Clinical Study Protocol

NCT Number: NCT04206605

Title: 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)

Study Number: SHP643-303

Document Version and Date: Protocol Amendment 3 (19-April-2021)

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

A summary of changes to previous protocol versions is appended to the end of the document.

PROTOCOL: SHP643-303

TITLE:	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)
SHORT TITLE:	Efficacy and Safety of Lanadelumab for Prevention Against Acute Attacks of Non-histaminergic Angioedema with Normal C1-Inhibitor (C1-INH)
STUDY PHASE:	Phase 3
DRUG:	Lanadelumab; TAK-743 (formerly SHP643, DX-2930)
IND NUMBER:	116647
EUDRACT NUMBER:	2019-001703-20
SPONSOR:	Takeda Development Center Americas, Inc. (TDCA) 95 Hayden Avenue, Lexington, MA 02421 USA 617-349-0200
PRINCIPAL/ COORDINATING INVESTIGATOR:	Multicenter study
PROTOCOL HISTORY:	Original Protocol (Global): 07 Aug 2019 Amendment 1 (VHP): 28 Apr 2020 Amendment 1.1 (All Regions except VHP): 14 May 2020 Amendment 2 (Global): 18 Aug 2020 Amendment 3 (Global): 19 April 2021

PROTOCOL SIGNATURE PAGE

Sponsor's (Takeda) Approval

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

Investigator's Acknowledgement

I have read this protocol for Study SHP643-303.

Title: 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)

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). A copy of this form must also be sent to the contract research organization (CRO)/Takeda medical monitor using the details below.

Fax number: +1-484-595-8155

E-mail: drugsafety@shire.com

For protocol- or safety-related questions or concerns during or outside of normal business hours the investigator must contact the IQVIA medical monitor. Contact details are available via the study specific contact list.

SUMMARY OF CHANGES FROM PREVIOUS VERSION

A summary of the changes incorporated into Amendment 3 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 Centers Americas, Inc. (TDCA) / Takeda	Cover Page Protocol Signature Page Product Quality Complaints Section 6.4 Appendix 1.5 Appendix 3.5
Removed IQVIA medical monitor contact information and added reference to the study specific contact list. The contact list contains the most accurate and up-to-date contact information.	Emergency Contact Information
The email address for reporting product quality complaints was updated to: ctmcomplaint@takeda.com	Product Quality Complaints
Revised to include appropriate Takeda forms for reporting adverse events (AEs) and pregnancy.	Emergency Contact Information Appendix 3.4 Appendix 3.8
Revised footnote to clarify that subjects <18 years of age will only be enrolled if allowed based on local site and / or country regulations.	Section 1.1 Section 4.1
Revised inclusion criterion #3 to clarify that subjects with C4 level not below the normal range should be enrolled.	Section 1.1 Section 5.1
Revised footnote f for Table 1 (Table 1 Schedule of Activities - Screening and Observation Period) to clarify that an additional confirmatory test may be performed during the observation period if C1-INH therapy washout was not completed during the screening period.	Section 1.3

Revised footnote g for Table 1 (Table 1 Schedule of Activities - Screening and Observation Period) to clarify that the 2-week washout period will be completed in the screening period only for subjects where it is deemed safe to complete.	Section 1.3
An "X" for site check-in call that was inadvertently missing at Visit 2 (Table 2 Schedule of Activities – Treatment Period) was added to align with Section 8.2.2.2 of the protocol.	Section 1.3
Revised Study DX-2930-04 from "ongoing" to "completed."	Section 2.6
Timeframe for male contraception was revised to align with female contraception (for the duration of the study and 70 days after the last dose of investigational product).	Section 5.4.2
Specific quantitative stopping criteria, particularly in regard to liver values was added.	Section 7.5.2
Added language to clarify that sample collection for genotype testing during the screening period is required; an additional sample for exploratory genetic analyses is optional.	Section 8.3.6.5

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 a product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product quality complaints include, but are not limited to, the following:

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

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

ctmcomplaint@takeda.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: SHP643-303	**Drug:** Lanadelumab
Title of the study: 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)	
Short title: Efficacy and Safety of Lanadelumab for Prevention Against Acute Attacks of Non-histaminergic Angioedema with Normal C1-Inhibitor (C1-INH)	
Study phase: Phase 3	
Number of subjects (total and per treatment arm): Approximately 75 subjects (male or female) aged 12 years[1] and above with non-histaminergic normal C1-INH angioedema will be randomized 2:1 to receive lanadelumab or placebo.	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 60 sites in North America (United States, Canada), Europe and Japan will participate.	
Study period (planned): Nov 2019 to Aug 2022	**Clinical phase:** 3
Objectives: **Primary:** To evaluate the efficacy of repeated subcutaneous (SC) administrations of lanadelumab in preventing angioedema attacks in adolescents (12 to <18 years of age) and adults with non-histaminergic angioedema with normal C1-INH. **Secondary:** • To evaluate the safety of repeated SC administrations of lanadelumab in preventing angioedema attacks in adolescents and adults with normal C1-INH angioedema. • To evaluate the pharmacokinetics (PK) of repeated SC administrations of lanadelumab in preventing angioedema attacks in adolescents and adults with normal C1-INH angioedema. • To evaluate the pharmacodynamics (PD) of repeated SC administrations of lanadelumab in preventing angioedema attacks in adolescents and adults with normal C1-INH. • To evaluate the immunogenicity of repeated SC administrations of lanadelumab in preventing angioedema attacks in adolescents and adults with normal C1-INH angioedema. • To evaluate the effect of lanadelumab on health-related quality of life (HR-QoL) assessments in adolescents and adults with normal C1-INH angioedema. **Exploratory:** • To evaluate the effect of lanadelumab on exploratory biomarker(s) of angioedema disease-state bioactivity in adolescents and adults with normal C1-INH angioedema.	
Rationale: Based on the mechanism of action and past case studies with icatibant (FIRAZYR®) (Bouillet et al., 2009; Wirth et al., 1991; Boccon-Gibod and Bouillet, 2012; Bouillet et al., 2017; Zanichelli et al., 2017; Cicardi and Zanichelli, 2010; Zanichelli et al., 2012; Regoli et al., 1998) and ecallantide (KALBITOR®) (Bhoola et al., 1992; Markland et	

[1] Enrollment of non-histaminergic normal C1-INH patients <18 years of age will be allowed based on local site and / or country regulations.

al., 1996; Cicardi and Zanichelli, 2010), there are strong scientific rationale and high unmet medical need to expand the use of lanadelumab as a prophylactic therapy for patients with likely bradykinin-mediated angioedema other than Type I/II HAE. The study aims to evaluate the efficacy and safety of lanadelumab for the prevention of angioedema attacks in subjects with non-histaminergic angioedema with normal C1-INH.

Investigational product, dose, and mode of administration:

Subjects who enter the blinded treatment period will receive SC administration lanadelumab 300 mg or placebo every 2 weeks (q2wks) for 26 weeks.

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.

The placebo product consists of the inactive formulation of the drug product. Placebo will be provided in a PFS and is filled to deliver a nominal volume of 2.0 mL subcutaneously.

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 and has demonstrated their understanding of self-administration.

Methodology:

This study targets to enroll approximately 75 subjects (12 years of age and above) with normal C1-INH angioedema. All enrolled subjects (who have signed informed consent form) must have an investigator-confirmed diagnosis of non-histaminergic angioedema with normal C1-INH at screening. Screened subjects who have been on any long-term prophylaxis (LTP) (eg, C1-INH, androgens, or anti-fibrinolytics), are required to undergo a minimum 2-week washout period prior to the observation period. This LTP washout period is permitted as long as the investigator determines that doing so would not place the subject at any undue safety risk, and that the subject is at least 18 years of age. During the observation period, all subjects must discontinue LTP. The attack rate in the observation period will serve as the baseline for this study. Subjects with any exposure to prophylactic plasma kallikrein (pKal) inhibitors prior to screening will be excluded from the study.

Enrolled subjects meeting all eligibility criteria at screening will enter an observation period of up to 8 weeks to determine the baseline angioedema attack rate and confirm their eligibility. Subjects meeting a minimum baseline angioedema attack rate of at least 1 investigator-confirmed angioedema attack per 4 weeks during the observation period may be allowed to exit the observation period at 4 weeks for randomization and will enter the treatment period. In addition, during the observation period, subjects (≥18 years of age) need to be treated with icatibant for at least 2 angioedema attacks or at least 1 moderate or severe attack. In the opinion of the investigator, subjects with no response to icatibant for acute angioedema attacks in the past medical history/screening, or no improvement or worsened attack severity 2 hours after icatibant treatment during the observation period (based on totality of assessments), will not be eligible. Subjects without at least 1 investigator-confirmed attack in the first 4 weeks may have their observation period extended for another 4 weeks. Subjects who have their observation period extended must complete the full 8-week observation period and must have at least 2 investigator-confirmed attacks during this time to be eligible to enter treatment period.

Subjects who do not meet the minimum attack rate during the observation period will be considered screen failures; subjects who screen fail will not be allowed to rescreen for the study.

After verification of eligibility in the observation period, subjects will be randomized 2:1 to receive repeated SC administrations of lanadelumab or placebo in a double-blind fashion.

Randomization will be stratified by baseline angioedema attack rate (1 to <2 attacks/4 weeks, and ≥2 attacks/4 weeks) and by subtype: 1) with known mutations (coagulation factor 12 [FXII], plasminogen [PLG], angiopoietin-1 [ANGPT1], or kininogen 1 [KNG1], genes associated with normal C1-INH angioedema); 2) with family history (a first-degree relative) and unknown mutations; and 3) with idiopathic non-histaminergic angioedema (INHA).

Acute angioedema attacks during the observation period and the treatment period will be managed with icatibant. Therefore, subjects ≥18 years of age need to be willing to be tested for their response to icatibant treatment for angioedema attacks that occur during the observation period. For subjects 12 to <18 years of age, standard of care therapy per local protocols should be provided.

Subjects may roll over into a 26-week long open-label extension (OLE) study (Study TAK-743-3001) upon completion of all assessments scheduled on Day 182. Those subjects who choose to roll over will provide consent no later than the last day of blinded treatment period (Day 182) and will be discharged from Study SHP643-303 after completion of all assessments on Day 182. Subjects who choose not to roll over to the OLE will continue to the planned 2 weeks of safety follow-up at the completion of all study assessments scheduled on Day 182.

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 for subjects with non-histaminergic normal C1-INH angioedema at the time of signing of the informed consent form (ICF).
2. Documented clinical history of recurrent attacks of angioedema in the absence of wheals/urticaria.
3. Investigator-confirmed diagnosis of non-histaminergic bradykinin-mediated angioedema with normal C1-INH as documented by a history of angioedema attack(s) at screening and occurrence of attacks during the observation period:
   - History of recurrent angioedema with at least an average of 1 angioedema attack per 4 weeks prior to screening and this attack rate must be confirmed during the observation period while treated with chronic high-dose antihistamine (cetirizine 40 mg/day or equivalent high-dose second-generation antihistamine medication).
   - Diagnostic testing results obtained during screening from a sponsor-approved central laboratory that confirm C1-INH function ≥50% of normal and C4 level not below the normal range. With prior sponsor approval, subjects may be retested during the observation period if results are incongruent with clinical history.
   - Clinical history of not responding to high-dose antihistamine treatment (cetirizine 40 mg/day or equivalent high-dose second-generation antihistamine medication), which must be confirmed during the observation period with at least 1 angioedema attack per 4 weeks with chronic high-dose antihistamine treatment and no significant difference (as assessed by the investigator and in consultation with the sponsor's medical monitor, as necessary) from the historic attack rate without high-dose antihistamine treatment.
4. Agree to adhere to the protocol-defined schedule of treatments, assessments, and procedures.
5. Subjects ≥18 years of age must be willing to use icatibant as the rescue medication during the observation and treatment period. During the observation period, subjects need to be treated with icatibant for at least 2 angioedema attacks or at least 1 moderate or severe attack. In the opinion of the investigator, subjects with no response to icatibant for acute angioedema attacks in the past medical history/screening, or no improvement or worsened attack severity 2 hours after icatibant treatment during the observation period (based on totality of assessments), will not be included. **Note:** For subjects 12 to <18 years of age, standard of care therapy per local protocols should be provided.
6. Males, or non-pregnant, non-lactating females who are of child-bearing potential and who agree to be abstinent[2] or agree to comply with the applicable contraceptive requirements of this protocol for the duration of the study. Female subjects of childbearing potential must have a negative serum pregnancy test at screening and must be willing to undergo pregnancy tests throughout the study. Females of non-childbearing potential are defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or

[2] Abstinence will be accepted as a highly effective method only if sexual abstinence is the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, symptothermal or post-ovulation), declaration of abstinence for the duration of exposure to IMP, or withdrawal (coitus interruptus) are not acceptable methods of contraception.

post-menopausal for at least 12 months.

7. 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).

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

   OR

   If the subject is a minor (ie, <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. Concomitant diagnosis of Type I or Type II HAE, or recurrent angioedema associated with urticaria.
2. Dosing with any investigational drug or exposure to an investigational device within 4 weeks prior to screening.
3. Exposure to angiotensin-converting enzyme (ACE) inhibitors or rituximab within 6 months prior to screening.
4. Use of any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
5. Response to omalizumab (prophylactic) or corticosteroid (acute/prophylactic) or epinephrine (acute) or anti-leukotrienes (prophylactic) treatments in the past.
6. Use of long-term prophylactic therapy for HAE, eg, C1-INH, attenuated androgens (eg, danazol, methyltestosterone, testosterone), or anti-fibrinolytics within 2 weeks prior to entering the observation period as long as the investigator determines that doing so would not place the subject at any undue safety risk, and that the subject is at least 18 years of age.
7. Any exposure to prophylactic plasma kallikrein inhibitors prior to screening.
8. Use of short-term prophylaxis for HAE within 7 days prior to entering the observation period. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.
9. Have any active infectious illness or fever defined as an oral temperature >38°C (100.4°F), tympanic >38.5°C (101.3°F), axillary >38°C (100.4°F), or rectal/core >38.5°C (101.3°F) within 24 hours prior to the first dose of study drug in the treatment period.
10. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) >3x upper limit of normal, or aspartate aminotransferase (AST) >3x upper limit of normal, or total bilirubin >2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome).
11. Pregnancy or breast feeding.
12 Subject has a known hypersensitivity to the investigational product or its components.
13. Have any uncontrolled underlying medical condition which would require treatment adjustment during the study treatment period that, in the opinion of the investigator or sponsor, may confound the results of the safety assessments or may place the subject at risk. Subjects with stable treatment for at least 3 months prior to screening and NOT expecting any change to their treatment regimen for 6 months during the study treatment period, will not be excluded.
14. 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:

- Planned duration of screening period: up to 8 weeks (including a 2-week LTP washout period, if applicable)
- Planned duration of baseline observation period: at least 4 weeks up to 8 weeks.
- Planned duration of treatment period: 26 weeks
- Planned duration of safety follow-up period: 2 weeks

Pharmacogenomic Sampling:

Blood samples will be collected (per local regulations and subject's consent) during the screening period and at predose on Day 0 for the purpose of 1) identifying genetic mutations to aid in subject stratification prior to randomization and 2) for future exploratory evaluation of genes or gene categories that may be associated with non-histaminergic angioedema with normal C1-INH disease susceptibility and drug action.

Statistical analysis:

The analysis sets are defined as:

- Treatment Period Full Analysis Set (FAS) will include all randomized subjects who receive any exposure to the investigational product during the treatment period. Subjects will be analyzed according to their randomized treatment assignment regardless of the treatment actually received.
- Steady State Period FAS will include all randomized subjects who receive any exposure to the investigational product during the steady state period. Subjects will be analyzed according to their randomized treatment assignment regardless of the treatment actually received.
- Safety Analysis Set (SAS) will include all subjects who receive any exposure to the investigational product. Subjects will be analyzed according to the treatment actually received regardless of randomized treatment assignment.
- Pharmacokinetic Set (PK Set) will include all subjects in the SAS who have at least 1 evaluable postdose PK concentration value.
- Pharmacodynamic Set (PD Set) will include all subjects in the SAS who have at least 1 evaluable postdose PD concentration value.

Efficacy Endpoints

Primary efficacy endpoint:

- Number of investigator-confirmed angioedema attacks during the treatment period (Day 0 through Day 182)

Rank-ordered Secondary Efficacy Endpoints:

1. Subjects that are attack-free during the treatment period (Day 0 through Day 182)
2. Number of investigator-confirmed moderate or severe angioedema attacks during the treatment period (Day 0 through Day 182)
3. Number of investigator-confirmed angioedema attacks during the presumed steady state period (Day 70 through Day 182)
4. Subjects that are attack-free during the presumed steady state period (Day 70 through Day 182)
5. Number of investigator-confirmed moderate or severe angioedema attacks during the presumed steady state period (Day 70 through Day 182)

Additional Secondary Efficacy Endpoints:

- Maximum attack severity during presumed steady state period (Day 70 through Day 182) and treatment period (Day 0 through Day 182)
- Time to first angioedema attack after Day 0
- Time to first angioedema attack after Day 70
- Achievement of at least a 50%, 70%, 90% and 100% reduction in the investigator-confirmed normalized number of attacks (NNA) per 4 weeks during each of the efficacy evaluation periods relative to the observation period

NNA

- Achievement of an efficacy evaluation period NNA <1.0 per 4 weeks during each of the efficacy evaluation periods

Subjects will use a diary to record the symptoms and occurrences of angioedema attacks according to the BAARP (non-histaminergic bradykinin-mediated angioedema attack assessment and recording procedures) criteria. An angioedema attack will be further reviewed and confirmed by the investigator. Any subject-reported or parent/caregiver-reported attack not confirmed by the investigator must have an alternate adverse event (AE) diagnosis reported.
There must be a full symptom-free calendar day or at least 24 hours preceding the onset of symptoms for an attack to be considered a new attack. Therefore,

- Attacks that progress from one site to another will be considered a single attack,
- Attacks that begin to regress and then worsen before complete resolution will be considered one attack, and
- Attacks that begin to appear to resolve, and then reappear without a symptom-free calendar day reported after the appearance of resolution will also be considered one attack.

NOTE: An angioedema attack does NOT include swelling due to trauma or symmetrical non-painful swelling of the lower extremities.

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

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

Safety Endpoints

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

Pharmacokinetic Endpoint

- Plasma concentrations of lanadelumab

Pharmacodynamic Endpoint

- Plasma cleaved high molecular weight kininogen (cHMWK) and pKal activity

Immunogenicity Endpoint

- Presence or absence of neutralizing or non-neutralizing antidrug antibodies (ADA) in plasma

Health Economics and Outcomes Research Endpoints

- Health-related quality of life will be measured using the angioedema quality of life (AE-QoL) questionnaire

Exploratory Endpoints

- Exploratory biomarker(s) of angioedema disease-state bioactivity

Statistical Methodology for Efficacy Endpoints

The primary efficacy endpoint, number of investigator-confirmed angioedema attacks during the treatment period (Day 0 through Day 182), will be compared between treatment group (lanadelumab versus placebo) using the Treatment Period FAS.

The primary efficacy endpoint will be analyzed using a generalized linear model for count data assuming a Poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential overdispersion. The model will include fixed effects for treatment group (categorical), normalized baseline attack rate (continuous), and stratification factor of subtype (categorical). The logarithm of time in days each subject was observed during the treatment period will be used as an offset variable in the model. From this model, the least squares mean rate and standard error for each treatment group as well as the mean rate ratios relative to the placebo

group and corresponding 95% confidence intervals will be estimated. These estimates will be reported as mean event rates per 4 weeks by transforming the estimates using the exponential function and scaling by the unit of time.

The primary endpoint will be tested by the following hypothesis:

H_0: $\lambda_{lanadelumab} / \lambda_{placebo} = 1$ versus H_1: $\lambda_{lanadelumab} / \lambda_{placebo} \neq 1$

Where $\lambda_{lanadelumab}$ refers to the mean investigator-confirmed angioedema attack rate in the lanadelumab group and $\lambda_{placebo}$ refers to the mean investigator-confirmed angioedema attack rate in the placebo group. The null hypothesis is that the mean investigator-confirmed angioedema attack rate ratio is 1 (no difference between treatment groups), versus the alternative hypothesis that the angioedema attack rate ratio is not 1. Estimated attack rate ratios less than 1 would indicate that subjects treated with lanadelumab, on average, have a lower incidence of investigator-confirmed angioedema attacks during the presumed steady-state treatment period. The hypothesis will be tested using the model-based least squares means estimate of the treatment difference (expressed as rate ratio relative to placebo) using a Wald-based chi-square test with Type I error set at 5%.

The rank-ordered secondary endpoints based on count data (ie, number of angioedema attacks during a specified period) will be analyzed using the same method as described for the primary efficacy endpoint with adjustments made to the offset term and analysis set based on the defined analysis period.

The rank-ordered secondary endpoints based on binary endpoints (ie, subjects that are attack-free during a specified analysis period) will be compared between treatment groups using the FAS specific to the analysis period of interests.

The number and percentage of subjects who are attack-free for the specified analysis period, as well as the difference between treatment arms and corresponding 95% confidence interval (CI) will be summarized. For subjects who discontinue the study prior to completion of the analysis period of interest, subjects will be classified as attack-free or not based on the observed contribution to the analysis period.

The rank-ordered binary endpoints will be tested by the following hypothesis:

H_0: $p_{lanadelumab} = p_{placebo}$ versus H_1: $p_{lanadelumab} \neq p_{placebo}$

Where $p_{lanadelumab}$ refers to the proportion of subjects that are attack-free during the specified analysis period in the lanadelumab group and $p_{placebo}$ refers to the proportion of subjects that are attack-free during the specified analysis period in the placebo group. The null hypothesis is that the proportion of attack-free subjects in the lanadelumab treatment group is equal to that in the placebo group, versus the alternative hypothesis that the proportions are not equal. A Cochran-Mantel-Haenszel (CMH) test, adjusting for baseline stratification factor(s) (categorical), will be used to test the null hypothesis, with Type I error set at 5%. A Mantel-Haenszel estimate for the common risk difference and corresponding stratified Newcombe confidence limits will be presented.

To adjust for the potential of inflated overall Type I error rate, the rank ordered secondary endpoints will be tested in a fixed sequence using a general gatekeeping approach consistent with the logical restrictions of the rank ordering of the endpoints. Secondary endpoints will not be declared statistically significant unless the primary endpoint is found to be statistically significant. Lower ranked secondary endpoints will not be declared statistically significant unless the primary and all of the higher ranked secondary endpoints are found to be statistically significant.

Statistical Methodology for Safety Endpoints

All safety analyses will be based on the SAS. Analyses will be summarized by treatment group.

Treatment-emergent AEs are defined as AEs with onset at the time of or following the start of treatment with study medication, 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. The number and percentage of subjects with TEAEs will be displayed for each treatment group by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries in terms of severity and relationship to study medication will also be provided. Related, serious, related serious AEs, and AESIs will be summarized separately in a similar fashion. Patient listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs, and AESIs will be produced.

Actual values and change from baseline in vital signs and clinical laboratory tests will be summarized by treatment

group with descriptive statistics at each assessment obtained.

Statistical Methodology for PK/PD Endpoints

No formal statistical hypothesis will be tested. Individual PK concentrations and PD levels will be provided in subject data listing(s) and tabularly summarized using descriptive statistics (number of subjects, arithmetic mean, standard deviation [SD], coefficient of variation, median, minimum, maximum, geometric mean, and coefficient of variation of geometric mean). Figures of individual and mean (±SD) concentration-time profiles of plasma lanadelumab and time-course of PD will be generated.

A population PK/PD modeling and simulation will be performed using data from this study and data from other studies and reported separately.

Sample Size Justification

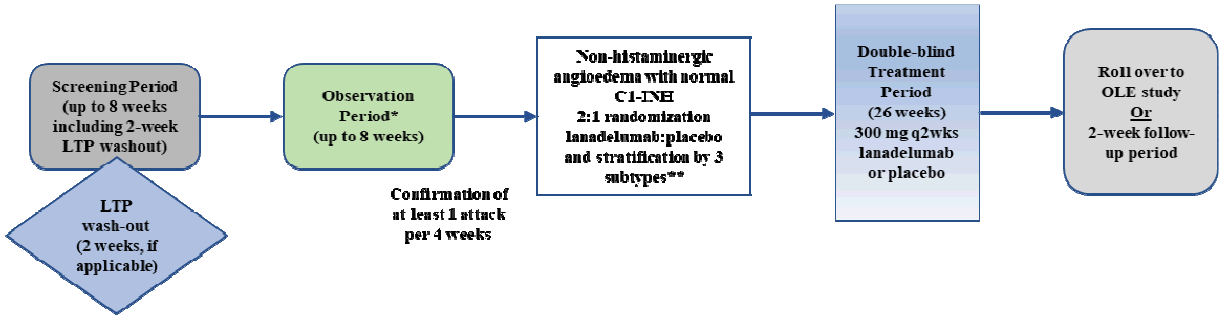
Approximately 75 subjects with non-histaminergic normal C1-INH angioedema will be randomized.

Power analyses were based on 10,000 simulations from a negative binomial distribution with dispersion parameter of 2 and 0.5 for lanadelumab and placebo-treated subjects, respectively, a 10% dropout with exponential loss-to-follow-up, and analyzed using a general linear model for count data assuming a Poisson distribution with Pearson chi-square scaling of standard errors to account for potential overdispersion. The randomization ratio was set at 2:1 for lanadelumab:placebo. The effect size of 60% reduction compared to placebo was based on the results observed in the pivotal study in subjects with HAE (Study DX-2930-03). In Study DX-2930-03, the lower 95% confidence limit for attack rate reduction (lanadelumab 300 mg q2wks group versus placebo) was 76.2%. Due to higher disease variability, a more conservative effect size assumption of 60% was assumed for subjects with non-histaminergic angioedema with normal C1-INH.

Assuming a treatment effect of at least a 60% reduction in the investigator-confirmed attack rate as compared with placebo and a placebo attack rate of 1 attack/4 weeks during the analysis period, a sample size of 75 subjects would provide at least 85% power (at α=0.025, 1-sided).

1.2 Schema

Figure 1 Study Schematic Diagram



C1-INH=C1-esterase inhibitor; LTP=long-term prophylaxis; OLE=open-label study; q2wks=every 2 weeks

* Confirmation of negative response to high-dose antihistamine treatment (cetirizine 40 mg/day or equivalent high-dose second-generation antihistamine medication) during the observation period. For subjects ≥18 years of age, investigator confirmation of response to icatibant rescue medication for at least 2 angioedema attacks or at least 1 moderate or severe attack is a requisite; subjects with no improvement or worsened attack severity 2 hours after icatibant treatment during the observation period (based on totality of assessments), will be excluded.

** The 3 subtypes are: 1) with known mutations; 2) with family history (a first-degree relative) and unknown mutations; 3) idiopathic nonhistaminergic angioedema [INHA].

Note: Subjects may roll over into an open-label extension study upon completion of all assessments scheduled on Day 182.

1.3 Schedule of Activities

Table 1 Schedule of Activities - Screening and Observation Period

Procedures	Screening[a] (up to 8 weeks)	OBSERVATION PERIOD (BY STUDY WEEK)[m]									See protocol section below for details
		Start of Observation Period	1	2	3	4	5	6	7	8	
Informed consent (written permission and assent)	X										8.3.1
Eligibility review	X	X									8.3.2
Demographics and medical/angioedema history	X										8.3.3 and 8.3.4.1
Prior/current medications, therapies, and procedures[b]	X		X----------X								6.6
Telephone contact[c]				X		X		X		X	8.2.1.3
Angioedema attack monitoring[b]	X	X----------X									8.2.1
Antihistamine treatment[d]			X----------X								8.2.1.3
Distribute icatibant and antihistamine treatment		X									8.2.1.2
Genotype testing[e]	X										8.3.6.5
C1-INH, C4, and C1q testing[f]	X										8.2.1.1
LTP washout[g]	X										8.2.1.1
Vital signs[h]	X										8.3.5.4
Physical exam[i]	X										8.3.5.1
12-lead ECG	X										8.3.5.7
Pregnancy test[j]	X										8.3.5.6
Clinical laboratory testing[k]	X										8.3.5.5

Virology testing: HBsAg, HCV, and HIV (serologies)[l]	X										8.3.5.5
Adverse events	X	X----------X									8.3.5.2

C1-INH=C1 esterase inhibitor; ECG=electrocardiogram; HbsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; LTP=long-term prophylactic therapy

[a] Subjects are allowed up to 8 weeks to complete all screening procedures. When all screening results are available, an eligibility review will be conducted by the site to determine if the subject meets all study eligibility criteria. As indicated in Table 2, a final eligibility review will be conducted prior to dosing on Day 0.

[b] All angioedema attacks will be reported after signing the ICF and assessed in accordance with BAARP (Appendix 5). From the start of the observation period, all 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 (Appendix 5).

[c] Study personnel will contact the subject or parent/caregiver by telephone on Weeks 2, 4, 6, and 8 to discuss study compliance (completion of the diary) and to evaluate the subject's attack frequency and other adverse events that may have occurred since the last contact. Telephone contacts will be documented in the source notes at the clinical site.

[d] Subjects will receive daily treatment with chronic high-dose antihistamine treatment (cetirizine 40 mg/day or equivalent high-dose second-generation antihistamine medication) throughout the observation period.

[e] A blood sample will be collected (per local regulations and subject's consent) at a single time point during screening for the purpose of identifying genetic mutations to aid in subject stratification prior to randomization. Confirmation of genetic mutations in the FXII, PLG, ANGPT1, or KNG1 genes, or other mutations associated with angioedema with normal C1-INH, must be obtained from the sponsor-approved central laboratory.

[f] C1-INH, C4, and C1q testing is required at screening from the sponsor-approved central laboratory. If C1-INH LTP is used, an additional confirmatory test may be performed after the C1-INH has washed out for at least 5 half-lives.

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

[h] Vital signs, including sitting or supine blood pressure, heart rate, body temperature, and respiratory rate.

[i] Physical examinations include measurement of height and weight.

[j] Pregnancy testing is required for all female subjects of childbearing potential; the test will be serum-based at the screening visit and may be serum- or urine-based at other visits.

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

[l] HIV (single assay antibody/Western Blot) and hepatitis (hepatitis B surface antigen, hepatitis C antibody) will be tested only at the screening visit.

[m] Subjects who do not complete the observation period due to COVID-19 related factors may be allowed to re-start the observation period if deemed eligible by the investigator and Sponsor's medical monitor.

Note: Subjects must stay in the observation period for minimum of 4 weeks and up to 8 weeks. Subjects meeting a minimum baseline angioedema attack rate of at least 1 investigator-confirmed angioedema attack per 4 weeks may be allowed to exit the observation period at 4 weeks for randomization. Subjects without at least 1 Investigator-confirmed attack in the first 4 weeks may have their observation period extended for another 4 weeks. Subjects who have their observation period extended must complete the full 8-week observation period and must have at least 2 investigator-confirmed attacks during this time to be eligible for randomization.

Table 2 Schedule of Activities - Treatment Period (Day 0 [Week 1] to Day 182 [Week 26]) and Follow-up Period (through Day 196 [Week 28])

Procedures	Treatment Period (In Weeks) — Shaded columns: scheduled on-site visits[s] — Non-Shaded columns: potential subject-elected off-site activity																								Follow-up Period[p] (2 weeks)	See protocol section below for details
Study Week	1-4				5-8				9-12				13-16				17-20				21-24				25-26		28	
Study Visit (± 4 days)	1[r]	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24[*]	25	26 /ET[o]	27 EOS[q]	
Study Day	0	4	14	28	35	42	49	56	63	70	77	84	91	98	105	112	119	126	133	140	147	154	161	168	175	182	196	
Confirmation of eligibility[a]	X																											8.2.1.3
Randomization	X																											6.2.2
Vital signs[b]	X		X	X				X				X				X				X				X		X		8.3.5.4
Physical exam[c]	X		X	X				X				X				X				X				X		X		8.3.5.1
12-lead ECG	X																									X		8.3.5.7
Pregnancy test[d]	X															X										X		8.3.5.6
Clinical laboratory testing[e]	X			X				X				X				X				X				X		X		8.3.5.5
Plasma PK and PD sample[f]	X		X	X				X				X				X				X				X		X		8.3.6.1 and 8.3.6.2
Plasma ADA sample[g]	X			X				X				X				X				X				X		X		8.3.6.3
Genotype sample[h]	X																											8.3.6.5
Blinded treatment q2wk administration	X		X	X		X		X		X		X		X		X		X		X		X		X[*]				6.2.3
Angioedema attack monitoring diary[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3.4.1
Health-related quality of life assessments[j]	X			X				X				X				X				X				X		X		8.3.6.6
Site check-in call[k]		X			X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X			8.2.2.2
Injection report[l]	X		X	X		X		X		X		X		X		X		X		X		X		X				8.3.6.9
Concomitant therapies, medications, procedures[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.6
Adverse events[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3.5.2
Discharge from study[n]																										X	X	8.2.2.3 and 8.2.3
Telephone contact																											X	8.2.3

ADA=antidrug antibodies; C1-INH=C1 esterase inhibitor; ECG=electrocardiogram; EOS=end of study; ET=early termination; PD=pharmacodynamic; PK=pharmacokinetic; q2wk=every 2 weeks

[a] Subjects meeting a minimum baseline angioedema attack rate of at least 1 investigator-confirmed angioedema attack per 4 weeks during the observation period may be allowed to exit the observation period at 4 weeks for randomization and will enter the treatment period. In addition, during the observation period, subjects (≥ 18 years of age) need to be treated with icatibant for at least 2 angioedema attacks or at least 1 moderate or severe attack. In the opinion of the investigator, subjects with no response to icatibant for acute angioedema attacks in the past medical history/screening, or no improvement or worsened attack severity 2 hours after icatibant treatment during the observation period (based on totality of assessments), will not be eligible. Subjects without at least 1 investigator-confirmed attack in the first 4 weeks may have their observation period extended for another 4 weeks. Subjects who have their observation period extended must complete the full 8-week observation period and must have at least 2 investigator-confirmed attacks during this time to be eligible to enter treatment period.

[b] 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.

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

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

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

[f] Blood samples for measurements of lanadelumab concentrations in plasma will be obtained predose (except on the Day 182/ET visit). Blood samples to measure cleaved high molecular weight kininogen (cHMWK) level and plasma kallikrein (pKal) activity will be obtained predose (except on the Day 182/ET visit).

[g] Blood samples for testing formation of ADA will be obtained predose (except on the Day 182/ET visit).

[h] A blood sample will be collected (per local regulations and subject's consent) at a single time point (predose) for future exploratory evaluation of genes or gene categories that may be associated with non-histaminergic angioedema with normal C1-INH and drug action.

[i] 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 (Appendix 5). 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.

[j] Health-related quality of life (HR-QoL) data will be obtained predose at the scheduled time points.

[k] Site personnel will call subjects within approximately 3 days after the planned self-administration of investigational product to ensure the administration occurred, to collect AEs and concomitant medications and to ensure all attacks have been appropriately documented.

[l] Collect the injection reports assessing the subject's or parent/caregiver's experience with SC injection of investigational product.

[m] On dosing days, collected predose and postdose.

[n] Subjects who elect to roll over into a 26-week long open-label extension (OLE) study, must provide consent no later than the last day of blinded treatment period on Day 182 (Visit 26). After the completion of all scheduled assessments on Day 182 (Visit 26), subjects will be discharged from this study and will enter the OLE study and receive their first dose of open-label lanadelumab. All other subjects will be discharged from the study after the completion of the end of study (EOS) assessments scheduled on Day 196 (Visit 27).

[o] Subjects who terminate from the study early will undergo (if possible) all of the assessments and procedures as Day 182 (Visit 26) at their final study visit.

[p] Subjects who choose not to roll over to the OLE, will continue to the planned 2-week safety follow-up period at the completion all assessments scheduled on Day 182 (Visit 26).

[q] Study personnel will contact the subject or parent/caregiver by telephone on Day 196 (Visit 27) to complete the EOS assessments. Telephone contacts will be documented in the source notes at the clinical site.

[r] Subjects should begin the treatment period (Visit 1) within 7 days after completion of the observation period. Any delayed start to the treatment period (i.e., >7 days from the observation period) due to unexpected event(s) should be discussed with the Sponsor

[s] 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 (e.g., 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.

[*] Last dose in blinded study medication at Visit 24 or Day 168 (±4 days).

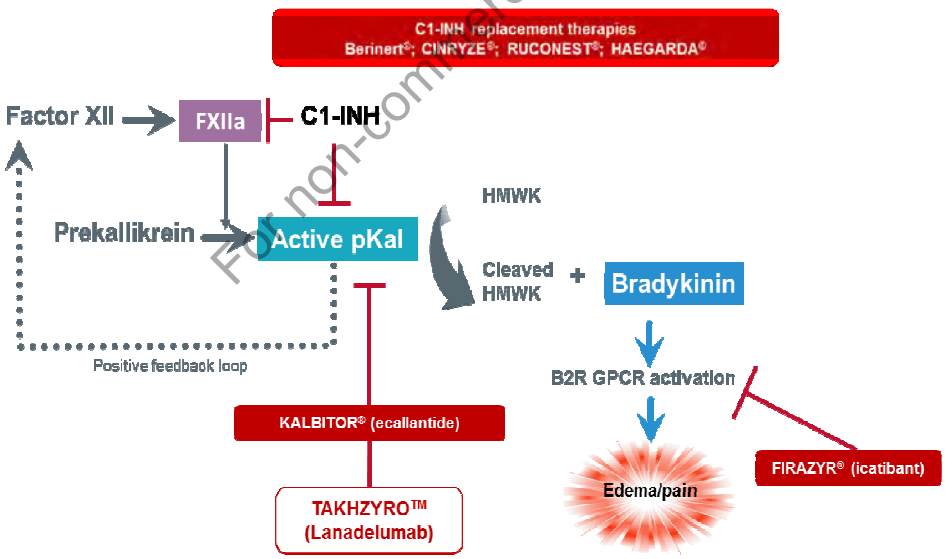
Note: Permissible assessment window during treatment period and follow-up period: Study Visit Day ±4 days

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; 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 non-histaminergic angioedema with normal C1-INH.

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 non-histaminergic normal C1-INH angioedema (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 (cHMWK), which is generated by pKal concomitant with bradykinin, was also elevated in the plasma from patients with 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 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

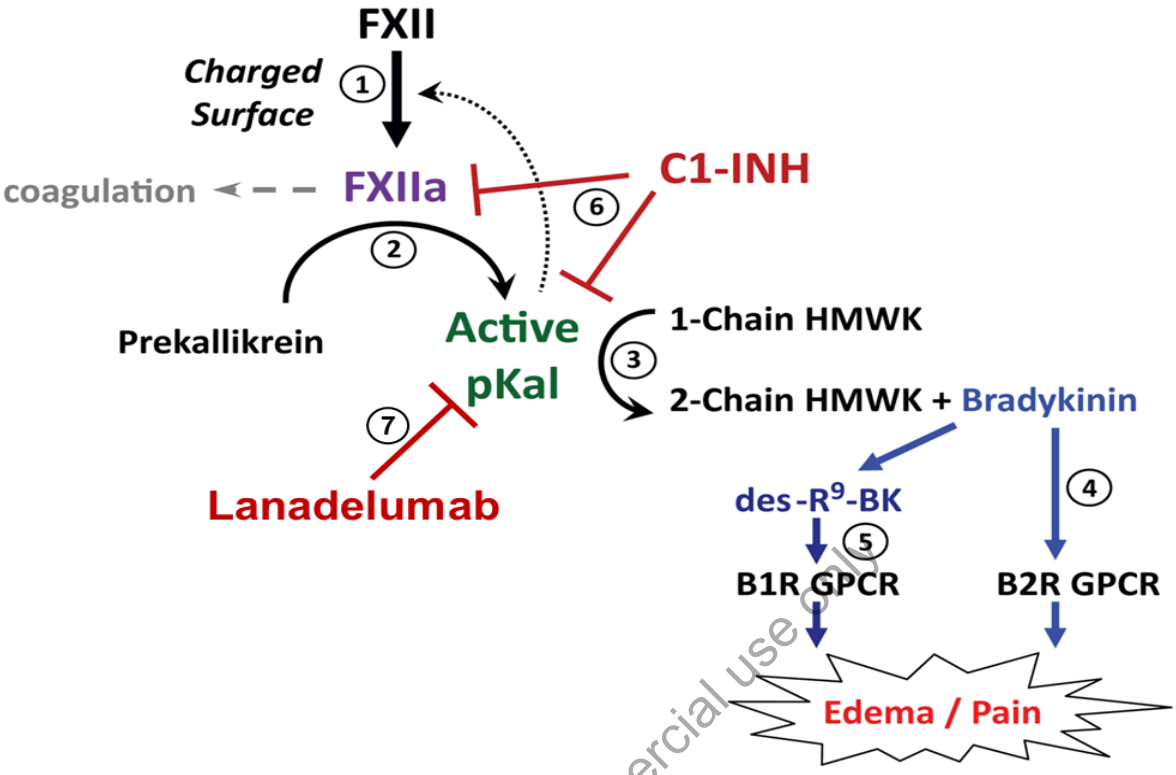
2.4.1 Drug Information

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

Dosage Form

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

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

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

Collectively, the nonclinical studies demonstrate that lanadelumab did not have adverse effects on vital functions or produce adverse target organ pathologies in rats or cynomolgus monkeys and support the safe use in patients with HAE as a prophylactic treatment by 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 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, serious adverse events (SAEs), discontinuations due to an adverse event (AE), or safety signals following lanadelumab treatment. One SAE of pneumonia was reported in a placebo-treated subject. Two subjects treated with lanadelumab tested positive for 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 and 400 mg suppressed pKal activity and reduced kininogen cleavage to the levels observed in healthy subjects. In a prespecified efficacy analysis, a statistically significant finding of HAE attack prevention by lanadelumab was observed. Specifically, in comparison to placebo, attack rate was reduced by 100% and 88% in the 300 and 400 mg lanadelumab treatment groups, respectively. The effects on HAE attacks were associated with drug exposure. Safety results from the multiple-ascending dose study in HAE patients, in conjunction with results from the single-ascending dose study in healthy subjects and the current nonclinical data package, supported the continued clinical development of lanadelumab in patients with HAE.

Lanadelumab clinical development program has 2 Phase 3 clinical studies in adolescent (≥12 to <18 years old) and adult subjects with documented diagnosis of Type I or Type II HAE: the completed pivotal, double-blind Study DX-2930-03 and the ongoing 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. Based on PD bioactivity, PK, safety, and efficacy of lanadelumab from the Phase 1 clinical studies and nonclinical studies, the dosing regimens identified for this study were: 300 mg q2wks, 300 mg q4wks, and 150 mg q4wks. The 3 proposed dose-regimen combinations provide a 6-fold range of steady-state trough concentrations and leverage both the biomarker and efficacy data generated in study DX-2930-02.

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

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

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

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

2.4.4 Adolescent Clinical Trial Experience

The Phase 3 clinical studies for lanadelumab, pivotal Study DX-2930-03 and the ongoing 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 to <40 and ≥40 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 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 ECGs. Overall, the safety and tolerability of lanadelumab were similar in the pediatric population (12 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 (CL/F) of lanadelumab after correcting for body weight. Based on the evaluation of PK, efficacy and safety, no dosing regimen adjustment has been recommended for adolescents (12 to <18 years). Refer to the latest lanadelumab IB.

2.5 Study Rationale

Based on the mechanism of action (Figure 2) and past case studies with icatibant (Bouillet et al., 2009; Wirth et al., 1991; Boccon-Gibod and Bouillet, 2012; Bouillet et al., 2017; Zanichelli et al., 2017; Cicardi and Zanichelli, 2010; Zanichelli et al., 2012; Regoli et al., 1998) and ecallantide (Bhoola et al., 1992; Markland et al., 1996; Cicardi and Zanichelli, 2010) there is strong scientific rationale to expand the use of lanadelumab as a prophylactic therapy for BMA patients other than those with Type I/II HAE. Prophylactic treatment with lanadelumab may be beneficial for other forms of BMA such as non-histaminergic angioedema with normal C1-INH based on the benefit/risk assessment of lanadelumab established in adolescents and adults with Type I or Type II HAE in the clinical development program, along with the convenience of a low volume, infrequent, SC administration for patients.

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, 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 completed 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 injection site reactions (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 electrocardiogram (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: 20-1280), 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 (see Schedule of Activities, Table 1 and Table 2).

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

2.7 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (Integrated Addendum to ICH E6[R1]: Guideline for Good Clinical Practice E6[R2] Current Step 4 version, 9 November 2016), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives (2001/20/EC; 2005/28/EC), and applicable national and local regulatory requirements.

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 efficacy of repeated SC administrations of lanadelumab in preventing angioedema attacks in adolescents (12 to <18 years of age) and adults with non-histaminergic angioedema with normal C1-INH.

3.1.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety of repeated SC administrations of lanadelumab in preventing angioedema attacks in adolescents and adults with normal C1-INH.
- To evaluate the PK of repeated SC administrations of lanadelumab in preventing angioedema attacks in adolescents and adults with normal C1-INH angioedema.
- To evaluate the PD of repeated SC administrations of lanadelumab in preventing angioedema attacks in adolescents and adults with normal C1-INH angioedema.
- To evaluate the immunogenicity of repeated SC administrations of lanadelumab in preventing angioedema attacks in adolescents and adults with normal C1-INH angioedema.
- To evaluate the effect of lanadelumab on health-related quality of life (HR-QoL) assessments in adolescents and adults with normal C1-INH angioedema.

3.1.3 Exploratory Objectives

To evaluate the effect of lanadelumab on exploratory biomarker(s) of angioedema disease-state bioactivity in adolescents and adults with normal C1-INH angioedema.

3.2 Study Endpoints

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

Table 3 Objectives and Endpoints

Objective	Endpoint(s)
Primary	
• To evaluate the **efficacy** of repeated SC administrations of lanadelumab in preventing angioedema attacks in adolescents (12 to <18 years of age) and adults with non-histaminergic angioedema with normal C1-INH.	**Primary Efficacy Endpoint** • Number of investigator-confirmed angioedema attacks during the treatment period (Day 0 through Day 182) **Rank-ordered Secondary Efficacy Endpoints** 1. Subjects that are attack-free during the treatment period (Day 0 through Day 182) 2. Number of investigator-confirmed moderate or severe angioedema attacks during the treatment period (Day 0 through Day 182) 3. Number of investigator-confirmed angioedema attacks during the presumed steady state period (Day 70 through Day 182) 4. Subjects that are attack-free during the presumed steady state period (Day 70 through Day 182) 5. Number of investigator-confirmed moderate or severe angioedema attacks during the presumed steady state period (Day 70 through Day 182) <u>Additional Secondary Efficacy Endpoints:</u> • Maximum attack severity during presumed steady state period (Day 70 through Day 182) and treatment period (Day 0 through Day 182) • Time to first angioedema attack after Day 0 • Time to first angioedema attack after Day 70 • Achievement of at least a 50%, 70%, 90% and 100% reduction in the investigator-confirmed NNA per 4 weeks during each of the efficacy evaluation periods relative to the observation period NNA • Achievement of an efficacy evaluation period NNA <1.0 per 4 weeks during each of the efficacy evaluation periods
Secondary	
• To evaluate the **safety** of repeated SC administrations of lanadelumab in preventing angioedema attacks in adolescents and adults with normal C1-INH angioedema.	• TEAEs, including AESIs and SAEs • Clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis) • Vital signs including blood pressure, heart rate, body temperature, and respiratory rate
• To evaluate the **PK** of repeated SC administrations of lanadelumab in preventing angioedema attacks in adolescents and adults with normal C1-INH angioedema.	• Plasma concentrations of lanadelumab

Table 3 Objectives and Endpoints

Objective	Endpoint(s)
• To evaluate the **PD** of repeated SC administrations of lanadelumab in preventing angioedema attacks in adolescents and adults with normal C1-INH angioedema.	• Plasma cHMWK and pKal activity
• To evaluate the **immunogenicity** of repeated SC administrations of lanadelumab in preventing angioedema attacks in adolescents and adults with normal C1-INH angioedema.	• Presence or absence of neutralizing or non-neutralizing ADA in plasma
• To evaluate the effect of lanadelumab on **HR-QoL** assessments in adolescents and adults with normal C1-INH angioedema.	• Measured by the AE-QoL questionnaire, which consists of 17 disease-specific quality-of-life items, to produce a total AE-QoL score and 4 domain scores (functioning, fatigue/mood, fear/shame, and nutrition). Change in total AE-QoL score during the treatment period (Day 0 through Day 182) will be assessed
Exploratory	
• To evaluate the effect of lanadelumab on **exploratory biomarker(s)** of angioedema disease-state bioactivity in adolescents and adults with normal C1-INH angioedema.	• Exploratory biomarker(s) of angioedema-disease state bioactivity (eg, pKal) in blood and plasma

ADA=antidrug antibodies; AE-QoL=angioedema quality of life; AESI=adverse event of special interest; C1-INH=C1 esterase inhibitor; cHMWK=cleaved high molecular weight kininogen; HR-QoL=health-related quality of life; NNA=normalized number of attacks; PD=pharmacodynamic; PK=pharmacokinetic; pKal=plasma kallikrein; SAE=serious adverse event; SC=subcutaneous; TEAE=treatment-emergent adverse event

4 STUDY DESIGN

4.1 Overall Design

Study SHP643-303 targets to enroll approximately 75 subjects (12 years of age and above[3]) with normal C1-INH angioedema. All enrolled subjects (who have signed informed consent form) must have an investigator-confirmed diagnosis of non-histaminergic angioedema with normal C1-INH at screening. Screened subjects who have been on any LTP (eg, C1-INH, androgens, or anti-fibrinolytics), are required to undergo a minimum 2-week washout period prior to the observation period. This LTP washout period is permitted as long as the investigator determines that doing so would not place the subject at any undue safety risk, and that the subject is at least 18 years of age. During the observation period, all subjects must discontinue LTP. The attack rate in the observation period will serve as the baseline for this study. Subjects with any exposure to prophylactic pKal inhibitors prior to screening will be excluded from the study.

Enrolled subjects meeting all eligibility criteria at screening will enter an observation period of up to 8 weeks to determine the baseline angioedema attack rate and confirm their eligibility. Subjects meeting a minimum baseline angioedema attack rate of at least 1 investigator-confirmed angioedema attack per 4 weeks during the observation period may be allowed to exit the observation period at 4 weeks for randomization and will enter the treatment period. In addition, during the observation period, subjects (≥18 years of age) need to be treated with icatibant for at least 2 angioedema attacks or at least 1 moderate or severe attack. In the opinion of the investigator, subjects with no response to icatibant for acute angioedema attacks in the past medical history/screening, or no improvement or worsened attack severity 2 hours after icatibant treatment during the observation period (based on totality of assessments), will not be eligible. Subjects without at least 1 investigator-confirmed attack in the first 4 weeks may have their observation period extended for another 4 weeks. Subjects who have their observation period extended must complete the full 8-week observation period and must have at least 2 investigator-confirmed attacks during this time to be eligible to enter treatment period.

Subjects who do not meet the minimum attack rate during the observation period will be considered screen failures; subjects who screen fail will not be allowed to rescreen for the study.

After verification of eligibility in the observation period, subjects will be randomized 2:1 to receive repeated SC administrations of lanadelumab or placebo in a double-blind fashion.

Randomization will be stratified by baseline angioedema attack rate (1 to <2 attacks/4 weeks, and ≥2 attacks/4 weeks) and by subtype: 1) with known mutations (FXII, PLG, ANGPT1, or KNG1 genes associated with normal C1-INH angioedema); 2) with family history (a first-degree relative) and unknown mutations; and 3) with idiopathic non-histaminergic angioedema (INHA).

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[3] Enrollment of non-histaminergic normal C1-INH patients <18 years of age will be allowed based on local site and /or country regulations.

Acute angioedema attacks during the observation period and the treatment period will be managed with icatibant. Therefore, subjects ≥18 years of age need to be willing to be tested for their response to icatibant treatment for angioedema attacks that occur during the observation period. For subjects 12 to <18 years of age, standard of care therapy per local protocols should be provided. Further details on icatibant and the management of acute angioedema attacks during the study are provided in Section 6.6.3.

During the 26-week treatment period all subjects will receive SC administration of investigational product q2wks. Section 4.3 provides justification for the dosing regimen proposed for this study. Further details on dosing and self-administration of lanadelumab are provided in Section 6.2.3 and Section 8.3.6.8.

Subjects with non-histaminergic angioedema with normal C1-INH may roll over into a 26-week long open-label extension (OLE) study (Study TAK-743-3001) upon completion of all assessments scheduled on Day 182. Those subjects who choose to roll over will provide consent no later than the last day of blinded treatment period (Day 182) and will be discharged from Study SHP643-303 after completion of all assessments on Day 182. Subjects who choose not to roll over to the OLE will continue to the planned 2 weeks of safety follow-up at the completion of all study assessments scheduled on Day 182.

Individual subject participation from screening through the completion of safety follow-up visit will be approximately 44 weeks (up to 8-week screening period [including a 2-week washout of LTP if applicable], up to 8-week baseline observation period, 26-week treatment period, and 2-week safety follow-up period). An overview of the study design scheme is provided in Figure 1. All study procedures are detailed in the schedule of assessments (Table 1 and Table 2). Details of procedures for collection of angioedema attack information are provided in Appendix 5.

4.2 Scientific Rationale for Study Design

This Phase 3, double-blinded, placebo-controlled study aims to evaluate the efficacy and safety of lanadelumab for the prevention of angioedema attacks in approximately 75 subjects with non-histaminergic angioedema with normal C1-INH for a 26-week treatment period. Subjects must experience at least 1 attack per 4 weeks in the observation period (investigator-confirmed baseline attack rate) for inclusion in the study (see Section 5 for inclusion/exclusion criteria).

The number of investigator-confirmed angioedema attacks during the treatment period is the direct way to evaluate the primary efficacy endpoint (see Section 9.6.1 for planned statistical analyses).

The non-histaminergic bradykinin-mediated angioedema attack assessment and reporting procedures (BAARP; see Appendix 5) will provide the standardized definition of an angioedema attack and define a standard set of procedures for the reporting and assessment of events reported by subjects to determine whether those events were true attacks. The secondary efficacy endpoints are also based on investigator-confirmed angioedema attacks (reporting, collection, and assessment in accordance with the BAARP). The secondary objectives of the study include

evaluation of safety endpoints, PD effects of lanadelumab, PK, immunogenicity, and effect on HR-QoL of chronically administered lanadelumab (Table 3).

The clinical pharmacology properties and proposed therapeutic target of lanadelumab in this study population with BMA support the same dose regimen demonstrated to be efficacious in subjects with Type I and Type II HAE, 300 mg q2wks.

Currently, there are no approved treatments for the BMA disease populations included in this study; therefore, use of an active comparator is not applicable. A placebo comparator has been chosen to evaluate and interpret the efficacy of lanadelumab. Per the protocol, for subjects ≥18 years of age, icatibant will be used as rescue medication during the observation and treatment period for the management of acute angioedema attacks. For subjects 12 to <18 years of age, standard of care therapy per local protocols will be provided. Since subjects on placebo are permitted to treat acute angioedema attacks either with icatibant or in accord with the investigator's usual care of their patients, the use of placebo arm as the comparator is justified.

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 HAE 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 coagulation factor XII (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 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).

Further support for the role of the plasma kallikrein-kinin system in non-histaminergic angioedema with normal C1-INH is supported by 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 q2wk dose regimen is the appropriate dose for this pivotal study in subjects with BMA other than Type I and Type II HAE.

4.4 Duration of Subject Participation and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 44 weeks. Individual subject participation from screening through the completion of safety follow-up visit will include: up to 8-week screening period (including a 2-week washout of LTP, if applicable), up to 8-week baseline observation period, 26-week treatment period, and 2-week safety follow-up period. The study will be completed in approximately 34 months.

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 (United States, Canada), 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 applicable population criteria below.

1. Males and females, 12 years of age and older for subjects with non-histaminergic normal C1-INH angioedema at the time of signing of the informed consent form (ICF).
2. Documented clinical history of recurrent attacks of angioedema in the absence of wheals/urticaria.
3. Investigator-confirmed diagnosis of non-histaminergic bradykinin-mediated angioedema with normal C1-INH as documented by a history of angioedema attack(s) at screening and occurrence of attacks during the observation period:
   - History of recurrent angioedema with at least an average of 1 angioedema attack per 4 weeks prior to screening and this attack rate must be confirmed during the observation period while treated with chronic high-dose antihistamine (cetirizine 40 mg/day or equivalent high-dose second-generation antihistamine medication).
   - Diagnostic testing results obtained during screening from a sponsor-approved central laboratory that confirm C1-INH function ≥50% of normal and C4 level not below the normal range. With prior sponsor approval, subjects may be retested during the observation period if results are incongruent with clinical history.
   - Clinical history of not responding to high-dose antihistamine treatment (cetirizine 40 mg/day or equivalent high-dose second-generation antihistamine medication), which must be confirmed during the observation period with at least 1 angioedema attack per 4 weeks with chronic high-dose antihistamine treatment and no significant difference (as assessed by the investigator and in consultation with the sponsor's medical monitor, as necessary) from the historic attack rate without high-dose antihistamine treatment.
4. Agree to adhere to the protocol-defined schedule of treatments, assessments, and procedures.
5. Subjects ≥18 years of age must be willing to use icatibant as the rescue medication during the observation and treatment period. During the observation period, subjects need to be treated with icatibant for at least 2 angioedema attacks or at least 1 moderate or severe attack. In the opinion of the investigator, subjects with no response to icatibant for acute angioedema attacks in the past medical history/screening, or no improvement or worsened attack severity 2 hours after icatibant treatment during the observation period (based on totality of assessments), will not be included. **Note**: For subjects 12 to <18 years of age, standard of care therapy per local protocols should be provided.

6. Males, or non-pregnant, non-lactating females who are of child-bearing potential and who agree to be abstinent[4] or agree to comply with the applicable contraceptive requirements of this protocol for the duration of the study. Female subjects of childbearing potential must have a negative serum pregnancy test at screening and must be willing to undergo pregnancy tests throughout the study. Females of non-childbearing potential are defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months.
7. 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).

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

   OR

   If the subject is a minor (ie, <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. Concomitant diagnosis of Type I or Type II HAE, or recurrent angioedema associated with urticaria.
2. Dosing with any investigational drug or exposure to an investigational device within 4 weeks prior to screening.
3. Exposure to angiotensin-converting enzyme (ACE) inhibitors or rituximab within 6 months prior to screening.
4. Use of any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
5. Response to omalizumab (prophylactic) or corticosteroid (acute/prophylactic) or epinephrine (acute) or anti-leukotrienes (prophylactic) treatments in the past.
6. Use of long-term prophylactic therapy for HAE, eg, C1-INH, attenuated androgens (eg, danazol, methyltestosterone, testosterone), or anti-fibrinolytics within 2 weeks prior to

[4] Abstinence will be accepted as a highly effective method only if sexual abstinence is the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, symptothermal or post-ovulation), declaration of abstinence for the duration of exposure to IMP, or withdrawal (coitus interruptus) are not acceptable methods of contraception.

entering the observation period as long as the investigator determines that doing so would not place the subject at any undue safety risk, and that the subject is at least 18 years of age.

7. Any exposure to prophylactic plasma kallikrein inhibitors prior to screening.
8. Use of short-term prophylaxis for HAE within 7 days prior to entering the observation period. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.
9. Have any active infectious illness or fever defined as an oral temperature >38°C (100.4°F), tympanic >38.5°C (101.3°F), axillary >38°C (100.4°F), or rectal/core >38.5°C (101.3°F) within 24 hours prior to the first dose of study drug in the treatment period.
10. Any of the following liver function test abnormalities: ALT >3x upper limit of normal, or AST >3x upper limit of normal, or total bilirubin >2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome).
11. Pregnancy or breast feeding.
12. Subject has a known hypersensitivity to the investigational product or its components.
13. Have any uncontrolled underlying medical condition which would require treatment adjustment during the study treatment period that, in the opinion of the investigator or sponsor, may confound the results of the safety assessments or may place the subject at risk. Subjects with stable treatment for at least 3 months prior to screening and NOT expecting any change to their treatment regimen for 6 months during the study treatment period, will not be excluded.
14. 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[5] 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).

[5] Abstinence will be accepted as a highly effective method only if sexual abstinence is the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, symptothermal or post-ovulation), declaration of abstinence for the duration of exposure to IMP, or withdrawal (coitus interruptus) are not acceptable methods of contraception.

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.

5.4.2 Male Contraception

Males, including males who are surgically sterile (post-vasectomy), with female partners of childbearing potential must agree to be abstinent[5] or else use a medically acceptable form of contraception throughout the study period and for 70 days following the last dose of investigational product.

6 STUDY INTERVENTION

6.1 Investigational Product

6.1.1 Identity of Investigational Product

The investigational product is lanadelumab, which 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. Additional information regarding the dosage forms is provided in the latest version of lanadelumab IB or the medication guide.

The reference/comparator product is placebo, which will be provided in in a PFS and is filled to deliver a nominal volume of 2.0 mL subcutaneously.

Commercial icatibant labeled for clinical trial use will be supplied as rescue medication for the treatment of acute angioedema attacks during the study for subjects ≥18 years of age (Section 6.6.3). The product will be supplied in a single-dose glass PFS delivering 3 mL of solution containing 30 mg icatibant and should be stored at or below 25°C (must not be frozen).

6.1.2 Blinding the Treatment Assignment

This study will be double-blinded. All study site personnel, subjects, healthcare providers, and the sponsor will be blinded to treatment.

To maintain the blind, lanadelumab and placebo will have an identical presentation, including its packaging and labeling, such that the contents of the PFS within the prepackaged study kits will be indistinguishable from each other. As described in Section 6.3.2, investigational product will be identified only by a unique study drug kit number. Each prepackaged study kit will contain 1 PFS of investigational product (nominal volume of 2 mL).

Knowledge of the PK/PD and ADA data would compromise the study blind. As such, the independent external laboratory performing the PK/PD analyses will keep the results in strict confidence until the study is unblinded.

Additionally, a limited number of representatives of the sponsor responsible for the interactive response technology (IRT) and product labeling will be unblinded to treatment assignment in order to review drug accountability on an ongoing basis throughout the study.

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

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

6.2.2 Allocation of Subjects to Treatment

This is a randomized, double-blind, placebo-controlled study. The actual treatment given to individual subjects is determined by a randomization schedule.

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

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined. Subjects will be randomized 2:1 to receive administrations of lanadelumab or placebo. Randomization will be stratified by baseline angioedema attack rate (1 to <2 attacks/4 weeks, and ≥2 attacks/4 weeks) and by subtype: 1) with known mutations (FXII, or PLG, or ANGPT1, or KNG1 genes, or other predefined mutations); 2) with family history (a first-degree relative) and unknown mutations; and 3) with INHA.

Individual subject treatment is automatically assigned by the IRT.

Once a randomization number/unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a randomization number/unique identifier is allocated incorrectly, the clinical research associate (CRA)/study monitor must be notified as soon as the error is discovered.

Investigational product packaging identification numbers, separate from randomization numbers/unique identifiers, may also be assigned to subjects for specific treatment assignment as dictated by the study. In these cases, the same investigational product packing identification number may not be assigned to more than 1 subject.

6.2.3 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 by the investigator or designee and has demonstrated their understanding of self-administration; refer to Section 8.3.6.8 for details.

All subjects will receive investigational product every 2 weeks from Visit 1 (Day 0) to Visit 24 (Day 168), for a total of 13 doses during the treatment period.

The presentation of investigational product is a PFS filled to deliver a nominal volume of 2.0 mL of drug product SC.

6.2.4 Unblinding the Treatment Assignment

The treatment assignment must not be unblinded during the study except in emergency situations where the identification of the investigational product is required for medical management of the subject. The investigator should contact the medical monitor as soon as possible after the treatment code has been broken and the investigator is unblinded.

In the event that the treatment assignment code is broken, the date and the signature of the person who broke the code are recorded on the IRT and the source documents, as applicable. The reason for breaking the code will be recorded in source documents, as appropriate, based on safety or deviation reporting. Upon breaking the blind, the subject is withdrawn from the study, but should be followed up for safety purposes. Any code-breaks that occur must be reported to the sponsor.

The data monitoring committee (DMC; see Section 9.2), in consultation with sponsor, may also request unblinding of an individual's treatment assignment for reasons of subject safety.

6.2.5 Dose Modification

No dose modifications (including dosing frequency) are allowed in this study.

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

6.3.1 Labeling

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

All investigational product is labeled with a minimum of the following: protocol number, MedID number, lot number, expiry date, dosage form, directions for use, storage conditions, the sponsor's name, and the statements "For clinical trial use only" and "Keep out of sight and reach of children". 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 (see Section 8.3.6.8), 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 2-8°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 provided that the blind of the study is not compromised.

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 CRO). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Validated electronic return systems (ie, IRT) do not require a shipment form. Returned investigational product must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

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

6.5 Subject Compliance

Subjects must be instructed to bring unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (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 the screening visit (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) and through the final study contact (including protocol-defined follow-up period) must be recorded in the subject's source document.

6.6.1 Prior Treatment

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

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 co-existing conditions, including those for acute attacks of angioedema attacks (see below), are permitted if not excluded during the study (see 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.
- If a subject (≥18 years of age) experiences an acute angioedema attack at any time during the study (including the observation and treatment period), icatibant should be administered as the rescue medication to treat the attack. Icatibant treatment is recommended within 6 hours and no later than 12 hours after the onset of the attack. Icatibant is to be administered by the SC route in the abdominal area. The entire volume in the syringe should be administered and the injection should occur over at least 30 seconds. If response is inadequate or symptoms recur, additional injections of 30 mg may be administered at intervals of at least 6 hours. Do not administer more than 3 injections in 24 hours. The subject will be allowed to self-administer icatibant if already trained by a healthcare provider or after receiving instructions on the use and appropriate training by study site personnel or healthcare provider. If a laryngeal attack occurs (ie, swelling of the airways), the subject should inject icatibant and proceed immediately to the nearest medical care facility. If it is the opinion of the investigator that the subject still needs medication for his/her acute angioedema attack after icatibant administration, then other standard of care therapy may be provided per locally approved product information. For subjects ≥12 to <18 years of age standard of care therapy per locally approved product information should be provided.

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 can also be re-scheduled 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) within 2 weeks prior to entering the observation period and during the study.
- Angiotensin-converting enzyme inhibitors or rituximab within 6 months prior to screening and during the study.
- Estrogen-containing medications with systemic absorption within 4 weeks prior to screening and during the study.
- Use of androgens (eg, stanozolol, danazol, oxandrolone, methyltestosterone, testosterone), for non-angioedema related medical conditions or for angioedema, within 2 weeks prior to entering the observation period and during the study.
- Any other investigational drug or device.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

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 26) as completely as possible (see Section 8.2.2.3). 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 are discontinued from the study because they do not meet the minimum angioedema attack rate during the observation period, or who are otherwise determined to be ineligible based on screening assessments will be considered to be screen failures.

Subjects who prematurely discontinue investigational product will not be replaced.

7.2 Reasons for Discontinuation

The reason for discontinuation (from treatment and/or study) must be determined by the investigator and recorded in the subject's source document. If a subject is discontinued for more than 1 reason, each reason should be documented in the source and the primary reason should be indicated.

Reasons for discontinuation include, but are not limited to:

- Withdrawal of consent (by a parent or both parents/legal authorized representative for adolescent subjects)
- Adverse Event
- Protocol deviation (eg, lack of compliance, use of experimental drug)
- Pregnancy
- Sponsor decision
- Investigator decision
- Death
- Lost to follow-up
- Lack of efficacy
- Other (must specify on the electronic case report form [eCRF])

7.3 Withdrawal from the Study

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

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

A minimum of 3 documented attempts must be made to contact any subject who is lost to follow-up at any time point prior to the last scheduled contact (office visit or 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.

Dosing for any individual subject will be discontinued if the following criteria are met with confirmed results in liver functional test:

1. Alanine aminotransferase (ALT) >3x ULN **OR**
2. Aspartate aminotransferase (AST) >3x ULN, **AND**
3. Total Bilirubin >2x ULN

If a subject meets the above criteria with confirmed test results, no other reason can be found to explain the combination of increased ALT or AST and total bilirubin, and both the investigator and sponsor deem this causality as related to study drug, the study may be suspended for further investigation, or possibly terminated.

Subjects who prematurely discontinue investigational product should undergo final visit of the treatment period procedures specified for Study Day 182 (Visit 26) as completely as possible (see Section 8.2.2.3).

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:

- **Observation period**: Subjects who do not complete the observation period due to COVID-19 related factors may be allowed to restart the observation period if deemed eligible by the investigator and Sponsor's medical monitor.

- **Treatment period (Visit 1)**: As indicated in Section 8.2.2.1, subjects should begin the treatment period (Visit 1) within 7 days after completion of the observation period. Any delayed start to the treatment period (ie, >7 days from the observation period) due to unexpected events, such as COVID-19, should be discussed with the Sponsor.

- **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
  - Blinded treatment q2wk administration
  - 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 and Table 2 for the schedule of study activities. Study assessments are detailed in Section 8.3.

8.2.1 Screening and Observation Period

8.2.1.1 Screening Period (up to 8 weeks, including 2-week LTP washout if applicable)

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

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

- Informed consent
- Demographics, medical history, and angioedema history
- Prior/current medications, therapies and procedures
- Angioedema attack monitoring
- Genotype sample collection (sample will be used to identify genetic mutations to aid in subject stratification prior to randomization)
- C1-INH function, C4, and C1q testing. If C1-INH therapy is used, the drug needs to be washed out for at least 5 half-lives before the testing sample is collected.
- LTP washout, if applicable
- Vital signs including blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR)
- Complete physical examination, including documentation of height and weight.
- 12-lead ECG
- Pregnancy test (serum-based; for female subjects of childbearing-potential)
- Clinical laboratory testing including hematology, serum chemistry, coagulation, and urinalysis
- Virology testing for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), and human immunodeficiency virus (HIV)
- Adverse events collection

Subjects are allowed up to 8 weeks to complete all screening procedures. When all screening results are available, an eligibility review will be conducted by the site to determine if the subject meets all study eligibility criteria. (**Note**: As indicated in Section 8.2.2.1, a final eligibility review will be conducted prior to dosing on Day 0.)

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

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or meets at least 1 of the exclusion criteria and has not been randomized and administered investigational product(s). Subjects cannot be rescreened once they have been designated as a screen failure.

8.2.1.2 Start of Observation Period

As indicated in Table 1, the following procedures and assessments are to be performed at the start of the observation period:

- Eligibility review
- Angioedema attack monitoring
- Adverse events collection
- Distribution of icatibant and antihistamine treatment

8.2.1.3 Observation Period (minimum of 4 weeks and up to 8 weeks)

Eligible subjects will enter an observation period to determine their baseline attack rate. LTP therapy is not allowed in this period. The observation period will be at least 4 weeks and may be extended up to 8 weeks, as described below.

Subjects will receive daily treatment with chronic high-dose antihistamine treatment (cetirizine 40 mg/day or equivalent high-dose second-generation antihistamine medication) throughout the observation period.

As indicated in Table 1, during the observation period, the following information will be collected on an ongoing basis:

- Angioedema attack data (**Note**: Subjects must report details of an angioedema attack to the study site within 72 hours of onset of the attack, in accordance with BAARP) [Appendix 5]). Subjects will also use the diary for recording of antihistamine treatment compliance and response to icatibant treatment for acute angioedema attacks.
- Prior/current medications, therapies, and procedures.
- Adverse events collection, including SAEs and AESIs.

Site check-in calls will occur at Weeks 2, 4, 6, and 8 of the observation period (Table 1) to discuss study compliance (completion of the diary) and to evaluate the subject's attack frequency and other AEs that may have occurred since the last contact. The preferred method of site check-in is a telephone call; however, an alternate method of contact may be considered as site policies permit. Telephone contact will be documented in the source notes at the clinical site.

Subjects meeting a minimum baseline angioedema attack rate of at least 1 investigator confirmed angioedema attack per 4 weeks during the observation period may be allowed to exit the observation period at 4 weeks for randomization and will enter the treatment period. In addition, during the observation period, subjects (≥18 years of age) need to be treated with icatibant for at least 2 angioedema attacks or at least 1 moderate or severe attack. In the opinion of the investigator, subjects with no response to icatibant for acute angioedema attacks in the past medical history/screening, or no improvement or worsened attack severity 2 hours after icatibant treatment during the observation period (based on totality of assessments), will not be eligible.

Subjects without at least 1 investigator-confirmed attack in the first 4 weeks may have their observation period extended for another 4 weeks. Subjects who have their observation period extended must complete the full 8-week observation period and must have at least 2 investigator-confirmed attacks during this time to be eligible to enter treatment period.

8.2.2 Treatment Period

8.2.2.1 Study Visit 1; Study Day 0

Visit 1 on Day 0 will be a scheduled on-site visit. After completion of the observation period, if eligible, subjects should begin the treatment period (Visit 1) within 7 days. Any delayed start to the treatment period (ie, >7 days from observation period) due to unexpected event(s) should be discussed with the Sponsor. The following procedures and assessments are to be performed on Day 0 prior to the first dose of investigational product administration. Any angioedema attack must be resolved prior to the first dose in the treatment period.

- Confirmation of study eligibility
- Randomization to blinded study treatment
- Vital signs, including body temperature, HR, BP, and RR
- Complete physical examination (including documentation of body weight)
- 12-lead ECG
- Pregnancy test (for female subjects of childbearing-potential)
- Clinical laboratory testing including hematology, serum chemistry, coagulation, and urinalysis
- Pharmacokinetic sample collection
- Pharmacodynamic sample collection
- Plasma ADA sample collection

- Genotype sample collection (for future exploratory genetic analyses)
- Health-related quality of life assessment (using the AE-QoL questionnaire)
- Prior therapies, medications, and procedures
- Angioedema attack data
- Adverse events collection, including SAEs and AESIs

As specified in Table 2, after the first dose of investigational product administration, the following post-treatment procedures and assessments will be performed:

- Investigational product injection report
- Vital signs including body temperature, HR, BP, and RR at 30 minutes postdose
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

8.2.2.2 Study Visit 2 (Study Day 4) to Study Visit 25 (Study Day 175)

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

- Vital signs including body temperature, HR, BP, and RR
- Physical examination (including documentation of body weight)
- Clinical laboratory testing, including hematology, serum chemistry, coagulation, and urinalysis
- Pharmacokinetic predose sample collection
- Pharmacodynamic predose sample collection
- Plasma ADA predose sample collection
- Angioedema attack data
- Health-related quality of life assessment (using the AE-QoL questionnaire)
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs
- Pregnancy test (for females of childbearing potential) - Visit 16 (Study Day 112) ONLY

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

- Investigational product injection report
- Vital signs including body temperature, HR, BP, and RR at 30 minutes postdose

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

On-site visits will be scheduled at Visits 1, 3, 4, 8, 12, 16, 20, and 24 (shaded columns in Table 2).

Site check-in calls will occur throughout the treatment period. If a subject does not have a scheduled on-site visit on study days specified in Table 2 (Visits 2, 5-7, 9-11, 13-15, 17-19, 21-23, and 25), 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.

8.2.2.3 Final Visit of Treatment Period (Study Visit 26; Study Day 182)

As indicated in Table 2, Visit 26 will be an on-site visit. The following procedures and assessments are to be performed:

- Vital signs including body temperature, HR, BP, and RR
- Physical examination (including documentation of body weight)
- 12-lead ECG
- Pregnancy test (for female subjects of childbearing-potential)
- Clinical laboratory testing, including hematology, serum chemistry, coagulation, and urinalysis
- Pharmacokinetic sample collection
- Pharmacodynamic sample collection
- Plasma ADA sample collection
- Health-related quality of life assessment (using the AE-QoL questionnaire)
- Angioedema attack data
- Concomitant therapies, medications, and procedures
- Adverse events collection, including SAEs and AESIs

Subjects who elect to roll over into a 26-week long OLE study, must provide consent no later than the last day of blinded treatment period on Day 182 (Visit 26). After the completion of all scheduled assessments on Day 182 (Visit 26), subjects will be discharged from this study and will enter the OLE study and receive their first dose of open-label lanadelumab.

8.2.3 Follow-up Period

The follow-up period for this study is 14 days (2 weeks). The final end of study (EOS) visit (Day 196, Visit 27) will be by telephone call from the site to collect information on angioedema attacks, concomitant therapies, medications, and procedures, and AEs. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Appendix 3.2). Subjects will be discharged from the study after the completion of the EOS assessments.

8.2.4 Early Termination

All procedures and assessments scheduled for final visit of the treatment period (Day 182, Visit 26) will be followed for the early termination (ET) visit (see Table 2).

8.2.5 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 and Table 2.

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

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

8.3.4 Efficacy

8.3.4.1 Collection of Angioedema Attack Data

Historical angioedema attack information will be collected at screening. Throughout the study (ie, from screening through follow-up), angioedema attack information will be solicited by site personnel during scheduled study visits and site check-ins, as shown Table 1 and Table 2. In addition, study subjects (or parent/caregivers, in the event the subject is <18 years old or is incapacitated) will be instructed to report details of the 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 5 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

As mentioned in Section 6.6.3, acute angioedema attacks during the study are to be managed with icatibant for subjects (≥18 years of age) and according to the local standard of care for subjects ≥12 to <18 years.

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 and Table 2). 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

In addition, height will be measured at screening visit 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 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. Adverse events, actions taken as a result of AEs, and follow-up results must be recorded in the eCRF as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.
- For any SAEs or AEs that require the subject to be discontinued from dosing, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s). Subjects who discontinue treatment will complete the procedures specified for the final visit of the treatment period (Day 182, Visit 26) 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 non-angioedema 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 6) and the DMID Pediatric Toxicity Table (Appendix 7).
- 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 5), 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)

Adverse events of special interest (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 and Table 2. Routine vital sign assessments will be taken with the subject in the sitting or supine position after 5 minutes at rest and will include body temperature, HR, BP, and RR. Blood pressure should be determined using the same arm and the same equipment, and the same position for each assessment throughout the study.

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

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

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

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

8.3.5.6 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 and Table 2; if pregnancy is suspected or on withdrawal (early termination visit) of the subject from the study. Pregnancy testing at the screening visit will be serum-based. All other 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 and Table 2. 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 Table 2. 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).

8.3.6.2 Pharmacodynamics

Blood samples for the measurement of cHMWK and pKal activity will be obtained at the study days specified in Table 2. 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).

8.3.6.3 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 Table 2. 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

Diagnostic Biomarkers

A blood sample will be obtained at the screening visit for evaluation of C1-INH function, C4, and C1q to confirm a diagnosis of non-histaminergic angioedema with normal C1-INH. Diagnostic testing will be performed by a sponsor-approved central laboratory. Subjects may be retested if results are incongruent with clinical history or believed by the investigator to be confounded by recent C1-INH use.

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 Table 2, 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 Genetics

The sponsor intends to apply genomic research across the TAK-743 development program. 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.

To support these aims, a 5.0 mL sample will be collected at screening for the purpose of identifying genetic mutations to aid in subject stratification prior to randomization (one time only) and an additional 5.0 mL sample will be collected at predose on Day 0 (baseline, one time only) for exploratory genetic analyses. The additional sample collection is optional, has no impact on participation in the main study, and requires a separate informed consent. To ensure subject confidentiality, samples will be stored and analyzed in a de-identified format. Samples will be stored in biorepositories for up to 15 years.

The scope of any present and/or future research will be restricted to candidate gene/proteins/markers related to responses to TAK-743 and BMA such as non-histaminergic angioedema with normal C1-INH.

The intent of this research is not to return results to subjects, unless required to do so by law. Subjects can request return of individual results, but it will not be possible to interpret these. No record of participation in any pharmacogenomic research, or any results derived from it should be recorded in a subject's personal medical records.

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.

For additional information and details, see Appendix 4.

8.3.6.6 Health-related Quality of Life

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 2.

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 8.

8.3.6.7 Healthcare Resource Utilization

Not applicable.

8.3.6.8 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 by the investigator or designee and has demonstrated their understanding of self-administration. Subjects may initiate self-administration after receiving the first 2 doses of investigational product administered by study staff at the study site. The subject is required to return to the site for visits as outlined in the Study Schedule of Activities (Table 2). 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.

8.3.6.9 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 2. 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 and Table 2).

Laboratory testing includes general safety parameters (hematology, serum chemistry, coagulation, and urinalysis), serology, pregnancy tests, C1-INH functional assay, C4 assay, C1q assay, PK, PD, plasma ADA testing, and pharmacogenomic/genotyping. All laboratory tests will be performed using established and validated methods.

When multiple sample collection types are performed at the same assessment time point, the samples will be drawn in the following order (depending on what sample types are to be collected at that time point): laboratory safety samples (hematology, coagulation, serum chemistry), C1-INH, C4, C1q, PK, ADA, PD. Subjects will be in a seated or supine position during blood collection.

As shown in Table 4, during this study it is expected that approximately 218 mL of blood will be drawn from all subjects (if they consent to provide blood samples for genetic testing as specified in Table 1 and Table 2), 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 218 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 4 Volume of Blood to Be Drawn from Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic		5	9	45
Pharmacodynamic		2.7	9	24.3
Antidrug antibody		5	8	40
C1-INH, C4, C1q		5	1	5
HBsAg, HIV, HCV		6	1	6
Safety	Clinical Chemistry	5	9	45
	Hematology and Coagulation	4.7	9	42.3
Genotyping		5	2	10
Total mL		38.4	48[a]	**217.6**

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

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

8.3.8 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.

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.

The SAP will be finalized prior to unblinding to preserve the integrity of the statistical analysis and study conclusions.

All statistical analyses will be performed using SAS® Version 9.4 or higher (SAS Institute, Cary, NC 27513).

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

No interim analysis or adaptive design is planned for this study. However, an independent DMC will be established to provide ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating subjects in the study.

The DMC will adhere to a prospectively determined charter, which will be written by the sponsor and approved by the DMC. The charter will define the responsibilities of the DMC and sponsor, the number and timing of the DMC meetings, the conduct of the meetings, and the data sets to be reviewed by the DMC. Analysis of the data for DMC review will be conducted according to the DMC charter and DMC SAP. Because no formal hypothesis testing for safety assessments is planned, multiplicity concerns regarding repeated analyses are not an issue.

Further details regarding the DMC can be found in the DMC charter, which will be available prior to the first administration of investigational product.

9.3 Sample Size and Power Considerations

Approximately 75 subjects with non-histaminergic normal C1-INH angioedema are planned to be randomized.

Power analyses were based on 10,000 simulations from a negative binomial distribution with dispersion parameter of 2 and 0.5 for lanadelumab and placebo-treated subjects, respectively, a 10% dropout with exponential loss-to-follow-up, and will be analyzed using a general linear model for count data assuming a Poisson distribution with Pearson chi-square scaling of standard errors to account for potential overdispersion. The randomization ratio was set at 2:1 for lanadelumab:placebo. The effect size of 60% reduction compared to placebo was based on the results observed in the pivotal study in subjects with HAE (Study DX-2930-03). In Study DX-2930-03, the lower 95% confidence limit for attack rate reduction (lanadelumab

300 mg q2wks group versus placebo) was 76.2%. Due to higher disease variability, a more conservative effect size assumption of 60% was assumed for subjects with non-histaminergic angioedema with normal C1-INH.

Assuming a treatment effect of at least a 60% reduction in the investigator-confirmed attack rate as compared with placebo and a placebo attack rate of 1 attack/4 weeks during the analysis period, a sample size of 75 subjects would provide at least 85% power (at α=0.025, 1-sided).

9.4 Statistical Analysis Set(s)

The analysis sets are defined as:

- Treatment Period Full Analysis Set (FAS) will include all randomized subjects who receive any exposure to the investigational product during the treatment period. Subjects will be analyzed according to their randomized treatment assignment regardless of the treatment actually received.
- Steady State Period FAS will include all randomized subjects who receive any exposure to the investigational product during the steady state period. Subjects will be analyzed according to their randomized treatment assignment regardless of the treatment actually received.
- Safety Analysis Set (SAS) will include all subjects who receive any exposure to the investigational product. Subjects will be analyzed according to the treatment actually received regardless of randomized treatment assignment.
- Pharmacokinetic Set (PK Set) will include all subjects in the SAS who have at least 1 evaluable postdose PK concentration value.
- Pharmacodynamic Set (PD Set) will include all subjects in the SAS who have at least 1 evaluable postdose PD concentration value.

9.5 Disposition, Demographics and Baseline Characteristics, and Exposure

9.5.1 Subject Disposition

The number of subjects randomized, treated with study drug, completing the study, and discontinuing prematurely by reason for withdrawal, will be summarized.

9.5.2 Demographics and Other Baseline Characteristics

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

9.5.3 Exposure and Treatment Compliance

Treatment compliance and the extent of exposure to investigational product will be described by the percentage of planned doses received by the subject, total number of doses received by the subject, and the number and percentage of subjects who received at least 80% of planned doses, summarized for each analysis population.

9.5.4 Prior and Concomitant Medications

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

9.6 Efficacy Analyses

9.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint, number of investigator-confirmed angioedema attacks during the treatment period (Day 0 through Day 182), will be compared between treatment group (lanadelumab versus placebo) using the Treatment Period FAS.

The primary efficacy endpoint will be analyzed using a generalized linear model for count data assuming a Poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential overdispersion. The model will include fixed effects for treatment group (categorical), normalized baseline attack rate (continuous), and stratification factor of subtype (categorical). The logarithm of time in days each subject was observed during the treatment period will be used as an offset variable in the model. From this model, the least squares mean rate and standard error for each treatment group as well as the mean rate ratios relative to the placebo group and corresponding 95% confidence intervals will be estimated. These estimates will be reported as mean event rates per 4 weeks by transforming the estimates using the exponential function and scaling by the unit of time.

The primary endpoint will be tested by the following hypothesis:

$H_0: \lambda_{lanadelumab} / \lambda_{placebo} = 1$ versus $H_1: \lambda_{lanadelumab} / \lambda_{placebo} \neq 1$

Where $\lambda_{lanadelumab}$ refers to the mean investigator-confirmed angioedema attack rate in the lanadelumab group and $\lambda_{placebo}$ refers to the mean investigator-confirmed angioedema attack rate in the placebo group. The null hypothesis is that the mean investigator-confirmed angioedema attack rate ratio is 1 (no difference between treatment groups), versus the alternative hypothesis that the angioedema attack rate ratio is not 1. Estimated attack rate ratios less than 1 would indicate that subjects treated with lanadelumab, on average, have a lower incidence of investigator-confirmed angioedema attacks during the presumed steady-state treatment period. The hypothesis will be tested using the model-based least squares means estimate of the treatment difference (expressed as rate ratio relative to placebo) using a Wald-based chi-square test with Type I error set at 5%.

9.6.2 Secondary Efficacy Endpoints

The rank-ordered secondary efficacy endpoints are as follows:

1. Subjects that are attack-free during the treatment period (Day 0 through Day 182).

2. Number of investigator-confirmed moderate or severe angioedema attacks during the treatment period (Day 0 through Day 182).
3. Number of investigator-confirmed angioedema attacks during the presumed steady state period (Day 70 through Day 182).
4. Subjects that are attack-free during the presumed steady state period (Day 70 through Day 182).
5. Number of investigator-confirmed moderate or severe angioedema attacks during the presumed steady state period (Day 70 through Day 182).

The rank-ordered secondary endpoints based on count data (ie, number of angioedema attacks during a specified period) will be analyzed using the same method as described for the primary efficacy endpoint with adjustments made to the offset term and analysis set based on the defined analysis period.

The rank-ordered secondary endpoints based on binary endpoints (ie, subjects that are attack-free during a specified analysis period) will be compared between treatment groups using the FAS specific to the analysis period of interest.

The number and percentage of subjects who are attack-free for the specified analysis period, as well as the difference between treatment arms and corresponding 95% confidence interval (CI) will be summarized. For subjects who discontinue the study prior to completion of the analysis period of interest, subjects will be classified as attack-free or not based on the observed contribution to the analysis period.

The rank-ordered binary endpoints will be tested by the following hypothesis:

H_0: $p_{lanadelumab} = p_{placebo}$ versus H_1: $p_{lanadelumab} \neq p_{placebo}$

Where $p_{lanadelumab}$ refers to the proportion of subjects that are attack-free during the specified analysis period in the lanadelumab group and $p_{placebo}$ refers to the proportion of subjects that are attack-free during the specified analysis period in the placebo group. The null hypothesis is that the proportion of attack-free subjects in the lanadelumab treatment group is equal to that in the placebo group, versus the alternative hypothesis that the proportions are not equal. A Cochran-Mantel-Haenszel (CMH) test, adjusting for baseline stratification factor(s) (categorical), will be used to test the null hypothesis, with Type I error set at 5%. A Mantel-Haenszel estimate for the common risk difference and corresponding stratified Newcombe confidence limits will be presented.

To adjust for the potential of inflated overall Type I error rate, the rank ordered secondary endpoints will be tested in a fixed sequence using a general gatekeeping approach consistent with the logical restrictions of the rank ordering of the endpoints. Secondary endpoints will not be declared statistically significant unless the primary endpoint is found to be statistically significant. Lower ranked secondary endpoints will not be declared statistically significant unless the primary and all of the higher ranked secondary endpoints are found to be statistically significant. The multiple testing procedure is detailed in Section 9.9.2.

Additional secondary efficacy endpoints are as follows:

- Maximum attack severity during presumed steady state period (Day 70 through Day 182) and treatment period (Day 0 through Day 182)
- Time to first angioedema attack after Day 0
- Time to first angioedema attack after Day 70
- Achievement of at least a 50%, 70%, 90% and 100% reduction in the investigator-confirmed normalized number of attacks (NNA) per 4 weeks during each of the efficacy evaluation periods relative to the observation period NNA
- Achievement of an efficacy evaluation period NNA <1.0 per 4 weeks during each of the efficacy evaluation periods

9.6.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints will be defined in the SAP**.**

9.7 Safety Analyses

All safety analyses will be based on the SAS. Analyses will be summarized by treatment.

Treatment-emergent adverse events are defined as AEs with onset at the time of or following the start of treatment with study medication, 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. The number and percentage of subjects with TEAEs will be displayed for each treatment group by system organ class (SOC) and PT using the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries in terms of severity and relationship to study medication will also be provided. Related, serious, related serious AEs, and AESIs will be summarized separately in a similar fashion. Patient listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs and AESIs will be produced.

Actual values and change from baseline in vital signs and clinical laboratory tests will be summarized for the treatment groups with descriptive statistics at each assessment obtained.

Usage of concomitant medications will be summarized descriptively for the treatment groups.

Abnormal physical examination findings will be listed.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and visit. Potentially clinically important findings will also be summarized or listed.

9.8 Other Analyses

9.8.1 Health-related Quality of Life Analyses

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

9.8.2 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

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

A descriptive summary analysis will be performed for cHMWK and pKal levels, C1-INH, and C4, as appropriate, using nominal time points.

The PK and PD properties of lanadelumab (including PK parameters, cHMWK, C1-INH, C4, and additional biomarkers as appropriate) will be evaluated by a population modeling and a simulation approach using data from this study and from all other studies in the lanadelumab clinical development program. A separate clinical pharmacology SAP will support the population PK and PD analysis and the analysis results will be reported separately.

9.8.3 Immunogenicity Analyses

Immunogenicity data will be summarized using descriptive statistics.

The effect on ADA and neutralizing antibodies on PK of lanadelumab, PD (cHMWK), and the number of investigator-confirmed angioedema attacks during the efficacy evaluation periods will be assessed and results will be provided in the population PK and PD analysis report.

9.9 Statistical/Analytic Considerations

9.9.1 Control of Type I Error

There will be 1 primary statistical comparison within this study with Type I error rate set at 5%.

9.9.2 Multiplicity Adjustment

The global family-wise Type I error rate (FWER) for the statistical tests of the primary and rank ordered secondary efficacy endpoints (rank specified in Section 9.6.2) will be controlled at 0.05. To strongly control the global FWER at this level, a general gatekeeping approach will be utilized in which the statistical tests will be conducted in a sequential manner. Testing will continue in sequence until the first test that the null hypothesis cannot be rejected; statistical significance cannot be declared for that test or for any of the remaining tests.

To further illustrate this approach, the test for the primary endpoint will be conducted first at the 5% significance level for the active treatment group compared with the placebo group and, if significant, the first secondary endpoint will be similarly tested at the 5% significance level. The testing sequence will continue in order through the remaining secondary endpoints for active treatment group to placebo comparison as long as the null hypothesis is rejected at the 5% significance level.

9.9.3 Handling of Missing Data

All available data will be included in the analysis. The length of time a subject was observed during the efficacy evaluation period will be included as an offset variable in the generalized linear model to adjust for differences in follow-up time.

9.9.4 Multicenter Studies

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

9.9.5 Subgroup Analyses

Subgroup analyses are planned to be conducted for the primary efficacy endpoint and AEs (non-angioedema attack treatment period AEs, related AEs, and severe AEs). Any p-values that are presented will be descriptive.

The following subgroups will be used:

- Age group
- Sex
- Race group
- Weight group
- Body mass index group
- Observation period angioedema attack rate group
- Subtype in angioedema
- Geographic region
- History of laryngeal angioedema attack

The subgroups will be analyzed using the same method as described for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint and the adverse events.

9.9.6 Sensitivity Analyses

Sensitivity analyses will be performed on the primary efficacy endpoint and/or secondary endpoints to evaluate the robustness of the results. These analyses will be described in detail in the statistical analysis plan.

The following sensitivity analyses are planned:

1. The primary analysis will be repeated using the SAS.
2. The primary analysis will be repeated using all subject-reported angioedema attacks instead of limiting the analysis to those attacks that were investigator-confirmed.
3. The primary analysis will be repeated using a generalized linear model assuming a negative binomial distribution.
4. The impact of missing data on the primary analysis will be explored using a tipping point analysis.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix 1 Regulatory, Ethical, and Study Oversight Considerations

Appendix 1.1 Regulatory and Ethical Considerations

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

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

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

Appendix 1.2 Sponsor's Responsibilities

Good Clinical Practice Compliance

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

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

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

Indemnity/Liability and Insurance

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

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

Public Posting of Study Information

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

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

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

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

Study Suspension, Termination, and Completion

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

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

Appendix 1.3 Investigator's Responsibilities

Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP 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 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], 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, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting.

Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan 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.

Data Handling

Data that may potentially unblind the treatment assignment (ie, investigational product serum concentrations, antibodies to investigational product, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

Appendix 1.5 Ethical Considerations

Informed Consent

It is the responsibility of the investigator to obtain written informed consent and assent, where applicable from all study subjects prior to any study-related procedures including screening assessments. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities.

A copy of the informed consent and assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

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

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

Institutional Review Board or Ethics Committee

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

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

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement. Investigational product supplies will not be released until the 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 HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO.

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

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

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

Study Results/Publication Policy

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

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

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

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

Hematology

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

Coagulation

- Prothrombin time
- Activated partial thromboplastin time (aPTT)
- International normalized ratio (INR)

Urinalysis

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

Virology (at screening only)

Hepatitis B surface antigen (HBsAg); hepatitis C virus (HCV); human immunodeficiency virus (HIV)

Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

Appendix 3.1 Adverse Event Definitions

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

Treatment-emergent Adverse Event

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

Serious Adverse Event

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

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

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

Unexpected Adverse Event

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the 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 5).

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 6) and DMID Pediatric Toxicity Table (Appendix 7).

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:

- aPTT prolongation in the absence of any associated bleeding or other evidence of clinical relevance will not be considered a clinically significant laboratory abnormality or AE. In the appropriate physiologic setting, such as IV heparin therapy, aPTT can be used to monitor bleeding risk. However, as noted in the 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 factor XII 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 8.2.3. 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 6) and DMID Pediatric Toxicity Table (Appendix 7). Angioedema attacks are also captured as AEs in this study; angioedema attacks assessed as described in BAARP (Appendix 5), 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 (see 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 8.2.3 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 informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

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

- Resolved with or without residual effects.
- A return to baseline for a pre-existing condition.
- Laboratory values have returned to baseline or stabilized.
- The investigator does not expect any further improvement or worsening of the event.

Fatal outcome (see Appendix 3.7)—if an autopsy is performed; the autopsy report is requested to be provided to the sponsor as soon as it is available.

Appendix 3.7 Fatal Outcome

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

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

Appendix 3.8 Pregnancy

All pregnancies are reported from the time informed consent is signed until the defined follow-up period stated in Section 8.2.3.

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 (see Appendix 1.5).

Appendix 4 Genetics

The sponsor intends to apply genetic research across the TAK-743 development program to explore how genomic variations may affect the clinical parameters associated with and response to TAK-743 (and any background products, comparators, and concomitant medications), and potentially the basis of the indication cohorts under study in the protocol, in this case BMA such as non-histaminergic angioedema with normal C1-INH. Collection of appropriate samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical studies, genetically guided treatment strategies, and a better understanding of disease etiology, which may lead to new therapeutic approaches.

Candidate genes which may be studied include those potentially related to the mechanism of action of TAK-743, as well as those potentially responsible for absorption, disposition, metabolism, and excretion of TAK-743. Future research may suggest other genes, gene categories, proteins, etc., as candidates for influencing not only response to TAK-743, but also susceptibility to BMA such as non-histaminergic angioedema with normal C1-INH for which TAK-743 may be evaluated. Thus, this additional genomic research may involve the future study of additional unnamed genes or gene categories that may be associated with non-histaminergic angioedema with normal C1-INH disease susceptibility and drug action.

Samples will be drawn during screening and prior to the first administration of investigational product. A 5.0 mL sample will be collected at a single time point during screening for the purpose of identifying genetic mutations to aid in subject stratification prior to randomization and an additional 5.0 mL sample will be collected at predose on Day 0 (baseline, one time only) for the purpose of exploratory genetic analyses. Samples may only be collected from subjects who provide separate informed consent, as detailed in the laboratory manual.

Samples will be labeled with the study protocol number, the subject's study identification number, and information related to the sample (eg, sample type [DNA, RNA, protein], study day/period, sample time). No personal identifiers will be recorded on the sample labels.

Subjects terminating early from the study due to AE, tolerability, or drug-related issues should, where possible, be approached for their remaining protocol-defined samples at the earliest possible time. Unscheduled samples should be labeled with free text capturing study protocol number, subject's study identification number, and information related to the sample (RNA or protein, sampling date, and time). Samples will be shipped to and stored at biorepositories as detailed in the laboratory manual. DNA, RNA, and protein will be extracted from the samples only when, and if, any separate exploratory research will be undertaken.

No record of participation in this pharmacogenomics portion of the protocol, or any results derived from it, should be recorded in the subjects' personal medical records. A record of participation in the pharmacogenomics portion of the protocol will, however, be captured in the study-specific source documentation records or CRF.

The sponsor, sponsor's representatives, biorepositories, and any specialty laboratories will be blinded to the subject's identity. The sample and/or extracted material will otherwise be stored for up to 15 years from the end of the study after which time it will be destroyed. Upon written

request, subjects will be permitted to withdraw their sample from the analysis and have their sample and/or extracted material destroyed. The link will also be destroyed at the same time as any remaining sample(s) are destroyed. Any results already generated from the samples will not be removed from any analyses that have already been performed.

Participation in this portion of the study is optional and does not impact the subject's eligibility for participation in the main clinical study. Subjects may continue to participate in the primary study if they refuse to provide a blood sample or if they withdraw their samples.

Results of the genetic analyses may contribute to the global understanding of BMA such as non-histaminergic angioedema with normal C1-INH and its treatment and 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. Any results generated will be for exploratory research purposes only and will not be made available unless required by law (ie, to regulatory authorities). Additionally, as any potential analysis does not form part of predefined analysis within the clinical study protocol, any results will be reported separately to the main clinical study report. Subjects may request the results of any analysis on their samples, although it will not be possible to interpret these.

APPENDIX 5 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 6 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

.... DIVISION OF MICROBIOLOGY AND INFECTIOUS ... DISEASES (DMID) ADULT TOXICITY TABLE 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 7 NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES (US NATIONAL INSTITUTES OF HEALTH; NATIONAL INSTITUTE OF ALLERGY AND INFECTION DISEASES)

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

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

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

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

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

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

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

ABBREVIATIONS: Abbreviations utilized in the Table:

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

ESTIMATING SEVERITY GRADE

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

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

SERIOUS OR LIFE-THREATENING AEs

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

COMMENTS REGARDING THE USE OF THESE TABLES

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

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

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

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

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

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

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

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

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

(Greater than 3 months of age)

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

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

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

(Greater than 3 months of age)

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

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

(Greater than 3 months of age)

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

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

(Greater than 3 months of age)

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

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

(Greater than 3 months of age)

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

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

	cells/hpf	cells/hpf		

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

(Greater than 3 months of age)

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

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

(Greater than 3 months of age)

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

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

(Greater than 3 months of age)

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

Appendix 8 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 9 Abbreviations

Abbreviation	Definition
ACE	angiotensin-converting enzyme
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)
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (synonymous with SGOT)
AUC	area under the curve
$AUC_{0-\infty}$	area under the curve from time 0 to infinity
AUC_{0-last}	area under the 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
BP	blood pressure
BMA	bradykinin-mediated angioedema
C1-INH	C1 inhibitor or C1 esterase inhibitor
CFR	Code of Federal Regulations
cHMWK	cleaved high molecular weight kininogen
C_{max}	maximum concentration
CRF	case report form
CRA	clinical research associate
CRO	contract research organization
DMC	data monitoring committee
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency

Abbreviation	Definition
EOS	end of study
ET	early termination
EU	European Union
EUDRACT	European Union clinical trials database
FDA	Food and Drug Administration
FWER	family-wise Type I error rate
GCP	Good Clinical Practice
HAE	hereditary angioedema
HIV	human immunodeficiency virus
HMWK	high molecular weight kininogen
HR	heart rate
HR-QoL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ISR	injection site reaction
LTP	long-term prophylaxis
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NNA	normalized number of attacks
OLE	open-label extension
PFS	prefilled syringe
PK	pharmacokinetic(s)
pKal	plasma kallikrein
PT	preferred term
q2wks	every 2 weeks
q4wks	every 4 weeks

Abbreviation	Definition
REB	research ethics board
RNA	ribonucleic acid
RR	respiratory rate
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
t_{max}	time to maximum concentration
UK	United Kingdom
US	United States
WHO	World Health Organization

Appendix 10 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	07 Aug 2019	Global
Amendment 1	28 Apr 2020	VHP
Amendment 1.1	14 May 2020	All Regions except VHP
Amendment 2	18 Aug 2020	Global
Amendment 3	19 April 2021	Global

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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**
Clarification that estrogen-containing medications are only excluded for patients with normal C1-INH angioedema; patients with AAE due to C1-INH deficiency are allowed to take estrogen-containing medications.	Section 5.4.1 Section 6.6.4
Repeated footnotes (a-d) for Table 1 removed.	Section 1.3
Table header formatting issues for Table 1 and Table 2.	Section 1.3
Revision of inclusion criterion #8 to clarify that females of childbearing potential must have a negative serum pregnancy test at screening and be willing to undergo pregnancy tests throughout the study.	Synopsis Section 5.1
Definition of abstinence, as outlined in the CTFG guidance on contraceptions, was added.	Synopsis Section 5.1 Section 5.4.2
Patients <18 years of age will not be enrolled at study sites in Germany.	Synopsis Section 4.1

SUMMARY OF CHANGES FROM PREVIOUS VERSION

A summary of the 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**
Revised emergency contact information to reflect the most up-to-date and accurate information.	Emergency Contact Information
Patients <18 years of age will not be enrolled at study sites in Germany.	Section 1.1 Section 4.1
Revised the number of sites and included Asia-Pacific as an additional region that will have participating sites.	Section 1.1
Definition of abstinence, as outlined in the CTFG guidance on contraceptions, was added.	Section 1.1 Section 5.1 Section 5.4.2
Revision of inclusion criterion #8 to clarify that females of childbearing potential must have a negative serum pregnancy test at screening and be willing to undergo pregnancy tests throughout the study.	Section 1.1 Section 5.1
Revised exclusion criterion #4 to exclude estrogen-containing medication within 4 weeks (versus 6 months) prior to screening.	Section 1.1 Section 5.2 Section 6.6.4
Added the following language to exclusion criterion #6 "… as long as the investigator determines that doing so would not place the subject at any undue safety risk, and that the subject is at least 18 years of age."	Section 1.1 Section 5.2
Removed the following language from exclusion criterion #9 and moved to description of Study Visit 1 (Study Day 0): "… any angioedema attack must be resolved prior to the first dose in the treatment period."	Section 1.1 Section 5.2 Section 8.1.2.1

Summary of Change(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
Extended the planned duration of the screening period to up to 8 weeks and overall study duration to approximately 44 weeks.	Section 1.1 Section 4.1 Section 4.4 Section 8.1.1.1
Revised the logarithm for the time in days for the primary efficacy endpoint to state "… during the treatment period…" (versus steady-state period)".	Section 1.1 Section 9.6.1
Repeated footnotes (a-d) for Table 1 removed.	Section 1.3
Table header formatting issues for Table 1 and Table 2.	Section 1.3
Clarification that estrogen-containing medications are only excluded for patients with normal C1-INH angioedema; patients with AAE due to C1-INH deficiency are allowed to take estrogen-containing medications.	Section 5.4.1 Section 6.6.4
Added pregnancy test at Visit 16 to align with Schedule of Activities.	Section 8.1.2.2
Revised subgroup analysis to state "…non-angioedema attack treatment period." (vs. non-HAE attack treatment period)	Section 9.9.5
Revised language on severity of AEs to be consistent across lanadelumab studies.	Appendix 3.3
Removed language regarding double coding.	Appendix 4

SUMMARY OF CHANGES FROM PREVIOUS VERSION

A summary of the changes incorporated into Amendment 2 is provided in the table below.

Summary of Change(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
Shire Global Drug Safety was updated 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
[redacted], MD was added as contact for IQVIA medical monitor.	Emergency Contact Information
The study population was revised to remove subjects with Acquired Angioedema (AAE) due to C1-INH deficiency. As a result of removing AAE subjects: • Title of study revised to remove AAE subjects • Total subjects have been reduced to approximately 75 • Study sites were reduced to approximately 60 • The cap for each non-histaminergic C1-INH angioedema subtype was removed • Objectives and endpoints were revised to remove AAE subjects. • Inclusion / Exclusion criteria were revised to remove AAE subjects. • Statistical analysis was revised to remove AAE subjects. • The Study Schema has been revised. • Removed note that estrogen-containing medications are allowed for AAE subjects	Section 1 Protocol Summary Section 2 Introduction Section 3 Objectives and Endpoints Section 4 Study Design Section 5.1 Inclusion Criteria Section 5.2 Exclusion Criteria Section 5.4.1 Female Contraception Section 6.2.2 Allocation of Subjects to Treatment Section 6.6.4 Prohibited Treatment Section 9 Statistical Considerations

Summary of Change(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
For study site regions, removed specific countries in Europe and added Japan.	Section 1.1 Synopsis Section 4.5 Sites and Regions
Clarified that LTP must be discontinued during the observation period and that the observation period will serve as the baseline attack rate.	Section 1.1 Synopsis Section 4 Study Design Section 8.2.1.3 Observation Period
Clarified that observation period is *up to* 8 weeks and provided additional detail on subject eligibility.	Section 1.1 Synopsis Section 1.3 Schedule of Activities Section 4 Study Design Section 8.2.1.3 Observation Period
The study number for the open-label extension study was added (Study TAK-743-3001).	Section 1.1 Synopsis Section 4 Study Design
"Antigen" in regards to C1-INH antigen was removed.	Section 1.1 Synopsis Section 5.1 Inclusion Criteria Section 8.3.6.4 Biomarkers Section 8.3.7 Volume of Blood to be Drawn from Each Subject
Inclusion criteria #9 and #10 were combined into a single exclusion criterion (now #7).	Section 1.1 Synopsis Section 5.1 Inclusion Criteria
"Concentration" in regards to plasma cHMWK and pKal levels was removed.	Section 1.1 Synopsis Table 3

Summary of Change(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
Clarified that the Screening period is *up to* 8 weeks.	Section 1.2 Schema Section 1.3 Schedule of Activities Section 8.2.1.1 Screening Period
An additional visit prior to the start of the observation period was added. This visit will allow for an eligibility review, angioedema attack and AE monitoring, and distribution of icatibant and antihistamine treatment.	Section 1.3 Schedule of Activities Section 8.2.1.2 Start of Observation Period
Clarified if C1-INH therapy has been used, the drug should be washed out for at least 5 half-lives before C1-INH, C4, and C1q testing.	Section 1.3 Schedule of Activities Section 8.2.1.1 Screening Period
Added study procedure modifications due to COVID-19 pandemic.	Section 1.3 Schedule of Activities Section 8.1 Changes to Study Procedures Due to the COVID-19 Pandemic
Removed Plasma PK and PD Sample from Visit 2 to Visit 3. Visit 2 is now an off-site visit. Reference to collecting samples predose on Study Day 4 was removed.	Section 1.3 Schedule of Activities Section 8.3.6.1 Clinical Pharmacology Section 8.3.6.2 Pharmacodynamics
Provided clarification that subjects should being Visit 1 in the treatment period within 7 days of the observation period. Any delay to the start of the treatment period should be discussed with the Sponsor.	Section 1.3 Schedule of Activities Section 8.2.2.1 Study Visit 1; Study Day 0
Added angioedema attack monitoring.	Section 8.2.1.1 Screening Period
Revised physical examinations to include body weight as part of *all* examinations.	Section 8.3.5.1 Physical Examination
Revised *Exploratory Endpoints* to *Exploratory Efficacy Endpoints* and added text indicating that exploratory efficacy endpoints will be defined in the SAP.	Section 9.6.3 Exploratory Efficacy Endpoints