# Clinical Study Protocol

NCT Number: NCT05460325

Title: A Multi-center, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of Lanadelumab (SHP643) in Chinese Subjects With Hereditary Angioedema

Study Number: SHP643-304

Document Version and Date: Amendment 2, 09 February 2023

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

**TAKEDA PHARMACEUTICALS**

| | |
|---|---|
| **Protocol:** | SHP643-304 |
| **Title:** | A Multi-center, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of Lanadelumab (SHP643) in Chinese Subjects with Hereditary Angioedema |
| **Short Title:** | Lanadelumab China Study |
| **Study Phase:** | Phase 3 |
| **Drug:** | Lanadelumab (SHP643); TAKHZYRO™ |
| **IND Number:** | Non-IND |
| **EUDRACT Number:** | Non-EUDRACT |
| **Sponsor:** | Takeda Development Center Americas, Inc.<br>95 Hayden Ave, Lexington, MA 02421, USA |
| **Principal / Coordinating Investigator:** | Dr. [redacted] |
| **Protocol History:** | Original Protocol: 26 Aug 2021<br>Protocol Amendment 1: 12 Apr 2022<br>Protocol Amendment 2: 9 Feb 2023 |



**Confidentiality Statement**

## PROTOCOL SIGNATURE PAGE

*Sponsor's (Takeda) Approval*

DocuSigned by:
[redacted]
10-Feb-2023 | 14:38:30 JST

*Signature:* [redacted], MD *Date:*

### Investigator's Acknowledgement

I have read this protocol for Study SHP643-304.

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

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

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

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

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

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

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

*Signature:* *Date:*

## SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

The main purpose of this amendment 2 is to add the potential to conduct an interim analysis to support the supplementary New Drug Application (sNDA) submission for China pediatric indication. The other purposes are to emphasize the consent requirement for adolescent subjects (<18 years of age) that reach the age of 18 years, extend the time frame of screening from up to 2 weeks to up to 4 weeks, and add the requirement to exclude subjects using any lanadelumab prior to the study to current exclusion criteria #2.

A summary of the changes incorporated into Amendment 2 is provided in the table below. Any minor revisions in grammar, spelling, punctuation, and format are not reflected in the summary of changes.

| **Protocol Amendment** | | |
|---|---|---|
| **Summary of Change(s) Since the Last Version of the Approved Protocol** | | |
| **Amendment Number**<br>**2** | **Amendment Date**<br>**9 Feb 2023** | **China** |
| **Description of Each Change and Rationale** | | **Section(s) Affected by Change** |
| The following information was added, an interim data analysis may be performed potentially to support the sNDA submission for China pediatric indication. The interim analysis will at least summarize the efficacy, safety and PK of treatment with lanadelumab in Chinese subjects with HAE when approximately 10 subjects complete the 26 weeks treatment period and 4 weeks follow-up period. | | Synopsis<br>Section 9.2 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee |
| To emphasize that for the adolescent subjects (<18 years of age) enrolled in the study that reach 18 years of age during study periods, a consent using the most current version of the informed consent form by subject is required. | | Table 1 Schedule of Study Activities<br>Section 8.1 Study Periods |
| To emphasize that both AESI and SAE should be reported to sponsor or CRO within 24 hours by investigator by adding AESI reporting requirement in administrative information and Table 1. | | Administrative Information<br>Table 1 Schedule of Study Activities<br>Appendix 3.4 Safety Reporting |
| Extended the time frame of screening from up to 2 weeks to up to 4 weeks for feasibility of study due to COVID-19. Accordingly, the maximum duration of participation was extended from 42 weeks to 44 weeks. | | Synopsis<br>Section 1.2 Schema<br>Section 4.1 Overall Design<br>Section 4.3 Duration of Subject Participation and Study Completion Definition<br>Section 8.1.1 Screening Visit and Washout Period |
| Added the requirement to exclude subjects using any lanadelumab prior to the study to current exclusion criteria #2. | | Synopsis<br>Section 5.2 Exclusion Criteria |

| **Protocol Amendment** | | |
|---|---|---|
| **Summary of Change(s) Since the Last Version of the Approved Protocol** | | |
| **Amendment Number**<br>**2** | **Amendment Date**<br>**9 Feb 2023** | **China** |
| **Description of Each Change and Rationale** | | **Section(s) Affected by Change** |
| Updated the study progress from "ongoing" to "completed" to two pediatric studies (Study SHP643-301 and Study SHP643-302). Added the summary of results of both studies that lanadelumab was generally well tolerated and a marked reduction in investigator-confirmed HAE attacks was observed in both HAE patient populations evaluated.<br>Added new ongoing studies: two Phase 3 studies in non-histaminergic angioedema subjects with normal C1 esterase inhibitor (C1-INH) (SHP643-303 and TAK-743-3001, and two prospective, non-interventional Phase 4 studies in HAE patients (Study SHP643-402 and Study SHP643-403). | | Section 2.2 Clinical Information |
| Remove liver toxicity (EU specific risk) as an important potential risk, per Investigator's Brochure Edition 10.0 Section 6.12. | | Section 2.4 Benefit/Risk Assessment |

AE=adverse event; AESI=adverse event of special interest; HAE=hereditary angioedema; PK=pharmacokinetic; SAE=serious adverse event; sNDA=supplementary New Drug Application

See Appendix 7 for protocol history, including all previous amendments.

## ADMINISTRATIVE INFORMATION

### Contacts

Certain events and study-related activities will require the investigator and/or subject to have appropriate contact information. The sponsor or contract research organization (CRO) will provide investigators with emergency medical contact information cards to be carried by each subject.

### SAE and AESI Reporting

If a subject experiences a serious adverse event (SAE) or an adverse event of special interest (AESI), the investigator must report the event to the sponsor or CRO **within 24 hours**, by completing an SAE or AE or hereditary angioedema (HAE) acute attack electronic case report form (eCRF) in English or report via the paper safety report form (as back-up) within 24 hours of becoming aware of any SAE or AESI respectively. The fax number and e-mail address are provided in the Form Completion Instruction.



### Protocol and Safety-Related Questions or Concerns

For protocol- or safety-related questions or concerns, the investigator must contact the Takeda OR IQVIA medical monitor:

**Takeda medical monitor**

Name: [redacted], MD

Phone: [redacted]

E-mail: [redacted]

**IQVIA medical monitor**

Name: [redacted]

Phone: [redacted]

E-mail: [redacted]

## PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Takeda within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis.

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

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



Please report the product quality complaint using Clinical Trial Material Compliant Form via the e-mail address:

ctmcomplaint@takeda.com

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

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# 1. PROTOCOL SUMMARY

## 1.1 Synopsis

| | |
|---|---|
| **Protocol number:** SHP643-304 | **Drug:** Lanadelumab |
| **Title of the study:** A Multi-center, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of Lanadelumab (SHP643) in Chinese Subjects with Hereditary Angioedema | |
| **Short title:** Lanadelumab China Study | |
| **Study phase:** Phase 3 | |
| **Number of subjects (total):** The planned total sample size for this study is approximately 20 subjects. | |
| **Principal Investigator:** Dr. [redacted] | |
| **Sites and Region:** The study will be conducted in approximately 5 sites in China. | |
| **Study period (planned):** 2022 to 2024 | |
| **Objectives:**<br>**Primary:**<br>• To evaluate the safety of repeated subcutaneous (SC) administrations of lanadelumab in Chinese subjects with hereditary angioedema (HAE).<br>**Secondary:**<br>• To evaluate the pharmacokinetics (PK) of repeated SC administrations of lanadelumab in Chinese subjects with HAE<br>• To evaluate the pharmacodynamics (PD) of repeated SC administrations of lanadelumab in Chinese subjects with HAE<br>• To evaluate the efficacy of repeated SC administrations of lanadelumab in Chinese subjects with HAE<br>• To evaluate the immunogenicity of repeated SC administration of lanadelumab and the effect on lanadelumab PK, PD, efficacy, and safety | |
| **Rationale:** The safety, PK, PD and efficacy of lanadelumab have been established by the global clinical development program for lanadelumab including two Phase 1 studies and one global Phase 3 pivotal study as well as Phase 3 extension study that are completed.<br>Lanadelumab is expected to fulfill an unmet medical need in China for the prevention of angioedema attacks in patients with Type I or Type II HAE. As part of the approval requirements and post-approval commitment, the China Health authority has requested that further efficacy and safety data be collected from Chinese patients with Type I or Type II HAE. For that, Takeda is planning this multi-center, open-label study to evaluate the safety, efficacy, PK, PD, and immunogenicity of lanadelumab in the Chinese population. | |
| **Investigational product, dose, and mode of administration:** The investigational product, lanadelumab, is a recombinant, fully human, immunoglobin G subclass 1, kappa light chain, monoclonal antibody expressed in Chinese hamster ovary cells. A single dose regimen of 300 mg lanadelumab will be administered to subjects every 2 weeks (q2wks) for 26 weeks for a total of 14 doses. Lanadelumab will be administered by SC injection in the upper arm, thigh, or abdominal area. | |
| **Methodology:**<br>This open-label study will enroll Chinese subjects of 12 years of age or older with a confirmed diagnosis of HAE (Type I or II).<br>The study includes a screening period that may require screening of 4 weeks, a washout period of 2 weeks, a run-in period of 4 to 8 weeks, a treatment period of 26 weeks, and a follow-up period of 4 weeks. Maximum study period will be 44 weeks. | |

Screening Visit and Washout Period:

Following informed consent, subjects will undergo screening assessments. Screened adult subjects who are on LTP (eg, androgens) for HAE are required to undergo a minimum 2-week washout period prior to the run-in period. This LTP washout period is permitted as long as the investigator determines that doing so would not place the subject in any undue safety risk and that the subject is at least 18 years of age (ie, LTP washout is not required in adolescent subjects [≥12 to <18 years of age]). Subjects who fail screening due to a single laboratory test result that does not meet eligibility criteria may have that laboratory test repeated at the discretion of the investigator. This will include a repeat of only the failed assessment rather than a repeat of all screening assessments.

Run-in Period:

Screened subjects who are not on LTP therapy for HAE or who have completed the required washout period will enroll and enter a run-in period of 4 to 8 weeks to determine their baseline attack rate. Only subjects meeting a minimum baseline attack rate of at least 1 investigator-confirmed attack per 4 weeks will be eligible for treatment. Subjects who experience 3 or more investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to the treatment period. Subjects without at least 1 investigator-confirmed attack after 4 weeks will have their run-in period extended by 4 weeks, during which time they need to have at least 2 investigator-confirmed attacks in 8 weeks to be eligible for treatment. Subjects who do not meet the minimum attack rate during the run-in period, or are otherwise determined to be ineligible due to screening assessments, will not be allowed to enter the treatment period of the study and will be replaced with new HAE subjects until approximately 20 subjects have entered the treatment period. Subjects who are found to be ineligible during the run-in period will not be allowed to rescreen into the study.

Treatment Period:

Subjects who enter the treatment period will receive lanadelumab 300 mg q2wks for 26 weeks. Subjects who complete the treatment period will receive a total of 14 doses of lanadelumab from Day 0 to Day 182 (±3 days).

Follow-up Period:

After completion of the 26 weeks treatment period, subjects will be followed for an additional 4 weeks and will attend the follow-up visit on Day 210 (±3 days).

In the event a monitor cannot visit the site in a timely manner due to the coronavirus disease 2019 (COVID-19) pandemic, alternative monitoring approaches such as remote source data verification or telephone contact may be used to ensure data quality and integrity and maintain subject safety. Alternative monitoring approaches should be used only where allowed by the local Health Authority and permitted by the institutional review board (IRB)/independent ethics committee (IEC).

Acute HAE attacks during the study will be managed in accordance with the investigator's usual care of their subjects, including use of individualized acute therapy/rescue medications. The acute therapy/rescue medications include FIRAZYR, fresh frozen plasma (FFP), or other local standard of care.



**Inclusion and Exclusion Criteria:**

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

**Inclusion Criteria:**

- Be of Chinese descent, defined as born in China and having Chinese parents and Chinese maternal and paternal grandparents.
- The subject is male or female and ≥12 years of age at the time of informed consent.
- Documented diagnosis of HAE Type I or Type II based upon all of the following:
  - Documented clinical history consistent with HAE (SC or mucosal, nonpruritic swelling episodes without accompanying urticaria).
  - Diagnostic testing results obtained during screening by a laboratory (approved by the sponsor) that confirm HAE Type I or Type II: C1 esterase inhibitor (C1-INH) functional level <40% of the normal level. Subjects with functional C1-INH level 40% to 50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may begin participating in the run-in period before these diagnostic results are available.

Subjects may be re-tested if results are incongruent with clinical history or believed by the investigator to be confounded by recent LTP use.

- At least one of the following: Age at reported onset of first angioedema symptoms ≤30 years, a family history consistent with HAE Type I or Type II, or C1q within normal range.

- Attack rate:
  - At the time of enrollment, subjects must experience at least 1 investigator-confirmed HAE attack per 4 weeks during the run-in period.
- The subject (or the subject's parent/legal guardian, if applicable) has provided written informed consent approved by the IRB/IEC.
  - If the subject is an adult, be informed of the nature of the study and provide written informed consent before any study-specific procedures are performed.

  OR
  - If the subject is a minor (ie, <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.
- Males, or non-pregnant, non-lactating females who are fertile and sexually active and who agree to be abstinent or agree to comply with the applicable contraceptive requirements of this protocol for the duration of the study, or females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or postmenopausal for at least 12 months.
- Agree to adhere to the protocol-defined schedule of assessments and procedures.

**Exclusion Criteria:**

1. Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema, HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.
2. Participation in a prior lanadelumab study or use any lanadelumab prior to the study.
3. Dosing with investigational drug or exposure to an investigational device within 4 weeks prior to entering to screening.
4. Exposure to angiotensin-converting enzyme inhibitors or any estrogen-containing medications with systematic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
5. Exposure to androgens (eg, danazol, methyltestosterone, testosterone) within 2 weeks prior to entering the run-in period.
6. Use of LTP therapy (defined as continued use) for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) for adult subjects within 2 weeks prior to entering the run-in period. Adolescent subjects (≥12 to <18 years of age) who are on LTP therapy for HAE are allowed to enter the study.
7. Use of short-term prophylaxis for HAE 7 days prior to entering the run-in period. Short-term prophylaxis is defined as FFP, C1-INH, attenuated androgens, or antifibrinolytics used to avoid angioedema complications from medically indicated procedures. Note: Currently, C1-INH therapies are not available in China.
8. Any of the following liver function abnormalities: alanine aminotransferase (ALT) >3× upper limit of normal (ULN), or aspartate aminotransferase (AST) >3× ULN or bilirubin >2× ULN (unless the bilirubin is a result of Gilbert's syndrome).
9. Pregnancy or breast feeding.
10. Subject has any condition that in the opinion of the investigator or sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (eg, history of substance abuse or dependence, significant pre-existing illnesses or major comorbidity the investigator considers may confound the interpretation of the study results).

**Maximum duration of subject participation in the study:** 44 weeks.

**Statistical analysis:**

**Analysis Sets**

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

**Sample Size and Power Considerations**

The planned total sample size for this study is approximately 20 subjects.

The sample size is considered adequate based on the objectives of the study and was based on clinical judgment and precedent studies of similar design and similar subject population and not on statistical considerations such as study power. With a sample size of 20 subjects exposed to lanadelumab, the probability of observing an event that occurs within the population at a rate of 10% is approximately 87%.



**Study Endpoints**

Primary:

- 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 (BP), heart rate (HR), body temperature, and respiratory rate
- 12-lead electrocardiogram (ECG)
- Physical examination

Secondary:

- Plasma concentrations of lanadelumab
- Plasma kallikrein (pKal) activity as measured by cleaved high molecular weight kininogen (cHMWK) level (ie, plasma concentrations of cHMWK)
- Number of investigator-confirmed HAE attacks during the efficacy evaluation periods
- Number of investigator-confirmed HAE attacks requiring acute treatment during the efficacy evaluation periods
- Number of investigator-confirmed moderate or severe HAE attacks during the efficacy evaluation periods
- Maximum attack severity during the efficacy evaluations periods
- Time to first HAE attack during the efficacy evaluation periods
- Achievement of attack-free status during the efficacy evaluation periods
- Number and percentage of subjects meeting the criterion of at least a 50%, 70%, 90% and 100% reduction in the investigator-confirmed normalized number of attacks (NNA) per 4 weeks relative to the run-in period NNA, and the number and percentage of subjects achieving NNA <1.0 per 4 weeks
- Presence or absence of antidrug antibody (ADA) in plasma (neutralizing or non-neutralizing antibodies in plasma)

- Effect on:
  - Lanadelumab plasma concentrations
  - cHMWK level
  - Number of investigator-confirmed HAE attacks during the efficacy evaluation periods

**Efficacy Analyses**

No statistical hypothesis testing will be performed.

- Continuous efficacy endpoints will be summarized using number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Whenever appropriate, raw (actual) values and changes from baseline will be summarized at each scheduled time point. Overall attack rates per month (28 days) will be estimated using summary statistics.
- Categorical efficacy endpoints (eg, attack severity) will be summarized in terms of the number and percentage of subjects in each category of the efficacy endpoint.
- Time-to-event endpoint (eg, time to the first HAE attack) will be summarized using Kaplan-Meier (KM) estimates. Summaries will include 25th, 50th (median) and 75% percentiles, if estimable, and the corresponding 95% confidence intervals. In addition, KM plots detailing each subject's contribution to the analysis will be provided.

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

Efficacy endpoints will be evaluated for the following 2 efficacy evaluation periods:

- Day 0 (after study drug administration) through Day 182
- Presumed steady-state period from Day 70 through Day 182

Sensitivity analysis will be performed to evaluate the robustness of the efficacy results during each efficacy evaluation period for the FAS population. The analysis will be repeated using all subject-reported HAE attacks instead of limiting the analysis to those attacks that were investigator confirmed.



**Safety Analyses**

No statistical hypothesis testing will be performed.

- Continuous safety endpoints (eg, change in laboratory parameter) will be summarized using number of subjects (n), mean, SD, median, minimum value, and maximum value. As appropriate, raw (actual) values and changes from baseline will be summarized overall and at each scheduled time point.
- Categorical endpoints (eg, presence or absence of an outcome measure) will be summarized using counts and percentages. Summaries will include, but are not limited to: number and percentage of subjects with an outcome measure, and laboratory shift tables (categorical change from baseline).

Baseline is defined as the last non-missing value prior to initial dosing with study drug (lanadelumab).

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

Adverse events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Only TEAEs will be analyzed, but all AEs including TEAEs and non-TEAEs will be provided in the AE subject listing. The analyses described in this section will be based on TEAEs; plainly referred to as AEs in this section for brevity.

- TEAE is defined as AE with onset at the time of or following initial dosing with study drug (lanadelumab), or medical conditions present prior to the start of study drug but increasing in severity or relationship at the time of or following the start of treatment, up to the last follow-up visit. For AEs with partial onset times, non-missing date parts will be used to determine if the AE is treatment emergent or not. If a determination cannot be made using the non-missing date as to when the AE occurred relative to study drug administration, then the AE will be classified as treatment emergent.

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

For this analysis, AEs will be classified to two analysis periods:

- Treatment Period AEs will include all AEs starting at or after the first exposure to study drug in this study to those starting before or at the subject's last visit date during the treatment period in this study (AEs starting at or after treatment on Day 0 through Day 182 visit).
- Follow-up Period AEs will include all AEs starting after the subject's last visit date of the treatment period in this study (AEs starting after the Day 182 visit).

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

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized by system organ class and preferred term (PT) for each analysis period. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, and related severe AEs. Similar summary tables for investigator-reported AESIs, or determined by the search tool of relevant Standardized MedDRA Queries, will also be generated.

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

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

Concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD). Usage of prior or concomitant medications (other than rescue medications) will be summarized descriptively by therapeutic class and PT. A separate, similar table will be provided for the subset of concomitant medications classified as rescue medications.

Clinical laboratory test results and vital signs, physical examination, and ECG findings will be summarized using descriptive statistics by visit. Clinical laboratory test results will be categorized according to reference ranges and the investigator's assessment of clinical assessment and summarized as shifts from baseline. Clinically significant laboratory test results and changes in vital signs will be listed and summarized. Listings of physical examination and ECG findings will include the investigator's assessment of clinical significance.



**Pharmacokinetic, Pharmacodynamic, and Immunogenicity Analyses**

Characterization of PK properties of lanadelumab in the Chinese population will be conducted via population PK modeling approach and reported separately.

Characterization of PK/PD properties of lanadelumab in the Chinese population will be conducted via population PK/PD modeling approach and reported separately.

No formal statistical hypothesis will be tested. Individual concentrations and PK parameters (not limited to $C_{trough}$) of lanadelumab will be provided in subject data listing(s) and summarized using descriptive statistics (number of subjects, arithmetic mean, SD, coefficient of variation [CV], median, minimum, maximum, geometric mean, and CV of geometric mean). Figures of individual and mean (±SD) concentration-time profiles for plasma lanadelumab will be generated. Tabular and graphical summaries will be analyzed based on the PK set and PD set, as appropriate.

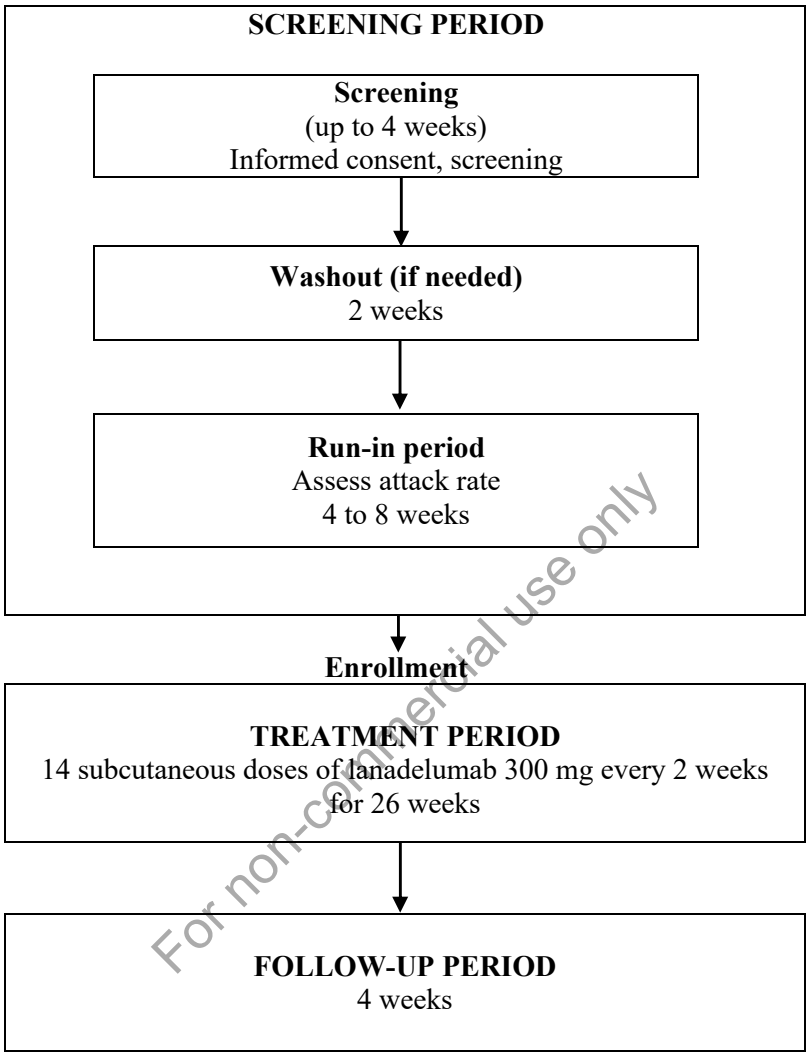
Immunogenicity data will be summarized using descriptive statistics.

**Interim Analysis**

An interim data analysis may be performed to support the supplementary New Drug Application (sNDA) submission for China pediatric indication. The interim analysis will at least summarize the efficacy, safety and PK of treatment with lanadelumab in Chinese subjects with HAE. The interim analysis will be conducted when approximately 10 subjects complete the 26 weeks treatment period and 4 weeks follow-up period.

## 1.2 Schema

**Figure 1. Study Schematic Diagram**



## 1.3 Schedule of Study Activities

### Table 1. Schedule of Study Activities

| | Screening Period | | Treatment Period[b] *Grey columns indicate option for self-administration at the site*[c] | | | | | | | | | | | | | | | Follow-up Visit[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening Visit and Washout | Run-in Period[a] | 1 | Site Check-in[d] | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
| Visit No. | | | 1 | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | |
| Day No. | | | 0 | 7 | 14 | 28 | 42 | 56 | 70 | 84 | 98 | 112 | 126 | 140 | 154 | 168 | 182/ET[e] | 210 |
| Dose No. | | | 1 | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | |
| Informed Consent[f] | X | | | | | | | | | | | | | | | | | |
| Eligibility Review | X | | X[g] | | | | | | | | | | | | | | | |
| LTP Therapy Washout[h] | X | | | | | | | | | | | | | | | | | |
| Lanadelumab 300 mg Treatment | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Injection Report[i] | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Diary Card[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Demographics | X | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | |
| C1-INH, C1q and C4 Testing[k] | X | | | | | | | | | | | | | | | | | |
| Pregnancy Test[l] (females) | X | | X | | | X | | X | | X | | X | | X | | | X | X |
| Vital Signs[m] | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination[n] | X | | X | | | X | | X | | | X | | | X | | | X | X |
| 12-Lead ECG[o] | X | | X | | | | | | | | | | | | | | X | |
| Clinical Laboratory Testing[p] | X | | X | | | X | | X | | | X | | | X | | | X | X |
| Serology Testing[q] | X | | | | | | | | | | | | | | | | | |
| Prior and Concomitant Therapy | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| HAE Symptoms or Attack Data[r,s] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PK Blood Sampling[t] | | | X | | X | | | X | | | X | | | X | | | X | X |
| PD Sample Collection[t] | | | X | | X | | | X | | | X | | | X | | | X | X |
| Plasma ADA Testing[t] | | | X | | | | | X | | | X | | | X | | | X | X |

## Table 1. Schedule of Study Activities

ADA=antidrug antibody; AE= adverse event; AESI=an adverse event of special interest; BP=blood pressure; C1-INH=C1 esterase inhibitor; $C_{max}$=maximum plasma drug concentration; ECG=electrocardiogram; eCRF=electronic case report form; ET=early termination; HAE=hereditary angioedema; HbsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HR=heart rate; LTP=long-term prophylaxis; PD=pharmacodynamic; PK=pharmacokinetic; RR=respiratory rate; SAE=serious adverse event; SC=subcutaneous

[a] Subjects will undergo a run-in period to determine their baseline HAE attack rate. Only subjects with a baseline rate of at least 1 investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and treatment. Subjects who experienced 3 or more investigator-confirmed attacks before the end of the 4 weeks could exit the run-in period early and proceed to enrollment and treatment. Subjects without at least 1 investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 investigator-confirmed attacks in 8 weeks to proceed to enrollment and treatment. To be eligible for enrollment, subjects who have their run-in extended have to complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered as screen failures.

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

[c] Subjects (and/or their parent/caregiver) are allowed to initiate self-administration under the investigator or designee supervision, after receiving the first 5 doses of lanadelumab at the study site administered by qualified personnel.

[d] Site personnel will contact the subject by phone to solicit for any attacks not already reported by the subject once between scheduled site visits or approximately 7 days after last contact with subject.

[e] In the event a subject prematurely discontinues from treatment and/or the study, ET visit procedures will be performed as soon as possible.

[f] For adolescent subjects (<18 years of age) enrolled in the study that reach 18 years of age during study periods, a consent using the most current version of the informed consent form by subject is required.

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

[h] Adult subjects (≥18 years of age) who are on LTP therapy for HAE will be required to undergo a minimum 2-week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the investigator determines that doing so would 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 had successfully completed the 2-week washout period before they can enter the run-in period. Adolescent subjects (≥12 to <18 years of age) who are on LTP therapy for HAE are not required to undergo LTP washout.

[i] An injection report will be completed by the subject (or caregiver) following each dose of lanadelumab. The injection report will collect information on the subject's experience with SC injection of lanadelumab. Study personnel will document the subject's responses in the subject's medical record and eCRF.

[j] At the time of the screening visit, a diary card will be dispensed to the subject or caregiver. As soon as the subject enters the run-in period, the subject (or caregiver) should complete the diary card at the end of each day to record if an HAE attack happens or not. An HAE attack worksheet, part of the diary card, should be completed if the subject encounters any HAE attack. The investigator should check completion of diary card at each visit.

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

[l] The pregnancy test is only for females of childbearing potential. Test will be conducted at the local laboratory and could be serum or urine based.

[m] There will be a ±15-minute window for all vital signs. At study visits in which investigational product will be administered, vital signs including sitting or supine BP, HR, body temperature, and RR, are to be obtained prior to dosing and 1 hour after dosing.

[n] Height and weight will be collected at the screening visit only. The physical examination has to be performed prior to dosing of study drug. Physical examination findings by body system will be classified as normal, abnormal not clinically significant, abnormal clinically significant, or not performed by the investigator.

## Table 1. Schedule of Study Activities

[o] Electrocardiograms (single recordings) will be performed and assessed by the local laboratory. The ECG has to be performed prior to dosing of study drug.

[p] Clinical laboratory testing will be conducted at the local laboratory and will include hematology (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, absolute platelet count), clinical chemistry (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin [total and direct], blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, creatine phosphokinase, glucose, phosphate, magnesium, potassium, sodium, total protein, uric acid), coagulation (prothrombin time, activated partial thromboplastin time, international normalized ratio), and urinalysis (bilirubin, glucose, ketones, blood, nitrite, pH, protein, specific gravity, microscopy [if indicated by macroscopic findings]). Blood samples for clinical laboratory testing will be collected pre-dose (ie, within 2 hours prior to dosing).

[q] Serology testing (HBsAg, HCV, and HIV) will be conducted at the local laboratory at screening.

[r] Historical attack information will be collected at screening. During the study, subjects (or caregivers, in the event the subject is <18 years old or is incapacitated) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack.

[s] Site personnel will also contact the subject once a week or at approximately 7 days after last contact with the subject during the run-in period and once between study visits or approximately 7 days after last contact with the subject during the treatment period in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not given through prior subject contact with the site.

[t] Blood samples for testing PK, PD and formation of antibodies to lanadelumab will be obtained at pre-dose (ie, within 2 hours prior to dosing) except on follow-up visit, with a window period of ±3 days for the corresponding visit except on Day 0. Testing for PK, PD, and ADAs will be conducted at a central laboratory.

Notes: If a subject experiences an SAE or an AESI, the investigator must report the event to the sponsor or CRO within 24 hours, by completing an SAE or AE or HAE acute attack eCRF in English or report via the paper safety report form (as back-up) within 24 hours of becoming aware of any SAE or AESI respectively.

Investigators are to report all SAEs to Takeda Global Patient Safety Evaluation (GPSE) Department through 30 days after the last dose of investigational product and SAEs considered related to investigational product >30 days after the last dose of investigational product.

Unscheduled visits may occur between the scheduled site visits as required. Assessments may be performed as clinically indicated at the discretion of the investigator.

[1] Please see Section 8.1.7 for activities to be followed during an unanticipated situation like coronavirus disease 2019 outbreak.

## 2. INTRODUCTION

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 (Zuraw et al. 2013). Hereditary angioedema manifests clinically as unpredictable, intermittent attacks of subcutaneous (SC) or submucosal edema of the face, larynx, gastrointestinal tract, limbs, and/or genitalia (Zuraw 2008). 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 et al. 2009; Goring et al. 1998; Lei et al. 2011; Nordenfelt et al. 2014; Roche et al. 2005).

In China, HAE has been recognized and diagnosed with C1-INH antigen and C4 levels since the 1980. However, due to the low disease awareness and shortage in C1-INH diagnosis assays, there are likely to be many undiagnosed patients. Currently there are only several publications from one clinical center that reports on Chinese HAE patients' clinical features and their treatment plans. Two reports describe the clinical features of 158 and 133 Chinese HAE patients. In one of the most current and largest study reports in China in which retrospective data from 158 HAE patients was analyzed, 156 patients were Type 1 (98.73%) and only 2 of were Type II (1.27%) and no report of Type 3 HAE patients. The number of reported cases is lower than expected based on the Chinese population which suggests the prevalence differs from estimates in other countries (ie, 1 per 50,000). However, incomplete historical clinical data and limited family history may not accurately depict the prevalence of HAE in China (Bork et al. 2000). Reported patient mean delay in diagnosis is 12.64 years, which is similar to what is reported in other countries. Reported patient swelling locations are extremities, face, gastrointestinal tract, laryngopharynx and genitalia. The face was the more commonly involved site at the first episode and GI was less frequent compared with the surveys from other countries. Gastrointestinal involvement was about 34.17% for Chinese patients which is relatively lower than reported in Western countries but similar to other Asian countries such as Japan and South Korea (Xu et al. 2013). This difference may also be due to the challenges for the diagnosis of GI attacks or swellings.



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. 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 a pKal inhibitor is a rational therapeutic strategy for HAE attack prevention. The importance of pKal as a drug target in HAE has been described in the literature (Kaplan and Joseph 2014).

TAKHZYRO™ (Lanadelumab-flyo, SHP643, formerly DX-2930) is a recombinant, Chinese hamster ovary (CHO) cell-expressed, fully human immunoglobin G subclass 1 (IgG1), kappa light chain, monoclonal antibody (mAb) that is a potent (Ki=125 pM) and specific inhibitor of the proteolytic activity of pKal. As of 24 Jul 2021, SC lanadelumab was approved for prevention of HAE attacks in over 50 countries, including the United States (US), European Union (EU), Canada, Australia, Switzerland, United Arab Emirates, Brazil, Serbia, Mexico, Israel, and China. As lanadelumab has a long half-life (approximately 14 days in HAE subjects), it is hypothesized that prophylactic treatment with lanadelumab will provide persistent suppression of pKal and thus prevention of angioedema attacks.

Lanadelumab is administered by SC administration and due to a prolonged half-life, has been studied as a twice or once monthly regimen, thus allowing infrequent SC administration.

### 2.1 Indication and Current Treatment Options in China

To date, there are no HAE medications commercially available in China. Lanadelumab (TAKHZYRO) was approved in China in December 2020 and icatibant (FIRAZYR) was approved in April 2021 but these drugs are not yet marketed in China. In some hospitals, patients may have access for the off-label use of fresh frozen plasma (FFP), due to containing Cl esterase inhibitor, for acute or short-term treatment. For long-term prophylaxis (LTP), oral weak androgens (eg, danazol 200 mg three times a day for 2 to 4 weeks, stanozolol, oxandrolone) or an antifibrinolytic, tranexamic acid (ε-aminocaproic acid) are used. Additionally, symptoms of an HAE attack, for example, severe abdominal pain, associated with vomiting, dehydration, and hypotension are treated only with supportive care. In cases of laryngeal attacks where laryngeal edema is life-threatening, more invasive measures such as intubation, cricothyrotomy or tracheostomy may be required.



Therapies currently available in China, however, have their respective limitations. For example, even though FFP has been shown to be effective, it has not been evaluated in controlled clinical studies and can pose potential safety risks to patients in regards to viral transmission, infusion reactions or allergic reactions such as urticaria (Tang et al. 2012; Zanichelli et al. 2015). Attenuated androgens although approved for use in some countries in Europe pose hepatoxic, cardiovascular and other safety risks to patients. The most recent World Allergy Organization guidelines recommend that weak androgens may be used as second-line therapy, with careful monitoring of dosage and clinical testing to mitigate safety risks. Antifibrinolytics are not recommended due to the lack of efficacy in LTP (Zhi et al. 2019).

Thus, the lanadelumab clinical development plan in China was initiated to meet an unmet medical need for a new prophylactic treatment for patients with HAE that provides a high level of efficacy to prevent angioedema attacks, a positive benefit/risk profile, and convenience of infrequent SC administration that can be self-administered.

## 2.2 Clinical Information

The indication of lanadelumab for routine prophylaxis to prevent attacks of HAE in patients 12 years and older was primarily supported by the efficacy results from a single, adequate, 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).



- Study DX-2930-01 demonstrated that lanadelumab was well tolerated by healthy subjects up to doses of 3.0 mg/kg without evidence of dose-limiting toxicity.
- Study DX-2930-02 reported no deaths, serious adverse events (SAEs), discontinuations due to an adverse event (AE), or safety signals following lanadelumab treatment. 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.
- Study DX-2930-03 (HELP Study™) showed that over the 26-week treatment period, all 3 lanadelumab dose regimens, 150 mg q4wks, 300 mg q4wks, and 300 mg every 2 weeks (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. 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 (71% to 83%), and attacks from Day 14 through Day 182 (75% to 89%). 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. Lanadelumab was generally well tolerated over the 26-week treatment period; no treatment-related SAEs or deaths were reported.

- Study DX-2930-04 (HELP Study Extension™) safety profile was consistent with the pivotal Study DX-2930-03; no treatment-related SAEs or deaths were reported. Efficacy was maintained and shown to be durable over the treatment period (132 weeks/33 months) of lanadelumab exposure across Study DX-2930-03 and Study DX-2930-04 for rollover subjects.

In addition, two Phase 1 studies were completed after the initial global marketing license for lanadelumab.

- Study SHP643-101 evaluated the PK properties and the safety of lanadelumab administered as a single SC 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.
- Study SHP643-102 determined the bioavailability of lanadelumab administered as a single SC dose of 300 mg with a prefilled syringe (PFS) or autoinjector (AI) and was conducted in healthy adult volunteer subjects. This study showed that the total systemic exposure of lanadelumab ($AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$) following a single SC administration of 300 mg via PFS was equivalent to that observed via AI. Overall, lanadelumab administered by a PFS or an AI was generally safe and well tolerated.



Two additional Phase 3 studies have been completed: a Phase 3 study in pediatric HAE subjects 2 to <12 years (Study SHP643-301) and a Phase 3 study in Japanese HAE subjects (≥12 years; Study SHP643-302). The results from these studies are consistent with previous global registration studies that included adult and adolescent (>12 years) HAE subjects. Lanadelumab was generally well tolerated. No deaths, treatment-related SAEs or subject withdrawal due to TEAEs were reported. No new safety concerns were identified; thus, the safety profile of lanadelumab remains favorable and unchanged. A marked reduction in investigator-confirmed HAE attacks was observed in both HAE patient populations evaluated (pediatric [2 to <12 years] and Japanese subjects). Efficacy was observed at26-weeks of treatment (same duration as the pivotal DX-2930-03 study) and was maintained over the 52-week treatment period.

Ongoing Phase 3 studies include: this Phase 3 study in Chinese HAE subjects (SHP643-304) and Phase 3 studies in non-histaminergic angioedema subjects with normal C1 esterase inhibitor (C1-INH) (SHP643-303 and TAK-743-3001). Two prospective, non-interventional Phase 4 studies in HAE patients are also ongoing (SHP643-402 and SHP643-403).

## 2.3 Study Rationale

The safety, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of lanadelumab have been established by the global clinical development program for lanadelumab including two Phase 1 studies and one global Phase 3 pivotal study as well as Phase 3 extension study that are completed.

Lanadelumab is expected to fulfill an unmet medical need in China for the prevention of angioedema attacks in patients with Type I or Type II HAE. As part of the approval requirements and post-approval commitment, the China Health authority has requested that further efficacy and safety data be collected from Chinese patients with Type I or Type II HAE. For that, Takeda is planning this multi-center, open-label study to evaluate the safety, efficacy, PK, PD, and immunogenicity of lanadelumab in the Chinese population.

## 2.4 Benefit/Risk Assessment



Lanadelumab, a first-in-class mAb against active pKal, represents a therapeutic innovation that will address the unmet medical needs within the HAE community and thus is expected to be of major public health interest. It is a fully human IgG1 mAb inhibitor of active pKal with a long half-life, which allows for convenient, infrequent SC self-administration (eg, q2wks).

Importantly for patients, lanadelumab's unique mechanism of action and properties allow reduced dosing frequency (eg, q2wks) with SC self-administration (10-60 seconds), which significantly reduces the burden of treatment as compared with a daily oral or twice weekly intravenous or SC treatment experienced by patients; therefore, lanadelumab offers a more effective and convenient therapy for patients suffering from HAE.

Four clinical studies supported the global marketing applications and licenses for lanadelumab for routine prophylaxis to prevent attacks of HAE in patients 12 years and older. The safety and tolerability data from these studies to date demonstrate that lanadelumab is safe and efficacious in HAE patients and have served as the basis of submission for global expansion.

Per the reference labeling (TAKHZYRO 2018), the most common adverse reactions are injection site reactions, upper respiratory infections, headache, rash, myalgia, dizziness, and diarrhea. Other adverse reactions that occurred at a higher incidence in TAKHZYRO-treated patients compared to placebo include hypersensitivity, increased aspartate aminotransferase (AST), and increased alanine aminotransferase (ALT).

Hypersensitivity is an important identified risk and is discussed in the warning and precautions of the reference labeling. Immunogenicity is an important potential risk and monitored closely. Based on the review of safety data from the completed and ongoing clinical trials, the known cumulative exposure and continuous pharmacovigilance monitoring for the risks, the benefit-risk continues to be favorable.

Lanadelumab is approved in several markets including the US and the EU.

Investigators should always refer to the latest version of the SHP643 investigator's brochure (IB) for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, pharmacokinetics, efficacy, and safety of SHP643.

### 2.5 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, 1996; ICH E6 R2, 2016), and applicable national and local regulatory requirements.

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

# 3. OBJECTIVES AND ENDPOINTS

## 3.1 Study Objectives

### 3.1.1 Primary Objective

The primary objective of this study is to evaluate the safety of repeated SC administrations of lanadelumab in Chinese subjects with HAE.

### 3.1.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the PK of repeated SC administrations of lanadelumab in Chinese subjects with HAE
- To evaluate the PD of repeated SC administrations of lanadelumab in Chinese subjects with HAE
- To evaluate the efficacy of repeated SC administrations of lanadelumab in Chinese subjects with HAE
- To evaluate the immunogenicity of repeated SC administration of lanadelumab and the effect on lanadelumab PK, PD, efficacy, and safety



## 3.2 Study Endpoints

**Table 2. Objectives and Endpoints**

| Objective | Endpoint(s) |
|---|---|
| **Primary** | |
| • To evaluate the safety of repeated SC administrations of lanadelumab in Chinese subjects with HAE. | • Treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and adverse events of special interest (AESIs)<br>• Clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis)<br>• Vital signs including blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR)<br>• 12-lead electrocardiogram (ECG)<br>• Physical examination |

## Table 2. Objectives and Endpoints

| Objective | Endpoint(s) |
|---|---|
| **Secondary** | |
| • To evaluate the PK of repeated SC administrations of lanadelumab in Chinese subjects with HAE. | • Plasma concentrations of lanadelumab |
| • To evaluate the PD of repeated SC administrations of lanadelumab in Chinese subjects with HAE. | • Plasma kallikrein (pKal) activity as measured by cleaved high molecular weight kininogen (cHMWK) level (ie, plasma concentrations of cHMWK) |
| • To evaluate the efficacy of repeated SC administrations of lanadelumab in Chinese subjects with HAE. | • Number of investigator-confirmed HAE attacks during the efficacy evaluation periods<br>• Number of investigator-confirmed HAE attacks requiring acute treatment during the efficacy evaluation periods<br>• Number of investigator-confirmed moderate or severe HAE attacks during the efficacy evaluation periods<br>• Maximum attack severity during the efficacy evaluations periods<br>• Time to first HAE attack during the efficacy evaluation periods<br>• Achievement of attack-free status during the efficacy evaluation periods<br>• Number and percentage of subjects meeting the criterion of at least a 50%, 70%, 90% and 100% reduction in the investigator-confirmed normalized number of attacks (NNA) per 4 weeks relative to the run-in period NNA, and the number and percentage of subjects achieving NNA <1.0 per 4 weeks |
| • To evaluate the immunogenicity of repeated SC administration of lanadelumab and the effect on lanadelumab PK, PD, efficacy, and safety. | • Presence or absence of antidrug antibody (ADA) in plasma (neutralizing or non-neutralizing antibodies in plasma)<br>• Effect on:<br>  • Lanadelumab plasma concentrations<br>  • cHMWK level<br>  • Number of investigator-confirmed HAE attacks during the efficacy evaluation periods |

# 4. STUDY DESIGN

## 4.1 Overall Design

This open-label study will enroll Chinese subjects of 12 years of age or older with a confirmed diagnosis of HAE (Type I or II).

The study includes a screening period that may require screening of 4 weeks, a washout period of 2 weeks, a run-in period of 4 to 8 weeks, a treatment period of 26 weeks, and a follow-up period of 4 weeks.

Screening Visit and Washout Period:

Following informed consent, subjects will undergo screening assessments. Screened adult subjects who are on LTP (eg, androgens) for HAE are required to undergo a minimum 2-week washout period prior to the run-in period. This LTP washout period is permitted as long as the investigator determines that doing so would not place the subject in any undue safety risk and that the subject is at least 18 years of age (ie, LTP washout is not required in adolescent subjects [≥12 to <18 years of age]). Subjects who fail screening due to a single laboratory test result that does not meet eligibility criteria may have that laboratory test repeated at the discretion of the investigator. This will include a repeat of only the failed assessment rather than a repeat of all screening assessments (for details see Section 8.1.1).



Run-in Period:

Screened subjects who are not on LTP therapy for HAE or who have completed the required washout period will enroll and enter a run-in period of 4 to 8 weeks to determine their baseline attack rate. Only subjects meeting a minimum baseline attack rate of at least 1 investigator-confirmed attack per 4 weeks will be eligible for treatment. Subjects who experience 3 or more investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to the treatment period. Subjects without at least 1 investigator-confirmed attack after 4 weeks will have their run-in period extended by 4 weeks, during which time they need to have at least 2 investigator-confirmed attacks in 8 weeks to be eligible for treatment. Subjects who do not meet the minimum attack rate during the run-in period or are otherwise determined to be ineligible due to screening assessments will not be allowed to enter the treatment period of the study and will be replaced with new HAE subjects until approximately 20 subjects have entered the treatment period. Subjects who are found to be ineligible during the run-in period will not be allowed to rescreen into the study.

Treatment Period:

Subjects who enter the treatment period will receive lanadelumab 300 mg every 2 weeks (q2wks) for 26 weeks. Subjects who complete the treatment period will receive a total of 14 doses of lanadelumab from Day 0 to Day 182 (±3 days).

Follow-up Period:

After completion of the 26 weeks treatment period, subjects will be followed for an additional 4 weeks and will attend the follow-up visit on Day 210 (±3 days).

All study procedures are detailed in the study schematic diagram (Figure 1) and schedule of study activities (Table 1).

In the event a monitor cannot visit the site in a timely manner due to the coronavirus disease 2019 (COVID-19) pandemic, alternative monitoring approaches such as remote source data verification or telephone contact may be used to ensure data quality and integrity and maintain subject safety. Alternative monitoring approaches should be used only where allowed by the local Health Authority and permitted by the institutional review board (IRB)/independent ethics committee (IEC).

Acute HAE attacks during the study will be managed in accordance with the investigator's usual care of their subjects, including use of individualized acute therapy/rescue medications. The acute therapy/rescue medications include FIRAZYR, FFP, or other local standard of care.



### 4.2 Justification for Dose

The lanadelumab clinical development program in subjects with Type I and Type II HAE established optimal efficacy at lanadelumab 300 mg q2wks dose with steady-state trough concentrations around 28400 ng/mL ($C_{ave,ss}$; CV=34.4). There were reductions of approximately 50% from baseline in cleaved high molecular weight kininogen (cHMWK), the endogenous substrate of kallikrein as a biomarker of its activity to evaluate the pharmacodynamic bioactivity of lanadelumab; and the HAE attack rate remained low with low cHMWK levels at 300 mg q2wks. This dose regimen was well tolerated and no discernible dose-dependent or limiting toxicity was observed for any related TEAEs.

Population pharmacokinetic analyses using global clinical PK data showed that age, gender and race did not meaningfully influence the pharmacokinetics of lanadelumab after correcting for body weight. Body weight is the only covariate identified to affect PK of lanadelumab. However, HAE patients with higher body weight were responders for the lanadelumab treatment, suggesting sufficient exposure provided (300mg q2wks) even in the subjects with heavier body weight (Inhaber et al. 2019).

The weight range in the global populations included in the population PK analyses was between 36.7 to 178 kg, which covers the available Chinese body weight distribution data (Zhang et al. 2018) and is expected to show the same efficacy response. These PK properties as part of clinical evidences support lanadelumab is an ethnically insensitive medicine. Thus, dosage 300 mg q2wks is expected to be efficacious and safe in Chinese HAE population.

### 4.3 Duration of Subject Participation and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 44 weeks.

For the definition of study completion date, see Section 8.1.4.

### 4.4 Sites and Regions

The study will be conducted in approximately 5 sites in China.

# 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

Each subject must meet all of the following criteria to enroll in the study:

1. Be of Chinese descent, defined as born in China and having Chinese parents and Chinese maternal and paternal grandparents.
2. The subject is male or female and ≥12 years of age at the time of informed consent.
3. Documented diagnosis of HAE Type I or Type II based upon all of the following:
   - Documented clinical history consistent with HAE (SC or mucosal, nonpruritic swelling episodes without accompanying urticaria).
   - Diagnostic testing results obtained during screening by a laboratory (approved by the sponsor) that confirm HAE Type I or Type II: C1-INH functional level <40% of the normal level. Subjects with functional C1-INH level 40% to 50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may begin participating in the run-in period before these diagnostic results are available. Subjects may be re-tested if results are incongruent with clinical history or believed by the investigator to be confounded by recent LTP use.
   - At least one of the following: Age at reported onset of first angioedema symptoms ≤30 years, a family history consistent with HAE Type I or Type II, or C1q within normal range.
4. Attack rate:
   - At the time of enrollment, subjects must experience at least 1 investigator-confirmed HAE attack per 4 weeks during the run-in period.
5. The subject (or the subject's parent/legal guardian, if applicable) has provided written informed consent approved by the IRB/IEC.
   - If the subject is an adult, be informed of the nature of the study and provide written informed consent before any study-specific procedures are performed.

     OR
   - If the subject is a minor (ie, <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.

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

## 5.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema, HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.
2. Participation in a prior lanadelumab study or use any lanadelumab prior to the study.
3. Dosing with investigational drug or exposure to an investigational device within 4 weeks prior to entering to screening.
4. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systematic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
5. Exposure to androgens (eg, danazol, methyltestosterone, testosterone) within 2 weeks prior to entering the run-in period.
6. Use of LTP therapy (defined as continued use) for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) for adult subjects within 2 weeks prior to entering the run-in period. Adolescent subjects (≥12 to <18 years of age) who are on LTP therapy for HAE are allowed to enter the study.
7. Use of short-term prophylaxis for HAE 7 days prior to entering the run-in period. Short-term prophylaxis is defined as FFP, C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures. Note: Currently, C1-INH therapies are not available in China.
8. Any of the following liver function abnormalities: ALT >3× upper limit of normal (ULN), or AST >3× ULN or bilirubin >2× ULN (unless the bilirubin is a result of Gilbert's syndrome).
9. Pregnancy or breast feeding.

10. Subject has any condition that in the opinion of the investigator or sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (eg, history of substance abuse or dependence, significant pre-existing illnesses or major comorbidity the investigator considers may confound the interpretation of the study results).

## 5.3 Reproductive Potential

### 5.3.1 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 adolescent subjects should be either:

- Premenarchal and either Tanner stage 1, or
- Females of childbearing potential with a negative urine and/or serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at the screening visit. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Female adult subjects should be either:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and age ≥51 years)
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- Of childbearing potential with a negative urine and/or serum β-hCG pregnancy test at the screening visit. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception include the following:

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

- Non-estrogen-containing hormonal contraceptives (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.

### 5.3.2 Male Contraception

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

# 6. STUDY INTERVENTION

## 6.1 Investigational Product

### 6.1.1 Identity of Investigational Product

The investigational product, lanadelumab, is a recombinant, fully human, IgG1, kappa light chain, mAb expressed in CHO cells. It is a potent and specific inhibitor (Ki=125 pM) of the proteolytic activity of active pKal.

Lanadelumab drug product is a sterile preservative-free solution for SC administration and is provided in strength of 300 mg/2 mL (150 mg/mL).

Lanadelumab drug product is supplied in a 5 mL single-use clear Type I glass vial fitted with a 13 mm chlorobutyl rubber stopper with FLUROTEC® on the plug and B2 coating on the top, and an aluminum crimp seal with a flip-off polypropylene cap. Each 300 mg vial is filled with a nominal volume of 2.0 mL of drug product. Each vial contains a slight overfill.

Additional information is provided in the current IB.



### 6.1.2 Blinding the Treatment Assignment

Not applicable, this is an open-label clinical study.

## 6.2 Dosing and Administration of Investigational Product

### 6.2.1 Dosing and Administration

A single dose regimen of 300 mg lanadelumab will be administered to subjects q2wks for 26 weeks for a total of 14 doses.

Lanadelumab will be administered by SC injection in the upper arm, thigh, or abdominal area. Self-administration will be permitted after a subject (and/or their parent/caregiver) has received appropriate training by the investigator or designee and understanding of the training must be confirmed by the investigator or designee. All subjects (adolescent or adult) who are considered suitable candidates (ie, those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer treatment. Subjects (and/or their parent/caregiver) are allowed to initiate self-administration under the investigator or designee supervision, after receiving the first 5 doses of lanadelumab at the study site administered by qualified study personnel. Once initiated, subjects may self-administer subsequent doses of lanadelumab at the investigational site per schedule of study activities (Table 1).

During an unanticipated situation like COVID-19 outbreak, subjects may self-administer investigational product at home (see details in Section 6.4 and Section 8.1.7).

### 6.2.2 Interactive Response Technology for Investigational Product Management

An interactive response technology (IRT) will be used for investigational product management tasks including investigational product supply management, inventory management and supply ordering, investigational product expiration tracking, and return of investigational product. Please refer to the instruction manual provided separately from this protocol that outlines the operating procedures regarding the IRT.

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

The study drug will be supplied by the sponsor and prepackaged in a study kit for investigational studies. Each study kit will contain 1 vial of investigational product. Both the vial and carton (kit) will be appropriately labeled according to local regulations and bear the unique study drug kit number. The investigative site will provide ancillary supplies. Subjects who elect to self-administer investigational product will be provided the following supplies as applicable:

- 1 to 2 dose(s) supply of investigational product
- Ancillary supplies, including alcohol pads, a temperature monitoring device, and a container for disposal
- Subject accountability form to record investigational product storage conditions and administration details



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

### 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, Med ID Number, Lot Number, Expiry Date (if applicable), Dosage Form, Directions for Use, Storage Conditions, Sponsor Name and Address, the statement “For clinical trial use only”, the statement, “Keep out of sight and reach of children”.

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

### 6.3.2 Packaging

Investigational product is packaged according to applicable local and regulatory requirements for investigational studies.

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

All supplies of the investigational products must be stored refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton and protected from light, in a securely locked area, accessible to authorized persons only, until needed for dose administration. Do not freeze.

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 site staff, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated site staff.



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, eg, fumigation of a storage room.

Before use, each vial of study drug should be inspected for appearance. Any vial containing visible particles or discoloration should not be used. Avoid shaking or vigorous agitation of the vial.

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

### 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. 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.

Home administration can only happen during an unanticipated situation like COVID-19 outbreak. In this situation, the site may use an alternative method for dispensing. If permitted by local regulations and ethics committees (ECs), the investigational product can be shipped from the site/the local depot directly to the subject's home address via courier. Subjects must be provided with instructions on how to receive, store, and ultimately return the investigational product.

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

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

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

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

Most doses of the study drug will be administered during site visits under the direct supervision of the investigator or qualified site personnel designated by the investigator. However, subjects (and/or their parent/caregiver) are allowed to initiate self-administration under the investigator or designee supervision, after receiving the first 5 doses of lanadelumab at the study site administered by qualified study personnel.

Subjects must be instructed how to have unused investigational product and empty/used investigational product packaging assessed for drug accountability. 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 Permitted and Prohibited Treatment

### 6.6.1 Permitted Treatment

The following therapies are allowed during the study:

- Therapies for co-existing conditions, including those for acute attacks of HAE (see Section 4.1), are permitted if not excluded in Section 6.6.2. Use of C1-INH will be permitted as an acute attack therapy but not as an LTP. Administration of the investigational product and study procedures will continue without alteration to the protocol-specified study schedule, even if the subject receives any treatment for an HAE attack.
- The use of short-term prophylactic treatment for HAE will be permitted if medically indicated and will be recorded in the appropriate electronic case report form (eCRF).
- Therapies to treat any AEs the subject experiences during the study are permitted and will also be recorded in the appropriate eCRF.
- FIRAZYR, which is approved in China for treatment of HAE attacks. FIRAZYR, as a rescue medication, will be provided to the study site by sponsor. Detailed information about FIRAZYR is provided in Appendix 5.

### 6.6.2 Prohibited Treatment

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

- LTP for HAE (eg, use of C1-INH for LTP, attenuated androgens, or antifibrinolytics)
- ACE inhibitors
- Estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy)
- Androgens (eg, stanozolol, danazol, oxandrolone, methyltestosterone, testosterone)
- Any other investigational drug or device

# 7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Treatment

If investigational product is discontinued, regardless of the reason, the evaluations listed for early termination will be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified evaluations at the follow-up visit. 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 and in electronic data capture (EDC).

## 7.2 Reasons for Discontinuation

The primary reason for discontinuation must be determined by the investigator and recorded in the subject's source document.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Protocol deviation
- Withdrawal by subject (by a parent or both parents/legal guardian for pediatric subjects)
- Lost to follow-up
- Lack of efficacy
- Pregnancy
- Study termination
- Other (if "Other" is selected, the investigator must specify in the eCRF)



## 7.3 Withdrawal from the Study

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

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

A minimum of 3 documented attempts must be made to contact any subject who is lost to follow-up at any time point prior to the last scheduled contact (in person or by phone or video). 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 be assessed for final safety evaluations and return any unused investigational product.

# 8. STUDY ASSESSMENTS AND PROCEDURES

See Table 1 for the schedule of study activities. Study assessments are detailed in Section 8.2.

## 8.1 Study Periods

The study includes a screening period that may require screening of 4 weeks, a washout period of 2 weeks, a run-in period of 4 to 8 weeks, a treatment period of 26 weeks, and a follow-up period of 4 weeks.

For adolescent subjects (<18 years of age) enrolled in the study that reach 18 years of age during study periods, a consent using the most current version of the informed consent form by subject is required.

### 8.1.1 Screening Visit and Washout Period

Informed consent, and assent when applicable, must be obtained for all subjects participating in the study prior to performing any study-related activities. Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the investigator. The screening visit procedures, including laboratory evaluations, are to be completed within the screening visit.



The investigator or qualified site personnel will confirm that all inclusion and exclusion criteria have been met.

Subjects who fail screening due to a single laboratory test result that does not meet eligibility criteria may have that laboratory test repeated at the discretion of the investigator. This will include a repeat of only the failed assessment rather than a repeat of all screening assessments (rescreening). In these cases, a new Subject Identification Code is not required. The repeat of a single screening assessment is allowed only once. A repeat assessment must take place within 4 weeks of the initial screening for any subject requiring repeat of a screening assessment. Other screen failures may be rescreened in the future (with new informed consent and screening period) if their clinical course results in a change that deems them eligible for the study.

Site personnel will train subjects and caregivers on identifying symptoms of an attack, the requirements for reporting attacks, and the information they will be expected to provide (see Section 8.2.2).

Adult subjects who are on LTP therapy for HAE will be required to undergo a minimum 2-week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the investigator determines that doing so would not place the subject at any undue safety risk and the subject was at least 18 years of age.

The investigator will confirm that the subject had successfully completed the 2-week washout period before they could enter the run-in period. Adolescent subjects (≥12 to <18 years of age) who are on LTP therapy for HAE are not required to undergo LTP washout.

Other assessments to be performed during screening visit are specified in Table 1.

### 8.1.2 Run-in Period

Subjects will undergo a run-in period to determine their baseline HAE attack rate as described in Section 4.1. Assessments during the run-in period include reporting of AEs, prior therapies, and HAE symptoms or attack data. Subjects who are found to be ineligible during the run-in period will not be allowed to rescreen into the study.

### 8.1.3 Treatment Period

There is a ±3-day window around each study visit, with a maximum of 17 days or a minimum of 11 days between any 2 doses.



#### 8.1.3.1 Visit 1 Dose 1 (Day 0)

Before Day 0 dosing, a post run-in eligibility review must take place. The procedures to be performed on Day 0 are presented in the schedule of study activities (Table 1).

#### 8.1.3.2 Site Check-in (Day 7)

Site personnel will contact the subject by phone to solicit for any attacks not already reported by the subject once between scheduled site visits or approximately 7 days after last contact with subject. Concomitant therapies and AEs will also be collected.

#### 8.1.3.3 Visit 2 Dose 2 (Day 14); Visit 3 Dose 3 (Day 28); Visit 4 Dose 4 (Day 42); Visit 5 Dose 5 (Day 56); Visit 8 Dose 8 (Day 98); Visit 11 Dose 11 (Day 140)

Study treatment will be administered at the site only during these study visits and the study procedures to be performed are presented in the schedule of study activities (Table 1).

#### 8.1.3.4 Visit 6 Dose 6 (Day 70); Visit 7 Dose 7 (Day 84); Visit 9 Dose 9 (Day 112); Visit 10 Dose 10 (Day 126); Visit 12 Dose 12 (Day 154); Visit 13 Dose 13 (Day 168)

Subjects (and/or their parent/caregiver) are allowed to initiate self-administration for these doses at the study site as described in Section 6.2.1. The study procedures to be performed are presented in the schedule of study activities (Table 1).

#### 8.1.3.5 Visit 14 Dose 14 (Day 182)/Early Termination

The final dose must be administered at the site and the study procedures must be completed as presented in the schedule of study activities (Table 1).

In the event a subject prematurely discontinued from treatment and/or the study, early termination visit procedures will be performed as soon as possible and recorded in the appropriate eCRF.

### 8.1.4 Follow-up Period and Visit 15 (Day 210)

The follow-up period for this protocol is 4 weeks.

At the end of this period, there will be a follow-up visit to query for SAEs, AEs, and concomitant treatments. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Appendix 3.2). The assessments specified in Table 1 will be performed at the follow-up visit.

The study completion date is defined as the date on which the last subject in the study completes the final protocol-defined assessments. This includes the follow-up visit.

### 8.1.5 Unscheduled Visit

Unscheduled visits may occur between scheduled site visits as required. Assessments may be performed as clinically indicated at the discretion of the investigator.

### 8.1.6 Additional Care of Subjects after the Study

No aftercare is planned for this study.

### 8.1.7 COVID-19-related Protocol Considerations

On a temporary basis, in order to maintain subject safety, confidentiality, and study integrity in the context of healthcare delivery challenges presented by the COVID-19 pandemic, subjects who may be impacted should contact study sites and investigators to determine the best course of action. Depending on the impact, in some cases it may be possible to arrange for alternative solutions as permitted by local regulations. 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 monitor, while maintaining subject safety and confidentiality as the priority.

Missing data, remote visits, changes to assessment approaches, and altered visit windows during the COVID-19 public health emergency may affect the study results. Thus, it is important to identify all protocol deviations and altered data collection or assessment methods. It is crucial that any deviations related to COVID-19 be clearly identified as such in the eCRF.

The following procedural changes may be considered:

- If necessary, informed consent from a potential or current trial participant may be obtained via electronic informed consent capabilities, or an electronic face-to-face consent interview when potential participants are unable to travel to the site.
- Subjects who discontinued from screening due to COVID-19-related factors but were otherwise qualified to participate in the trial may be rescreened if the medical monitor agrees.
- Options for additional investigational dosing in the home setting to prevent missed doses at site visits.

  Note: Home administration can only happen during an unanticipated situation like COVID-19 outbreak. In this situation, all procedures required at that visit need to be completed, except vital signs, ECG, physical examination, and blood collection. In addition, if investigator or subject has safety concerns regarding the self-injection at home, please reach out to sponsor medical monitor or site for more guidance. See Section 6.4 for the drug supply for administration.
- Remote checks instead of site visits (if appropriate) may be performed as a safety check on subject well-being.
- Transfer to investigational sites away from risk zones to complete required visits.



## 8.2 Study Assessments

### 8.2.1 Demographic and Other Baseline Characteristics

Subject demographic information including gender, age, and race will be collected at screening.

#### 8.2.1.1 Medical History and Prior and Concomitant Medications

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

Medical history will capture the subject's current relevant medical status (current disease processes), past relevant medical status (past disease processes), history of surgery, and allergies.

At screening, subject HAE attack history will be collected. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant attack location(s), average duration, acute attack therapy use, and history of LTP.

All non-study treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, non-pharmacological treatment such as psychotherapy) received within 30 days prior to the screening visit and through the final study contact (including protocol-defined follow-up period) must be recorded in the subject's source document and in EDC.

#### 8.2.1.2 C1-INH, C1q, and C4 Testing

Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment. Subjects may be re-tested if results are incongruent with clinical history or believed by the investigator to be confounded by recent LTP use. Analysis for these assays will be conducted at a central laboratory.

### 8.2.2 Efficacy

The collection, reporting, and assessment of attacks in this study will be done in accordance with the HAE Attack Assessment and Reporting Procedures (HAARP) (Appendix 4.1). Site personnel will be trained on HAARP prior to screening subjects at their site.

During screening, site personnel will train subjects and caregivers on identifying symptoms of an attack, the requirements for reporting attacks and the information they will be expected to provide. The subject (and caregiver) will confirm their understanding of what is required of them for reporting attacks to the site.

At screening, subject HAE attack history will be collected. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant attack location(s), average duration, acute attack therapy use, and history of LTP.

During the study, subjects (or caregivers, in the event the subject is <18 years old) will be instructed to notify and report details to the study site within 72 hours of the onset of an HAE attack. In the event that a subject is incapacitated following an attack, this information can be provided to the site by a family member or other individual with detailed knowledge of the event. Diary card will be provided to assist in tracking any HAE attacks subjects experience. Weekly communication between the subjects and the site, including reports of HAE attacks, must be documented in the eCRF.

Subjects (or caregivers) will be asked to provide the following information when reporting an attack:

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

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

Site personnel will review the information provided and solicit additional information as necessary to document the attack, as described in HAARP.

Subjects washing out of LTP will be contacted by the site at the end of the 2-week washout period. The investigator must confirm the subject has successfully completed the 2-week washout period before they can enter the run-in period. Confirmation of washout will be captured in the eCRF.

Site personnel will contact the subject or caregiver weekly, or approximately 7 days after their last contact with the subject, throughout the run-in period. If the subject experiences 1 or more investigator-confirmed HAE attacks by the end of Week 4, the subject will have fulfilled the run-in requirement and may proceed to the treatment period. Subjects who experience 3 or more investigator-confirmed attacks can exit the run-in period early and proceed to the treatment period. If the subject experiences no investigator-confirmed HAE attacks at the end of 4 weeks, the subject will remain in the run-in period for an additional 4 weeks. The maximum duration of the run-in period is 8 weeks. If run-in has been extended and the subject has 2 or more investigator-confirmed HAE attacks by the end of Week 8, the subject will have fulfilled the run-in requirement and may proceed to the treatment period. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in will be considered as screen failures.



During the treatment period, site personnel will contact the subject or caregiver once between scheduled study visits or approximately 7 days after their last contact to solicit for any HAE attack information not already reported.

Throughout the duration of the study, during each study visit at the investigative site, site personnel will solicit for any new HAE attack information that was not already provided to the site.

In this study HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to study drug, will be recorded on the AE page of the eCRF. For all SAEs that are reported as HAE attacks, the principal investigator or physician designee will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack.

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

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

To be confirmed as an HAE attack, the event must have symptoms or signs consistent with an attack in at least one 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 clinically determine that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (eg, urticaria), the reported event persists well beyond the typical time course of an HAE attack, 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 the previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.

### 8.2.3 Safety

#### 8.2.3.1 Physical Examination

A physical examination will be performed by the investigator. A physical examination will include the body systems listed below:

- Height and weight (at screening visit only)
- General appearance
- Ears, nose, and throat

- Head and Neck
- Ophthalmological
- Respiratory
- Cardiovascular
- Abdomen
- Neurological
- Extremities
- Dermatological
- Lymphatic

Abnormalities identified at the screening visit and at subsequent study visits will be recorded in the subject's source documents and in EDC. Physical examination findings by body system will be classified as normal, abnormal not clinically significant, abnormal clinically significant, or not performed by the investigator.



#### 8.2.3.2 Adverse Events

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed. Hypersensitivity reactions and events of disordered coagulation are classified as AESIs. All AEs, regardless of seriousness, severity, or causal relationship to study drug, will be recorded on the AE page of the eCRF. See Appendix 3 for definitions, assessment, collection time frame, and reporting procedures for AE, TEAE, SAE, AESI, unexpected AE, and suspected unexpected serious adverse reaction (SUSAR).

Investigators are to report all SAEs to the Takeda Global Patient Safety Evaluation (GPSE) Department through 30 days after the last dose of investigational product and SAEs considered related to investigational product >30 days after the last dose of investigational product.

#### 8.2.3.3 Vital Signs

There will be a ±15-minute window for all vital signs. At study visits in which study drug will be administered, vital signs including sitting or supine BP, HR, body temperature, and RR, are to be obtained prior to dosing and 1 hour after dosing.

The investigator will assess whether a change from baseline in vital signs may be deemed clinically significant and whether the change should be considered and recorded as an AE.

Vital sign values should be classified according to clinical significance as determined by the investigator. Categorical vital signs and the clinically significant vital signs will be summarized.

#### 8.2.3.4 Clinical Laboratory Tests

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

A complete list of the clinical laboratory tests to be performed including hematology, clinical chemistry, coagulation, urinalysis, and serology is provided in Appendix 2. Clinical laboratory tests will be conducted at a local laboratory.

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, serology), C1-INH, C4, C1q, PK, ADAs, and PD.



#### 8.2.3.5 Pregnancy Test

A urine or serum pregnancy test will be performed on all females of childbearing potential at the screening visit, monthly throughout the treatment period, and at the follow-up visit according to the schedule of study activities (Table 1) using local laboratory.

#### 8.2.3.6 Electrocardiogram

A standard 12-lead ECG (single recording) will be performed and assessed by the local laboratory according to the schedule of study activities (Table 1).

The date and time of each ECG and its results will be documented in the source documents and in EDC.

### 8.2.4 Other Assessments

#### 8.2.4.1 Pharmacokinetics

Blood samples for the measurement of plasma lanadelumab concentration will be obtained pre-dose (ie, within 2 hours before dosing) according to the schedule of study activities (Table 1) with a window period of ±3 days for the corresponding visit except on Day 0. Pharmacokinetic analysis will be conducted at a central laboratory.

#### 8.2.4.2 Pharmacodynamics

To evaluate the PD effects of lanadelumab upon pKal activity, blood samples will be obtained at pre-dose (ie, within 2 hours before dosing) according to the schedule of study activities (Table 1) with a window period of ±3 days for the corresponding visit except on Day 0. Pharmacodynamic analysis will be conducted at a central laboratory.

#### 8.2.4.3 Plasma Antidrug Antibody Testing (Immunogenicity)

Plasma samples for testing for formation of antibodies to lanadelumab will be obtained pre-dose (ie, within 2 hours before dosing) according to the schedule of study activities (Table 1) with a window period of ±3 days for the corresponding visit except on Day 0. Immunogenicity analysis will be conducted at a central laboratory.



### 8.2.5 Volume of Blood to Be Drawn from Each Subject

The amount of blood to be drawn for each assessment is provided in the operations manual. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

### 8.2.6 Blood Sample Collection, Storage, and Shipping

Blood samples for laboratory assessments, PK, PD, and formation of antibodies will be collected at the site, according to the schedule of study activities (Table 1), by 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.

### 8.2.7 Injection Report

An injection report will be completed by the subject (or caregiver) following each dose of lanadelumab, according to the schedule of study activities (Table 1).

The injection report will collect information on the subject's experience with SC injection of lanadelumab. Study personnel will document the subject's responses in the subject's medical record and eCRF.

### 8.2.8 Diary Card

A diary card will be completed by the subject (or caregiver) as soon as the subject enters the run-in period, according to the schedule of study activities (Table 1). The diary card will be dispensed to the subject (or caregiver) at the time of the screening visit. If the subject passes all screening assessments, the investigator or designee will inform the subject via phone call or video to start completing the diary card. The subject (or caregiver) should complete the diary card at the end of each day to record if an HAE attack happens or not. If the subject encounters any HAE attack, an HAE attack worksheet (part of diary card) should be completed; subjects (or caregivers, in the event the subject is <18 years old) should notify and report details to the study site within 72 hours of the onset of the HAE attack (see Section 8.2.2). The investigator should check completion of diary card at each visit. Study personnel will document the subject's responses in the subject's medical record and eCRF.

# 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.

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

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



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

An interim data analysis may be performed to support the supplementary New Drug Application (sNDA) submission for China pediatric indication. The interim analysis will at least summarize the efficacy, safety and PK of treatment with lanadelumab in Chinese subjects with HAE. The interim analysis will be conducted when approximately 10 subjects complete the 26 weeks treatment period and 4 weeks follow-up period.

No adaptive design, or data monitoring committee is planned for this study.

## 9.3 Sample Size and Power Considerations

The planned total sample size for this study is approximately 20 subjects.

The sample size is considered adequate based on the objectives of the study and was based on clinical judgment and precedent studies of similar design and similar subject population and not on statistical considerations such as study power. With a sample size of 20 subjects exposed to lanadelumab, the probability of observing an event that occurs within the population at a rate of 10% is approximately 87%.

### 9.4 Statistical Analysis Set(s)

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

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

### 9.5 Analysis of Disposition

The numbers of subjects enrolled, completing, or withdrawing, along with reasons for withdrawal, will be tabulated for the FAS population.



### 9.6 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) for the FAS population.

### 9.7 Demographics and Baseline Characteristics Analyses

Baseline and demographic variables will be descriptively summarized for the FAS population.

### 9.8 Treatment Compliance and Extent of Exposure

Treatment compliance and extent of exposure will be described by calculating the percentage of planned doses received by the subject and the total number of doses received by the subject and summarized for the FAS population.

### 9.9 Efficacy Analyses

The efficacy endpoints are described in Section 3.2.

No statistical hypothesis testing will be performed.

- Continuous efficacy endpoints will be summarized using number of subjects (n), mean, SD, median, minimum, and maximum. Whenever appropriate, raw (actual) values and changes from baseline will be summarized at each scheduled time point. Overall attack rates per month (28 days) will be estimated using summary statistics.

- Categorical efficacy endpoints (eg, attack severity) will be summarized in terms of the number and percentage of subjects in each category of the efficacy endpoint.
- Time-to-event endpoint (eg, time to the first HAE attack) will be summarized using Kaplan-Meier (KM) estimates. Summaries will include 25th, 50th (median) and 75% percentiles, if estimable, and the corresponding 95% confidence intervals. In addition, KM plots detailing each subject's contribution to the analysis will be provided.

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

Efficacy endpoints will be evaluated for the following 2 efficacy evaluation periods:

- Day 0 (after study drug administration) through Day 182
- Presumed steady-state period from Day 70 through Day 182

Sensitivity analysis will be performed to evaluate the robustness of the efficacy results during each efficacy evaluation period for the FAS population. The analysis will be repeated using all subject-reported HAE attacks instead of limiting the analysis to those attacks that were investigator confirmed.



### 9.10 Safety Analyses

The safety endpoints are described in Section 3.2.

No statistical hypothesis testing will be performed.

- Continuous safety endpoints (eg, change in laboratory parameter) will be summarized using number of subjects (n), mean, SD, median, minimum value, and maximum value. As appropriate, raw (actual) values and changes from baseline will be summarized overall and at each scheduled time point.
- Categorical endpoints (eg, presence or absence of an outcome measure) will be summarized using counts and percentages. Summaries will include, but are not limited to: number and percentage of subjects with an outcome measure, and laboratory shift tables (categorical change from baseline).

Baseline is defined as the last non-missing value prior to initial dosing with study drug (lanadelumab).

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

Adverse events will be coded using MedDRA coding dictionary. Only TEAEs will be analyzed, but all AEs including TEAEs and non-TEAEs will be provided in the AE subject listing. The analyses described in this section will be based on TEAEs; plainly referred to as AEs in this section for brevity.

- TEAE is defined as AE with onset at the time of or following initial dosing with study drug (lanadelumab), or medical conditions present prior to the start of study drug but increasing in severity or relationship at the time of or following the start of treatment, up to the last follow-up visit. For AEs with partial onset times, non-missing date parts will be used to determine if the AE is treatment emergent or not. If a determination cannot be made using the non-missing date as to when the AE occurred relative to study drug administration, then the AE will be classified as treatment emergent.

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



For this analysis, AEs will be classified to two analysis periods:

- Treatment Period AEs will include all AEs starting at or after the first exposure to study drug in this study to those starting before or at the subject's last visit date during the treatment period in this study (AEs starting at or after treatment on Day 0 through Day 182 visit).
- Follow-up Period AEs will include all AEs starting after the subject's last visit date of the treatment period in this study (AEs starting after the Day 182 visit).

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

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized by SOC and PT for each analysis period. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, and related severe AEs. Similar summary tables for investigator-reported AESIs, or determined by the search tool of relevant Standardized MedDRA Queries, will also be generated.

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

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

Concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD). Usage of prior or concomitant medications (other than rescue medications) will be summarized descriptively by therapeutic class and PT. A separate, similar table will be provided for the subset of concomitant medications classified as rescue medications.

Clinical laboratory test results and vital signs, physical examination, and ECG findings will be summarized using descriptive statistics by visit. Clinical laboratory test results will be categorized according to reference ranges and the investigator's assessment of clinical assessment and summarized as shifts from baseline. Clinically significant laboratory test results and changes in vital signs will be listed and summarized. Listings of physical examination and ECG findings will include the investigator's assessment of clinical significance.



### 9.11 Other Analyses

The PK, PD, and Immunogenicity endpoints are described in Section 3.2.

#### 9.11.1 Pharmacokinetic, Pharmacodynamic, and Immunogenicity Analyses

Characterization of PK properties of lanadelumab in the Chinese population will be conducted via population PK modeling approach and reported separately.

Characterization of PK/PD properties of lanadelumab in the Chinese population will be conducted via population PK/PD modeling approach and reported separately.

No formal statistical hypothesis will be tested. Individual concentrations and PK parameters (not limited to $C_{trough}$) of lanadelumab will be provided in subject data listing(s) and summarized using descriptive statistics (number of subjects, arithmetic mean, SD, coefficient of variation [CV], median, minimum, maximum, geometric mean, and CV of geometric mean). Figures of individual and mean (±SD) concentration-time profiles for plasma lanadelumab will be generated. Tabular and graphical summaries will be analyzed based on the PK set and PD set, as appropriate.

Immunogenicity data will be summarized using descriptive statistics.

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# Appendix 1 Regulatory, Ethical, and Study Oversight Considerations

## Appendix 1.1 Regulatory and Ethical Considerations

This study is conducted in accordance with current applicable regulations including ICH E6, 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, contract research organization [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 eCRFs 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.

### 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.



## Appendix 1.3 Investigator's Responsibilities

### Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and E6 R2 (2017), and applicable local and national 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 multi-center 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 (multi-center study), in compliance with 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 multi-center studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.



**Documentation and Retention of Records**

**Electronic Case Report Forms**

Electronic case report forms (eCRFs) are supplied by the sponsor or 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 eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic 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 eCRF.

The clinical research associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data. Alternative approaches may be used to ensure data quality, data integrity, and subject safety (eg, remote source data review via phone or video) as permitted by regional and local regulations. Additional details are in the monitoring plan.

### 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 eCRF 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) or an auditor.

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

### Audit/Inspection

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

### Financial Disclosure

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

## Appendix 1.4 Data Management Considerations

### Data Collection

The investigators' authorized site personnel must enter the information required by the study eCRF 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 eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF 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 sponsor'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 personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

## Appendix 1.5 Ethical Considerations

### Informed Consent

It is the responsibility of the investigator to obtain written informed consent and assent where applicable from all study subjects prior to any study-related procedures including screening assessments. All consent and assent documentation must be in accordance with applicable regulations and GCP.

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

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

The principal investigator provides the sponsor with a copy of the consent form and assent 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**

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.

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

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

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. 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

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/EC 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 multi-center study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multi-center publication of the compiled and analyzed study results. If such a multi-center 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 multi-center 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:

Clinical Chemistry

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

Hematology

- Hemoglobin
- Hematocrit
- Red blood cell count
- White blood cell count with differential
- Mean corpuscular volume
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Absolute platelet count

Coagulation

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

Serology

- HBsAg
- HCV
- HIV

Urinalysis

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

Others

- C1-INH
- C1q
- C4
- Urine and/or serum pregnancy test
- Pharmacokinetic test
- Pharmacodynamic test
- Antidrug antibody test

# 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 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 one 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).

**Adverse Events of Special Interest**

Adverse events of special interest (AESIs) will be captured and monitored during this study. Investigators will report all AESIs 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 mAb as a class, these events are considered AESI for this study. Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with hypersensitivity reactions, regardless of causality, within 24 hours from the time of study drug administration. Investigators will report hypersensitivity reactions that occur after 24 hours, only if the reactions are suspected to be related to study drug.

- Events of Disordered Coagulation
  - Bleeding AESI

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

- Hypercoagulable AESI

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

**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 from the pharmacological properties of a product.

**Suspected Unexpected Serious Adverse Reaction**

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

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

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



**Symptoms of the Disease under Study**

As discussed in Section 8.2.2 of this protocol, angioedema attacks will be captured as AEs in this study and will be evaluated in accordance with HAARP (Appendix 4.1).

**Clinical Laboratory and Other Safety Assessment**

A change in the value of a clinical laboratory parameter, vital sign measure, physical examination 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.

If, at the end of the treatment period, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, physical examination 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, physical examination or ECG parameter is clinically significant and represents an AE.

When laboratory abnormalities are considered to be AEs, the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (Appendix 4.2) or DMID Pediatric Toxicity Tables (Appendix 4.3) will be used to assess severity. Where discrepancies in the ULN 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.

Collection of ECG parameters will be conducted and assessed by a local laboratory for all study subjects.



**Appendix 3.2 Collection of Adverse Events**

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

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

## Appendix 3.3 Assessment of Adverse Events

### Severity Categorization

If the subject experiences a change in the severity of an AE, the event should be captured once with the maximum severity recorded. However, 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 AEs will be assessed according to DMID Adult Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases) (Appendix 4.2) and the DMID Pediatric Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases) (Appendix 4.3). 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



Any treatment-emergent ECG abnormality that is considered by the investigator as clinically significant and requiring intervention/therapy will be assessed as a severe AE.

### 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:

**Table A1. Adverse Event Relationship Categorization**

| | |
|---|---|
| Related | The temporal relationship between the event and the administration of the investigational product is compelling enough and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident. |
| Not related | The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event. |



### 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

## Appendix 3.4 Safety Reporting

### Reference Safety Information

The RSI for this study is the IB which the sponsor has provided under separate cover to all investigators.

### Reporting Procedures

The investigator should complete a SAE electronic case report form (eCRF), an AE or a HAE acute attack eCRF for AESI in English and transmit to Takeda Global Patient Safety Evaluation (GPSE) within 24 hours of becoming aware of the event.

If EDC fails to work, SAE/AESI will be reported via Takeda safety report form within the same timeframe. It is applicable to all initial and follow-up SAE/AESI reports. Of Note: HAE is the indication for treatment and should be considered expected as the events are considered disease related (progression of underlying disease) and not subject to expedited reporting.

### Appendix 3.5 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to investigational product) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 8.1.4 and must be reported to the Takeda GPSE 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 Department within 24 hours of the reported first becoming aware of the event.

### Appendix 3.6 Serious Adverse Event Onset and Resolution Dates

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

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



### Appendix 3.7 Fatal Outcome

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

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

## Appendix 3.8 Pregnancy

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

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours of the first awareness to the Takeda GPSE using the paper Pregnancy Report Form. The fax number and e-mail address are provided in the Form Completion Instruction.

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 post-partum.



Pregnancy complications such as abortion/miscarriage, or congenital abnormality are considered SAEs and must be reported using the same procedure as describing the SAE reporting.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the same procedure as describing the SAE reporting 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 safety reporting procedure whether or not they result in an AE/SAE as described in Appendix 3.4.

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

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

- Abuse – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society

- Misuse – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- Overdose – Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed dose
- Medication Error – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

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

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

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

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



**Appendix 3.10 Urgent Safety Measures**

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

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

The investigator may implement urgent safety measures to protect study subjects from immediate hazard to their health or safety. The measures should implement immediately and does not require prior authorization from the sponsor. In the event(s) of an apparent direct hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, and within 1 calendar day after the change is implemented.

The sponsor will also ensure the responsible EC(s) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

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

The sponsor/CRO is responsible for reporting all SUSARs and any other applicable (serious) adverse drug reactions to regulatory authorities, investigators and ECs/institutions as applicable, in accordance with safety regulations in the countries where the study is conducted. The sponsor/CRO will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational product or that would be sufficient to consider changes in the investigational products administration or in the overall conduct of the trial.

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

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

## Appendix 4 Scales and Assessments

The following assessments will be utilized in this study:

| Full Title of Scale/Assessment |
|---|
| HAE ATTACK ASSESSMENT AND REPORTING PROCEDURES (HAARP) |
| National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases) |
| National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases) |

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 4.1 HAE ATTACK ASSESSMENT AND REPORTING PROCEDURES (HAARP)

## 1 PURPOSE

This document applies to clinical trials that involve investigator adjudication/assessment of angioedema attacks. The purpose of this document is to provide a definition of an HAE attack and to define a standardized set of procedures for the reporting and assessment of events reported by subjects to determine whether those events are true HAE attacks.

## 2 DEFINITION OF AN ATTACK

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

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



Despite the presence of these symptoms, the investigator may still determine clinically that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an attack (eg, urticaria), the reported event persists well beyond the typical time course of an attack (eg, greater than 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 resolution of the prior attack's symptoms.

Attack resolution is defined as the subject no longer having symptoms of the attack. Prodromal symptoms by themselves are not considered an attack.

Subject report of use of acute HAE attack treatment for an attack by itself is not confirmation that an attack occurred.

# 3 REPORTING AND ASSESSMENT OF ATTACK DATA

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

During the relevant study periods, as defined in the applicable study protocol, subjects (or caregivers, for subjects <18 years old) will be instructed to contact the site within 72 hours of the start of symptoms of an attack. In the situation that a subject is incapacitated and is unable to contact the site, a family member or other individual with detailed knowledge of the event can provide the information. Diary card will be provided to assist in tracking any HAE attacks subject's experience. Any tools or devices the subject uses to track this information are not intended to serve as source documents for the study.

Site personnel will review the information provided by the subject or caregiver and solicit additional information as necessary to document the attack. Information documented by the site will be considered source for the study.

A designated individual at the site (the collector) will contact the subject or 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. 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 caregiver.



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

## 3.1 Subject-reported Symptoms

Subjects and caregivers can use any existing methods by which they track information about their attacks or diary card will be provided by the study site. However, subjects (or a caregiver) will need to track attacks in such a way as to be able to contact the study site as soon as possible, but not later than 72 hours (3 full days) after the first symptoms appear, to report the information.

### 3.1.1 Attack Information

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

- Date and time when symptoms of an attack were first experienced
- Description of symptoms experienced, including location(s)
- Impact on activity and whether any assistance or medical intervention was required, including hospitalizations or emergency department visits
- Any medications used to treat the attack
- If the attack resolved, date and time the subject was no longer experiencing symptoms

Subjects 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 should not withhold or delay any treatment they would normally receive to treat their attack in order 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 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 on identifying symptoms of an attack, the requirements for reporting attacks and the information they will be expected to provide. The subject will confirm their understanding of what is required of them for reporting attacks to the site. Sites will assess the subject's compliance with the reporting requirements throughout the study and may retrain the subject if necessary in order to maintain the integrity of the data provided to the site.

### 3.1.4 Reporting Multiple Attacks

If a subject experiences symptoms they attribute to more than one unique attack they can report this as multiple attacks to the site. Based on the definition of an attack, it will be the determination of the investigator or designee as to whether events reported as being separate are confirmed as separate attacks or not.

### 3.1.5 Caregiver Report

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

### 3.1.6 Subject Contact with Sites

Site personnel will establish a recommended method and time window for each subject 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 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. The date and time for check-ins can be modified based on when the last contact with the subject was made. When the site is contacted by a subject 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 misses a call from the site. A study schedule for each subject's on-site visits will be provided to the subject by the site.

### 3.2.1 Review of Subject Report of Symptoms

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

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

### 3.2.2 Documenting a Reported Attack

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

- Date and time of contact with the subject

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

Additional probing questions about what the subject experienced to determine:

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



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

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

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

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

### 3.2.3 Site Training

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

- definition of an HAE attack
- requirements of subjects and caretakers for reporting attacks

- reporting worsening symptoms and multiple attacks
- information to be collected from subjects and caregivers as well as the additional probing questions to gather context for the attack information provided
- assessment of attack severity
- entry of the attack data into the eCRF
- reporting HAE attacks as adverse events
- requirements for investigator assessment of attacks

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

All responsible persons involved in the collection of information from subjects or assessing attacks must be listed on FDA Form 1572 or equivalent regulatory document as applicable.



### 3.3 HAE Attacks as Adverse Events

At the time of each contact and scheduled study visit, site personnel will ask if the subject experienced any adverse events or changes to the medications they are taking.

Hereditary angioedema attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to study drug, will be recorded on the AE page of the eCRF.

Any AE reported to the site meeting criteria for an SAE must be reported to sponsor (see Appendix 3.5). For all SAEs that are reported as HAE attacks, the principal investigator or physician designee will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack.

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

# 4 INVESTIGATOR ATTACK ASSESSMENT

The principal investigator for a study site may identify a physician designee to assess subject symptom information and make attack determinations. Sites should be limited to two individuals responsible for assessing attacks, one of them being the principal investigator. Assessors must be experienced with HAE and familiar with the study subject's disease history.

The assessor must review the information and determine whether the event is an actual attack or not. If needed, the assessor can contact the subject and/or caregiver to clarify information or ask for any additional detail. The determination will be documented along with the date and time the determination was made. Any event deemed not an attack must be accompanied by an explanation and alternative diagnosis 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, the subject's caregiver or any other site personnel. Assessors may consult with one another about a particular subject's attack but only one 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 4.2 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious 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<br>High: 400-600 mg/dL | Low: <100 mg/dL<br>High: >600 mg/dL | Low: < 50 mg/dL<br>--- | 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+<br>or<br>200 mg - 1 gm loss/day | 2-3+<br>or<br>1- 2 gm loss/day | 4+<br>or<br>2-3.5 gm loss/day | nephrotic syndrome<br>or<br>> 3.5 gm loss/day |
| Hematuria | microscopic only<br><10 rbc/hpf | gross, no clots<br>>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 4.3 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious 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-<br>No Treatment Needed | Moderate-<br>Treatment Needed | Severe-<br>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 | evere-Little ral 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/<br>Lower Motor Neuropathy | | Mild transient<br>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 5 Firazyr

FIRAZYR is a competitive antagonist selective for the bradykinin B2 receptor with an affinity similar to bradykinin. FIRAZYR inhibits bradykinin from binding the B2 receptor and thereby treats the clinical symptoms of an acute, episodic attack of hereditary angioedema (HAE).

FIRAZYR is indicated for the treatment of acute attacks of HAE in adults, adolescents, and children aged 2 years and older.

FIRAZYR drug product is a clear and colorless to light yellow liquid for subcutaneous (SC) administration.

FIRAZYR drug product is supplied in a prefilled syringe in strength of 30 mg/3 mL, with a FLUROTEC-coated plunger stopper. A hypodermic needle (25 G; 16 mm) is included in the pack.

During an unanticipated situation like COVID-19 outbreak, the site may use an alternative method for dispensing FIRAZYR. If permitted by local regulations and ECs, FIRAZYR can be shipped from the site/the local depot directly to the subject's home address via courier. Subjects must be provided with instructions on how to receive, store, and ultimately return FIRAZYR.



### Dosing

For adults, the recommended dose of FIRAZYR is 30 mg administered as a single slow SC injection into the abdomen. In the majority of cases, a single injection of FIRAZYR is sufficient to treat an attack. If there is insufficient relief or recurrence of symptoms, a second injection of FIRAZYR can be administered after 6 hours. If the second injection produces insufficient relief or a recurrence of symptoms is observed, a third injection of FIRAZYR can be administered after additional 6 hours. Not more than 3 injections of FIRAZYR should be administered to the subject within a 24-hour period.

For pediatrics (aged 2 to 17 years), the recommended dose of FIRAZYR is based on body weight and is provided in the following table. Suggest investigator remind adolescent subjects to monitor their weight regularly and dose FIRAZYR according to the recommendation.

| Body Weight | Dose (Injection Volume) |
|---|---|
| 12 kg to 25 kg | 10 mg (1.0 mL) |
| 26 kg to 40 kg | 15 mg (1.5 mL) |
| 41 kg to 50 kg | 20 mg (2.0 mL) |
| 51 kg to 65 kg | 25 mg (2.5 mL) |
| >65 kg | 30 mg (3.0 mL) |

**Method of administration**

FIRAZYR is intended to administer as a slow SC injection, preferably in the abdominal area. Disinfect the injection site and administer FIRAZYR by SC injection for over at least 30 seconds. Each FIRAZYR syringe is intended for single-use only.

For subjects who have never received FIRAZYR previously, the first treatment should be given in a medical institution or under the guidance of a physician. FIRAZYR may be self-administered or administered to adults by a caregiver only after receiving training in SC injection technique by a healthcare professional. Children and adolescents aged 2 to 17 years may be administered with FIRAZYR by a caregiver only after receiving training in SC injection technique by a healthcare professional. The decision on initiating caregiver-administration or self-administration of FIRAZYR should only be taken by a physician experienced in the diagnosis and treatment of HAE.

**Storage**

FIRAZYR is stored between 2□ to 25□ (36°F to 77°F). It should not be frozen.

Refer to the FIRAZYR product leaflet for additional details on FIRAZYR and its administration.

## Appendix 6 Abbreviations

| Abbreviation | Definition |
|---|---|
| ACE | angiotensin-converting enzyme |
| ADA | antidrug antibody |
| AE | adverse event |
| AESI | adverse event of special interest |
| AI | autoinjector |
| 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 |
| BP | blood pressure |
| C1-INH | C1 esterase inhibitor |
| CFR | Code of Federal Regulations |
| cHMWK | cleaved high molecular weight kininogen |
| CHO | Chinese hamster ovary |
| COVID-19 | coronavirus disease 2019 |
| CRA | clinical research associate |
| CRO | contract research organization |
| $C_{trough}$ | steady-state trough concentration |
| CV | coefficient of variation |
| DMID | Division of Microbiology and Infectious Diseases |
| EC | ethics committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture/collection |
| EMA | European Medicines Agency |
| EU | European Union |

| Abbreviation | Definition |
|---|---|
| EUDRACT | European Union Clinical Trials Register |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FFP | fresh frozen plasma |
| GCP | Good Clinical Practice |
| GPSE | Global Patient Safety Evaluation |
| HAARP | HAE Attack Assessment and Reporting Procedures |
| HAE | hereditary angioedema |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HR | heart rate |
| IB | investigator's brochure |
| ICH | International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | independent ethics committee |
| IgG1 | immunoglobin G subclass 1 |
| INR | International Normalized Ratio |
| IRB | institutional review board |
| IRT | interactive response technology |
| KM | Kaplan-Meier |
| LTP | long-term prophylaxis |
| mAb | monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NNA | normalized number of attacks |
| PD | pharmacodynamic(s) |
| PFS | prefilled syringe |
| PK | pharmacokinetic(s) |
| pKal | plasma kallikrein |
| PT | preferred term |

| Abbreviation | Definition |
|---|---|
| q2wks | every 2 weeks |
| RR | respiratory rate |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAS | statistical analysis system |
| SC | subcutaneous(ly) |
| SD | standard deviation |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| US | United States |
| WHO-DD | World Health Organization-Drug Dictionary |

## Appendix 7 Protocol History

| Document | Date | Global/Country/Site Specific |
|---|---|---|
| Protocol Amendment 2 | 9 Feb 2023 | China |
| Protocol Amendment 1 | 12 Apr 2022 | China |
| Original Protocol | 26 Aug 2021 | China |

## Previous Protocol Amendment Summaries of Changes

| Protocol Amendment | | |
|---|---|---|
| **Summary of Change(s) Since the Last Version of the Approved Protocol** | | |
| **Amendment Number**<br>**1** | **Amendment Date**<br>**12 Apr 2022** | **China** |
| **Description of Each Change and Rationale** | | **Section(s) Affected by Change** |
| Added the details and changed the section heading as per the updated protocol template.<br>Added name and contact information of Takeda medical monitor. | | Contacts |
| Updated the text for the analyses of safety parameters (ie, clinical laboratory test, vital signs, physical examination, and ECG findings) for clarification.<br>Updated the text for the classification of physical examination and vital signs according to clinical significance. | | Section 1.1 Synopsis<br>Table 1 Schedule of Study Activities<br>Section 8.2.3.1 Physical examination<br>Section 8.2.3.3 Vital Signs<br>Section 9.10 Safety Analyses |
| Added the circumstances for repeating a laboratory test during the screening period for subjects who fail screening due to a single laboratory test result that does not meet eligibility criteria, based on Section 8.1.1. | | Section 1.1 Synopsis<br>Section 4.1 Overall Design |
| Clarified that rescreening will not be allowed for any subjects who are found to be ineligible during the run-in period. | | Section 1.1 Synopsis<br>Section 4.1 Overall Design<br>Section 8.1.2 Run-in Period |
| Added details about management of acute HAE attacks during the study as per the investigator's discretion. | | Section 1.1 Synopsis<br>Section 4.1 Overall Design |
| Updated exclusion criterion #6 to indicate that use of LTP therapy for HAE within 2 weeks prior to entering the run-in period is exclusionary only for adult subjects, for clarification. | | Section 1.1 Synopsis<br>Section 5.2 Exclusion Criteria |
| Added a row for injection report in the schedule of study activities table, and added details of injection report to provide clear guidance of the study execution in Table 1 footnote "h" and Section 8.2.7. | | Table 1 Schedule of Study Activities<br>Section 8.2.7 Injection Report |
| Added a row for diary card in the schedule of study activities table, and added details of diary card to provide clear guidance of the study execution in Table 1 footnote "i" and Section 8.2.8. | | Table 1 Schedule of Study Activities<br>Section 8.2.8 Diary Card |

| Protocol Amendment | | |
|---|---|---|
| **Summary of Change(s) Since the Last Version of the Approved Protocol** | | |
| **Amendment Number**<br>**1** | **Amendment Date**<br>**12 Apr 2022** | **China** |
| **Description of Each Change and Rationale** | | **Section(s) Affected by Change** |
| Added the option that a subject's parent/caregiver can also administer the investigational product to the subject instead of only by the subject themselves, in case any subject is too young or unable to do self-administration.<br>Added the option that subjects are allowed to initiate self-administration under the supervision from investigator or designee, instead of only under the investigator supervision. | | Table 1 Schedule of Study Activities<br>Section 6.2.1 Dosing and Administration<br>Section 6.3 Labeling, Packaging, Storage, and Handling of Investigational Product<br>Section 6.5 Subject Compliance<br>Section 8.1.3.4 Visit 6 Dose 6 (Day 70); Visit 7 Dose 7 (Day 84); Visit 9 Dose 9 (Day 112); Visit 10 Dose 10 (Day 126); Visit 12 Dose 12 (Day 154); Visit 13 Dose 13 (Day 168) |
| Removed the sentence "subjects who self-administer will fill/complete a self-administration questionnaire" due to the reason that the study will use injection report to collect administration-related information. | | Table 1 Schedule of Study Activities<br>Section 6.5 Subject Compliance |
| Clarified that unscheduled visits may occur in between the scheduled site visits, and necessary assessments will be performed at the discretion of investigator. | | Table 1 Schedule of Study Activities<br>Section 8.1.5 Unscheduled Visit |
| Added sentence to clarify the activities to be followed during an unanticipated situations like COVID-19 outbreak. Cross-reference to Section 8.1.7 included as this provides guidance on how to respond if an emergency happens as a result of COVID-19 or a similar unanticipated situation. | | Table 1 Schedule of Study Activities |
| Corrected the typographical error for the number of reported cases in Chinese population, from 1 per 50,00 to 1 per 50,000. | | Section 2 Introduction |
| Added clinical information (ie, efficacy and safety result summary) for Study SHP643-302 per the latest IB. | | Section 2.2 Clinical Information |
| Added a sentence about regulatory approval status of lanadelumab. | | Section 2.4 Benefit/Risk Assessment |
| Removed the term 'children' as there are no children being enrolled in this study. | | Section 5.3.1 Female Contraception |
| Clarified to follow schedule of study activities (Table 1) for self-administration of lanadelumab at the investigational site.<br>Added that home administration of investigational product may be considered during an unanticipated situation like COVID-19 outbreak and refer to details in Section 6.4 and Section 8.1.7. | | Section 6.2.1 Dosing and Administration |
| Added the subsection of interactive response technology, which is added for the investigational product management tasks. | | Section 6.2.2 Interactive Response Technology for Investigational Product Management |

| Protocol Amendment | | |
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| **Summary of Change(s) Since the Last Version of the Approved Protocol** | | |
| **Amendment Number**<br>**1** | **Amendment Date**<br>**12 Apr 2022** | **China** |
| **Description of Each Change and Rationale** | | **Section(s) Affected by Change** |
| Added details of alternative method for dispensing the investigational product directly to the subject's home address during an unanticipated situations like COVID-19 outbreak. This provides guidance on how to respond if an emergency happens as a result of COVID-19 or a similar unanticipated situation. | | Section 6.4 Drug Accountability |
| Updated subject instructions to bring unused investigational product and empty/used investigational product packaging to every visit with new instructions to assess drug accountability for unused investigational product and empty/used investigational product packaging. This is to deal with an unanticipated situations like COVID-19 outbreak when subjects are receiving home administration and cannot visit site. | | Section 6.5 Subject Compliance |
| Updated the text 'office visit or telephone contact' with 'in person or by phone or video' as per the updated template language.<br>Updated the text 'return to the site for final safety evaluations and return any unused investigational product' with 'be assessed for final safety evaluations and return any unused investigational product'. This is to deal with an unanticipated situations like COVID-19 outbreak when subjects cannot visit site. | | Section 7.4 Subjects "Lost to Follow-up" Prior to the Last Scheduled Visit |
| Clarified that screen failure situations other than an ineligible laboratory test result would require a new ICF to be signed in the future at the discretion of the investigator if the subject's clinical course results in a change that deems them eligible for the study. | | Section 8.1.1 Screening Visit and Washout Period |
| Added details of home administration of investigational product during an unanticipated situation like COVID-19 outbreak, for clarification. | | Section 8.1.7 COVID-19-related Protocol Considerations |
| Replaced 'memory aid' by 'diary card', which is added under this protocol amendment and will be provided to assist in tracking any HAE attacks subjects experience.<br>Removed the sentence "Any AE reported to the site meeting criteria for an SAE must be reported to the sponsor" as already reported in Section 8.2.3.2. | | Section 8.2.2 Efficacy<br>Appendix 4.1 |
| Added a sentence "All AEs, regardless of seriousness, severity, or causal relationship to study drug, will be recorded on the AE page of the eCRF", for clarification. | | Section 8.2.3.2 Adverse Events |
| Removed appendix (previously Appendix 6) on bioanalysis and added a new section to provide details of blood sample collection, storage, and shipping to align with the laboratory manual. | | Section 8.2.6 Blood Sample Collection, Storage, and Shipping |
| Added sentence that alternative approaches such as remote source data review via phone or video could be used for monitoring purpose per the updated protocol template. | | Appendix 1.3 |

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| Added physical examination as other safety assessment along with vital sign measurement and ECG assessment to be consistent with other parts of the protocol. | | Appendix 3.1 |
| Corrected the typographical error for the time by which the subject or caregiver should contact the study site from '2 hours' to '72 hours' after appearance of first symptoms of an HAE attack. | | Appendix 4.1 |
| Added details of alternative method for dispensing of FIRAZYR during an unanticipated situations like COVID-19 outbreak.<br>Added text suggesting that the investigator remind adolescent subjects to monitor their weight regularly and to dose FIRAZYR as per the recommendation. | | Appendix 5 |
| Removed the appendix (previously Appendix 4) on contraceptive guidance as similar text is already provided in Section 5.3. | | Not applicable |

AE=adverse event; COVID-19=coronavirus disease 2019; ECG=electrocardiogram; HAE=hereditary angioedema; IB=investigator's brochure; ICF=informed consent form; LTP=long-term prophylaxis; SAE=serious adverse event