whether a subject is receiving lanadelumab q2wks or q4wks. Therefore, procedures and assessments are presented separately for each dosing regimen below.

Subjects on q2wk Dosing Regimen

Visit 26 will be an on-site visit for all subjects on the q2wk regimen. As indicated in Table 2, 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
- 12-lead ECG

- Clinical laboratory testing, including hematology, serum chemistry, coagulation, and urinalysis
- Health-related quality of life assessments (AE-QoL)
- HAE attack data (Note: Subjects must report details of an HAE attack to the study site within 72 hours of onset of the attack, in accordance with HAARP [CCI redacted]).
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

As specified in Table 2, after lanadelumab administration (q2wks; Section 6.2.3), the following post treatment procedures and assessments will be performed:

- Lanadelumab injection report
- Vital signs including body temperature, HR, BP and RR at 1 hours and 2 hours post-dose (see Section 8.2.5.4 regarding elimination of the 2 hour post-dose measurement).
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

Site personnel will contact the subject once between Visit 26 and the next scheduled study visit at Visit 27 (or approximately 7 days after last contact with subject) to solicit for any attacks not already reported by the subject and to collect information on AEs and concomitant medications. The preferred method of site contact is a telephone call; however, alternate methods of contact may be considered as site policies permit.

Subjects on q4wk Dosing Regimen

Visit 26 will be an on-site visit for all subjects on the q4wk regimen. Completion of treatment or last dose administration will occur at Visit 26 (Day 350) for subjects on the q4wk regimen.

As indicated in Table 2, 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
- 12-lead ECG
- Clinical laboratory testing, including hematology, serum chemistry, coagulation, and urinalysis
- Pharmacokinetic predose sample collection
- Pharmacodynamic predose sample collection
- Plasma ADA predose sample collection

- Health-related quality of life assessments (AE-QoL)
- HAE attack data (Note: Subjects must report details of an HAE attack to the study site within 72 hours of onset of the attack, in accordance with HAARP [redacted]).
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

As specified in Table 2, after lanadelumab administration (q4wks; Section 6.2.3), the following post treatment procedures and assessments will be performed:

- Lanadelumab injection report
- Vital signs including body temperature, HR, BP and RR at 1 hours and 2 hours post-dose (see Section 8.2.5.4 regarding elimination of the 2 hour post-dose measurement).
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

Site personnel will contact the subject once between Visit 26 and the next scheduled study visit at Visit 27 (or approximately 7 days after last contact with subject) to solicit for any attacks not already reported by the subject and to collect information on AEs and concomitant medications. The preferred method of site contact is a telephone call; however, alternate methods of contact may be considered as site policies permit.

8.1.2.5 Final Treatment Period Visit at Study Visit 27 (Study Day 364)

Note: The procedures and assessments at Visit 27 will differ depending on whether a subject is receiving lanadelumab q2wks or q4wks. Therefore, procedures and assessments are presented separately for each dosing regimen below.

Subjects on q2wk Dosing Regimen

Visit 27 will be an on-site visit for all subjects on the q2wk regimen. Completion of treatment or last dose administration will occur at Visit 27 (Day 364) for subjects on the q2wk regimen.

As indicated in Table 2, 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
- 12-lead ECG
- Clinical laboratory testing, including hematology, serum chemistry, coagulation, and urinalysis
- Pharmacokinetic predose sample collection
- Pharmacodynamic predose sample collection

- Plasma ADA predose sample collection
- Health-related quality of life assessments (AE-QoL)
- HAE attack data (Note: Subjects must report details of an HAE attack to the study site within 72 hours of onset of the attack, in accordance with HAARP CCI).
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

As specified in Table 2, after lanadelumab administration (q2wks; Section 6.2.3), the following post treatment procedures and assessments will be performed:

- Lanadelumab injection report
- Vital signs including body temperature, HR, BP and RR at 1 hours and 2 hours post-dose (see Section 8.2.5.4 regarding elimination of the 2 hour post-dose measurement).
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

Subjects on q4wk Dosing Regimen

Visit 27 will be an on-site visit for all subjects on the q4wk regimen. This is a non-dosing visit for subjects on the q4wk regimen.

As indicated in Table 2, the following procedures and assessments will be performed at this visit:

- Vital signs including body temperature, HR, BP and RR
- Physical examination
- 12-lead ECG
- Clinical laboratory testing, including hematology, serum chemistry, coagulation, and urinalysis
- Health-related quality of life assessments (AE-QoL)
- HAE attack data (Note: Subjects must report details of an HAE attack to the study site within 72 hours of onset of the attack, in accordance with HAARP CCI).
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

8.1.3 Follow-up Period

A site check-in will occur approximately every 7 days between the last visit in the treatment period at Day 364 and the on-site follow-up visit at Day 378/392. Subjects participating in Study TAK-743-5007 will receive a site check in at approximately Day 371; for all other subjects, the approximate study days for site check-in are Day 371, Day 378, and Day 385. The preferred

method of site contact is a telephone call; however, alternate methods of contact may be considered as site policies permit.

At the end of the follow-up period at Day 378/ Day 392 there will be a scheduled on-site EOS visit, at which the following assessments and procedures will be performed:

- Vital signs including body temperature, HR, BP and RR
- Physical examination
- 12-lead ECG
- Clinical laboratory testing, including hematology, serum chemistry, coagulation, and urinalysis
- Pregnancy test (for female subjects)
- Pharmacokinetic sample collection
- Pharmacodynamic sample collection
- Plasma ADA sample collection
- Health-related quality of life assessments (AE-QoL)
- HAE attack data (Note: Subjects must report details of an HAE attack to the study site within 72 hours of onset of the attack, in accordance with HAARP [redacted]).
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs. Note: All AEs and SAEs that are not resolved at the time of this contact will be followed to closure [redacted].

8.1.4 Early Termination

All procedures and assessments scheduled for the EOS visit will be followed for the early termination (ET) visit (see Table 2).

8.1.5 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 and Table 2.

8.2.1 Informed Consent

Informed consent and assent forms must be approved for use by the reviewing IRB, research ethics board (REB) or IEC. Informed consent must be obtained for all subjects participating in the study (or their parent/caregiver, as applicable) 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 consent/assent of the subject (or their parent/caregiver, as applicable) as determined by the investigator.

8.2.2 Eligibility Review

The investigator or qualified site personnel will confirm that all inclusion criteria have been met (Sections 5.1) and none of the exclusion criteria have been met (Section 5.2).

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 Efficacy

8.2.4.1 Collection of Hereditary Angioedema Attacks

Historical HAE attack information will be collected at screening. Throughout the study (ie, from screening through follow-up), HAE attack information will be solicited by site personnel during scheduled study visits and site check-ins, as shown Table 1 and Table 2. 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 HAARP [redacted]. Site personnel will be trained on HAARP prior to screening subjects at their site.

8.2.4.2 Management of Acute Angioedema Attacks

As mentioned in Section 4.1, acute HAE attacks during the study are to be managed according to the local standard of care. In case of insufficient response to the first dose, additional rescue medications will be allowed.

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 complete physical examination will be performed by the investigator or his/her qualified designee according to the Study Schedule of Activities (Table 1 and Table 2). The date and time of each examination, and any findings, will be recorded on the source documents and 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:

- General appearance
- Ears, nose, and throat
- Head and Neck
- Ophthalmological
- Respiratory
- Cardiovascular
- Abdomen
- Neurological
- Extremities
- Dermatological
- Lymphatic

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

8.2.5.2 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 efficacy 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. Adverse events, 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, CCI , 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 8.2.5.3, 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 CCI . Information on SAE collection time frame, onset/resolution dates, and SAEs with a fatal outcome is presented in CCI .

The efficacy 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) Adult Toxicity Table CCI and the DMID Pediatric Toxicity Table CCI .
- 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 angioedema attack will be assessed in accordance with HAARP CCI , 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 3 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 and reported to the Shire Global Drug Safety Department.

8.2.5.3 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 pKal 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, international normalized ratio [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.

8.2.5.4 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 and Table 2. 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 to dosing and at 1 hour and 2 hours after completion of the injection of lanadelumab. After a subject has received 4 doses of lanadelumab in the study, the vital sign measurement at 2 hours post-dose may be eliminated at subsequent visits based on the discretion of the investigator and the absence of safety signals. There will be a ±15 minute time window for all vital sign measurements

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 (ie, the predose measurement at Visit 1/Day 0) in vital signs may be deemed clinically significant and whether the change should be considered and recorded as an AE.

8.2.5.5 Clinical Laboratory Tests for Safety Assessments

A complete list of clinical laboratory tests to be performed to assess general safety parameters is provided in CCI [redacted]. All safety laboratory assessments will be performed at a central laboratory.

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.

8.2.5.6 Pregnancy Test

For all females, pregnancy testing (β-hCG) will be performed at the time points specified in Schedule of Activities in Table 1 and Table 2; 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.

8.2.5.7 Electrocardiogram

A standard 12-lead ECG (single recording) will be performed at the time points specified in Schedule of Activities in Table 1 and Table 2. The date and time of each ECG and its results will be documented in the source documents and eCRF.

8.2.6 Other Study Assessments

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 1 and Table 2. Samples should be obtained prior to dosing (ie, within 2 hours prior to dosing), with the exception of the EOS/ET visit.

8.2.6.2 Pharmacodynamics

Blood samples for the measurement of cHMWK will be obtained at the study days specified in Table 1 and Table 2. Samples should be obtained prior to dosing (ie, within 2 hours prior to dosing), with the exception of the EOS/ET visit.

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 1 and Table 2. Samples should be obtained prior to dosing (ie, within 2 hours prior to dosing), with the exception of the EOS/ET visit.

8.2.6.4 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. Diagnostic testing will be performed by a Sponsor-approved central laboratory. 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%, and results of C1q assay are required for eligibility in subjects without a documented family history consistent with HAE Type I or II. 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 the medical monitor is advised for proper documentation of eligibility.

8.2.6.5 Health-related Quality of Life

Health-related quality of life will be assessed using the AE-QoL questionnaire, at the study visits specified in Table 1 and Table 2.

The AE-QoL questionnaire is a self-administered validated instrument to assess HRQoL among patients with recurrent angioedema (including HAE) (Weller et al., 2012). The AE-QoL consists of 17 disease-specific quality-of-life items, each of the 17 items has a five-point response scale ranging from 1 (Never) to 5 (Very Often). Per the developers' guidelines (Weller et al., 2012), the questionnaire is scored to produce a total score and four domain scores (functioning, fatigue/mood, fear/shame, and nutrition). Raw domain scores (mean of the item scores within each scale) and the raw total score (mean of all item scores) are rescaled using linear transformations into final percentage scores ranging 0 to 100, based on the maximum possible score, where the lower the score the lower the impairment. The MCID for the total score is 6 (Weller et al., 2012).

The AE-QoL has good psychometric properties, including reliability (test-retest and internal consistency), construct validity (convergent/divergent and known groups), ability to detect change and responder definition (Weller et al., 2012). The AE-QoL has been shown to be a content valid, reliable, construct valid, sensitive and interpretable measure of HR-QoL for patients with HAE.

8.2.6.6 Healthcare Resource Utilization

Not applicable.

8.2.6.7 Self-administration of Lanadelumab

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

Self-administration will be permitted after a subject (and/or their parent/caregiver) has received appropriate training by the investigator or designee and has demonstrated their understanding of self-administration. The subject is required to return to the site for visits as outlined in the schedule of events. At these on-site visits, the subject (or parent/caregiver) may continue to self-administer lanadelumab or may opt to have lanadelumab administered by study personnel or healthcare provider.

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

- The subject's (or 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 (or PFS) of investigational product for drug accountability purposes.
- Additional information, as provided in the Pharmacy Manual.

If a subject (or parent/caregiver) is self-administering lanadelumab at home or another offsite location, site personnel will perform a site check-in (within 3 days after the study day) to ensure that self-administration of lanadelumab has occurred as scheduled. During this site check-in, the site will also solicit for any HAE attacks not already reported by the subject and collect information on AEs and concomitant medications. The preferred method of site contact is a telephone call; however, alternate methods of contact may be considered as site policies permit.

8.2.6.8 Injection Report

An Injection Report will be completed by the subject (or parent/caregiver) following each dose of lanadelumab, according to the assessment schedule in Table 1 and Table 2. 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.

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 and Table 2).

Laboratory testing includes general safety parameters (hematology, serum chemistry, coagulation, and urinalysis), serology, pregnancy tests, C1-INH functional assay, C4 assay, 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), C1-INH, C4, C1q, PK, anti-drug antibodies, PD. Subjects will be in a seated or supine position during blood collection.

As shown in Table 5, during this study it is expected that approximately 251 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 251 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 5: Volume of Blood to Be Drawn from Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic samples		5	9	45
Pharmacodynamic samples		2.7	9	24.3
HBsAg, HIV, HCV (virology)		6	1	6
C1-INH, C4, C1q at screening		5	1	5
Anti-drug antibody testing samples		5	9	45
Safety	Clinical Chemistry	5	13	65
	Coagulation and Hematology	4.7	13	61.1
Total		33.4	55[a]	**251.4**

CI-INH=C1 esterase inhibitor; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus

[a] This represents the total number of samples collected during the study. Up to 5 samples will be drawn at any given visit.

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

9.1.1 General Considerations

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

9.3 Sample Size and Power Considerations

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

9.4 Statistical Analysis Set(s)

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

Pharmacokinetic set (PK Set) is defined as all subjects in the FAS who have at least 1 evaluable post dose PK concentration value. All PK analyses will be based on the PK set.

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

9.5 Disposition, Demographics and Baseline Characteristics, and Exposure

9.5.1 Subject Disposition

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

9.5.2 Demographics and Other Baseline Characteristics

Baseline HAE characteristics 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 system organ class (SOC) and preferred term (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 Efficacy Analyses

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

- Continuous efficacy endpoints will be summarized using number of subjects (n), mean, SD, median, minimum, and maximum. Whenever appropriate, raw (actual) values and changes from baseline will be summarized at each scheduled time point. Additionally, the attack rates will be calculated using the number of attacks divided by the duration of time for each subject for each efficacy evaluation period.
- Categorical efficacy endpoints (eg, attack severity) will be summarized in terms of the number and percentage of subjects in each category of the efficacy endpoint.
- Time-to-event endpoint (eg, time to the first HAE attack) will be summarized using Kaplan-Meier (KM) estimates. Summaries will include 25th, 50th (median), and 75%

percentiles, if estimable, and the corresponding 95% confidence intervals. In addition, KM plots detailing each subject's contribution to the analysis will be provided.

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

If applicable, efficacy endpoints will be evaluated for the following 4 efficacy evaluation periods:

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

9.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the achievement of attack-free status for the efficacy evaluation period of Day 0 through Day 182. A subject is considered as attack free during an efficacy evaluation period if the subject has no investigator-confirmed HAE attacks during that efficacy evaluation period. For subjects who discontinue treatment during an efficacy evaluation period, the evaluation period will end at the time of treatment discontinuation and attack-free status will be evaluated for the period of time that the subject was in the evaluation period.

The number and percentage of subjects achieving attack-free for the efficacy evaluable period of Day 0 through Day 182 will be summarized for the FAS. A 95% confidence interval for the proportion of subjects achieving attack-free will be derived using the exact method.

9.6.2 Other Efficacy Endpoints

Other efficacy endpoints are as follows:

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

- Time to first HAE attack after Day 0 for the efficacy evaluation period of Day 0 through Day 182.
- Time to first HAE attack after Day 0 for the efficacy evaluation period of Day 70 through Day 182.
- Achievement of at least a 50%, 70% and 90% reduction in the investigator-confirmed normalized number of attacks (NNA) per 4 weeks relative to the run-in period NNA for each of the efficacy evaluation periods.
- Achievement of an efficacy evaluation period NNA <1.0 per 4 weeks, <0.75 per 4 weeks, <0.50 per 4 weeks, and <0.25 per 4 weeks for each of the efficacy evaluations periods.
- Achievement of attack-free status for each of the efficacy evaluation periods of Day 0 through Day 364, Day 70 through Day 182, and Day 70 through Day 364.
- Achievement of attack-free status for monthly increments through Day 364.
- Achievement of attack-free intervals.
- Percentage of attack free days during each of the efficacy evaluation period.

9.6.2.1 Statistical Methods Analyzing Other Efficacy Endpoints

Normalized Number of Investigator-confirmed Hereditary Angioedema Attacks

The normalized number of investigator-confirmed HAE attacks (NNA) during each efficacy evaluation period will be expressed as a monthly (28 days) HAE attack rate and will be analyzed using the FAS.

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

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

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

The number of investigator-confirmed HAE attacks per month will be summarized by month (per 28-day interval) for the FAS. The summary will include descriptive statistics for run-in period 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 FAS:

- 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

Time to First Attack

The time to the first investigator-confirmed HAE attack (days) after Day 0 for the efficacy evaluation period of Day 0 through Day 182 and Day 70 through Day 182 will be calculated from the date and time of the first dose of lanadelumab for that efficacy evaluation period to the date and time of the first investigator-confirmed HAE attack after the first 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 Kaplan-Meier methods.

Characteristics of Investigator-confirmed Hereditary Angioedema Attacks

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

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. For efficacy evaluation period summaries, mean attack duration will be summarized for all subjects or only subjects with attacks. The subject-level average attack duration will be categorized into 12-hour intervals and tabulated by category (<12 hours, 12-24 hours, >24-48 hours, and >48 hours).

- HAE Attack Severity: For each subject, the mean severity of all investigator-confirmed HAE attacks will be calculated using a numerical rating and summarized. For efficacy evaluation period summaries, mean attack severity will be summarized for all subjects or only subjects with attacks. 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 reclassified 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 on the angioedema attack page of the eCRF.
- Supportive Treatment Use: The number and percentage of subjects with supportive treatment use for an HAE attack, as well as the number of supportive treatment, will be tabulated by supportive treatment type (IV fluids, pain medication, oxygen, anti-emetic, and other) as reported on the angioedema attack page of the eCRF.

Achievement of At Least 50%, 70%, and 90% Reduction in the Investigator-confirmed Normalized Number of Attacks per 4 Weeks Relative to the Run-in Period

For each subject, a treatment period HAE attack rate and run-in period HAE attack rate will be calculated. The percentage reduction will be calculated as the run-in period HAE attack rate minus the treatment period HAE attack rate divided by the run-in period HAE attack rate. Number and percentage of subjects achieving for each of the three predefined threshold will be summarized for each of the efficacy evaluation period. The three classes of responders are nested within each other and not mutually exclusive.

Achievement of an Efficacy Evaluation Period Normalized Number of Attacks <1.0, <0.75, <0.50, and <0.25 per 4 Weeks

For each subject, a treatment period NNA will be calculated. The number and percentage of subjects achieving each of the four predefined threshold will be summarized for each of the efficacy evaluation period. The four classes of responders are nested within each other and not mutually exclusive.

Achievement of Attack-free Status

The number and percentage of subjects that are attack-free will be summarized for each of the efficacy evaluation periods of Day 70 through Day 182, Day 0 through Day 364, and Day 70 through Day 364. For subjects who discontinue treatment during an efficacy evaluation period, the evaluation period will end at the time of treatment discontinuation and attack-free status will be evaluated for the period of time that the subject was in the evaluation period.

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

The number and percentage of subjects achieving attack-free status for monthly increments (Month 1, Month 2, Month 3, etc) through Day 364 (Month 13) will be summarized. A two-sided 95% CI for the proportion of subjects achieving attack-free will be derived using the exact method.

For subjects who discontinue the study during a monthly increment, the evaluation period will end at the date of study discontinuation with time 23:59 and attack-free status will be evaluated for the period of time that the subject was in the evaluation period.

Achievement of investigator-confirmed HAE attack-free intervals

A subject is considered as attack free during a time period if the subject has no investigator-confirmed HAE attacks during that time period. Subjects who discontinued during a time period are considered as non-responders for that time period.

The number and percentage of subjects who achieve investigator-confirmed HAE attack free intervals which will include but may not be limited to 1 month (4 weeks; 'Day 0 to one day before Day 28 visit'), 3 months (12 weeks; 'Day 0 to one day before Day 84 visit'), or until the Day 182 visit (approximately 6 months or 24 weeks; 'Day 0 to Day 182 visit') during the treatment period will be tabulated by treatment group.

Percentage of Attack-free Days

The percentage of HAE attack free days will be calculated by counting the number of days in the efficacy evaluation period without an HAE attack and dividing by the number of days the subject contributed to the efficacy evaluation period. An attack-free day is defined as a calendar day with no investigator-confirmed HAE attack. Descriptive statistics for the percentage of HAE attack free days will be summarized.

9.6.3 Exploratory Endpoints

Not applicable.

9.7 Safety Analyses

No statistical hypothesis testing will be performed. All safety summaries will be based on the FAS.

- Continuous safety endpoints (eg, change in laboratory parameter) will be summarized using number of subjects (n), mean, standard deviation (SD), median, minimum value, and maximum value. As appropriate, raw (actual) values and 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, TEAEs related to the investigational product, TEAEs leading to withdrawal, severe TEAEs and absolute count of events will be summarized by PT and SOC.
- 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 visit. Potentially clinically important findings will also be summarized or listed.

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 investigator-reported 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 SMQ-defined AESI, as well as the total number of SMQ-defined AESIs, will be summarized by SOC and PT for each analysis period. Separate summary tables will be created for each AESI category and for those events with the SMQ-defined AESIs classified as related, serious, related serious, severe, and related severe. 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 upper limit of normal (ULN), and clinically significant result more than the ULN will be summarized by study visit. If more than one

laboratory result is reported per study visit per parameter, the result yielding the most severe classification will be selected for analysis.

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

All laboratory test results will be presented in subject listings.

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

9.8.1 Health-related Quality of Life Analyses

The AE-QoL total score and domain scores will be summarized using descriptive statistics by scheduled visit. A change in scores from baseline (Day 0) to Day 182 and Day 364 will be reported

9.8.2 Pharmacokinetic/Pharmacodynamic Analyses

No formal statistical hypothesis will be tested. Individual PK concentrations and cHMWK levels will be provided in subject data listing(s) and summarized using descriptive statistics (number of subjects, arithmetic mean, SD, coefficient of variation [CV%], median, minimum, maximum, geometric mean, and %CV of geometric mean). Figures of individual and mean (± SD) concentration-time profiles plasma lanadelumab will be generated. Tabular and graphical summaries will be analyzed based on the PK set and PD set, as appropriate

9.8.3 Immunogenicity Analyses

Immunogenicity data will be summarized using descriptive statistics, and the effect on lanadelumab plasma concentrations, cHMWK, and the number of investigator confirmed HAE attacks during the efficacy evaluation periods will be evaluated.

9.9 Statistical/Analytic Considerations

9.9.1 Multiplicity Adjustment

Not applicable; no hypothesis testing is planned

9.9.2 Control of Type I Error

Not applicable; no hypothesis testing is planned

9.9.3 Handling of Missing Data

All available data will be included in the analysis. No imputation of missing data will be performed.

9.9.4 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.

9.9.5 Subgroup Analyses

Subgroup analyses may be performed; details will be described in the SAP, as applicable.

9.10 Sensitivity Analyses

The primary analysis and some of the other efficacy analyses will be repeated using all subject-reported HAE attacks instead of limiting the analysis to those attacks that were investigator-confirmed. See Table 6 for details of sensitivity analyses on other efficacy endpoints using all subject-reported HAE attacks.

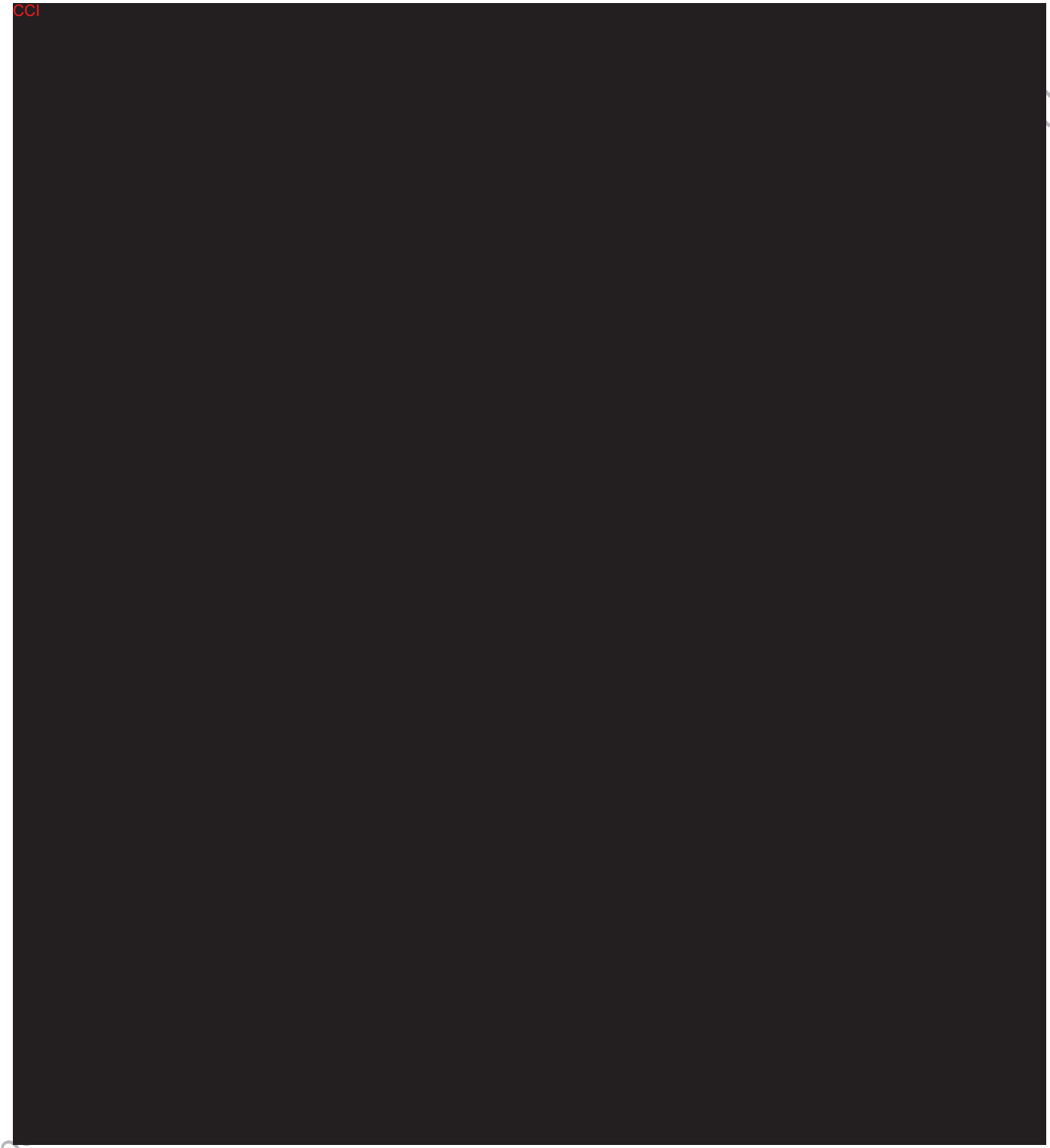
Table 6: Sensitivity Analysis for Other Efficacy Endpoints

Other Efficacy Endpoints	Sensitivity Analysis Using All Attacks
Number of HAE attacks	x
Number of HAE attacks requiring acute treatment	x
Number of moderate or severe HAE attacks	x
Characteristics of HAE attacks	x
Number of high-morbidity HAE attacks	x
Time to first HAE attack after Day 0 or Day 70	x
Achievement of attack reduction from run-in period	x
Achievement of predefined attack rate	x
Achievement of attack-free	x
Percentage of attack-free days	x

HAE=hereditary angioedema

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

CCI



CCI

CCI

CCI

CCI

CCI

[redacted]

CCI

CCI

[redacted]

CCI

[redacted]

CCI

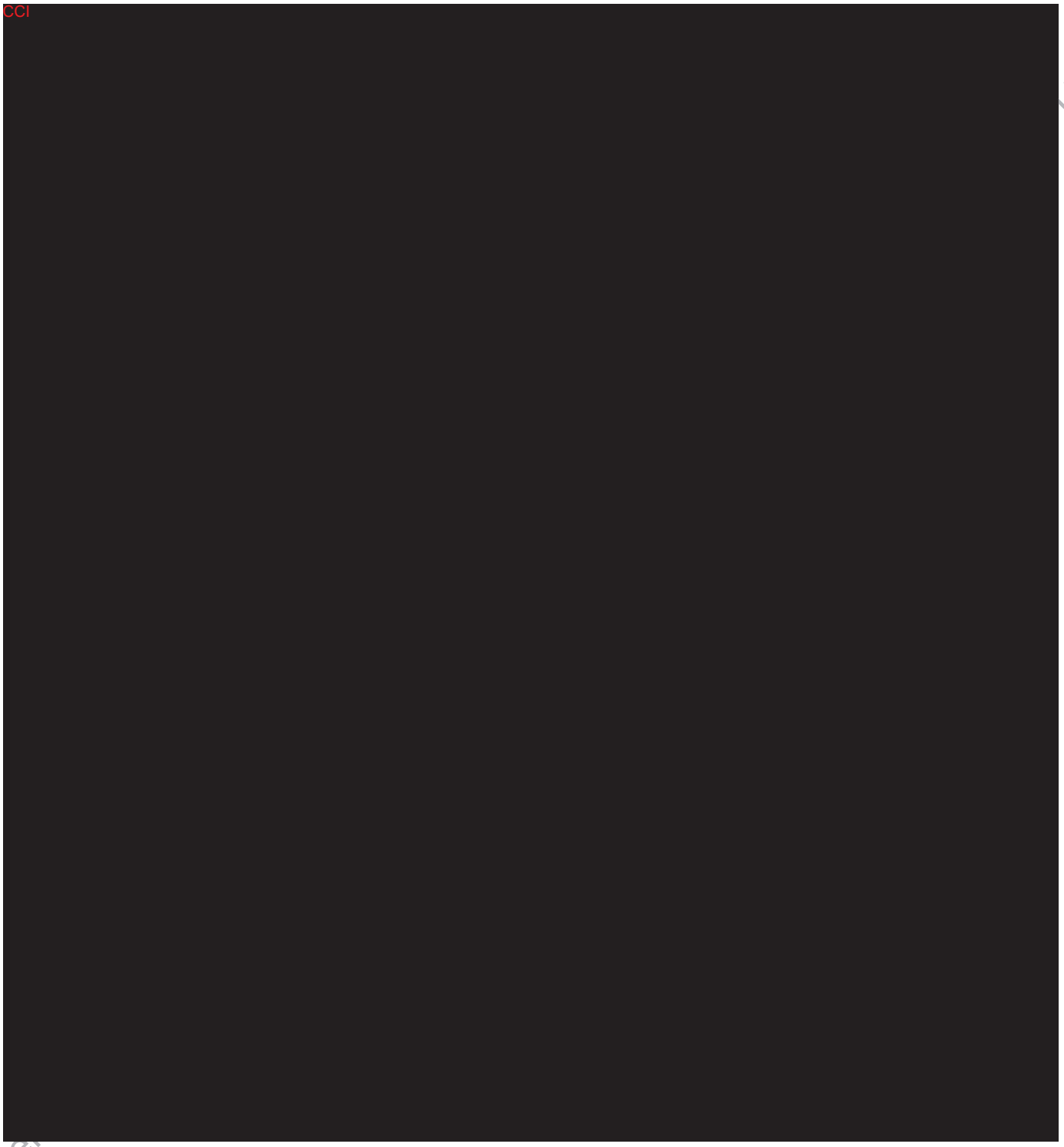
[redacted]

CCI

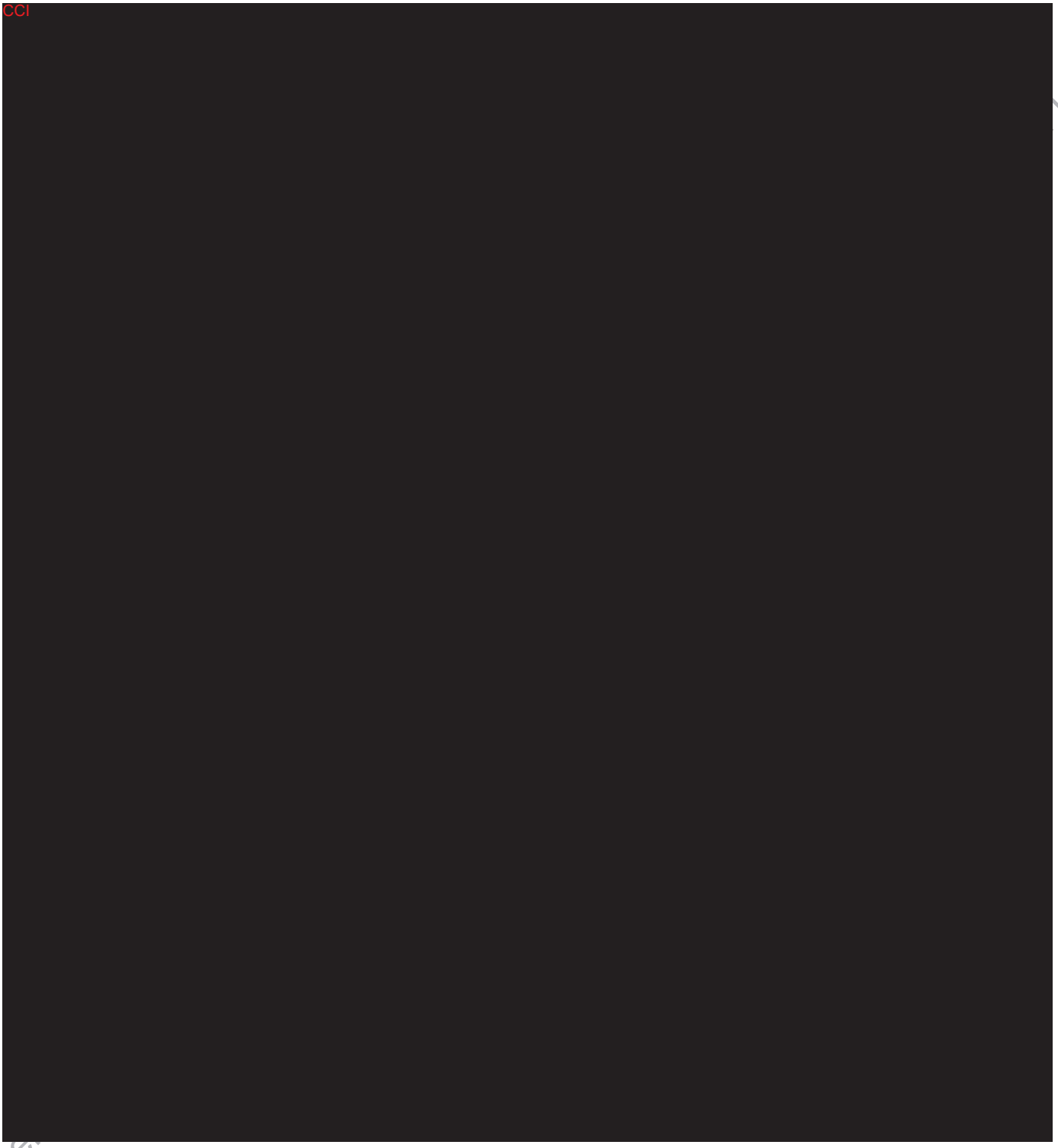
CCI

CCI

CCI



CCI



CCI

CCI

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

CCI

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

CCI

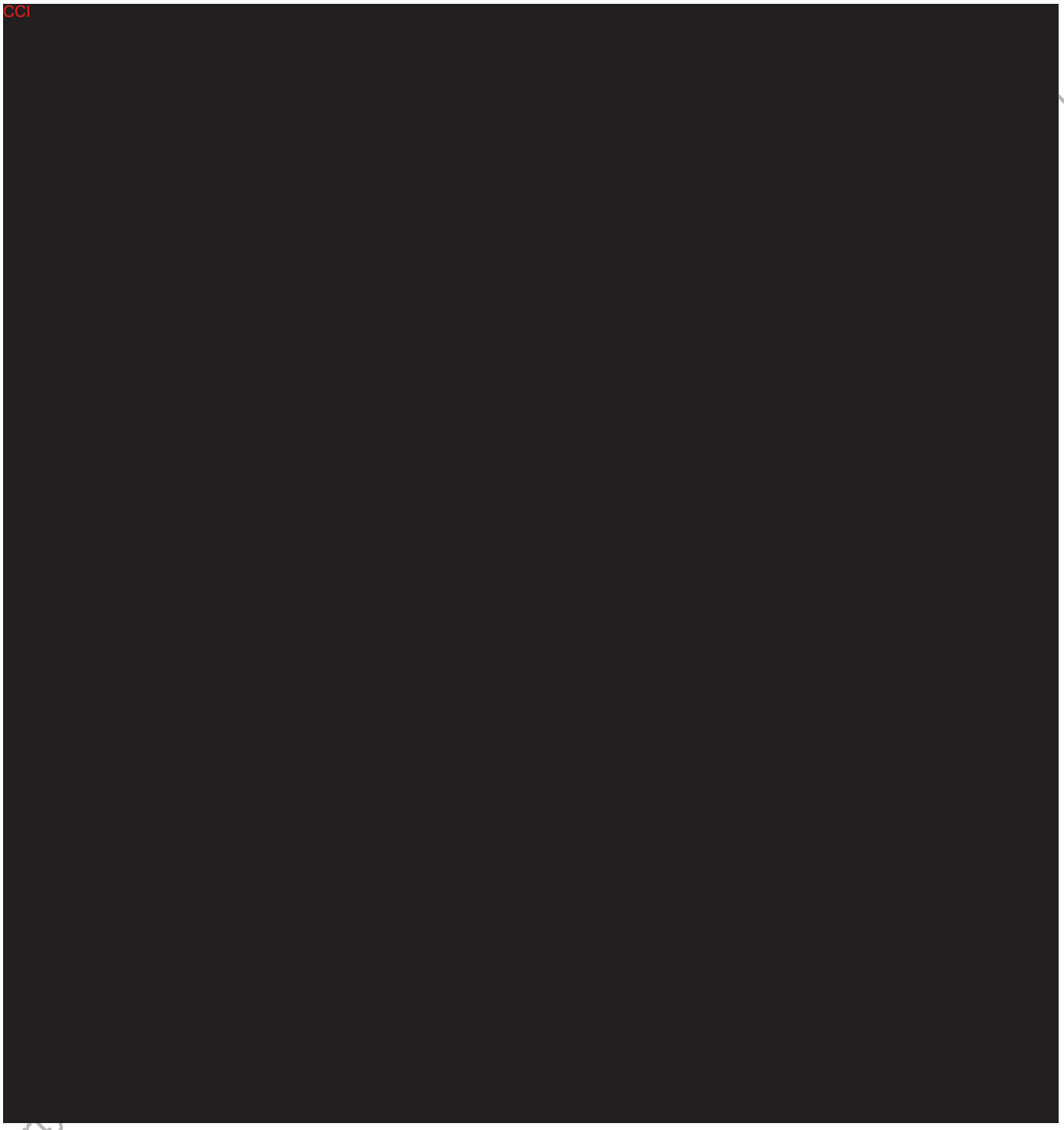
[redacted]

CCI

CCI

CCI

CCI



CCI

CCI

CCI

[redacted]

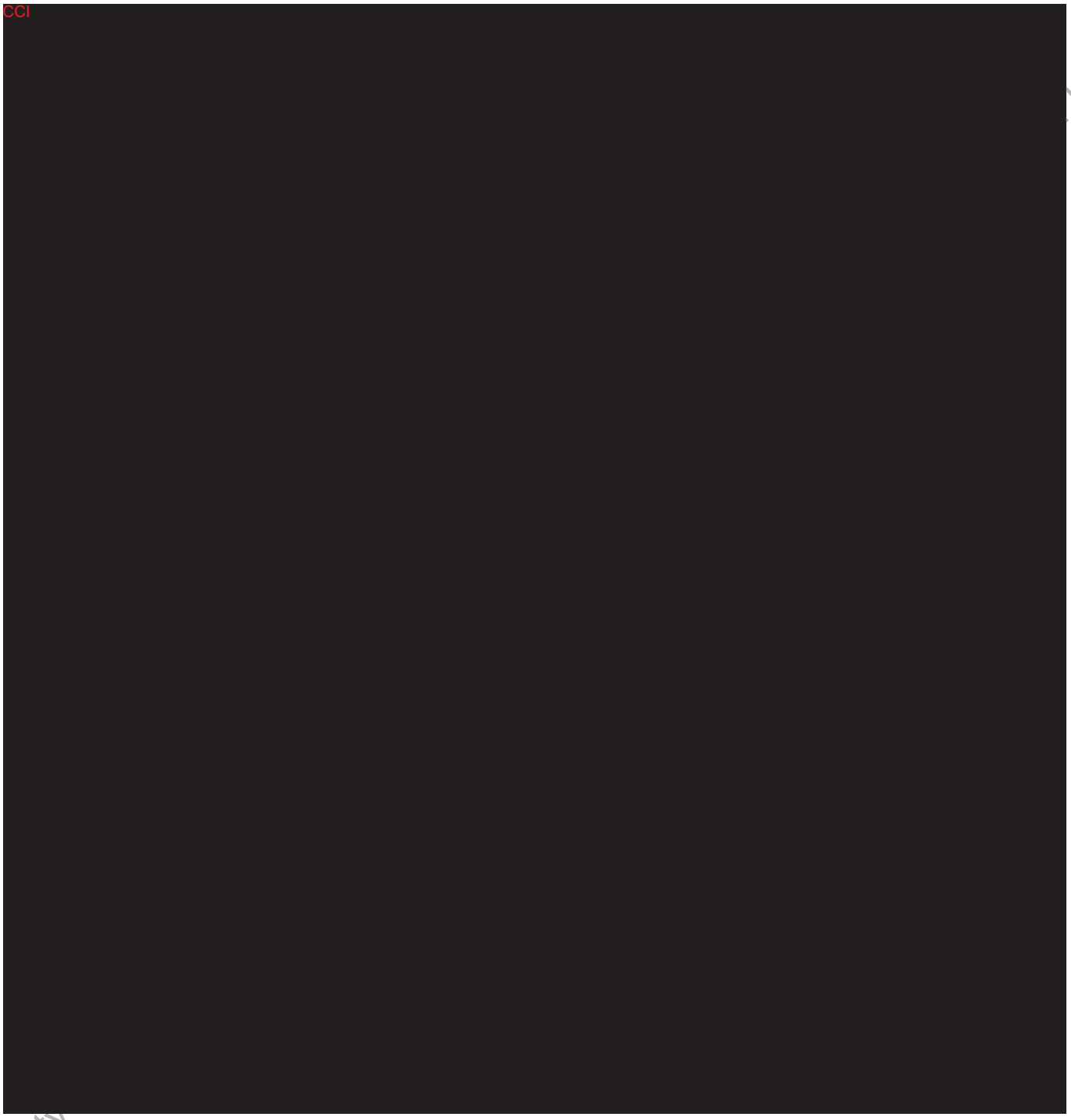
CCI

[redacted]

CCI

CCI

CCI



CCI

[redacted]

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

[redacted]

CCI

[redacted]

CCI

CCI

CCI

CCI

[redacted]

CCI

CCI

[redacted]

CCI

CCI

[redacted]

11. REFERENCES

Baldrick, P. 2010. Juvenile animal testing in drug development - Is it useful? *Regulatory Toxicology and Pharmacology,* 57, 291-299.

Banerji, A. 2013. The burden of illness in patients with hereditary angioedema. *Ann Allergy Asthma Immunol,* 111, 329-36.

Banerji, A., Busse, P., Shennak, M., Lumry, W., Davis-Lorton, M., Wedner, H. J., Jacobs, J., Baker, J., Bernstein, J. A., Lockey, R., Li, H. H., Craig, T., Cicardi, M., Riedl, M., Al-Ghazawi, A., Soo, C., Iarrobino, R., Sexton, D. J., TenHoor, C., Kenniston, J. A., Faucette, R., Still, J. G., Kushner, H., Mensah, R., Stevens, C., Biedenkapp, J. C., Chyung, Y.and Adelman, B. 2017. Inhibiting Plasma Kallikrein for Hereditary Angioedema Prophylaxis. *N Engl J Med,* 376, 717-728.

Bork, K. 2014a. Current drugs in early development for hereditary angioedema: potential for effective treatment. *Expert Opin Investig Drugs,* 23, 887-91.

Bork, K. 2014b. An evidence based therapeutic approach to hereditary and acquired angioedema. *Current Opinion in Allergy and Clinical Immunology,* 14, 354-362.

Bork, K., Hardt, J.and Witzke, G. 2012. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol,* 130, 692-7.

Bygum, A. 2009. Hereditary angio-oedema in Denmark: a nationwide survey. *The British journal of dermatology,* 161, 1153-8.

Caballero, T., Aygoren-Pursun, E., Bygum, A., Beusterien, K., Hautamaki, E., Sisic, Z., Wait, S.and Boysen, H. B. 2014. The humanistic burden of hereditary angioedema: results from the Burden of Illness Study in Europe. *Allergy Asthma Proc,* 35, 47-53.

Cicardi, M., Bork, K., Caballero, T., Craig, T., Li, H. H., Longhurst, H., Reshef, A.and Zuraw, B. 2012. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy,* 67, 147-57.

Cornpropst, M., Dobo, S., Collier, J., Rose, A., Wilson, R., Babu, Y. S., Collis, P., Zong, J.and Sheridan, W. P. 2016. BCX7353, a Potent Inhibitor of Plasma Kallikrein, Shows Sustained Maximal Enzyme Inhibition When Dosed Orally Once Daily: Results from a Phase I Trial in Healthy Subjects. *Journal of Allergy and Clinical Immunology, The,* 137, AB401.

Craig, T., Pursun, E. A., Bork, K., Bowen, T., Boysen, H., Farkas, H., Grumach, A., Katelaris, C. H., Lockey, R., Longhurst, H., Lumry, W., Magerl, M., Martinez-Saguer, I., Ritchie, B., Nast, A., Pawankar, R., Zuraw, B.and Maurer, M. 2012. WAO Guideline for the Management of Hereditary Angioedema. *World Allergy Organ J,* 5, 182-199.

Craig, T. J., Levy, R. J., Wasserman, R. L., Bewtra, A. K., Hurewitz, D., Obtulowicz, K., Reshef, A., Ritchie, B., Moldovan, D., Shirov, T., Grivcheva-Panovska, V., Kiessling, P. C., Keinecke, H. O.and Bernst 2009. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *Journal of Allergy and Clinical Immunology, The,* 124, 801-808.

Davis, A. E. 2005. The pathophysiology of hereditary angioedema. *Clinical Immunology,* 114, 3-9.

El-Hachem, C., Amiour, M., Guillot, M.and Laurent, J. 2005. Hereditary angioneurotic edema: a case report in a 3-year-old child. *Archives de pédiatrie,* 12, 1232-6.

Fouche, A. S., Saunders, E. F. H.and Craig, T. 2014a. Depression and anxiety in patients with hereditary angioedema. *Annals of Allergy, Asthma & Immunology,* 112, 371-375.

Fouche, C., Kenealy, T., Mace, J.and Shaw, J. 2014b. Practitioner perspectives from seven health professional groups on core competencies in the context of chronic care. *J Interprof Care,* 28, 534-40.

Gordon, E. M., Donaldson, V. H., Saito, H., Su, E.and Ratnoff, O. D. 1981. Reduced titers of Hageman factor (factor XII) in Orientals. *Annals of internal medicine,* 95, 697-700.

Goring, H. D., Bork, K., Spath, P. J., Bauer, R., Ziemer, A., Hintner, H.and Wuthrich, B. 1998. Hereditary angioedema in the German-speaking region. *Hautarzt,* 49, 114-22.

Horiuchi, T., Ohi, H., Ohsawa, I., Fujita, T., Matsushita, M., Okada, N., Seya, T., Yamamoto, T., Endo, Y., Hatanaka, M., Wakamiya, N., Mizuno, M., Nakao, M., Okada, H., Tsukamoto, H., Matsumoto, M., Inoue, N., Nonaka, M.and Kinoshita, T. 2012. Guideline for hereditary angioedema (HAE) 2010 by the Japanese Association for Complement Research - secondary publication. *Allergology international : official journal of the Japanese Society of Allergology,* 61, 559-62.

Iwamoto, K., Tanaka, A., Hiragun, M., Kawai, M., Mihara, S., Takenaka, M., Shibuya, M., Inomata, N., Hatano, Y., Shimizu, F., Kousaka, T.and Hide, M. 2012. Novel and recurrent C1 inhibitor gene mutations in nine Japanese patients with hereditary angioedema. *Journal of dermatological science,* 68, 68-70.

Kenniston, J. A., Faucette, R. R., Martik, D., Comeau, S. R., Lindberg, A. P., Kopacz, K. J., Conley, G. P., Chen, J., Viswanathan, M., Kastrapeli, N., Cosic, J., Mason, S., DiLeo, M., Abendroth, J., Kuzmic, P., Ladner, R. C., Edwards, T. E., TenHoor, C., Adelman, B. A., Nixon, A. E.and Sexton, D. J. 2014. Inhibition of plasma kallikrein by a highly specific active site blocking antibody. *J Biol Chem,* 289, 23596-608.

Leeb-Lundberg, L. M. F., Marceau, F., Müller-Esterl, W., Pettibone, D. J.and Zuraw, B. L. 2005. International Union of Pharmacology. XLV. Classification of the Kinin Receptor Family: from Molecular Mechanisms to Pathophysiological Consequences. *Pharmacological Reviews,* 57, 27-77.

Lei, W. T., Shyur, S. D., Huang, L. H., Kao, Y. H.and Lo, C. Y. 2011. Type I hereditary angioedema in Taiwan -- clinical, biological features and genetic study. *Asian Pac J Allergy Immunol,* 29, 327-31.

Lumry, W. R. 2013. Overview of epidemiology, pathophysiology, and disease progression in hereditary angioedema. *American journal of managed care, The,* 19, s103-10.

Lumry, W. R., Miller, D. P., Newcomer, S., Fitts, D.and Dayno, J. 2014. Quality of life in patients with hereditary angioedema receiving therapy for routine prevention of attacks. *Allergy and asthma proceedings,* 35, 371-6.

Martin, P. L.and Weinbauer, G. F. 2010. Developmental Toxicity Testing of Biopharmaceuticals in Nonhuman Primates. *International Journal of Toxicology,* 29, 552-568.

Maurer, M., Magerl, M., Ansotegui, I., Aygoren Pursun, E., Betschel, S., Bork, K., Bowen, T., Balle Boysen, H., Farkas, H., Grumach, A., Hide, M., Katelaris, C., Lockey, R., Longhurst, H., Lumry, W., Martinez-Saguer, I., Moldovan, D., Nast, A., Pawankar, R., Potter, P., Riedl, M., Ritchie, B., Rosenwasser, L., Sanchez-Borges, M., Zhi, Y., Zuraw, B.and Craig, T. 2018. The international WAO/EAACI guideline for the management of hereditary angioedema - the 2017 revision and update. *Allergy*.

Morford, L. L., Bowman, C. J., Blanset, D. L., Bogh, I. B., Chellman, G. J., Halpern, W. G., Weinbauer, G. F.and Coogan, T. P. 2011. Preclinical safety evaluations supporting pediatric drug development with biopharmaceuticals: strategy, challenges, current practices. *Birth Defects Res B Dev Reprod Toxicol,* 92, 359-80.

Nanda, M. K., Elenburg, S., Bernstein, J. A.and Assa'ad, A. H. 2015. Clinical Features of Pediatric Hereditary Angioedema. *Journal of Allergy and Clinical Immunology: In Practice, The,* 3, 392-395.

Nielsen, E., Johansen, H., Holt, J.and Mollnes, T. 1994. C1 inhibitor and diagnosis of hereditary angioedema in newborns. *Pediatric Research,* 35, 184-187.

Nordenfelt, P., Dawson, S., Wahlgren, C. F., Lindfors, A., Mallbris, L.and Bjorkander, J. 2014. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. *Allergy Asthma Proc,* 35, 185-90.

Nzeako, U. C., Frigas, E.and Tremaine, W. J. 2001. Hereditary angioedema, a broad review for clinicians. *Archives of Internal Medicine,* 161, 2417-2429.

Ohi, H., Itabashi, T.and Shinohara, N. 2017. Educational Activities Significantly Improved Diagnosis of the Rare Disease Hereditary Angioedema. *The Journal of Angioedema,* 2, 18-20.

Ohsawa, I., Honda, D., Nagamachi, S., Hisada, A., Shimamoto, M., Inoshita, H., Mano, S.and Tomino, Y. 2015. Clinical manifestations, diagnosis, and treatment of hereditary angioedema: survey data from 94 physicians in Japan. *Ann Allergy Asthma Immunol,* 114, 492-8.

Pappalardo, E., Cicardi, M., Duponchel, C., Carugati, A., Choquet, S., Agostoni, A.and Tosi, M. 2000. Frequent de novo mutations and exon deletions in the C1inhibitor gene of patients with angioedema. *Journal of Allergy and Clinical Immunology, The,* 106, 1147-1154.

Read, N., Lim, E., Tarzi, M. D., Hildick-Smith, P., Burns, S.and Fidler, K. J. 2014. Paediatric hereditary angioedema: a survey of UK service provision and patient experience. *Clin Exp Immunol,* 178, 483-8.

Renne, T.and Gruber, A. 2012. Plasma kallikrein: novel functions for an old protease. *Thromb Haemost,* 107, 1012-3.

Roach, B., Kim, Y., Jerome, E.and Michael, A. F. 1981. Influence of age and sex on serum complement components in children. *American journal of diseases of children (1960),* 135, 918-20.

Roche, O., Blanch, A., Caballero, T., Sastre, N., Callejo, D.and Lopez-Trascasa, M. 2005. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. *Ann Allergy Asthma Immunol,* 94, 498-503.

Sabharwal, G.and Craig, T. 2017. Pediatric hereditary angioedema: an update. *F1000Research,* 6.

Stray-Pedersen, Sorte, Samarakoon, Gambin, Chinn, Coban Akdemir, Erichsen, Forbes, Gu, Yuan, Jhangiani, Muzny, Rødningen, Sheng, Nicholas, Noroski, Seeborg, Davis, Canter, Mace, Vece, Allen, Abhyankar, Boone, Beck, Wiszniewski, Fevang, Aukrust, Tjønnfjord, Gedde-Dahl, Hjorth-Hansen, Dybedal, Nordøy, Jørgensen, Abrahamsen, Øverland, Bechensteen, Skogen, Osnes, Kulseth, Prescott, Rustad, Heimdal, Belmont, Rider, Chinen, Cao, Smith, Caldirola, Bezrodnik, Lugo Reyes, Espinosa Rosales, Guerrero-Cursaru, Pedroza, Poli, Franco, Trujillo Vargasand Aldave Becerr 2017. Primary immunodeficiency diseases: Genomic approaches delineate heterogeneous Mendelian disorders. *Journal of Allergy and Clinical Immunology, The,* 139, 232-245.

Tosi, M. 1998. Molecular genetics of C1 inhibitor. *Immunobiology,* 199, 358-65.

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

Yamamoto, T., Horiuchi, T., Miyahara, H., Yoshizawa, S., Maehara, J., Shono, E., Takamura, K., Machida, H., Tsujioka, K., Kaneko, T., Uemura, N., Suzawa, K., Inagaki, N., Umegaki, N., Kasamatsu, Y., Hara, A., Arinobu, Y., Inoue, Y., Niiro, H., Kashiwagai, Y., Harashima, S., Tahira, T., Tsukamoto, H.and Akashi, K. 2012. Hereditary angioedema in Japan: genetic analysis of 13 unrelated cases. *The American journal of the medical sciences,* 343, 210-4.

Zuraw, B.and Christiansen, S. 2016. HAE Pathophysiology and Underlying Mechanisms. *Clinical Reviews in Allergy & Immunology,* 51, 216-229.

Zuraw, B. L. 2008. Clinical practice. Hereditary angioedema. *N Engl J Med,* 359, 1027-36.

Zuraw, B. L., Bernstein, J. A., Lang, D. M., Craig, T., Dreyfus, D., Hsieh, F., Khan, D., Sheikh, J., Weldon, D., Bernstein, D. I., Blessing-Moore, J., Cox, L., Nicklas, R. A., Oppenheimer, J., Portnoy, J. M., Randolph, C. R., Schuller, D. E., Spector, S. L., Tilles, S. A., Wallace, D., American Academy of Allergy, A., Immunology, American College of Allergy, A.and Immunology 2013. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol,* 131, 1491-3.