Clinical Study Protocol

NCT Number: NCT04444895

Title: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of Lanadelumab for Prevention Against Acute Attacks of Non-histaminergic Angioedema with Normal C1-Inhibitor (C1-INH)

Study Number: TAK-743-3001

Document Version and Date: Amendment 1, 14 September 2020

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

Protocol:	TAK-743-3001
Title:	An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of Lanadelumab for Prevention Against Acute Attacks of Non-histaminergic Angioedema with Normal C1-Inhibitor (C1-INH)
Short Title:	Open-Label Study of Long-Term Safety and Efficacy of Lanadelumab for Prevention of Acute Attacks of Non-histaminergic Angioedema with Normal C1-Inhibitor
Study Phase:	Phase 3
Drug:	Lanadelumab; TAK-743 (formerly SHP643, DX-2930)
IND Number:	116647
EUDRACT Number:	2019-004823-20
Sponsor:	Takeda Development Center Americas (TDCA) 95 Hayden Avenue, Lexington, MA 02421 USA 617-349-0200
Protocol History:	Original Protocol (20 January 2020) Amendment 1 (14 September 2020)

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

Sponsor's (Takeda) Approval

Signature and Date:	DocuSigned by: [redacted]
[redacted], MD, PhD and [redacted]	

Investigator's Acknowledgement

I have read this protocol for Study TAK-743-3001.

Title: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of Lanadelumab for Prevention Against Acute Attacks of Non-histaminergic Angioedema with Normal C1-Inhibitor (C1-INH)

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)	[***The investigator completes the bottom section of the protocol signature page***]

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the "Takeda Safety Report Form" within 24 hours to the Takeda Global Patient Safety Evaluation (GPSE) Group. The fax number and e-mail address are provided on the form (sent under separate cover).

Fax number: +1-484-595-8155

E-mail: drugsafety@shire.com

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

Name: [redacted]**, MD**

Phone: [redacted]

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

Phone: +1 973 659 6677 (USA)
+33 186 990 019 (Europe)

SUMMARY OF CHANGES FROM PREVIOUS VERSION

A summary of changes incorporated into Amendment 1 is provided in the table below.

Summary of Change(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
Sponsor has been revised from Shire to Takeda Development Center Americas (TDCA) / Takeda.	Cover Page Protocol Signature Page Product Quality Complaints Section 6.4 Drug Accountability Appendix 1.5 Ethical Considerations
[redacted], MD was added as contact for IQVIA medical monitor.	Emergency Contact Information
Revised to include appropriate Takeda forms for reporting adverse events (AEs) and pregnancy. Shire Global drug Safety Department was revised to Takeda Global Patient Safety Evaluation (GPSE) Group.	Emergency Contact Information Section 8.3.5.2 Adverse Events Appendix 3.4 Safety Reporting Appendix 3.5 Serious Adverse Event Collection Time Frame Appendix 3.8 Pregnancy
For study site regions, removed specificity to European Union (revised to Europe) and removed Israel. Section 4.5 was revised to be consistent with synopsis.	Section 1.1 Synopsis Section 4.5 Sites and Regions
References to acquired angioedema (AAE) due to C1-INH deficiency were removed.	Section 1.1 Synopsis Section 2 Introduction
Removed exclusion criteria 4, 5, 6 and 7.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria

Summary of Change(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
Corrected errors referring to treatment period. The treatment period for this study is 182 days.	Section 1.1 Synopsis Section 4.4 Duration of Subject Participation and Study Completion Definition
Pharmacokinetic and Pharmacodynamic analysis populations were added.	Section 1.1 Synopsis Section 9.4 Statistical Analysis Set(s) Section 9.7.1 Analysis of Pharmacokinetic Data Section 9.7.2 Analysis of Pharmacodynamic Data
"Concentration" in regards to plasma cHMWK and pKal levels was removed.	Section 1.1 Synopsis Table 2
Exploratory biomarkers was revised to state "…angioedema-disease state bioactivity, including pKal activity."	Section 1.1 Synopsis Table 2
Added legend for shaded and non-shaded columns to clarify on-site versus elected off-site visits.	Table 1
Added a footnote to clarify which Visit 1 study assessments will not be duplicated from Study SHP643-303.	Table 1
Provided clarification that demography data will be re-entered at Visit 1; but for medical history, only new medical history will be entered.	Table 1 Section 8.2.2.1 Study Visit 1; Study Day 0
Clarified that height should be measured at Visit 1 for subjects that are <18 years of age at the time of consent in Study SHP643-3001.	Table 1 Section 8.2.2.1 Study Visit 1; Study Day 0 Section 8.3.5.1 Physical Examination

Summary of Change(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
Visits 5 and 9 were revised to subject-elected off-site visits.	Table 1 Section 8.2 Study Periods
Section references to study assessments were added.	Table 1
Timing of site check-in calls was added and clarified that additional site calls to subjects may be done as needed.	Table 1
Provided clarification on which assessments should be collected pre-dose versus post-dose.	Table 1
Added study procedure modifications due to COVID-19 pandemic.	Table 1 Section 8.1 Changes to Study Procedures Due to the COVID-19 Pandemic
Removed footnote regarding genotyping and other biomarker assay collection at Visit 1, 7, 11, and 14.	Table 1 Section 8.3.7 Volume of Blood to be Drawn from Each Subject
Revised to be more concise and include final results from DX-2930-04 study.	Section 2.4.3 Clinical Studies with Lanadelumab
Secondary objective regarding the subject experience with the prefilled syringe was revised to state "to evaluate subject experience of injection."	Table 2
Combined off-site Visit 2 with all other off-site visits.	Section 8.2 Study Periods
Added additional instructions and clarification on site check-in to subjects.	Section 8.2 Study Periods
Added section on collection of angioedema attack data.	Section 8.3.4.1 Collection of Angioedema Attack Data
Clarified that secondary efficacy analyses will be performed using the Safety Population and the Reduced-Dose Safety Population.	Section 9.5.2 Secondary Efficacy Analysis

Summary of Change(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
Revised *HAE* attack to *angioedema* attack.	Section 9.5.2 Secondary Efficacy Analysis
Added a sentence to severity categorization of AEs to be consistent across lanadelumab studies.	Appendix 3.3 Assessment of Adverse Events

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Takeda 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 Takeda 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 the 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 (eg, 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 Quality Complaint Data Collection Form" via the email address:

PQC@shire.com

Telephone number (provided for reference if needed):
Takeda, Lexington, MA (USA)
1-800-828-2088

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

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol number: TAK-743-3001	**Drug:** Lanadelumab
Title of the study: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of Lanadelumab for Prevention Against Acute Attacks of Non-histaminergic Angioedema with Normal C1-Inhibitor (C1-INH)	
Short title: Open-Label Study of Long-Term Safety and Efficacy of Lanadelumab for Prevention of Acute Attacks of Non-histaminergic Angioedema with Normal C1-Inhibitor	
Study phase: Phase 3	
Number of subjects (total and per treatment arm): Approximately 75 subjects aged 12 years and older with non-histaminergic normal C1-INH angioedema who complete Study SHP643-303.	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 60 sites in North America, Europe, and Japan will participate.	
Study period (planned): August 2020 to January 2023	**Clinical phase:** 3
Objectives: **Primary:** To evaluate the long-term safety of repeated subcutaneous (SC) administrations of lanadelumab in adolescents and adults with non-histaminergic angioedema with normal C1-INH **Secondary:** • To evaluate the long-term efficacy of lanadelumab in preventing angioedema attacks • To characterize pharmacokinetics (PK) and pharmacodynamics (PD) following long-term SC administration of lanadelumab • To assess the immunogenicity of chronically administered lanadelumab • To evaluate the effect of lanadelumab on health-related quality of life (HR-QoL) • To evaluate subject experience of injection • To evaluate the safety and efficacy of lanadelumab in subjects switched to the dosing regimen of 300 mg every 4 weeks (q4wks) lanadelumab **Exploratory:** • To evaluate exploratory biomarker(s) of angioedema disease-state bioactivity in plasma	
Rationale: This open-label extension study will be preceded by the initiation of Study SHP643-303, a phase 3, multicenter, randomized, placebo-controlled, double-blind study to evaluate the efficacy and safety of lanadelumab for prevention against acute attacks of non-histaminergic angioedema with normal C1-inhibitor (C1-INH). The rationale for this study is to continuously evaluate the long-term safety of repeated SC treatment with lanadelumab and the long-term efficacy of lanadelumab in preventing angioedema attacks for subjects with non-histaminergic angioedema with normal C1-INH who roll over from Study SHP643-303.	

Investigational product, dose, and mode of administration:

The drug product is a sterile, preservative-free, ready-to-use solution of lanadelumab at a concentration of 150 mg/mL. Drug product will be provided in a prefilled syringe (PFS) at a dosage strength of 300 mg (300 mg/2 mL). Each PFS is filled to deliver a nominal volume of 2.0 mL of drug product subcutaneously.

During the open-label extension treatment period, subjects may receive lanadelumab 300 mg every 2 weeks (q2wks) or may consider lanadelumab 300 mg q4wks if they have been well-controlled (eg, attack-free) for 26 consecutive weeks across Study SHP643-303 and Study TAK-743-3001. The dose frequency change to q4wks will be based on the investigator's discretion and consultation with the sponsor's medical monitor.

Investigational product will be administered by SC injection in the abdominal area (preferred), thigh, or upper arm. Self-administration of investigational product will be permitted after a subject and/or parent/caregiver has received appropriate training by the investigator or designee in the antecedent study (SHP643-303) or in this study and has demonstrated their understanding of self-administration.

Methodology:

Study TAK-743-3001 is an open-label, long-term safety and efficacy extension study of Study SHP643-303, to evaluate lanadelumab in preventing acute angioedema attacks in patients with non-histaminergic angioedema with normal C1-INH who roll over from Study SHP643-303.

All subjects must complete the double-blind treatment period at Day 182 of Study SHP643-303 and consent to enter Study TAK-743-3001. Subjects who discontinue from Study SHP643-303 after enrollment are not eligible to enroll in Study TAK-743-3001.

Subjects should be asked about their interest in Study TAK-743-3001 after enrollment into SHP643-303 to anticipate enrollment and preparedness for Study TAK-743-3001. Willing subjects must sign informed consent for Study TAK-743-3001 on or after Day 168 of SHP643-303 and prior to any procedures in Study TAK-743-3001.

Subjects who are eligible to roll over into Study TAK-743-3001, but elect not to, may not enroll in Study TAK-743-3001 at a later time. The first Study TAK-743-3001 visit (Day 0) will occur on the same day as the Study SHP643-303 Day 182 study visit. Subjects will complete all Study SHP643-303 final study assessments (Day 182) at which time they will be discharged from that study. No assessments conducted between the Study SHP643-303 Day 182 study visit and the first Study TAK-743-3001, visit (Day 0) will be duplicated. Results of the final SHP643-303 assessments on Day 182 will be used as the pre-dose results for Day 0 of Study TAK-743-3001.

All subjects, caregivers, investigators and study site personnel will remain blinded to the SHP643-303 treatment assignment until the conclusion of Study TAK-743-3001.

All subjects must adhere to the Schedule of Activities (Table 1) for the entire duration of the study. See Schedule of Activities (Table 1) for additional information on study visits.

Following their first open-label dose, subjects will continue to receive repeated SC administrations of open-label 300 mg lanadelumab q2wks or may be considered to receive lanadelumab 300 mg q4wks if they have been well-controlled (eg, attack free) for 26 consecutive weeks across Study SHP643-303 and Study TAK-743-3001 per the scheduled dosing in the Study Activities Schedules. The dose frequency change to q4wks will be based on the investigator's discretion and consultation with the sponsor's medical monitor. The treatment period will last up to 182 days from the date of the first open-label dose. The number of doses administered during this period will not exceed 13 doses. The Day 168 study visit is the last visit at which a dose may be administered.

All doses should be administrated within the accepted ±4-day window around dose administration schedule (q2wks or q4wks in Table 1).

If a subject experiences an acute angioedema attack at any time during the study that in the opinion of the investigator requires medical intervention, standard of care therapy should be provided based on subject's medical history and per locally approved product information. Administration of lanadelumab and study procedures will continue without alteration to the protocol study activities schedules, even if a subject receives treatment for a breakthrough angioedema attack on the day of a scheduled dose of study drug (if self-administering) or scheduled study visit.

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 study treatment. Subjects must complete appropriate training in the antecedent study (SHP643-303) or in this study by the investigator or designee and understanding of the training must be documented by the investigator or designee.

Once trained, subjects may self-administer subsequent doses of lanadelumab at the investigational site (when visits are scheduled study site visits) or the subject's home or other agreed upon location (when the study permits off-site dosing -- See Schedule of Activities [Table 1] for details). Adolescent subjects self-administering investigational product will be supervised by a parent/legal guardian/caregiver. Alternatively, a parent/legal guardian/caregiver, after completing appropriate training, will be allowed to administer lanadelumab to an adolescent without study site personnel supervision. Site personnel will call subjects within approximately 3 days after the planned off-site self-administrations to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all angioma attacks have been appropriately documented.

Throughout the study, study site personnel will document information in source documents (ie, the subject's medical record) and electronic case report form (eCRF) regarding the subject's experience with self-administration and SC administration of lanadelumab.

After completion of the treatment period, all subjects will undergo safety evaluations during a 2-week follow-up period.

If, at any time, a dose-related safety signal is identified either from this study or Study SHP643-303, the Sponsor may decide to modify the open-label lanadelumab dose and/or frequency.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

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

1. Males and females, 12 years of age and older diagnosed with non-histaminergic normal C1-INH angioedema at the time of enrollment into the antecedent Study SHP643-303.
2. Subjects must have completed the treatment period (through Day 182) of Study SHP643-303 without reporting a clinically significant treatment-emergent adverse event (TEAE) that would preclude subsequent exposure to lanadelumab.
3. Agree to adhere to the protocol-defined schedule of treatments, assessments, and procedures.
4. Males, or non-pregnant, non-lactating females who are of child-bearing potential 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 non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months.
5. The subject (or the subject's parent/legal guardian, if applicable) has provided written informed consent approved by the institutional review board/research ethics board/ethics committee (IRB/REB/EC) at any time prior to study start. If the subject is a minor (ie, <18 years of age), have a parent/legal guardian 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.

Exclusion Criteria:

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

1. Discontinued from Study SHP643-303 after enrollment but before Visit 26 for any reason.
2. Presence of important safety concerns identified in Study SHP643-303 that would preclude participation in this study.
3. Dosing with an investigational product (IP, not including IP defined in antecedent Study SHP643-303) or exposure to an investigational device within 4 weeks prior to Day 0.
4. Subject has a known hypersensitivity to the investigational product or its components.
5. Have any condition (surgical or medical) that, in the opinion of the investigator or sponsor, may compromise their safety or compliance, preclude the successful conduct of the study, or interfere with interpretation of the results (eg, significant pre-existing illness or other major comorbidities that the investigator considers may confound the interpretation of study results).

Maximum duration of subject participation in the study:

Subjects who provide informed consent will roll over from Study SHP643-303. Eligible subjects will be enrolled and undergo a treatment period of up to 182 days. At the conclusion of the treatment period, subjects will be

followed for an additional 2 weeks.

All subjects will receive open-label lanadelumab during a treatment period of up to 182 days.

The last dose of open-label lanadelumab administered may be given at the Day 168 study visit.

There will be a ±4-day window around each study visit (+4 days for follow-up call at Visit 15). Subjects will be monitored at the study site through 1-hour post-dose for scheduled study site visits. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.

Statistical analysis:

Analysis Populations

The Safety Population will include all subjects who received any study drug after entering Study TAK-743-3001 (ie, any exposure to open-label lanadelumab).

The Dose-Reduced Safety Population will include all subjects in the Safety Population who receive 300 mg q4wks open-label lanadelumab.

The Pharmacokinetic population will include all subjects in the safety population who have at least 1 evaluable postdose PK concentration value.

The Pharmacodynamic population will include all subjects in the safety population who have at least 1 evaluable postdose PD concentration value.

Criteria for Evaluation

Primary Endpoint:

Safety measures, including:

- Adverse events (AEs), including serious adverse events (SAEs) and adverse events of special interest (AESI)
- Clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis)
- Vitals signs including blood pressure, heart rate (HR), body temperature
- Weight and height (height for subjects <18 years old)
- 12-lead ECGs

Secondary Endpoints:

- Number of investigator-confirmed angioedema attacks during the treatment period
- Number of moderate or severe angioedema attacks during the treatment period
- Number of high-morbidity angioedema attacks during the treatment period; a high-morbidity angioedema attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation <24 hours), hemodynamically significant (systolic blood pressure <90 mmHg, requires intravenous (IV) hydration, or associated with syncope or near-syncope) or laryngeal.
- Analysis of pharmacokinetics (PK) effects through measurement of plasma concentrations of lanadelumab.
- Evaluation of the pharmacodynamic (PD) effects of lanadelumab through plasma cHMWK and fluorogenic plasma kallikrein (pKal) assay with FXIIa activation.
- Presence of anti-drug antibodies (ADAs), including evaluation of neutralizing antibodies (if any confirmed positive anti-drug antibodies are detected)
- Health-related quality of life assessments will be assessed using the AE-QoL questionnaire.
- Lanadelumab Injection Report
- Safety measures, including:
  - AEs, including SAEs and AESIs
  - Clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis)
  - Vitals signs including blood pressure (BP), HR, body temperature
  - Weight and height (height for subjects <18 years old)
  - 12-lead ECGs
- Efficacy measures, including:
  - Number of investigator-confirmed angioedema attacks during the treatment period

- Number of moderate or severe angioedema attacks during the treatment period
- Number of high-morbidity angioedema attacks during the treatment period; a high-morbidity angioedema attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation <24 hours), hemodynamically significant (systolic blood pressure <90 mmHg, requires IV hydration, or associated with syncope or near-syncope) or laryngeal.

Exploratory Endpoints:

- Exploratory biomarker(s) of angioedema-disease state bioactivity, including pKal activity

Safety Analyses

Adverse Events

Treatment-emergent AEs are defined as AEs with onset at the time of or following the first exposure to open-label 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.

In this study, angioedema attacks will be captured as AEs and will be evaluated in accordance with Non-histaminergic Bradykinin-mediated Angioedema Attack Assessment and Reporting Procedures (BAARP).

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.

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. The number of deaths due to an AE, hospitalization due to an AE and study discontinuation due to an AE will be summarized.

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized by system organ class (SOC), and preferred term (PT). This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, and related severe AEs.

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

Laboratory Test Results, Vital Signs, and Electrocardiography Results

Baseline is the last non-missing value prior to first exposure to study drug in Study SHP643-303.

Actual values and change from baseline in clinical laboratory test results and vital signs will be summarized by study visit.

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. 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 within each category will be summarized by study visit.

The number and percentage of subjects with normal, abnormal not clinically significant and abnormal clinically significant ECG results will be summarized.

Efficacy Analyses

Number of Investigator-confirmed Angioedema Attacks

The number of investigator-confirmed angioedema attacks during the treatment period (Day 0 through Day 182) expressed as a monthly angioedema attack rate, will be analyzed using each analysis population.

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

The baseline investigator-confirmed monthly angioedema attack rate will be calculated for each subject as the number of investigator-confirmed monthly angioedema attacks occurring during the baseline observation period of

Study SHP643-303 divided by the number of days the subject contributed to the baseline observation period multiplied by 28 days.

The baseline, treatment period, and treatment period change from baseline in the investigator-confirmed angioedema attack rate will be summarized for each analysis population. The summary will include the total number of investigator-confirmed angioedema attacks reported during each period and subject-time in months that each subject contributed to each period. Figures will be created for each analysis population plotting the on-study investigator-confirmed angioedema attacks reported during the treatment period relative to Day 0 for each subject.

Similar summary tables will be presented for the following efficacy endpoints for each analysis population:

- Number of moderate or severe investigator-confirmed angioedema attacks during the treatment period.
- Number of high-morbidity investigator-confirmed angioedema attacks during the treatment period; a high-morbidity angioedema attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation <24 hours), hemodynamically significant (systolic blood pressure <90 mmHg, requires IV hydration, or associated with syncope or near-syncope) or laryngeal.

Other Analyses

Plasma concentrations of lanadelumab and plasma kallikrein activity will be summarized by nominal PK and PD sampling times.

The number and percentage of subjects with positive antibodies (and whether neutralizing or non-neutralizing) and exploratory biomarkers will be summarized by study visit and overall.

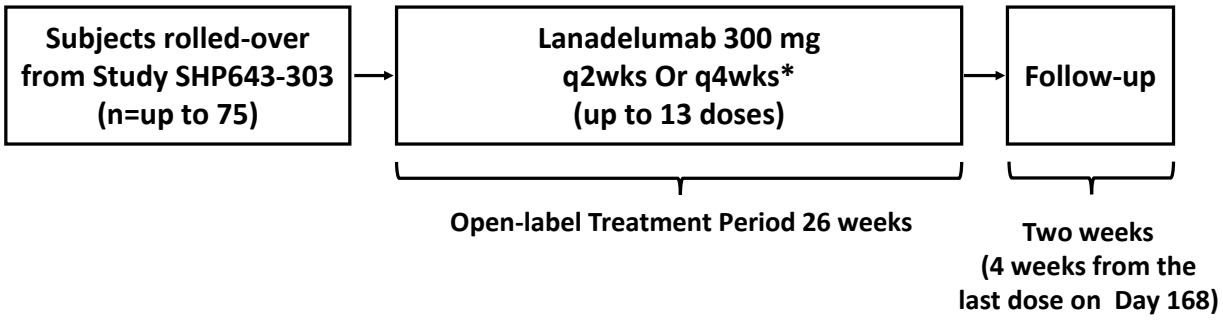
Quality of life assessments will be summarized by study visit.

Sample Size Determination

No formal sample size calculation was performed. The sample size is not based on any statistical considerations. This study is designed to evaluate the safety and efficacy of open-label treatment with lanadelumab in subjects who completed Study SHP643-303.

1.2 Schema

Figure 1 Study Schematic Diagram



q2wks=every 2 weeks; q4wks=every 4 weeks

* Subjects may consider switching to lanadelumab 300 mg q4wks if they have been well-controlled (eg, attack-free) for 26 consecutive weeks across Study SHP643-303 and Study TAK-743-3001. The dose frequency change to q4wks will be based on the investigator's discretion and consultation with the sponsor's medical monitor.

Note: Subjects with non-histaminergic angioedema with normal C1-INH may roll over from SHP643-303 study into an open-label extension study upon completion of all assessments (in SHP643-303) scheduled on Day 182.

1.3 Schedule of Activities

Table 1 Schedule of Activities – Day 0 through Day 196

Activities Occurring at	Treatment Period, Visit Window ±4 days Shaded columns =scheduled on-site visits[o] for all subjects. Non-Shaded columns =potential subject-elected off-site activity and/or self-administration dosing.														Follow-up Period[q] (+4 days)	See Protocol Section below for details
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Dose Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ET[p]**	**EOS/ Follow-up**	
Study Day (±4 days)	**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	
Informed Consent	•[a]															8.3.1
Eligibility Review	•															8.3.2
Lanadelumab 300 mg q2wks[e,f]	•	•	•	•	•	•	•	•	•	•	•	•	•			6.2.1
Lanadelumab 300 mg q4wks[e,f]	•		•		•		•		•		•		•			6.2.1
Demographic and Medical History	•[b,c]															8.3.3 and 8.3.3.1
Pregnancy Test[g] (females)	•[b]		•				•				•			•		8.3.5.6
Vital Signs[h]	•		•				•				•			•		8.3.5.4
Physical Exam[i]	•[b,d]		•				•				•			•		8.3.5.1
Clinical Laboratory Testing[j]	•[b]		•				•				•			•		8.3.5.5
12-Lead ECG	•[b]													•		8.3.5.7
Prior (4 weeks) & Concomitant Therapy	•[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	6.6
Adverse Events	•[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	8.3.5.2
Angioedema Attack Monitoring Diary[k]	•[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	8.3.4.1
Health-related Quality of Life Assessments[l]	•[b]		•				•				•			•		8.3.6.5
Site Check-in Call[m]		•		•	•	•		•	•	•		•	•			8.2.2.4
Lanadelumab Injection Report[n]	•	•	•	•	•	•	•	•	•	•	•	•	•			8.3.6.8
PK, PD, ADA & Biomarker Sample collection	•[b]						•				•			•		8.3.6.1, 8.3.6.2, 8.3.6.3, 8.3.6.4

ADA=anti-drug antibody; ECG=Electrocardiogram; EOS=end-of-study visit; ET=early termination visit; PK=Pharmacokinetic; PD=Pharmacodynamic

[a] Subjects must sign informed consent for Study TAK-743-3001 on or after Day 168 of Study SHP643-303. Day 182 of Study SHP643-303 is also Day 0 of Study TAK-743-3001, and informed consent should be completed on this visit, if not already provided.

[b] These assessments will be carried over from the last study visit (Day 182) from Study SHP643-303; no study assessments will be duplicated.

[c] Demography data from Study SHP643-303 will be re-entered (in clinical database) for Study TAK-743-3001. However, medical history reported in the Study SHP643-303 will *not* be re-entered into the eCRF for Study TAK-743-3001; only *new* medical history data will be entered.

[d] Height should be measured for subjects aged <18 years at time of consent for Study SHP643-3001.

[e] Doses are administered within ±4 days of lanadelumab administration schedule. During the open-label extension treatment period, subjects may receive lanadelumab 300 mg every 2 weeks (q2wks) or may consider lanadelumab 300 mg every 4 weeks (q4wks) if they have been well-controlled (eg, attack free) for 26 consecutive weeks across Study SHP643-303 and Study TAK-743-3001. The dose frequency change to q4wks will be based on the investigator's discretion and discussion with the sponsor's medical monitor.

[f] At each on-site visit in which a dose of lanadelumab is administered, assessments will be collected *prior* to administration of investigational product. The following assessments will also be collected *post-dose*: vital signs, lanadelumab injection report, concomitant therapies, medications, procedures, and AE collection.

[g] Pregnancy testing may be urine- or serum-based and will be performed for females of childbearing potential.

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

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

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

[k] During the treatment and follow-up period, subjects or parents/caregivers will use a diary to record symptoms and occurrences of angioedema attacks and any medications taken by the subject for the management of attacks. Angioedema attacks will be monitored daily and recorded as they occur. Subjects or parents/caregivers are instructed to notify and report details of an attack to the study site within 72 hours of the onset of an angioedema attack, in accordance with BAARP. Any subject-reported or parent/caregiver-reported attack not confirmed by the investigator must have an alternate AE diagnosis recorded in the source documents and electronic case report form.

[l] Health-related quality of life (HRQoL) data will be obtained predose at the scheduled dosing time points.

[m] Site personnel will call subjects within approximately 3 days after the planned self-administration to ensure the administration occurred, to collect AEs and concomitant medications, and to ensure all angioma attacks have been appropriately documented. Additional site calls to the subject may be done as needed.

[n] Injection reports will be collected assessing the subject's or parent/caregiver's experience with SC injection of investigational product.

[o] To extend flexibility to patients during the COVID-19 public health emergency, an in-person visit may be substituted with a remote visit. The type of remote visit (eg, telehealth visit or home health care visit) will be documented in the study records and eCRF. See Section 8.1 of the protocol for additional details.

[p] Subjects who terminate the study early will undergo (if possible) all of the study assessments and procedures at Visit 14/ET.

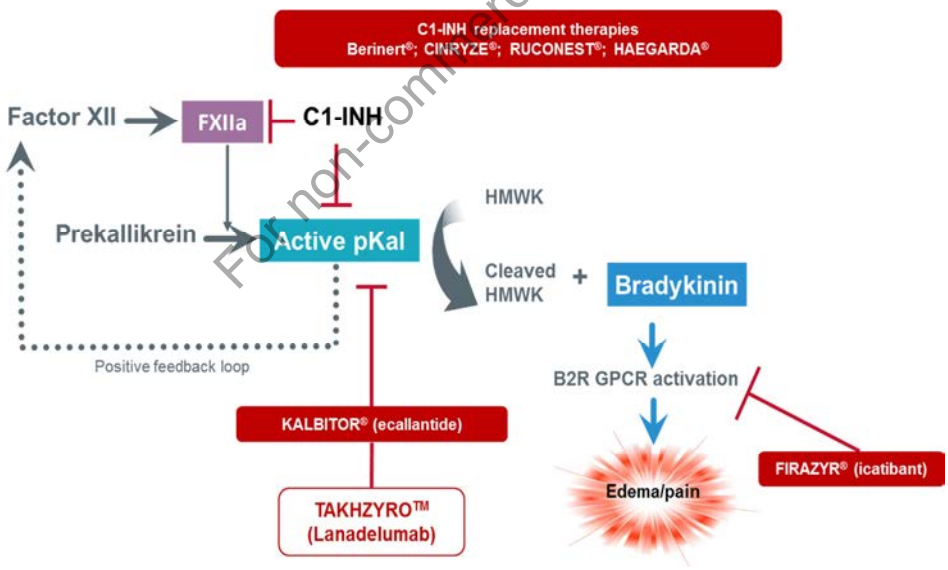
[q] Visit 15 assessments may be collected by telephone.

2. INTRODUCTION

2.1 Disease Etiology and Pathophysiology

Hereditary angioedema (HAE) is a long-term, debilitating, and life-threatening disease caused by mutations in the C1 esterase inhibitor (C1-INH) SERPING1 gene (Tosi, 1998), resulting in heterozygous deficiency (Type I HAE) or dysfunction (Type II HAE) of C1-INH plasma protein (Sosada et al., 2013). HAE manifests clinically as unpredictable, intermittent attacks of subcutaneous or submucosal edema of the face, larynx, gastrointestinal tract, limbs, and/or genitalia (Zuraw, 2008). Despite lacking a precise understanding of the triggering events that initiate an HAE attack, identification of the key components of the kallikrein-kinin pathway has facilitated the development of multiple therapeutic strategies to treat HAE (Figure 2). Unregulated plasma kallikrein (pKal) is recognized as the key pathophysiologic defect responsible for the development of HAE attacks (Schneider et al., 2007). Blocking bradykinin production with pKal inhibitors or blocking bradykinin B2 receptors are rational therapeutic strategies to treat or prevent HAE attacks. The importance of kallikrein-kinin pathway components as drug targets in HAE have been described in the literature and demonstrated by the approval of ecallantide and icatibant to treat acute attacks and approval of lanadelumab for attack prevention (Kaplan and Joseph, 2014; Busse et al., 2019; Duffey and Firszt, 2015).

Figure 2 Multiple Therapeutic Strategies to Treat HAE Target the Kallikrein-Kinin Pathway



B2R=bradykinin type 2 receptor; C1-INH=C1 esterase inhibitor; GPCR=G protein-couple receptor; HAE=hereditary angioedema; HMWK=high molecular weight kininogen; pKal=plasma kallikrein

In addition to Type I or Type II HAE, bradykinin is also an important mediator for other types of non-histaminergic angioedema, such as: A) non-histaminergic angioedema with normal C1-INH and B) acquired angioedema (AAE) due to C1-INH deficiency.

Unlike HAE Type I/II, which are well-characterized forms readily diagnosed by low levels of functional C1-INH along with a positive family history in most cases and that have several approved treatments, for the other forms of non-histaminergic angioedema an unclear pathophysiology and lack of consistent diagnostic criteria have limited the opportunity for the clinical investigation and new treatment development (Craig et al., 2014). Consequently, there are still no approved treatments for non-histaminergic angioedema patients (Bygum and Vestergaard, 2013), who are unresponsive to conventional antihistamine/glucocorticoid treatment (Craig et al., 2014). The clinical research for non-histaminergic angioedema has made significant progress recently. Similar to what is observed with Type I or II HAE, kallikrein-kinin pathway potentially plays a critical role in the underlying pathophysiology of non-histaminergic angioedema, including both non-histaminergic normal C1-INH angioedema and AAE due to C1 deficiency (Castelli et al., 2013; Zuraw, 2018). For example, pKal from patients with non-histaminergic normal C1-INH angioedema exhibits a similar enhanced propensity for activation as was observed for C1-INH deficient patients, which was higher than that of healthy controls or patients with histaminergic angioedema (Lara-Marquez et al., 2018). In addition, bradykinin has been shown to be elevated in plasma from non-histaminergic angioedema patients during acute attacks (Cugno et al., 2017). Cleaved high molecular weight kininogen (WK), which is generated by pKal concomitant with bradykinin, was also elevated in the plasma from patients with AAE due to C1-INH deficiency and non-histaminergic angioedema with normal C1-INH (Cugno et al., 1995; Baroso et al., 2016). Furthermore, mutations identified to date in HAE with normal C1-INH have been associated with dysregulation of the plasma kallikrein-kinin system. For example, patients with HAE with normal C1-INH and a mutation in coagulation factor XII (FXII) that substitutes a threonine at position 309 to either a lysine or an arginine have a form of FXII that is more prone to activation by plasmin and leads to a truncated enzyme that has 15-fold higher catalytic efficiency towards prekallikrein activation (de Maat et al., 2016; Ivanov et al., 2019). A mutation in the gene encoding plasminogen (PLG) in HAE patients with normal C1-INH substitutes a lysine at position 330 with a glutamate and has been hypothesized to be associated with increased activation of the plasma kallikrein-kinin system by plasmin (Bork et al., 2018). The reported missense mutation in the angiopoietin-1 gene (ANGPT1) from HAE patients with normal C1-INH is hypothesized to increase bradykinin B2 receptor activation (Bafunno et al., 2018). Recently, a mutation in the kininogen gene (KNG1) to substitute a methionine to a lysine at position 379 was reported and the effect of this mutation on bradykinin metabolism is under investigation (Bork et al., 2019). Therefore, it is hypothesized that lanadelumab has the potential to be an effective therapy and address an unmet medical need for these patients with likely bradykinin-mediated angioedema (BMA).

2.2 Epidemiology

The exact prevalence of HAE is unknown; however, current estimates range from 1 per 10,000 to 1 per 150,000 persons, with many authors agreeing that 1 per 50,000 is likely the closest estimate (Bygum, 2009; Goring et al., 1998; Lei et al., 2011; Nordenfelt et al., 2014; Roche et al., 2005).

The prevalence for AAE due to C1-INH deficiency or non-histaminergic normal C1-INH angioedema are even much lower (Busse and Buckland, 2012; Agostoni et al., 2004; Aygören-Pürsün et al., 2018; Maurer et al., 2018) compared to Type I or Type II HAE. Non-histaminergic angioedema with normal C1-INH is a very rare disease, with clinical features similar to those of HAE with C1-INH deficit (Maurer et al., 2018). Until recently it was assumed that HAE is a disease that results exclusively from a genetic deficiency of the C1-INH. In the year 2000, families with HAE and normal levels of C1-INH were described (Bork et al., 2000). Since then several patients and families with that condition have been reported. Most of the patients by far were women. In part of the affected women, oral contraceptives, hormone replacement therapy containing estrogens, and pregnancies were more prone to trigger the clinical symptoms (Bork, 2010). According to the latest classification (Zuraw et al., 2012; Zuraw, 2018), within the non-histaminergic normal C1-INH angioedema, the following subtypes are defined:

1) normal C1-INH angioedema with demonstrated genetic mutations associated with the disease; eg, mutations in the coagulation factor F12 gene (HAE-FXII), plasminogen gene (HAE-PLG), angiopoietin-1 gene (HAE-ANGPT1), or kininogen 1 gene [HAE-KNG1], or other mutations associated with non-histaminergic normal C1-INH angioedema (de Maat et al., 2016; Ivanov et al., 2018; Bork et al., 2018; Bork et al., 2019);
2) normal C1-INH angioedema with unknown genetic mutations, but with family history of recurrent angioedema in a first-degree relative;
3) idiopathic non-histaminergic angioedema (INHA) (Cicardi et al., 1999) with similar features to normal C1-INH angioedema with unknown genetic mutations, but with no clear family history.

The frequency of non-histaminergic angioedema with normal C1-INH is not clearly known; the information available from the current literature indicate that in 1 case, in a cohort of 138 Brazilian patients with HAE, the preponderance of HAE with C1-INH deficiency was 77.5% (n=107) followed by HAE with normal C1-INH at 22.5% (n=31) (Alonso et al., 2017). Similarly, in a cohort of Italian patients in 2016, the minimum prevalence of normal C1-INH with the FXII mutation was 37:59,394,000 inhabitants and normal C1-INH without this mutation was 60:59,394,000, which was equivalent to 1:1,605,243 for FXII-HAE and 1:989,900 for without this mutation (Bova et al., 2017).

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).

Unlike HAE Types I and II, there are no approved treatments for the other forms of non-histaminergic angioedema (Bygum and Vestergaard, 2013), which are unresponsive to conventional antihistamine/glucocorticoid treatment (Craig et al., 2014).

Lanadelumab is expected to fulfill an unmet medical need for patients with non-histaminergic angioedema with normal C1-INH by providing a long-term safe, effective and convenient intervention to prevent angioedema attacks. Lanadelumab may provide significant benefit to these patients with other forms of BMA, given the similarity in the pathophysiology and the demonstrated efficacy in preventing angioedema attacks in patients with Types I and II HAE. In the HAE 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) can be considered if the patient is well controlled (eg, stably attack-free for more than 6 months) in adolescent and adults. A similar convenient dosing interval of q2wks is being proposed for patient populations in this study. In addition, lanadelumab has a convenient route of administration (subcutaneous; SC), with the flexibility to allow self-administration.

The targeted indication for lanadelumab (TAK-743/SHP643) currently under study is prophylaxis to prevent attacks of non-histaminergic angioedema with normal C1-INH in patients 12 years and older.

2.4 Product Background and Clinical Information

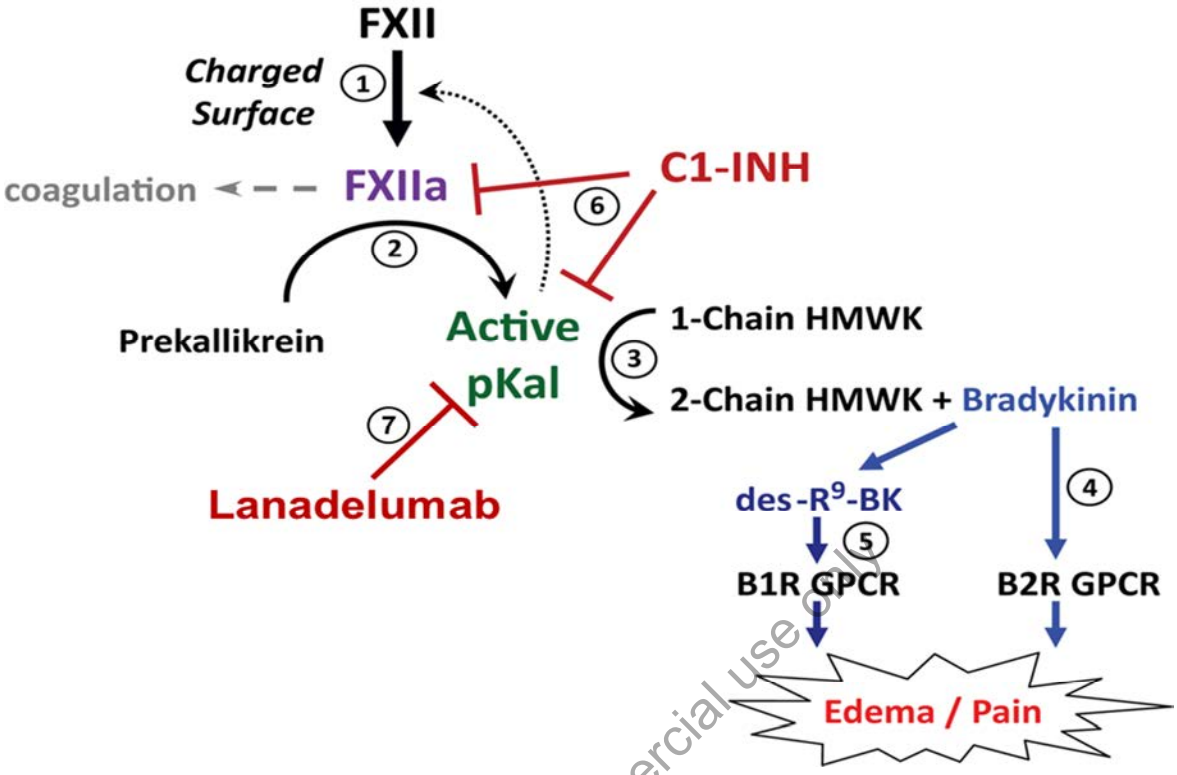
2.4.1 Drug Information

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 high molecular weight kininogen (HMWK). Inhibition of bradykinin generation prevents the vascular leak and swelling during an angioedema attack initiated when bradykinin binds to the B2 receptor (Figure 3).

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 3 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 Factor 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.

Source: Kenniston et al., 2014

Dosage Form

The drug product is a sterile, preservative-free, ready-to-use solution of lanadelumab at a concentration of 150 mg/mL. Drug product will be provided in a single-use prefilled syringe (PFS) at a dosage strength of 300 mg (300 mg/2mL). Each PFS is filled to deliver a nominal volume of 2.0 mL of drug product subcutaneously.

Route of Administration

Lanadelumab is formulated as a liquid for injection and is intended for SC administration in the abdomen (preferred), 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 has 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 plasma 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 months 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 SC 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). Refer to the latest version of the lanadelumab investigator's brochure (IB) for details.

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

Clinical study DX-2930-02 evaluated the safety, tolerability, and PK of 2 doses of lanadelumab (30, 100, 300, or 400 mg) separated by 14 days in HAE patients and demonstrated that lanadelumab was well tolerated following 2 doses up to 400 mg. There were no deaths, 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 antidrug 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 patients. 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 mg and 400 mg lanadelumab treatment groups, respectively. The effects on HAE attacks were associated with drug exposure.

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

Study DX-2930-03 (HELP Study™) was a multicenter, randomized, double-blind, placebo-controlled, parallel group efficacy and safety study to evaluate lanadelumab for long-term prophylaxis (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. The dosing regimens in this study were: 300 mg q2wks, 300 mg q4wks, and 150 mg q4wks.

The primary objective of the study was to evaluate the efficacy of lanadelumab in preventing HAE attacks. The secondary objective was evaluation of the safety of repeated SC administration

of lanadelumab. Each subject underwent a treatment period consisting of 13 doses of blinded investigational medicinal product (IMP) for a period of 26 weeks from the date of the first dose on Day 0 through 2 weeks after the final dose (for the 150 mg q4wks and 300 mg q4wks regimens, every second dose was placebo). Over the 26-week treatment period, all 3 lanadelumab dose regimens, 150 mg q4wks, 300 mg q4wks, and 300 mg q2wks, resulted in a highly statistically significant percentage reduction in the least squares mean investigator-confirmed HAE attack rate compared with placebo of 76%, 73%, and 87% (adjusted $p<0.001$), respectively, for the primary endpoint. During the estimated steady-state 16-week period (Day 70 through Day 182), the percentage reduction in the mean monthly HAE attack rates for lanadelumab-treated subjects compared with placebo was 78% in the 150 mg q4wks arm, 81% in the 300 mg q4wks arm, and 91% in the 300 mg q2wks arm. Furthermore, all 3 lanadelumab regimens demonstrated highly statistically significant attack rate reductions compared with placebo for all secondary efficacy analyses (adjusted $p<.001$ for all comparisons): attacks requiring acute treatment (74% to 87%), moderate or severe attacks (70% to 83%), and attacks from Day 14 through Day 182 (75% to 89%). 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 (HR-QoL) based on angioedema quality of life (AE-QoL) scores. 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 adverse event (TEAE). Two subjects (1 lanadelumab treated and 1 placebo) discontinued the study due to a TEAE.

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 completed enrollment; the study enrolled 212 total subjects, including 109 who rolled over from DX-2930-03 and 103 nonrollover subjects. The safety profile in study DX-2930-04 is 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 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 over the treatment period (33 months) of lanadelumab exposure across Study DX-2930-03 and Study DX-2930-04 for rollover subjects. Improved HR-QoL based on AE-QoL scores were observed for rollover and nonrollover subjects.

2.4.4 Adolescent Clinical Trial Experience

The Phase 3 clinical studies for lanadelumab, pivotal Study DX-2930-03 and the open-label extension Study DX-2930-04, evaluated the adult and adolescent population; inclusion of adolescents in these studies was justified based on the similarity of the pathophysiology and clinical presentation of HAE in adults and adolescents, as well as by the lack of any safety signal identified in nonclinical and clinical studies to date. As of the data cut for the global marketing license or authorization application for lanadelumab, 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 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 (standard deviation [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 years to <40 years and ≥40 years to <65 years. A similar observation was made for subjects <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 26.1 months of data from the Phase 3 long-term safety clinical study in patients with HAE, including adolescents (Study DX-2930-04 Interim Analysis 2 data cutoff on 31 Aug 2018).

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

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

Population PK analyses for adolescents and adults in Phase 3 studies, indicate no apparent influence of age on clearance 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 years to <18 years). Refer to the latest lanadelumab Investigator's Brochure (IB).

2.5 Study Rationale

This open-label extension study will be preceded by the initiation of Study SHP643-303, a phase 3, multicenter, randomized, placebo-controlled, double-blind study to evaluate the efficacy and safety of lanadelumab for prevention against acute attacks of non-histaminergic angioedema with normal C1-INH. The rationale for this study is to continuously evaluate the long-term safety of repeated subcutaneous treatment with lanadelumab and the long-term efficacy of lanadelumab in preventing angioedema attacks for subjects with non-histaminergic angioedema with normal C1-INH who roll over from Study SHP643-303.

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 patients 12 years and older (Section 2.4.3 and Section 2.4.4; refer to the latest version of the lanadelumab IB).

From a benefit/risk perspective, lanadelumab was generally well tolerated by subjects with HAE across the clinical program and has not shown safety limitations. There were no deaths and few subjects withdrew due to TEAEs. There were no discontinuations of treatment due to TEAEs in adolescent subjects in any of the Phase 3 studies (until the interim analysis 2 data cutoff for Study DX-2930-04 on 31 Aug 2018).

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 (ISR), a majority of which were generally mild, lasted <0.5 hours in duration, and did not lead to study discontinuation. The safety profile in the ongoing Phase 3 open-label study (DX-2930-04) was consistent with that of the pivotal study.

As of the data cutoff on 31 Aug 2018, the most frequently reported AEs in the lanadelumab-treated population across Study DX-2930-03 and Study DX-2930-04 were injection site pain (49.5%), viral upper respiratory tract infection (35.9%), headache (25.5%), upper respiratory tract infection (21.4%), injection site erythema (15.9%), and injection site bruising (12.3%).

Overall, 60% (132/220) of lanadelumab-treated subjects reported a total of 1834 related TEAEs across Study DX-2930-03 and Study DX-2930-04. The vast majority of related TEAEs were ISRs, eg: injection site pain (45.9%, 101/220), injection site erythema (15%, 33/147), injection site bruising (9.1%, 20/220), injection site swelling (5.5%, 12/220), and injection site pruritus

(5.0%, 11/220) in ≥5.0% of lanadelumab-treated population. The most frequently occurring non-ISR related AE was headache, reported by 5.0% (11/220) of lanadelumab-treated population. Other related non-ISR AEs reported by ≥2 subjects included hypersensitivity (2.3%, 5/220), alanine aminotransferase (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) as a non-ISR TEAE reported by ≥2 subjects (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.

As of the data cutoff date on 31 Aug 2018 for Study DX-2930-04, 109 (51.4%) subjects had a total of 1567 ISR TEAEs during the treatment period. These ISRs occurred across a collective 8013 doses, equivalent to a mean of 37.8 doses per subject. Most of the ISRs were related to lanadelumab (1382 of 1567 ISR TEAEs). None of the ISRs were serious or severe. Most ISRs were mild in severity (98.7% [1547 of 1567 ISR TEAEs]) and reports of moderate ISRs were infrequent; the most frequent single event, injection site pain, had a maximum severity of mild in 89 subjects and moderate in 2 subjects. The majority of ISRs (91.2%) resolved within a day, while 76.3% 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 the lanadelumab-treated population and there were no events of anaphylaxis observed in either Phase 3 study. 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 AESIs, 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 AESIs of hypersensitivity were reported in the placebo group.

As of the data cutoff on 31 Aug 2018, 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 5 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. While coagulopathy is a theoretical risk with drugs affecting the plasma kallikrein-kinin system and lanadelumab may cause activated partial thromboplastin time (aPTT) prolongation (Appendix 3.1), there does not seem to be a clinical association with abnormal bleeding events based on the lack of effect on hemostasis in Studies DX-2930-03 and DX-2930-04. Therefore, disordered coagulation (bleeding events or hypercoagulable events) is no longer considered an AESI for lanadelumab in this protocol.

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 to 1280), and 2/84 or 2.4% lanadelumab-treated subjects tested positive for antibodies classified as neutralizing. As of the data cutoff for the second interim analysis, 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 patients with non-histaminergic angioedema with normal C1-INH is being initiated after establishing the efficacy and safety profile of lanadelumab in adolescent and adult HAE patients. Additionally, the type and frequency of safety assessments in this study will be similar to the pivotal Phase 3 study in HAE patients (Table 1).

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 (ICH GCP, 1996; ICH E6 R2, 2016), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives (2001/20/EC; 2005/28/EC), and applicable national and local regulatory requirements.

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

3. OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

- To evaluate the long-term safety of repeated SC administrations of lanadelumab in adolescents and adults with non-histaminergic angioedema with normal C1-INH

3.1.2 Secondary Objectives

- To evaluate the long-term efficacy of lanadelumab in preventing angioedema attacks
- To evaluate PK and PD following long-term SC administration of lanadelumab
- To assess the immunogenicity of chronically administered lanadelumab
- To evaluate the effect of lanadelumab on health-related quality of life (QoL)
- To evaluate subject experience of injection
- To evaluate the safety and efficacy of lanadelumab in subjects switched to the dosing regimen of 300 mg q4wks lanadelumab

3.1.3 Exploratory Objectives

- To evaluate exploratory biomarker(s) of angioedema disease-state bioactivity in plasma

3.2 Study Endpoints

Table 2 Objectives and Endpoints

Objective	Endpoint(s)
Primary	
• To evaluate the long-term **safety** of repeated SC administrations of lanadelumab in adolescents and adults with non-histaminergic angioedema with normal C1-INH	**Primary Safety Endpoints** Safety measures, including • AEs including SAEs and adverse events of special interest (AESIs) • Clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis) • Vitals signs including blood pressure (BP), heart rate (HR), body temperature • Weight and height (height for subjects <18 years old) • 12-lead ECGs
Secondary	
• To evaluate the long-term **efficacy** of lanadelumab in preventing angioedema attacks	• Number of investigator-confirmed angioedema attacks during the treatment period • Number of moderate or severe angioedema attacks during the treatment period • Number of high-morbidity angioedema attacks during the treatment period; a high-morbidity angioedema attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation <24 hours), hemodynamically significant (systolic blood pressure <90 mmHg, requires IV hydration, or associated with syncope or near-syncope) or laryngeal.

Table 2 Objectives and Endpoints

Objective	Endpoint(s)
• To characterize the PK and PD profile of SC administration of lanadelumab	• Analysis of PK effects through measurement of plasma concentrations of lanadelumab. • Evaluation of the PD effects of lanadelumab through plasma cHMWK and fluorogenic pKal assay with FXIIa activation.
• To assess the immunogenicity of chronically administered lanadelumab	• Presence of ADAs, including evaluation of neutralizing antibodies (if any confirmed positive anti-drug antibodies are detected)
• To evaluate the effect of lanadelumab on health-related quality of life (QoL)	• Health-related QoL assessments will be assessed using the AE-QoL questionnaire.
• To evaluate subject experience of injection	• Lanadelumab Injection Report
• To evaluate the safety and efficacy of lanadelumab in subjects switched to the dosing regimen of 300 mg q4wks lanadelumab	Safety measures, including: • AEs, including SAEs and AESIs • Clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis) • Vitals signs including BP, HR, body temperature • Weight and height (height for subjects <18 years old) • 12-lead ECGs Efficacy measures, including: • Number of investigator-confirmed angioedema attacks during the treatment period • Number of moderate or severe angioedema attacks during the treatment period • Number of high-morbidity angioedema attacks during the treatment period; a high-morbidity angioedema attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation <24 hours), hemodynamically significant (systolic blood pressure <90 mmHg, requires IV hydration, or associated with syncope or near-syncope) or laryngeal.
Exploratory	
• To evaluate exploratory biomarker(s) of angioedema disease-state bioactivity in plasma	• Exploratory biomarker(s) of angioedema-disease state bioactivity, including pKal activity

ADA=anti-drug antibodies; AE=adverse event; AESI=adverse event of special interest; BP=blood pressure, C1-INH=C1 inhibitor or C1 esterase inhibitor, cHMWK=cleaved high molecular weight kininogen; FXIIa=coagulation factor XIIa; ECG=electrocardiogram; HR=heart rate; IV=intravenous; PD=pharmacodynamic; PK=pharmacokinetic; pKal=plasma kallikrein; QoL=quality of life; SAE=serious adverse event; SC=subcutaneous

4. STUDY DESIGN

4.1 Overall Design

Study TAK-743-3001 is an open-label, long-term safety and efficacy extension study of Study SHP643-303 to evaluate lanadelumab in preventing acute angioedema attacks in patients with non-histaminergic angioedema with normal C1-INH who roll over from Study SHP643-303.

All subjects must complete the double-blind treatment period at Visit 26/Day 182 of Study SHP643-303 and consent to enter Study TAK-743-3001. Subjects who discontinue from Study SHP643-303 after enrollment but before Visit 26 are not eligible to enroll in Study TAK-743-3001.

Subjects should be asked about their interest in Study TAK-743-3001 after enrollment into SHP643-303 to anticipate enrollment and preparedness for Study TAK-743-3001. Willing subjects must sign informed consent for Study TAK-743-3001 on or after Day 168 of SHP643-303 and prior to any procedures in Study TAK-743-3001.

Subjects who are eligible to roll over into Study TAK-743-3001, but elect not to, may not enroll in Study TAK-743-3001 at a later time. The first Study TAK-743-3001 visit (Day 0) will occur on the same day as the Study SHP643-303 Day 182 study visit. Subjects will complete all Study SHP643-303 final study assessments (Visit 26/Day 182) at which time they will be discharged from that study. No assessments conducted between the Study SHP643-303 Day 182 study visit and the first Study TAK-743-3001, visit (Day 0) will be duplicated. Results of the final SHP643-303 assessments on Day 182 will be used as the pre-dose results for Day 0 of Study TAK-743-3001.

All subjects, caregivers, investigators and study site personnel will remain blinded to the SHP643-303 treatment assignment until the conclusion of Study TAK-743-3001.

All subjects must adhere to the Schedule of Activities (Table 1) for the entire duration of the study. See Schedule of Activities (Table 1) for additional information on study visits.

Following their first open-label dose, subjects will continue to receive repeated SC administrations of open-label 300 mg lanadelumab q2wks or may be considered to receive lanadelumab 300 mg q4wks if they have been well-controlled (eg, attack free) for 26 consecutive weeks across Study SHP643-303 and Study TAK-743-3001 per the scheduled dosing in the Study Activities Schedules. The dose frequency change to q4wks will be based on the investigator's discretion and consultation with the sponsor's medical monitor. The treatment period will last up to 168 days from the date of the first open-label dose. The number of doses administered during this period will not exceed 13 doses. The Day 168 study visit is the last visit at which a dose may be administered.

All doses should be administrated within the accepted ±4-day window around dose administration schedule (q2wks or q4wks in Table 1).

If a subject experiences an acute angioedema attack at any time during the study that in the opinion of the investigator requires medical intervention, standard of care therapy should be provided based on subject's medical history and per locally approved product information. Administration of lanadelumab and study procedures will continue without alteration to the protocol study activities schedules, even if a subject receives treatment for a breakthrough angioedema attack on the day of a scheduled dose of study drug (if self-administering) or scheduled study visit.

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 study treatment. Subjects must complete appropriate training in the antecedent study (SHP643-303) or in this study by the investigator or designee and understanding of the training must be documented by the investigator or designee. Once trained, subjects may self-administer subsequent doses of lanadelumab at the investigational site (when visits are scheduled study site visits) or the subject's home or other agreed upon location (when the study permits off-site dosing -- See Schedule of Activities [Table 1] for details). Adolescent subjects self-administering investigational product will be supervised by a parent/legal guardian/caregiver. Alternatively, a parent/legal guardian/caregiver, after completing appropriate training in the antecedent study (SHP643-303) or in this study, will be allowed to administer lanadelumab to an adolescent without study site personnel supervision. Site personnel will call subjects within approximately 3 days after the planned off-site self-administrations to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all angioma attacks have been appropriately documented.

Throughout the study, study site personnel will document information in source documents (ie, the subject's medical record) and electronic case report form (eCRF) regarding the subject's experience with self-administration and SC administration of lanadelumab.

After completion of the treatment period, all subjects will undergo safety evaluations during a 2-week follow-up period.

If, at any time, a dose-related safety signal is identified either from this study or Study SHP643-303, the Sponsor may decide to modify the open-label lanadelumab dose and/or frequency.

4.2 Scientific Rationale for Study Design

This open-label extension study will be preceded by the initiation of Study SHP643-303, a phase 3, multicenter, randomized, placebo-controlled, double-blind study to evaluate the efficacy and safety of lanadelumab for prevention against acute attacks of non-histaminergic angioedema with normal C1-INH and AAE due to C1-INH deficiency. The rationale for this study is to continuously evaluate the long-term safety of repeated subcutaneous treatment with lanadelumab and the long-term safety and efficacy of lanadelumab in preventing angioedema attacks for subjects with non-histaminergic angioedema with normal C1-INH who roll over from Study SHP643-303.

4.3 Justification for Dose

Reports in the literature suggest that, similar to Type I or II HAE, the pathophysiology of non-histaminergic angioedema with normal C1-INH is potentially attributed to the dysregulation of pKal activity and elevated bradykinin. For example, pKal from patients with non-histaminergic normal C1-INH angioedema had a comparable enhanced propensity for activation as was observed for C1-INH deficient patients, which was higher than that of healthy controls or patients with histaminergic angioedema (Lara-Marquez et al., 2018). In addition, bradykinin has been shown to be elevated in plasma from patients during an attack (Cugno et al., 2017). Cleaved high molecular weight kininogen, which is generated by pKal concomitant with bradykinin, was elevated in the plasma from patients with angioedema with normal C1-INH (Cugno et al., 1994; Baroso et al., 2016). Furthermore, mutations identified to date in HAE with normal C1-INH have been associated with dysregulation of the plasma kallikrein-kinin system. For example, patients with HAE with normal C1-INH and a substitution mutation in FXII at position threonine 309 to either a lysine or an arginine yields a form of FXII that is more prone to activation by plasmin and leads to a truncated enzyme that has 15-fold higher catalytic efficiency towards prekallikrein activation (de Maat et al., 2016; Ivanov et al., 2019). A mutation in the gene encoding PLG in HAE patients with normal C1-INH substitutes a lysine at position 330 with a glutamate and has been hypothesized to be associated with increased activation of the plasma kallikrein-kinin system by plasmin (Bork et al., 2018). The reported missense mutation in ANGPT1 from HAE patients with normal C1-INH is hypothesized to increase bradykinin B2 receptor activation (Bafunno et al., 2018).

Further support for the role of the plasma kallikrein-kinin system in non-histaminergic angioedema with normal C1-INH includes case studies with doses of icatibant (Boccon-Gibod and Bouillet, 2012; Bouillet et al., 2017; Zanichelli et al., 2017; Cicardi and Zanichelli, 2010) or ecallantide (Cicardi and Zanichelli, 2010) approved for HAE with C1-INH deficiency. Several reports indicate that icatibant or ecallantide reduces attack duration in angioedema patients with normal C1-INH (Boccon-Gibod and Bouillet, 2012; Bouillet et al., 2017; Cronin and Maples, 2012).

Meanwhile, target-mediated drug disposition for therapeutic monoclonal antibodies, which is linked to the high affinity and high specificity of antibody molecules for their targets (Grimm, 2009), have been frequently reported. However, it has recently been recognized that 2 elimination pathways are involved in the disposition of therapeutic monoclonal antibodies: (1) ‘nonspecific’ elimination via phagocytic and endothelial cells of the reticuloendothelial system clearing both antigen-bound and free monoclonal antibodies – this usually is not saturable and thus follows linear kinetics; and (2) antigen specific target-mediated disposition that is dependent on binding to target antigen to be eliminated – this usually is a saturable process and therefore may follow nonlinear kinetics (Ryman and Meibohm, 2017). The lanadelumab clinical development program in subjects with Types I and II HAE characterized the clinical PK and PD properties of lanadelumab and established the optimal benefit risk profile of lanadelumab dose regimen. The clinical pharmacology package of lanadelumab suggests the elimination of lanadelumab may not be involved in target-mediated drug disposition, following linear kinetics.

Thus, the clinical pharmacology properties and proposed therapeutic target of lanadelumab in the new indications support the same dose regimen demonstrated to be efficacious in subjects with Type I and Type II HAE.

Therefore, the lanadelumab 300 mg q2wks dose regimen is considered to be the appropriate dose for the antecedent SHP643-303study and this open-label extension study in subjects with BMA other than Type I and Type II HAE.

4.4 Duration of Subject Participation and Study Completion Definition

Subjects who provide informed consent will roll over from Study SHP643-303. Eligible subjects will be enrolled and undergo a treatment period of up to 182 days. At the conclusion of the treatment period, subjects will be followed for an additional 2 weeks.

All subjects will receive open-label lanadelumab during a treatment period of up to 182 days.

The last dose of open-label lanadelumab administered may be given at the Day 168 study visit.

There will be a ±4-day window around each study visit (+4 days for follow-up call at Visit 15). Subjects will be monitored at the study site through 1-hour postdose for scheduled study site visits. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.

The subject's maximum duration of participation is expected to be approximately 196 days. The last subject last visit will be completed in approximately January 2023.

The Study Completion Date is defined as the date on which the last subject in the study completes the final protocol-defined assessment(s). This includes the follow-up visit or contact, whichever is later (refer to Section 8.2.3 for the defined follow-up period for this protocol).

4.5 Sites and Regions

This is a multicenter study. Approximately 60 sites in North America, Europe, and Japan will participate.

5. STUDY POPULATION

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. Males and females, 12 years of age and older diagnosed with non-histaminergic normal C1-INH angioedema at the time of enrollment into the antecedent Study SHP643-303.
2. Subjects must have completed the treatment period (through Visit 26/Day 182) of Study SHP643-303 without reporting a clinically significant TEAE that would preclude subsequent exposure to lanadelumab.
3. Agree to adhere to the protocol-defined schedule of treatments, assessments, and procedures.
4. Males, or non-pregnant, non-lactating females who are of child-bearing potential 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 non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months.
5. The subject (or the subject's parent/legal guardian, if applicable) has provided written informed consent approved by the institutional review board/research ethics board/ethics committee (IRB/REB/EC) at any time prior to study start. If the subject is a minor (ie, <18 years of age), have a parent/legal guardian 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.

5.2 Exclusion Criteria

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

1. Discontinued from Study SHP643-303 after enrollment but before Visit 26 for any reason.
2. Presence of important safety concerns identified in Study SHP643-303 that would preclude participation in this study.
3. Dosing with an investigational product (IP, not including IP defined in antecedent Study SHP643-303) or exposure to an investigational device within 4 weeks prior to Day 0.
4. Subject has a known hypersensitivity to the investigational product or its components.
5. Have any condition (surgical or medical) that, in the opinion of the investigator or sponsor, may compromise their safety or compliance, preclude the successful conduct of the study, or interfere with interpretation of the results (eg, significant pre-existing illness

or other major comorbidities that the investigator considers may confound the interpretation of study results).

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 was observed (see the latest version of lanadelumab IB).

5.4.1 Female Contraception

Sexually active females of childbearing potential should use an 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.

Female subjects should be one of the following:

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

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

5.4.2 Male Contraception

Male subjects must be advised to use acceptable contraceptives throughout the study period and for 160 days following the dose of investigational product. Male subjects must be advised not to donate sperm during the course of the study and within 160 days of the dose of investigational product. Acceptable methods of contraception for male subjects include:

- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam).

6. STUDY INTERVENTION

6.1 Investigational Product

6.1.1 Identity of Investigational Product

The investigational product is a sterile, preservative-free, ready-to-use solution of lanadelumab at a concentration of 150 mg/mL. Drug product will be provided in a PFS at a dosage strength of 300 mg (300 mg/2 mL). Each PFS is filled to deliver a nominal volume of 2.0 mL of drug product subcutaneously.

During the open-label extension treatment period, subjects may receive lanadelumab 300 mg q2wks or may consider lanadelumab 300 mg q4wks if they have been well-controlled (eg, attack free) for 26 consecutive weeks across Study SHP643-303 and Study TAK-743-3001. The dose frequency change to q4wks will be based on the investigator's discretion and consultation with the sponsor's medical monitor.

Commercial icatibant will not be supplied as rescue medication for the treatment of acute angioedema attacks. If a subject experiences an acute angioedema attack at any time during the study, standard of care therapy may be provided per locally approved product information.

6.1.2 Blinding the Treatment Assignment

Not applicable.

6.2 Administration of Investigational Product

6.2.1 Dosing

Investigational product will be administered by SC injection in the abdominal area (preferred), thigh, or upper arm. Self-administration of investigational product will be permitted after a subject (and/or parent/caregiver) has received appropriate training in the antecedent study (SHP643-303) or in this study by the investigator or designee and has demonstrated their understanding of self-administration.

6.2.2 Unblinding the Treatment Assignment

Not applicable.

6.2.3 Dose Modification

During the open-label extension treatment period, subjects may consider lanadelumab 300 mg q4wks if they have been well-controlled (eg, attack-free) for 26 consecutive weeks across Study SHP643-303 and Study TAK-743-3001. The dose frequency change to q4wks will be based on the investigator's discretion and 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, medical identification 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". Any additional labeling requirements for participating countries will also be included on the label.

Space is allocated on the label so that the site representative can record 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 will be supplied by the sponsor and pre-packaged in a study kit for the study. Each study kit will contain 1 PFS. Both the 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 and parents/caregivers who elect to self-administer investigational product to the subject (Section 8.3.6.7), 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 PFS should be returned to the study kit cartons/boxes and transported to the site for drug accountability. Written instructions on investigational product handling and self-administration procedures will be provided to the trained subjects and parent/caregiver prior to initiating self-administration. Refer to the Pharmacy Manual for additional details on investigational product 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 syringe/carton labels as they are distributed.

Investigational product should be stored in a refrigerator at 2°C to 8°C. Prefilled syringes should be removed from refrigeration and allowed to get to room temperature before administration. Do not freeze. The PFS should be protected from light in the original carton. Refer to the latest version of the IB for current stability data.

Before use, each PFS of study drug should be inspected for appearance. Any PFS 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 PFS.

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

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/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 Takeda-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 products 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 contract research organization [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, interactive response technology) 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 (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

6.6 Prior and Concomitant Therapy

All non-study treatment (including but not limited to all prescriptions, over-the-counter medications, herbal treatments, vitamins and supplements, behavioral treatment, non-pharmacological treatments and procedures, such as psychotherapy, surgical, diagnostic, or dental as appropriate), received within 28 days (4 weeks) prior to Visit 1 (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 will be obtained from Study SHP643-303.

Prior treatments that have a stop date in Study SHP643-303 will not be re-recorded in the Study TAK-743-3001 clinical database. However, any prior medication that started in Study SHP643-303 (or before) and are still ongoing at the time of rollover into TAK-743-3001 will be recorded in the source documents and clinical database.

6.6.2 Concomitant Treatment

Concomitant treatment refers to all treatment 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 coexisting conditions, including those for acute attacks of angioedema attacks (see below), are permitted if not excluded during the study (Section 6.6.4).
- The use of periprocedural prophylactic treatment for angioedema will be permitted if medically indicated.
- Therapies to treat any AEs the subject experiences during the study will be permitted.
- Commercial icatibant will not be supplied as rescue medication for the treatment of acute angioedema attacks. If a subject experiences an acute angioedema attack at any time during the study, standard of care therapy may be provided per locally approved product information.

Administration of investigational product and study procedures will continue without alteration to the protocol-specified study schedule, even if the subject has symptoms of an angioedema attack the day of investigational product administration and/or receives treatment for an angioedema attack. The administration of investigational product may also be rescheduled as long as the minimum and maximum timeframe between doses are met based on subject preference or physician discretion.

6.6.4 Prohibited Treatment

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

- Long-term prophylaxis for angioedema attacks (eg, use of C1-INH for LTP, attenuated androgens, or anti-fibrinolytics) during the study.
- Angiotensin-converting enzyme inhibitors or rituximab during the study.
- Estrogen-containing medications with systemic absorption during the study.
- Use of androgens (eg, stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) for non-angioedema related medical conditions or for angioedema during the study.
- Any other investigational drug or device.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

Subjects who prematurely discontinue investigational product, regardless of the reason, should undergo the final visit of the treatment period procedures specified for Study Day 182 (Visit 14) as completely as possible (Section 8.2.2.4). Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for discontinuation, date of discontinuation of the investigational product, and the total amount of investigational product administered must be recorded in the source documents.

Subjects who prematurely discontinue investigational product will not be replaced.

7.2 Reasons for Discontinuation

The reason for discontinuation 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 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 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 telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that the subject return to the site for final safety evaluations and return any unused investigational product.

7.5 Stopping Rules

7.5.1 Study Level Stopping Rules

Study data, including SAEs and AESIs, as defined in Section 8.3.5.3, 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 is determined.

7.5.2 Individual Stopping Rules

Dosing for any individual subject will be discontinued if the subject experiences an investigational product-related SAE (or an investigational product-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 final visit of the treatment period procedures specified for Study Day 182 (Visit 14) as completely as possible (Section 8.2.2.4).

7.5.3 Follow-up for Subjects Meeting Stopping Criteria

Subjects who 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 Changes to Study Procedures Due to the COVID-19 Pandemic

Given the public health emergency associated with the COVID-19 pandemic, in-person visits may be substituted with a remote visit (eg, telehealth visit or home health care visit). However, all attempts should be made to perform study assessments at the study site if feasible per COVID-19 regulations in your region. As the COVID-19 pandemic may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case-by-case basis by the principal investigator in consultation with the study team and the medical team as needed, while maintaining patient safety and confidentiality as the priority.

Procedural changes due to COVID-19 may include the following:

- **On-site Visits:** To extend flexibility to patients during the COVID-19 public health emergency, an in-person visit may be substituted with a remote visit. The type of remote visit (eg, telehealth visit or home health care visit) will be documented in the study records and eCRF. At a minimum, the following should be collected to assess subject safety and overall clinical status:
    - Adverse events
    - Concomitant medications
    - Angioedema attacks
    - Any additional assessment(s) deemed necessary by the investigator for patient safety

    Deviations from the protocol-specific procedures (eg, not collecting a protocol-specified specimen, such as bloodwork) will be recorded as related to COVID-19.

    Missed clinical visits due to COVID-19 must be recorded on the eCRF.

- **Direct-to-patient (DTP) delivery of study drug**: Alternative study drug deliveries may include dispensing additional study drug at clinic visits or DTP delivery of the study drug from the investigational site to subjects in compliance with national laws or temporary national emergency measures.

8.2 Study Periods

Refer to Table 1 for the Schedule of Study Activities. Study assessments are detailed in Section 8.3.

8.2.1 Screening Period

Informed consent must be obtained before any study-specific procedures are performed. Subjects must sign informed consent for Study TAK-743-3001 on or after Day 168 of Study SHP643-303.

Day 182 of Study SHP643-303 is also Day 0 of Study TAK-743-3001, and informed consent must be completed on this visit, if not already provided.

8.2.2 Treatment Period

8.2.2.1 Study Visit 1; Study Day 0

As indicated in Table 1, 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 of investigational product:

- Informed Consent
- Confirmation of study eligibility
- Demographics

  Note: Demography data from Study SHP643-303 will be re-entered (in clinical database) for Study TAK-743-3001.
- Documentation of height (for subjects aged <18 years at time of consent for Study SHP643-3001)

Subjects will undergo the following assessments on Day 0 after lanadelumab is administered as a SC injection:

- Vital signs (30 minutes [±15 minutes] after completion of the injection of investigational product), including body temperature, HR, BP, and respiratory rate (RR)
- Lanadelumab Injection Report
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

All subjects who take part in this protocol will have participated in Study SHP643-303. Subjects will enter this protocol on the same day as their last Study Visit (Day 182) in Study SHP643-303. The following assessments will be carried over into this study:

- Medical History

  Note: Medical history reported in the Study SHP643-303 will not be re-entered into the eCRF for Study TAK-743-3001; only *new* medical history data will be entered.
- Complete physical examination
- 12-lead ECG
- Pregnancy test (for female subjects of childbearing-potential)
- Clinical laboratory testing including hematology, serum chemistry, coagulation, and urinalysis
- PK sample collection
- PD sample collection

- Plasma ADA sample collection
- Biomarker sample collection
- Health-related QoL assessment (using the AE-QoL questionnaire)
- Prior therapies, medications, and procedures
- Angioedema attack data
- Adverse events collection, including SAEs and AESIs

8.2.2.2 Study Visits 3, 7, 11; Study Days 28, 84, 140

As indicated in Table 1, Visits 3, 7, and 11 on Study Days 28, 84, and 140 respectively, will be scheduled on-site visits. The following procedures and assessments are to be performed on Days 28, 84, and 140 prior to investigational product administration:

- Vital signs (within 60 minutes prior to the injection of investigational product), including body temperature, HR, BP, and RR
- Complete physical examination (including documentation of body weight)
- Pregnancy test (for female subjects of childbearing potential)
- Clinical laboratory testing including hematology, serum chemistry, coagulation, and urinalysis
- Concomitant therapies, medications, and procedures
- PK sample collection (on Visits 7 and 11 only)
- PD sample collection (on Visits 7 and 11 only)
- Plasma ADA sample collection (on Visits 7 and 11 only)
- Biomarker sample collection (on Visits 7 and 11 only)
- Health-related QoL assessment (using the AE-QoL questionnaire)
- Angioedema attack data
- Adverse events collection, including SAEs and AESIs

Subjects will undergo the following assessments on Days 28, 56, 84, 112, 140 and 182 after lanadelumab is administered as a SC injection:

- Vital signs (30 minutes [±15 minutes] after completion of the injection of investigational product), including body temperature, HR, BP, and RR
- Lanadelumab Injection Report
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

8.2.2.3 Study Visits 2, 4, 5, 6, 8, 9, 10, 12, 13; Study Days 14, 42, 56, 70, 98, 112, 126, 154, and 168

As indicated in Table 1, Visits 2, 4, 5, 6, 8, 9, 10, 12, and 13 on Study Days 14, 42, 56, 70, 98, 112, 126, 154, and 168, respectively, will be potential subject-elected off-site activity and/or self-administration dosing days. The following procedures and assessments are to be performed prior to investigational product administration:

- Concomitant therapies, medications, and procedures
- Angioedema attack data
- Adverse events collection, including SAEs and AESIs

Subjects will undergo the following assessments after lanadelumab is administered as a SC injection:

- Lanadelumab Injection Report
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

If a subject does not have a scheduled on-site visit on study days specified in Table 1, site personnel will perform a site check-in (within 3 days of the study day) to collect AEs and concomitant medications and to ensure all angioedema attacks have been appropriately documented and, if applicable, ensure that self-administration of investigational product (by subject or parent/caregiver) has occurred as scheduled. The preferred method of site check-in is a telephone call; however, an alternate method of contact may be considered as site policies permit. Additional site calls to the subject may be done as needed.

8.2.2.4 End of Treatment - Study Visit 14; Study Day 182

As indicated in Table 1, Visit 14 on Day 182 will be a scheduled on-site visit. The following procedures and assessments are to be performed on Day 182:

- Vital signs, including body temperature, HR, BP, and RR
- Complete physical examination (including documentation of body weight)
- Pregnancy test (for female subjects of childbearing-potential)
- Clinical laboratory testing including hematology, serum chemistry, coagulation, and urinalysis
- 12-lead ECG
- Concomitant therapies, medications, and procedures
- PK sample collection
- PD sample collection
- Plasma ADA sample collection

- Biomarker sample collection
- Health-related QoL assessment (using the AE-QoL questionnaire)
- Angioedema attack data
- Adverse events collection, including SAEs and AESIs

8.2.2.5 Follow-up Period -- Study Visit 15; Study Day 196

As indicated in Table 1, the Follow-up period for this study is 14 days (2 weeks) (+4 days). The final end of study (EOS) visit (Day 196, Visit 15) will be by telephone call from the site.

- Concomitant therapies, medications, and procedures
- Angioedema attack data
- Adverse events collection, including SAEs and AESIs

All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (Appendix 3.2). Subjects will be discharged from the study after the completion of the EOS assessments.

8.2.3 Early Termination

All procedures and assessments scheduled for final visit of the treatment period (Day 182, Visit 14) will be followed for the early termination (ET) visit (Table 1).

8.2.4 Additional Care of Subjects after the Study

No aftercare is planned for this study.

8.3 Study Assessments

Refer to the Study Schedule of Activities in Table 1.

8.3.1 Informed Consent

Informed consent and assent forms must be approved for use by the reviewing IRB, REB or EC. 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/EC 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.

8.3.2 Eligibility Review

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

8.3.3 Demographic and Other Baseline Characteristics

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

8.3.3.1 Medical and Medication History

New medical and medication history will be collected and recorded in the subject's source documents.

8.3.4 Efficacy

Throughout the study (ie, from Day 0 through follow-up), angioedema attack information will be solicited by site personnel during scheduled study visits and site check-ins, as shown in Table 1. 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 angioedema attack to the study site within 72 hours of the onset of the attack.

The collection, reporting and assessment of angioedema attacks in this study will be done in accordance with the Non-histaminergic Bradykinin-mediated Angioedema Attack Assessment and Reporting Procedures (BAARP) provided in Appendix 4 of this protocol. Site personnel will be trained on BAARP prior to screening subjects at their site.

8.3.4.1 Collection of Angioedema Attack Data

Angioedema attack information will be solicited by site personnel during scheduled study visits and site check-ins, as shown Table 1. 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 angioedema attack to the study site within 72 hours of the onset of the attack.

The collection, reporting and assessment of angioedema attacks in this study will be done in accordance with the BAARP provided in Appendix 4 of this protocol. Site personnel will be trained on BAARP prior to screening subjects at their site

8.3.4.2 Management of Acute Angioedema Attacks

Commercial icatibant will not be supplied as rescue medication for the treatment of acute angioedema attacks. If a subject experiences an acute angioedema attack at any time during the study, standard of care therapy may be provided per locally approved product information.

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 angioedema attack.

8.3.5 Safety

8.3.5.1 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). The date and time of each

examination 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
- Body weight for all patients

Note: Height should be documented for subjects aged <18 years at time of consent for study SHP643-3001 (Visit 1 ONLY).

8.3.5.2 Adverse Events

Each subject will be monitored for the occurrence of AEs, including SAEs and AESIs, from signing of the informed consent form (ICF) 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, angioedema attacks, will also be captured as AEs in this study (see details below).
- Subjects having TEAEs will be monitored until resolution with relevant clinical assessments and laboratory tests, as determined by the investigator. Up to the EOS visit, AEs, actions taken as a result of AEs, and follow-up results must be recorded in the eCRF; post-EOS visit follow-up results will be recorded 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 the procedures specified for the final visit of the treatment period (Day 182, Visit 14) 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 angioedema attack AEs). Any AE meeting criteria for an SAE, as defined in Appendix 3.1, 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 8.3.5.3, 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 Appendix 3.1, Appendix 3.2, Appendix 3.3, and Appendix 3.4, respectively. Information on SAE collection time frame, onset/resolution dates, and SAEs with a fatal outcome is presented in Appendix 3.5, Appendix 3.6, and Appendix 3.7, respectively.

The efficacy endpoint, angioedema 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- or caregiver-reported angioedema attack:

- Non-angioedema attack AEs will include the subset of AEs that are not identified in the eCRF as a subject-reported angioedema attack. Essentially, this will be AEs excluding the subject-reported angioedema attack events. **These nonangioedema 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 (Appendix 5) and the DMID Pediatric Toxicity Table (Appendix 6).
- Angioedema attack AEs will include the subset of AEs identified in the eCRF as a subject-reported angioedema attack. This will include, but will not be limited to, investigator-confirmed angioedema attacks. **These angioedema 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 BAARP (Appendix 4), which includes an assessment using BAARP criteria and an assessment using DMID criteria.

For all SAEs that are reported as angioedema attacks, the investigator will review the event within 24 hours of initial notification and, in accordance with BAARP, evaluate if it represented a confirmed angioedema attack. For all non-serious AEs that are reported as angioedema attacks, the investigator will review the event within 3 days of initial notification and, in accordance with BAARP, evaluate if it represented a confirmed angioedema 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 angioedema attacks will be recorded in the eCRF. Note: Non-histaminergic angioedema with normal C1-INH is the indication for treatment and should be considered subject to expedited reporting.

Emergency department visits for angioedema attacks and angioedema attacks resulting in hospital admissions will be captured in the eCRF and reported to the Takeda Global Patient Safety Evaluation (GPSE) Group.

8.3.5.3 Adverse Events of Special Interest (AESIs)

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

Hypersensitivity Reactions

As hypersensitivity reactions have been observed for monoclonal antibodies as a class, these events are considered AESIs 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.

8.3.5.4 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. 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.

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

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

8.3.5.5 Clinical Laboratory Tests

All clinical laboratory tests will be performed according to the laboratory's standard procedures. 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.

A complete list of the clinical laboratory tests to be performed is provided in Appendix 2.

8.3.5.6 Pregnancy Test

For all females of childbearing potential, pregnancy testing β-hCG will be performed at the time points specified in the Schedule of Activities in Table 1; if pregnancy is suspected or on withdrawal (early termination visit) of the subject from the study. All pregnancy testing in this study may be urine- or serum-based.

8.3.5.7 Electrocardiogram

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

8.3.6 Other Study Assessments

8.3.6.1 Clinical Pharmacology

Blood samples for the measurement of plasma lanadelumab concentration will be obtained at the study days specified in in Table 1. Samples should be obtained prior to dosing (ie, within 2 hours prior to dosing), with the exception of Day 4 and Day 182/ET visit. Residual sample may be used for exploratory biomarker analysis (see Section 8.3.6.4).

8.3.6.2 Pharmacodynamics

Blood samples for the measurement of cHMWK and pKal activity will be obtained at the study days specified in in Table 1. Samples should be obtained prior to dosing (ie, within 2 hours prior to dosing), with the exception of Day 4 and Day 182/ET visit. Residual sample may be used for exploratory biomarker analysis (see Section 8.3.6.4).

8.3.6.3 Immunogenicity (Antidrug 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 in Table 1. Samples should be obtained prior to dosing (ie, within 2 hours prior to dosing), with the exception of the Day 182/ET visit. Residual sample may be used for exploratory biomarker analysis (see Section 8.3.6.4).

8.3.6.4 Biomarkers

Exploratory Biomarkers

During the treatment period, residual aliquots of blood samples for PK, PD, and ADA assessments, which will be collected at the time points indicated in in Table 1, may also be tested for exploratory biomarkers of angioedema disease-state bioactivity (eg, pKal activity). The intent of this exploratory research is to aid in biomarker development, design and interpretation of clinical studies, exploration of guided treatment strategies, and to increase disease understanding.

Samples will be stored in biorepositories for up to 15 years. Any results of this exploratory research will be reported separately from the main clinical study report. Results may be used internally to help support the design of additional clinical studies, form part of scientific publication, or be made known to the regulatory authorities as part of a new drug application. The sponsor has no obligation to perform this additional exploratory research.

8.3.6.5 Health-related Quality of Life (QoL)

Health-related quality of life will be assessed using the AE-QoL questionnaire, with the assessments to occur at predose on the study visits specified in Table 1.

The AE-QoL questionnaire is a self-administered validated instrument to assess HR-QoL among patients with recurrent angioedema (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 minimal clinically important difference 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.

Further information concerning AE-QoL assessment included in the study is provided in Appendix 7.

8.3.6.6 Healthcare Resource Utilization

Not applicable.

8.3.6.7 Self-administration of Investigational Product

Self-administration of investigational product is allowed 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 in the antecedent study (SHP643-303) or in this study by the investigator or designee in the antecedent study (SHP643-303) or in this study and has demonstrated their understanding of self-administration. The subject is required to return to the site for visits as outlined in the Study Schedule of Activities (Table 1). At these on-site visits, the subject (or parent/caregiver) may continue to self-administer investigational product or may opt to have the product administered by study personnel or healthcare provider.

The investigator or designee will train subjects (and/or parents/caregivers) who elect to self-administer investigational product 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 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 investigational product 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 study treatment has occurred as scheduled. During this site check-in, the site will also solicit for any angioedema 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.

8.3.6.8 Injection Report

An injection report will be completed by the subject (or parent/caregiver) following each dose administration of investigational product, according to the assessment schedule in Table 1. The injection report will collect information on the subject's (or parent/caregiver) experience with SC injection of investigational product. Study personnel will document the subject's responses in the subjects' medical record and eCRF.

8.3.7 Volume of Blood to Be Drawn from Each Subject

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

Laboratory testing includes general safety parameters (hematology, serum chemistry, coagulation, and urinalysis), serology, pregnancy tests, PK, PD, 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), PK, ADA, and PD. Subjects will be in a seated or supine position during blood collection.

As shown in Table 3, during this study it is expected that approximately 109 mL of blood will be drawn from all subjects as specified in Table 1, regardless of age or sex. 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 109 mL. When more than one 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 3 Volume of Blood to Be Drawn from Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic		5	4	20
Pharmacodynamic		2.7	4	10.8
Antidrug antibody		5	4	20
Safety	Clinical Chemistry	5	6	30
	Hematology and Coagulation	4.7	6	28.2
Total mL		22.4	24[a]	**109**

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

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 109 mL regardless of sex. 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.

8.3.8 Blood Sample Collection, Storage, and Shipping

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

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Process

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

For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, SD, minimum, and maximum values will be presented. Where applicable, estimates from statistical model of least squares means, standard errors, and 95% confidence intervals for least squares means will be provided. Plots of the supporting data detailing each subject's contribution to the analysis will be provided.

The Statistical Analysis Plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy 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, North Carolina, USA).

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

No interim analysis, adaptive design, or data monitoring committee (DMC) is planned for this study.

9.3 Sample Size and Power Considerations

No formal sample size calculation was performed. The sample size is not based on any statistical considerations. This study is designed to evaluate the safety and efficacy of open-label treatment with lanadelumab in subjects with normal C1-INH angioedema who participated in Study SHP643-303.**Statistical Analysis Set(s)**

9.4.1 Safety Population

The Safety Population will include all subjects who received any study drug after entering Study TAK-743-3001 (ie, any exposure to open-label lanadelumab). Unless otherwise specified, summary tabulations conducted in the Safety Population will be presented by the subject's SHP643-303 treatment group (placebo or lanadelumab 300 mg q2wks) and overall.

9.4.2 Reduced-Dose Safety Population

The Reduced-Dose Safety Population is a subset of the Safety Population and includes subjects who switched from lanadelumab 300 mg q2wks to a lanadelumab 300 mg q4wks dosing regimen during the TAK743-3001 study. The TAK-743-3001 treatment period for this analysis population will be partitioned by dosing regimen, such that the safety and efficacy data can be appropriately attributed to each dosing regimen. Unless otherwise specified, summary tabulations conducted on the Reduced-Dose Safety Population will be presented by dosing regimen (lanadelumab 300 mg q2wks and lanadelumab 300 mg q4wks).

9.4.3 Pharmacokinetic Population

The pharmacokinetic population will include all subjects in the safety population who have at least 1 evaluable postdose PK concentration value.

9.4.4 Pharmacodynamic Population

The pharmacodynamic population will include all subjects in the safety population who have at least 1 evaluable postdose PD concentration value.

9.5 Efficacy Analyses

9.5.1 Primary Efficacy Analysis

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

9.5.2 Secondary Efficacy Analysis

Efficacy analyses will be performed using the Safety Population and the Reduced-Dose Safety Population.

Number of Investigator-confirmed Angioedema Attacks

The number of investigator-confirmed angioedema attacks during the treatment period (Day 0 through Day 182) expressed as a monthly angioedema attack rate will be analyzed.

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

The baseline investigator-confirmed angioedema attack rate will be calculated for each subject as the number of investigator-confirmed angioedema attacks occurring during the baseline observation period during Study SHP643-303 divided by the number of days the subject contributed to the baseline observation period, multiplied by 28 days.

The baseline, treatment period, and treatment period change from baseline in the investigator-confirmed angioedema attack rate will be summarized for each analysis population. The summary will include the total number of investigator-confirmed angioedema attacks

reported during the treatment period and subject-time in months that each subject contributed to the treatment period. Figures will be created for each analysis population plotting the on-study investigator-confirmed angioedema attacks reported during the treatment period relative to Day 0 for each subject.

In addition, the number of investigator-confirmed angioedema attacks per month (defined as 28 days) will be summarized descriptively by month (per 28-day interval) for each analysis population. The summary will include the number, change from baseline, and percent change from baseline of investigator-confirmed angioedema attacks. Investigator-confirmed angioedema attacks will be grouped into 28-day intervals using the start date of the angioedema 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 27 days. Each successive interval will start the last day of the prior interval plus 1 day and end 28 days later.

Similar summary tables will be presented for the following efficacy endpoints:

- Number of moderate or severe investigator-confirmed angioedema attacks during the treatment period.
- Number of high-morbidity investigator-confirmed angioedema attacks during the treatment period; a high-morbidity angioedema attack is defined as any attack that has at least one of the following characteristics: severe in intensity, results in hospitalization (except hospitalization for observation <24 hours), hemodynamically significant (systolic blood pressure <90, requires intravenous (IV) hydration, or associated with syncope or near-syncope) or laryngeal.

9.5.3 Multiplicity Adjustment

No multiplicity adjustment will be performed for this study. Any statistical testing will be considered exploratory.

9.5.4 Control of Type I Error

No control of Type I error will be performed. Any statistical testing will be considered exploratory.

9.5.5 Exploratory Efficacy Endpoints

A discussion of exploratory efficacy endpoints is provided in the SAP.

9.6 Safety Analyses

All safety analyses will be performed separately on the Safety Population and Reduced-Dose Safety Population. If not otherwise specified, the treatment period for the Reduced-Dose Safety Population is defined as the time interval during which a subject receives lanadelumab 300 mg every 4 weeks dosing regimen.

9.6.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Separate summaries will be presented for each analysis population.

Treatment-emergent AEs are defined as AEs with onset at the time of or following the first exposure to open-label 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 parts 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 TEAEs; 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 open-label 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 to the Day 182 visit).
- Follow-up Period: AEs will include all AEs starting at or after the subject's last visit date of the treatment period in this study (AEs starting after the Day 182 visit).

For AEs with partial onset times, non-missing date parts will be used to determine if the AE falls within the period. If a determination cannot be made using the non-missing date parts as to if the AE falls within the period, the AE will be conservatively counted as a treatment-period AE.

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 system organ class (SOC), and preferred term (PT) for each analysis period. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, related severe AEs, and investigator-reported AESIs for treatment period and follow-up period.

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

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

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

9.6.2 Laboratory Test Results

Baseline is defined as the last non-missing value prior to the first exposure to lanadelumab, ie, baseline is the last non-missing value prior to first exposure to study drug in Study SHP643-303.

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

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, non-clinically significant result less than the lower limit of normal, within the normal range, non-clinically significant result more than the upper limit of normal, and clinically significant result more than the upper limit of normal 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.

9.6.3 Vital Signs

Baseline is defined as the last non-missing value prior to the first exposure to lanadelumab, ie, baseline is the last non-missing value prior to first exposure to study drug in Study SHP643-303.

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 a 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.

9.6.4 Electrocardiography

The number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECG results, or ECG not performed, will be summarized by study visit. Subjects with clinically significant ECG results will be listed. This listing will include all results for a subject across study time points to identify any trends.

9.7 Other Analyses

If not otherwise specified, all other analyses will be performed separately on the Safety Population and Reduced-Dose Safety Population. Additional analyses of PK, PD, biomarker data, and potential effect of ADA on PK, PD and biomarkers will be described in a separate PK/PD report. Additional analysis of QoL data will be described in a separate QoL report.

9.7.1 Analysis of Pharmacokinetic Data

Pharmacokinetic analyses will be performed using the Pharmacokinetic Population. Plasma concentration of lanadelumab will be summarized by nominal PK sampling time.

9.7.2 Analysis of Pharmacodynamic Data

Pharmacodynamic analyses will be performed using the Pharmacodynamic Population. Plasma kallikrein activity will be summarized by nominal PD sampling time.

9.7.3 Analysis of Biomarker Data

Additional biomarkers will be summarized by nominal sampling time.

9.7.4 Analysis of Immunogenicity Data

Blood samples will be collected and tested for the presence of ADA. Endpoint titers and assessment of in vitro neutralization will be reported for samples testing positive. The number and percentage of negative, positive, and/or with neutralizing antibodies antibody samples will be reported and will be summarized by study visit and overall.

9.7.5 Health-related Quality of Life Analyses

The HR-QoL total score and domain scores will be summarized using descriptive statistics by scheduled visit. A change in scores from baseline (Day 0 of Study TAK-743-3001) will be summarized. A change in scores from baseline on Day 0 of Study SHP-643-03 will be summarized.

9.7.6 Analysis of Experience with Study Drug Self-administration

For the Safety Population, the responses to each item of the self-administration and subcutaneous injection survey will be tabulated by study visit.

The number and percentage of subjects who performed study drug administration via study staff administration in-clinic, self-administration in-clinic, and self-administration at home will be tabulated by study visit.

The number and percentage of subjects with >80% self-administration, with >80% administration by study staff in-clinic, or subjects with <80% self-administration and <80% administration by study staff in-clinic will be tabulated for the Safety Population.

The number and percentage of study drug administration with a duration of 0 seconds to 10 seconds, 11 seconds to 20 seconds, 21 seconds to 30 seconds, 31 seconds to 60 seconds, greater than 1 minute to less than or equal to 2 minutes, greater than 1 minute to less than or equal to 3 minutes, greater than 3 minutes to less than or equal to 4 minutes, greater than 4 minutes to less than or equal to 5 minutes, and greater than 5 minutes will be summarized for the doses that was self-administered at home, self-administered in-clinic, administered by the study staff in-clinic, and overall.

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APPENDIX 1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Appendix 1.1 Regulatory and Ethical Considerations

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

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

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

Appendix 1.2 Sponsor's Responsibilities

Good Clinical Practice Compliance

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

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

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

Indemnity/Liability and Insurance

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

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

Public Posting of Study Information

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

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

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

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

Study Suspension, Termination, and Completion

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

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

Appendix 1.3 Investigator's Responsibilities

Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP E6 R2 (2016), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

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

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

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

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

Protocol Adherence and Investigator Agreement

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

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

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

Documentation and Retention of Records

Case Report Forms

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

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

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

The clinical research associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan and the CRF completion guidelines. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

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

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

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

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

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

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

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

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

Audit/Inspection

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

Financial Disclosure

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

Appendix 1.4 Data Management Considerations

Data Collection

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

Data Management

Data are to be entered into a clinical database as specified in the CRF completion guidelines for the study, or similar. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

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

Appendix 1.5 Ethical Considerations

Informed Consent

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

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

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

Institutional Review Board or Ethics Committee

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

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

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Investigational product supplies will not be released until the CRO has received written IRB/EC approval.

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

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

Privacy and Confidentiality

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

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

After subjects have consented to take part in the study, the sponsor and/or its representatives review their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market lanadelumab; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected, if permitted under local laws governing privacy.

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

Study Results/Publication Policy

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

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

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

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

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

APPENDIX 2 CLINICAL LABORATORY TESTS

The following clinical laboratory assessments will be performed as mentioned in Section 8.3.5.5. See Section 8.3.7 for volume of blood to be drawn.

Chemistry

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

Hematology

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

Coagulation

- Prothrombin time
- aPTT
- International normalized ratio (INR)

Urinalysis

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

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

Appendix 3.1 Adverse Event Definitions

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

Treatment-emergent Adverse Event

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

Serious Adverse Event

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

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

- Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

Unexpected Adverse Event

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

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

Suspected Unexpected Serious Adverse Reaction

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

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

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

Symptoms of the Disease under Study

As discussed in Section 8.3.5.2 of this protocol, angioedema attacks will be captured as AEs in this study and will be evaluated in accordance with BAARP (Appendix 4).

Clinical Laboratory and Other Safety Assessment

A change in the value of a clinical laboratory parameter, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of investigational product, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the investigational product, and the range of variation of the respective parameter within its reference range, should also be considered.

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

When laboratory abnormalities are considered to be AEs, the severity of these AEs will be assessed according to the DMID Adult Toxicity Table (Appendix 5) and DMID Pediatric Toxicity Table (Appendix 6).

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

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

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

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

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

Appendix 3.2 Collection of Adverse Events

All AEs/SAEs are collected from the time the informed consent document is signed until the defined follow-up period stated in Section 8.2.2.5. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered.

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

Appendix 3.3 Assessment of Adverse Events

Severity Categorization

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

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

In this study, the severity of all AEs will be assessed according to the DMID Adult Toxicity Table (Appendix 5) and DMID Pediatric Toxicity Table (Appendix 6). Angioedema attacks are also captured as AEs in this study; angioedema attacks assessed as described in BAARP (Appendix 4), which includes an assessment using BAARP criteria and an assessment using DMID criteria.

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

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

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

Relationship Categorization

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

The following additional guidance may be helpful:

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

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

Related: Factors consistent with an assessment of Related include:

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

Outcome Categorization

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

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

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

Appendix 3.4 Safety Reporting

Reference Safety Information

The RSI for this study is the latest version of the lanadelumab IB, which the sponsor has provided under separate cover to all investigators.

Reporting Procedures

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

The investigator must complete, sign, and date the Takeda Safety Report Form, verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested), and fax or e-mail the form to the Takeda GPSE Group. A copy of the Takeda Safety Report Form (and any applicable follow-up reports) must also be sent to the CRO/Takeda medical monitor using the details specified in the emergency contact information section of the protocol.

Appendix 3.5 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to investigational product) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 8.2.2.5 and must be reported to the Takeda GPSE Group and the CRO/Takeda medical monitor within 24 hours of the first awareness of the event.

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

Appendix 3.6 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

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

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

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

Appendix 3.7 Fatal Outcome

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

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

Appendix 3.8 Pregnancy

All pregnancies are reported from the time informed consent is signed until the defined follow-up period stated in Section 8.2.2.5.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Takeda GPSE Group using the Takeda Pregnancy Report Form. A copy of the Takeda Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Takeda medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

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

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion or congenital abnormality are considered SAEs and must be reported using the Takeda Safety Report Form.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Takeda Safety Report Form as well as the Takeda Pregnancy Report Form. The test date of the first positive serum/urine β-hCG test or ultrasound result will determine the pregnancy onset date.

Appendix 3.9 Abuse, Misuse, Overdose and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Appendix 3.1.

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

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

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)

- **Overdose** – Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed dose
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

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

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

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

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

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

Appendix 3.10 Urgent Safety Measures

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

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

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

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

The sponsor and the clinical CRO is responsible for notifying the relevant regulatory authorities of related, unexpected SAEs.

In addition, the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the TAK-743 program.

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

APPENDIX 4 NON-HISTAMINERGIC BRADYKININ-MEDIATED ANGIOEDEMA ATTACK ASSESSMENT AND REPORTING PROCEDURES (BAARP), VERSION 4.0

Title: Non-histaminergic Bradykinin-mediated Angioedema Attack Assessment and Reporting Procedures (BAARP)

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

Sponsor:

Dyax Corp., a Takeda company
300 Shire Way, Lexington, MA 02421 USA

Original (v1.0): 14 September 2015

Version 2.0: 29 June 2017

Version 3.0: 06 May 2019

Version 4.0: 07 August 2019

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LIST OF ABBREVIATIONS

AAE	acquired angioedema
AE	adverse event
BAARP	Non-histaminergic Bradykinin-mediation Angioedema Attack Assessment and Reporting Procedures
C1-INH	C1 inhibitor
eCRF	electronic case report form
HAE	hereditary angioedema
SAE	serious adverse event

1. PURPOSE

This document applies to clinical trials that involve investigator adjudication/assessment of non-histaminergic bradykinin-mediated angioedema attacks that occur with hereditary angioedema (HAE) with C1 inhibitor (C1-INH) deficiency, normal C1-INH angioedema, and acquired angioedema (AAE) due to C1-INH deficiency. The purpose of this document is to provide a definition of non-histaminergic bradykinin-mediated angioedema attacks (subsequently simplified to "angioedema attacks") and to define a standardized set of procedures for the subject (or parent/caregiver) reporting and investigator assessment of events reported by subjects to determine whether those events meet the criteria of an angioedema attack as defined in this document.

2. DEFINITION OF AN ANGIOEDEMA ATTACK

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

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

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

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

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

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

Prodromal symptoms by themselves are not considered an attack.

Subject- (or parent/caregiver-) reported use of an acute treatment for an attack by itself is not confirmation that the attack meets the protocol-defined criteria of an angioedema attack.

3. REPORTING AND ASSESSMENT OF ANGIOEDEMA ATTACK DATA

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

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

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

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

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

3.1 Subject (or Parent/Caregiver) Reported Symptoms

Subjects (or parents/caregivers) will use the sponsor-provided Daily Angioedema Attack Diary. On days a subject experiences an attack, additional information will be captured in the Angioedema Attack Worksheet that is part of the diary. Subjects (or parents/caregivers) will contact the study site as soon as possible, but no later than 72 hours (3 full days) after the first symptoms appear, to report the information. The study site will utilize the sponsor-provided Angioedema Attack Source Worksheet to document the reported attack.

3.1.1 Angioedema Attack Information

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

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

- Impact on activity and whether any assistance or medical intervention was required, including hospitalizations or emergency department visits
- Name, date, and time of administration of any medications used to treat the attack, including both acute therapies and other medications. **NOTE**: During the observation period (as described in the study protocol), if icatibant is administered to treat the attack, the date and time of initial symptom improvement with icatibant treatment should be recorded.
- If the attack resolved, date and time the subject was no longer experiencing symptoms
- Any other pertinent information related to the attack

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

3.1.2 Worsening Symptoms

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

3.1.3 Subject Training

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

3.1.4 Reporting Multiple Angioedema Attacks

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

3.1.5 Subject (or Parent/Caregiver) Contact with Sites

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

3.2 Site Contact with the Subject

Sites will establish a recommended day and time window for check-in calls between study visits, as outlined in the study protocol. The site needs to review the subject's Daily Angioedema Attack Diary to ensure all required information has been filled out. The date and time for check-ins can be modified based on when the last contact with the subject (or parent/caregiver) was made. When the site is contacted by a subject (or parent/caregiver) reporting symptoms of an attack, the site should make sure they have the ability to record the information provided in a complete and accurate way. Back-up plans should be established in case the subject (or parent/caregiver) misses a call from the site. A study schedule for each subject's on-site visits will be provided to the subject (or parent/caregiver) by the site.

3.2.1 Review, Documenting, and Assessing a Reported Angioedema Attack

During contact with the subject (or parent/caregiver), whether initiated by the subject (or parent/caregiver) or at a regular check-in, site personnel should ask the subject (or parent/caregiver) to provide them information about new or ongoing angioedema attacks experienced by the subject, review the subject's Daily Angioedema Attack Diary, and ensure information in the Diary is accurate.

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

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

- Date and time of contact with the subject (or parent/caregiver)
- Date and time the subject first experienced symptoms
- Description of symptoms experienced, including location(s)
- Description of any attack triggers
- Impact on daily activity and whether any assistance was required
- If the attack has resolved or is ongoing. If the attack has resolved, the date and time the subject was no longer experiencing any symptoms of the attack.
- Name, date, and time of administration of any medications used to treat the attack including acute therapy or other non-angioedema attack treatments. **NOTE**: During the observation period, if icatibant is administered to treat the attack, the date and time of initial symptom improvement with icatibant treatment should be recorded.
- If hospitalization occurred
- If a trip to the emergency department occurred

Additional probing questions about what the subject experienced to determine:

- If the subject only experienced prodromal symptoms
- If the subject experienced anything different than their typical attack

- If there were any possible alternative etiologies of the symptoms. For example, a viral gastroenteritis outbreak in the household could explain abdominal symptoms

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

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

The site will also document the date and time of investigator or designee review, the official designation of the event as an attack or not, and if applicable, the reason why an event is not considered an angioedema attack. Any subject-reported (or parent/caregiver-reported) attack not confirmed by the investigator must have an alternate adverse event (AE) diagnosis reported.

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

3.2.2 Site Training

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

- Review information reported in the Daily Angioedema Attack Diary
- Definition of an angioedema attack
- Requirements of subjects (or parents/caretakers) for reporting attacks
- Reporting worsening symptoms and multiple attacks
- Information to be collected from subjects (or parents/caregivers) as well as the additional probing questions to gather context for the attack information provided
- Assessment of attack severity
- Entry of the attack data into the eCRF
- Reporting angioedema attacks as AEs
- Requirements for investigator assessment of attacks

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

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

3.3 Angioedema Attacks as Adverse Events

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

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

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

For all non-serious AEs that are reported as angioedema attacks, the principal investigator or physician designee will review the event within 3 days of initial notification and, in accordance with BAARP, evaluate if it represented a confirmed angioedema attack. If necessary for the evaluation, the investigator or designee may contact the subject for additional information. Any subject-reported attack not confirmed by the investigator must have an alternate AE diagnosis recorded in the source documents and eCRF. All subject-reported and investigator-confirmed angioedema attacks will also be recorded in the source documents and the study's database.

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

4. INVESTIGATOR ATTACK ASSESSMENT

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

Assessors must be experienced with non-histaminergic bradykinin-mediated angioedema and familiar with the study subject's disease history.

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

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

APPENDIX 5 NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLES (US NATIONAL INSTITUTES OF HEALTH; NATIONAL INSTITUTE OF ALLERGY AND INFECTION DISEASES)

NOVEMBER 2007
DRAFT

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

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

- The population being studied
  - Does the clinical trial evaluate healthy subjects, subjects with a particular disease or condition?
- The stage of test article development
  - Is the clinical trial a Phase I, II, III or IV?
- The type of test article
  - Does the clinical trial evaluate a drug, device, vaccine or other biologic agent?
- The prior human and preclinical experience with the test article
  - Are there any specific findings that require adjustment of the toxicity table?

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

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

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

ABBREVIATIONS: Abbreviations utilized in the Table:

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

ESTIMATING SEVERITY GRADE

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

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

SERIOUS OR LIFE-THREATENING AEs

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

COMMENTS REGARDING THE USE OF THESE TABLES

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

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/mm^3	13,000-15,000 /mm^3	15,000-30,000/mm^3	>30,000 or <1,000 /mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	---
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ---	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

CHEMISTRIES (continued)

	Grade 1	Grade 2	Grade 3	Grade 4
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP; No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

RESPIRATORY				
	Grade 1	Grade 2	Grade 3	Grade 4
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

MUSCULOSKELATEL				
	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint distruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

SKIN				
	Grade 1	Grade 2	Grade 3	Grade 4
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC				
	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25-50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

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

NOVEMBER 2007
DRAFT

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

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

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

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

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

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

ABBREVIATIONS: Abbreviations utilized in the Table:

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

ESTIMATING SEVERITY GRADE

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

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

SERIOUS OR LIFE-THREATENING AEs

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

COMMENTS REGARDING THE USE OF THESE TABLES

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

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

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

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

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

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

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

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

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

(Greater than 3 months of age)

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

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

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

(Greater than 3 months of age)

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

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

(Greater than 3 months of age)

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

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

(Greater than 3 months of age)

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

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

(Greater than 3 months of age)

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

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

	cells/hpf	cells/hpf		

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

(Greater than 3 months of age)

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

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

(Greater than 3 months of age)

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

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

(Greater than 3 months of age)

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

APPENDIX 7 SCALES AND ASSESSMENTS

The following scales/assessments will be utilized in this study:

Full Title of Scale/Assessment	Version Number	Date Issued
Angioedema quality of life (AE-QoL) questionnaire	Version 2010	2012

A separate master file containing each scale/assessment listed above will be provided to the site. Updates to scales/assessments during the study (if applicable) will be documented in the table above and a new master file containing the revised scale/assessment will be provided to the site.

APPENDIX 8 ABBREVIATIONS

Abbreviation	Definition
AAE	acquired angioedema
ADA	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
AE-QoL	angioedema quality of life (questionnaire)
ALT	alanine aminotransferase (synonymous with SGPT)
ANGPT1	angiopoietin-1 gene
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (synonymous with SGOT)
AUC	area under the plasma time-concentration curve
$AUC_{0-\infty}$	area under the plasma time-concentration curve from time 0 to infinity
AUC_{0-last}	area under the plasma time-concentration curve from time 0 to the time of last concentration measured
BAARP	Non-histaminergic Bradykinin-mediated Angioedema Attack Assessment and Reporting Procedures
β-hCG	beta-human chorionic gonadotropin
B19V	parvovirus B19
BP	blood pressure
BMA	bradykinin-mediated angioedema
BUN	blood urea nitrogen
C1-INH	C1 inhibitor or C1 esterase inhibitor
CFR	Code of Federal Regulations
cHMWK	cleaved high molecular weight kininogen
C_{max}	maximum observed concentration
CPK	Creatine phosphokinase
CRF	case report form
CRA	clinical research associate
CRO	contract research organization
DMC	data monitoring committee
DMID	Division of Microbiology and Infectious Diseases

Abbreviation	Definition
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EOS	end of study
ePPND	enhanced pre-and post-natal development
ET	early termination
FDA	Food and Drug Administration
FXII	coagulation factor XII
GCP	Good Clinical Practice
HAE	hereditary angioedema
HIPAA	Health Insurance Portability and Accountability Act
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HMWK	high molecular weight kininogen
HR	heart rate
HR-QoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFU	Instructions for Use
IMP	investigational medicinal product
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
ISR	injection site reaction
IUD	intrauterine device
IUS	intrauterine hormone-releasing systems

Abbreviation	Definition
KNG1	kininogen gene
LTP	long-term prophylaxis
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
PFS	prefilled syringe
PD	Pharmacodynamic(s)
PK	pharmacokinetic(s)
pKal	plasma kallikrein
PLG	plasminogen gene
PT	preferred term
q2wks	every 2 weeks
q4wks	every 4 weeks
QoL	quality of life
RBC	red blood cell
REB	research ethics board
RR	respiratory rate
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SMQ	Standard MedDRA Queries
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
t_{max}	time to maximum concentration
ULN	upper limit of normal
UK	United Kingdom
US	United States

Abbreviation	Definition
WBC	white blood cell

APPENDIX 9 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	20 January 2020	Global
Amendment 1	14 September 2020	Global