Statistical Analysis Plan

NCT Number: NCT04444895

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

Study Number: TAK-743-3001

Document Version and Date: Version 2.0, 29 June 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.

STATISTICAL ANALYSIS PLAN

Study Number: TAK-743-3001

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

Phase: Phase 3

Version: 2.0

Date: 29 JUN 2023

Prepared by: [redacted]

Based on: Protocol Version: Amendment 1.0

Protocol Date: 14 SEP 2020

REVISION HISTORY

Version	SAP Section	Primary Rationale for Revision
2.0	6.6 Protocol Deviation	Protocol deviation section is updated to describe the handling of the site level deviations and important protocol deviations.
2.0	6.7.2.1 Number of Investigator-confirmed Angioedema Attacks	Added subgroup analysis for number of investigator-confirmed angioedema attacks based on the three levels of baseline subtype (with known mutations, with family history, and with idiopathic non-histaminergic angioedema) from Study SHP643-303. Added 95% CI to summaries of the number of investigator-confirmed angioedema attacks.
2.0	6.8.5 Achievement of Treatment Period NNA per 4 weeks <1.0, <0.75, <0.50, and <0.25 during each of the efficacy evaluation periods	To be consistent with parent Study SHP643-303, removed analyses for the achievement of treatment period attack rate <0.75 attacks per 4 weeks, <0.50 attacks per 4 weeks, and <0.25 attacks per 4 weeks.
2.0	7.7 Health-related Quality of Life Analyses	Summaries of change in total scores and 4 domain scores from baseline are updated per the protocol and the baseline definition of safety analysis.
2.0	10.2.2 Definition of Baseline	The baseline definition for safety analysis is updated to clearly define handling of baseline for rollover subjects that were on lanadelumab or placebo in parent Study SHP643-303. Added the definition for PK/PD analyses.
2.0	10.2.14 Clinical Significance Attributions for Laboratory Results	Added Section 10.2.14 Clinical Significance Attributions for Laboratory Results.
Original version 1.0	Not Applicable	Not Applicable

TABLE OF CONTENTS

List of in-text tables

ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug Antibody
AE	Adverse Event
AE-QoL	Angioedema Quality of Life
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BILI	Bilirubin
BLQ	Below Limit of Quantitation
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
cHMWK	Cleaved High Molecular Weight Kininogen
C1-INH	C1 Esterase Inhibitor
C1q	Complement Component 1q
C4	Complement Component 4
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CO_2	Carbon Dioxide
CPK	Creatine Phosphokinase
CRF	Case Report Form
CTMS	Clinical Trial Management System
CV%	Coefficient of Variation
ECG	Electrocardiogram
EOS	End of Study
ET	Early Termination
FAS	Full Analysis Set
BAARP	Non-histaminergic bradykinin-mediated angioedema attack assessment and reporting procedures
HR	Heart Rate

Abbreviation	Definition
HRQoL	Health-Related Quality of Life
INR	International Normalized Ratio
IP	Investigational Product
ISR	Injection Site Reaction
IV	Intravenous
JNDA	Japanese New Drug Application
KM	Kaplan-Meier
LLOQ	Lower Limit of Quantitation
LLN	Lower Limit of Normal
LTP	Long-term Prophylaxis
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
msec	Millisecond
NNA	Normalized Number of Attacks
PD	Pharmacodynamic
pH	Potential Hydrogen
PK	Pharmacokinetic
PT	Preferred Term (MedDRA®)
QoL	Quality of Life
RD-SFAS	Reduced Dose Safety Analysis Set
RR	Respiratory Rate
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFAS	Safety Analysis Set
SC	Subcutaneous
SD	Standard Deviation
SMQ	Standardized MedDRA® Query
SOC	System Organ Class

Abbreviation	Definition
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO-DD	World Health Organization Drug Dictionary

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

Text directly copied from the protocol is *italicized*.

1.1 Objectives

1.1.1 Primary Objective

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

1.1.2 Secondary Objective(s)

- *To evaluate the long-term efficacy of lanadelumab in preventing angioedema attacks*
- *To characterize pharmacokinetics (PK) and pharmacodynamics (PD) following long-term SC administration of lanadelumab*
- *To assess the immunogenicity of chronically administered lanadelumab*
- *To evaluate the effect of lanadelumab on health-related quality of life (HR-QoL)*
- *To evaluate subject experience of injection*
- *To evaluate the safety and efficacy of lanadelumab in subjects switched to the dosing regimen of 300 mg every 4 weeks (q4wks) lanadelumab*

1.1.3 Exploratory Objective(s)

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

1.2 Endpoints

1.2.1 Primary Endpoint(s)

Objective	*Endpoint(s)*
Primary	
• *To evaluate the long-term **safety** of repeated SC administrations of lanadelumab in adolescents and adults with non-histaminergic angioedema with normal C1-INH*	***Primary Safety Endpoints*** *Safety measures, including* • *AEs including SAEs and adverse events of special interest (AESIs)* • *Clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis)* • *Vitals signs including blood pressure (BP), heart rate (HR), body temperature* • *Weight and height (height for subjects <18 years old)* • *12-lead ECGs*

1.2.2 Secondary Endpoint(s)

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

1.2.3 Exploratory Endpoint(s)

Objective	*Endpoint*
Exploratory	
• *To evaluate exploratory biomarker(s) of angioedema disease-state bioactivity in plasma*	• *Exploratory biomarker(s) of angioedema-disease state bioactivity, including pKal activity*

1.3 Estimand(s)

Table 1 Estimand Framework

Estimand: Primary

	Attributes				
Definition	**Treatment**	**Population**	**Variable (or Endpoint)**	**Strategy for Addressing Intercurrent Event**	**Population-Level Summary**
Proportion of patients with BMA who would develop treatment emergent AE (including each AESI (hypersensitivity reactions and all serious events) if exposed to lanadelumab during the treatment period	TAK-743 300 mg every 2 weeks and TAK-743 300 mg every 4 weeks for those subjects who had dose frequency change	≥ 12-year-old subjects with BMA defined through inclusion and exclusion criteria as stated in the protocol and who received at least 1 dose of lanadelumab during the study.	Occurrence of Treatment emergent AEs following first lanadelumab dose	1/ Rescue medication: treatment policy (Events will be counted regardless of whether or not rescue medication/supportive treatment use had occurred.) 2/ Premature study discontinuation before the end of the treatment period related to study medication: while on treatment (Events will be counted while the subject is on the study) 3/ Premature study discontinuation before the end of the treatment period unrelated to study medication: while on treatment (Events will be counted while the subject is on the study) 4/ Study medication interruption: treatment policy (Events will be counted regardless of the treatment interruption)	Number and proportion of subjects who experience treatment-emergent AEs during Treatment Period

Estimand: Secondary					
	Attributes				
Definition	Treatment	Population	Variable (or Endpoint)	Strategy for Addressing Intercurrent Event	Population-Level Summary
A secondary estimand is the effect of lanadelumab on the rate of angioedema attacks during the treatment period (Day 0 to Day 182)	TAK-743 300 mg every 2 weeks and TAK-743 300 mg every 4 weeks for those subjects who had dose frequency change	≥ 12-year-old subjects with BMA defined through inclusion and exclusion criteria as stated in the protocol and who received at least 1 dose of lanadelumab during the study.	Number of investigator-confirmed angioedema attacks during the Treatment Period (Day 0 to Day 182).	1/ Rescue medication: treatment policy (Events will be counted regardless of whether or not rescue medication/supportive treatment use had occurred.) 2/ Premature study discontinuation before the end of the treatment period related to study medication: while on treatment (Events will be counted while the subject is on-study) 3/ Premature study discontinuation before the end of the treatment period unrelated to study medication: while on treatment (Events will be counted while the subject in on-study) 4/ Study medication interruption: treatment policy (Events will be counted regardless of the interruption)	Normalized number of investigator-confirmed angioedema attack per 4 weeks during Treatment Period and comparison to normalized number of investigator-confirmed angioedema attacks per 4 weeks during baseline observation period for study SHP643-303.

2.0 STUDY DESIGN

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

All subjects must complete the double-blind treatment period at Visit 26/Day 182 of Study SHP643-303 and consent to enter Study TAK-743-3001. Subjects who discontinue from Study

SHP643-303 after enrollment but before Visit 26 are not eligible to enroll in Study TAK-743-3001.

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

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

All subjects must adhere to the Schedule of Activities (Table 5) for the entire duration of the study. See Schedule of Activities (Table 5) for additional information on study visits.

Following their first open-label dose, subjects will continue to receive repeated SC administrations of open-label 300 mg lanadelumab q2wks or may be considered to receive lanadelumab 300 mg q4wks if they have been well-controlled (eg, attack free) for 26 consecutive weeks across Study SHP643-303 and Study TAK-743-3001 per the scheduled dosing in the Study Activities Schedules. The dose frequency change to q4wks will be based on the investigator's discretion and consultation with the sponsor's medical monitor. The treatment period will last up to around182 days from the date of the first open-label dose. The number of doses administered during this period will not exceed 13 doses. The Day 168 study visit is the last visit at which a dose may be administered.

All doses should be administrated within the accepted ±4-day window around dose administration schedule (q2wks or q4wks in Table 6*).*

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

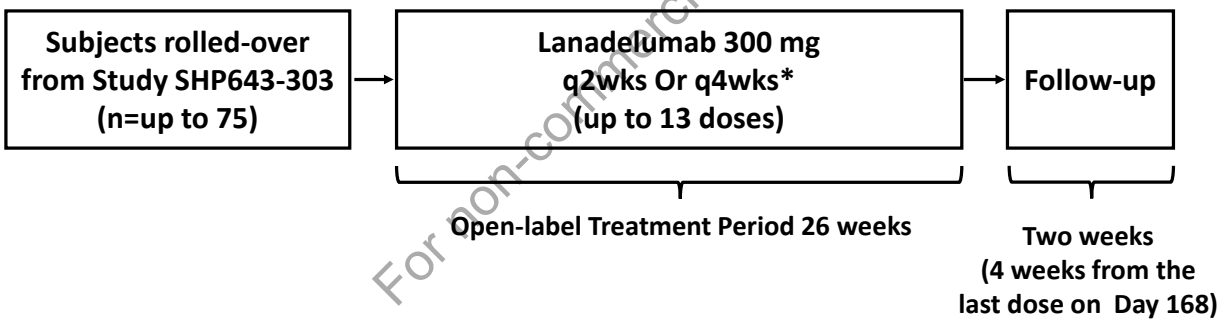
All subjects (adolescent or adult) who are considered suitable candidates (ie, those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer study treatment. Once trained, subjects may self-administer subsequent doses of lanadelumab at the investigational site (when visits are scheduled study site visits) or the subject's home or other agreed upon location (when the study permits off-site dosing -- See Schedule of Activities [Table 6] *for details).*

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

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

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

Figure 1 Study Schematic Diagram



q2wks=every 2 weeks; q4wks=every 4 weeks.

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

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

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

The statistical objective is to evaluate long-term safety and efficacy of lanadelumab by estimating the number and proportion of subjects with treatment emergent adverse events and the angioedema attack rate (attacks/4 weeks). No formal hypothesis testing will be performed.

3.1 Statistical Hypotheses

Not applicable.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

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

5.0 ANALYSIS SETS

5.1 Screened Set (SC Set)

The Screened Set will consist of all subjects who have signed informed consent.

5.2 Safety Analysis Set (SFAS)

The Safety Analysis Set will include all subjects who received any study drug after entering Study TAK-743-3001 (ie, any exposure to open-label lanadelumab). Unless otherwise specified, summary tabulations conducted in the Safety Analysis Set will be presented by the subject's SHP643-303 treatment group (placebo or lanadelumab 300 mg q2wks) and overall. In addition, for efficacy analyses, within each previous treatment group (placebo or lanadelumab 300 mg q2wks) and overall, data will be presented by the actual dosing regimen a subject receives, 300 mg every 2 weeks and 300 mg every 4 weeks. For safety analyses, within each previous treatment group (placebo or lanadelumab 300 mg every 2 weeks) data will be presented by the actual dosing regimen a subject receives, 300 mg every 2 weeks and 300 mg every 4 weeks. For the overall safety analysis set, data will not be presented by actual dosing regimen and the total will only be presented.

5.3 Reduced-Dose Safety Analysis Set (RD-SFAS)

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

will be presented by dosing regimen (lanadelumab 300 mg q2wks and lanadelumab 300 mg q4wks).

5.4 Pharmacokinetic Set (PK Set)

The Pharmacokinetic Set (PK Set) will include all subjects in the SFAS who have at least 1 evaluable post dose PK concentration value.

5.5 Pharmacodynamic Set (PD Set)

The Pharmacodynamic Set (PD Set) will include all subjects in the SFAS who have at least 1 evaluable post dose PD concentration value.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. CIs intervals will be presented using the same number of decimal places as the parameter estimate where applicable.

6.1.1 Handling of Treatment Misallocations

Not Applicable.

6.1.2 Analysis Approach for Continuous Variables

All continuous endpoints in this study will be summarized descriptively. *For continuous variables, the number of subjects, mean, median, SD, minimum, and maximum values will be presented.*

6.1.3 Analysis Approach for Binary Variables

All binary and categorical endpoints in this study will be summarized descriptively. *For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented.*

6.1.4 Analysis Approach for Time-to-Event Variables

Time to the first investigator-confirmed angioedema attack will be summarized using Kaplan-Meier (KM) estimates of the 25th, 50th (median), and 75th percentiles with associated two-sided 95% CI, as well as percentage of events and censored observations. Plots of the supporting data detailing each subject's contribution to the analysis will be provided where applicable.

6.2 Disposition of Subjects

The number of subjects who were included in each defined analysis set (Safety Analysis Set, Reduced-Dose Safety Analysis Set, Pharmacokinetic Set, and Pharmacodynamic Set) will be

summarized for the screened subjects. The number of subjects included in each analysis set will be summarized by study site and country as well.

The number and percentage of subjects who completed the treatment period (defined as those subjects who complete study Visit 14/Day 182), follow-up period, or prematurely discontinued the study will be presented for the Safety Analysis Set and Reduced-Dose Safety Analysis Set. Reasons for premature discontinuation from study will be summarized (number and percentage) for the Safety Analysis Set and Reduced-Dose Safety Analysis Set. The duration of enrollment, in days will be summarized for each site, country and overall. Duration of enrollment will be calculated as (last date of contact for any subject at that site- the first date of informed consent for any subject at that site + 1).

Disposition of all subjects, including screen failures, will be presented in a listing for the Screened Set. Inclusion criteria not met and exclusion criteria met will be listed.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Descriptive summaries of demographic and baseline characteristics will be presented for the Safety Analysis Set (SFAS) and Reduced Dose Safety Analysis Set (RD-SFAS). Demography data from Study SHP643-303 will be re-entered in the clinical database from Study TAK-743-3001.

The following demographic characteristics will be summarized:

- Age at informed consent date (years),
- Age category (<18, 18 to <40, 40 to <65, ≥65 years) at informed consent date,
- Sex (Male, Female, Unknown, Intersex/Undifferentiated),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown),
- Race (White, Black or African American, Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska Native, Multiple, Other),
- Race group (White, Other),
- Geographical region (North America, Europe, Japan, and Other),
- Weight (kg),
- Weight category (<50, 50 to <75, 75 to <100, ≥100 kg),
- Height (cm),
- Body mass index (BMI) (kg/m^2), calculated as 10000*weight (kg)/ height (cm)^2,
- BMI group for subjects ≥ 18 years of age (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2),

- BMI percentile group for subjects < 18 years of age based on growth charts from the Centers for Disease Control and Prevention (CDC) (Underweight: <5th percentile, Healthy or Overweight: 5th to <95th percentile, Obese: >=95th percentile),
    - Official and validated SAS programs created by CDC will be used to calculate the percentile of BMI. For more information on the CDC SAS programs, see http://www.cdc.gov/growthcharts/computer_programs.htm.

All baseline and demographic data will be presented in subject listings.

6.3.2 Medical History and Concurrent Medical Conditions

Medical history will be collected at Visit 1 and will be coded using MedDRA Version 23.1 or newer. Medical history reported in the Study SHP643-303 will not be re-entered into the eCRF for Study TAK-743-3001; only new medical history data will be entered.

The medical history will be summarized by system organ class (SOC) and preferred term (PT) for the Safety Analysis Set. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency.

All medical history will be presented in subject listings for the Safety Analysis Set.

6.3.3 Baseline Characteristics

The following baseline angioedema characteristics will be summarized in a separate table:

- Age at onset of angioedema symptoms (years),
- History of laryngeal attacks (yes, no),
- Primary attack location (laryngeal, abdominal, peripheral, or a combination of these locations),
- Number of attacks in the last 1, 3, and 12 months prior to screening,
- Average attack duration (in days) in the last 12 months prior to screening,
- Average severity of angioedema attacks in the last 12 months prior to screening (mild, moderate, severe),
- Average attack duration category (less than 12 hours, 12-24 hours, 24-48 hours, greater than 48 hours, not applicable) in the last 3 months prior to screening,
- Number of attacks of different severity (mild, moderate, severe) in the last 3 months prior to screening,
- Observation period of Study SHP643-303 angioedema attack rate (attacks/4 weeks),
- Observation period of Study SHP643-303 angioedema attack rate categories (1-<2 attacks/4 weeks, ≥2 attacks/4 weeks),

- Observation period of Study SHP643-303 angioedema attack rate strata (1-<2 attacks/4 weeks, ≥2 attacks/4 weeks), and
- Type of LTP therapy before entering the observation period of Study SHP643-303 (C1-INH, Androgens, Anti-fibrinolytics, or not on LTP).
- The three levels of subtype will be summarized 1) with known mutations (FXII, PLG, ANGPT1, or KNG1 genes, or other predefined mutations associated with normal C1-INH angioedema) – with summary to include the genotype categories; 2) with family history (a first-degree relative) and unknown mutations; and 3) with idiopathic non-histaminergic angioedema (INHA).

The LTP (C1-INH, Androgens, or Anti-fibrinolytics) treatment a subject was on prior to the observation period of Study SHP643-303 was determined by applying the algorithm below to prior medications (i.e., medications with start and stop date prior to the start date of observation period, imputing partial dates as described in Section 10.2.10) reported for that subject that lasted for ≥4 days:

LTP	Algorithm to Identify Medications
C1-INH	ATC level 4 in ('B06AC') and preferred drug name not in ('icatibant', 'ecallantide', 'icatibant acetate')
Androgens	ATC level 4 in ('G03BA', 'G03BB', 'A14AA') or preferred drug name in ('danazol', 'oxandrolone')
Anti-fibrinolytics	ATC level 4 in ('B02AA', 'B02AB')

6.4 Medication History and Concomitant Medications

6.4.1 Prior Treatment/Medications

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

6.4.2 Concomitant Medications/Procedure

Concomitant medications will be coded using the WHO Drug Dictionary dated 01 SEP 2019. Concomitant therapies and procedures will be coded using MedDRA Version 23.1 or newer.

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant medication/therapy is defined as any medication/therapy with a start date and time prior to the date and time of the first dose of IP and continuing after the first dose of IP or with a start date

and time between the dates and times of the first dose of IP and end of the study, inclusive. For medications/therapy/procedure with partial onset times, non-missing date parts will be used to determine whether the medication is concomitant or prior medication. If a determination cannot be made using the non-missing date parts as to when the medication occurred relative to study drug administration, then the medication will be classified as concomitant.

The summaries of concomitant medication/therapy/procedure will be presented separately for:

- Concomitant Medications/therapies/procedures (excluding those taken for an angioedema attack)
- Concomitant Medications/therapies/procedures taken for an angioedema attack

The concomitant medications will be summarized by the number and proportion of subjects within each ATC Level 2 therapeutic class and PT for the SFAS. Tabulations will be presented sorted by therapeutic class in alphabetical order and by PT within each therapeutic class by descending frequency. The concomitant therapies and procedures will be summarized by the number and proportion of subjects within each SOC and PT for the SFAS. Tabulations will be presented sorted by therapeutic class in SOC and by PT within each SOC by descending frequency. Multiple medication usage by a subject in the same category (i.e., therapeutic class or preferred name) will be counted only once.

Concomitant medications/therapies/procedures will be summarized for the Treatment Period and Follow-up Periods inclusive. Partial date imputation for medications is described in Section 10.2.10.

All concomitant therapies, procedures and medication will be listed for the Screened Set.

6.5 Study Drug Administration and Injection Report

For the SFAS, the responses to each item of the study drug administration and injection report will be tabulated by study visit.

The number and percentage of subjects who performed study drug administration via study staff administration in-clinic, self-administration in-clinic (including “Self-Administration in the Study Clinic under Supervision by Study Staff” and “Parent/Caregiver Administration in the Study Clinic under Supervision by Study Staff”), and self-administration at home (including “Self-Administration at Home or Other outside Clinic” and “Parent/Caregiver Administration at Home or Other Outside Clinic”) will be tabulated by study visit.

The number and percentage of subjects with >80% self-administration (including “Self-Administration in the Study Clinic under Supervision by Study Staff” and “Parent/Caregiver

Administration in the Study Clinic under Supervision by Study Staff", "Self-Administration at Home or Other outside Clinic" and "Parent/Caregiver Administration at Home or Other Outside Clinic"), with >80% administration by study staff in-clinic, or subjects with <80% self-administration and <80% administration by study staff in-clinic will be tabulated for the Safety Analysis Set.

The number and percentage of study drug administration with a duration of 0 seconds to 10 seconds, 11 seconds to 20 seconds, 21 seconds to 30 seconds, 31 seconds to 60 seconds, greater than 1 minute to less than or equal to 2 minutes, greater than 2 minute to less than or equal to 3 minutes, greater than 3 minutes to less than or equal to 4 minutes, greater than 4 minutes to less than or equal to 5 minutes, and greater than 5 minutes will be summarized for the doses that was self-administered at home (including "Self-Administration at Home or Other outside Clinic" and "Parent/Caregiver Administration at Home or Other Outside Clinic"), self-administered in-clinic (including "Self-Administration in the Study Clinic under Supervision by Study Staff" and "Parent/Caregiver Administration in the Study Clinic under Supervision by Study Staff"), administered by the study staff in-clinic, and overall.

A listing of study drug administration and injection report will be provided.

6.6 Protocol Deviations

Protocol deviations as obtained from a clinical trial management system (CTMS) will be assessed throughout the study. All identified deviations will be reported in the CTMS. Protocol deviations from the CTMS will be coded to severity categories ("critical", "major" and "minor") and importance criteria ("yes", "no") and provided as part of the CTMS transfer to Biostatistics.

Protocol deviations will be collected at both the site and subject level. Deviations at the site level will be tracked as non-compliance after CTMS enhancements for all subjects who were enrolled at that site at the time of the deviation. Protocol deviations and study site non-compliances will be summarized by deviation type, and severity for the SFAS, respectively. All protocol deviations and non-compliances will be included in the separate listings for the screened set. Protocol deviations identified as related to the impact of COVID-19 will be flagged in the subject listings.

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy and/or reliability of study data or that may significantly affect a subject's rights, safety, or well-being. These deviations will be identified with a flag in the listings, and a sub-category of important protocol deviations will also be summarized in the subject level protocol deviation and study site non-compliances tables.

6.7 Efficacy Analysis

No statistical hypothesis testing will be performed. The totality of results across all efficacy endpoints will be the measure of overall treatment benefit.

All efficacy analyses will be based on the SFAS and specified efficacy analyses will be based on the RD-SFAS. Efficacy data, including derived efficacy parameters defined in the subsections below, will be presented in subject data listings.

For all efficacy analyses, unique angioedema attacks, as defined in Section 10.2.5.1 will be used.

Handling of missing start or end date and time for angioedema attacks is described in Section 10.2.9.

Efficacy endpoints will be presented for the following two efficacy evaluation periods:

- Day 0 (after study drug administration) through Day 182 (the end of the Treatment Period)
- Presumed steady state period from Day 70 through Day 182 only for subjects who were on placebo in the Study SHP643-303. This is because subjects who were on placebo in the Study SHP643-303 are treatment naïve when they enter into the Study TAK743-3001.

Detailed definition of these periods is given in Section 10.2.4. For the efficacy evaluation period starting from Day 70, only subjects who reach the visit of Day 70 will be included in the analysis and this number of subjects will be used as denominator for percentage calculation.

An HAE attack will be counted for a specific efficacy evaluation period only if that HAE attack started during that period. For example, if a HAE attack starts before Day 70 and is ongoing after Day 70, it will not be counted for the efficacy period Day 70 through Day 182.

6.7.1 Primary Endpoint(s) Analysis

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

6.7.2 Secondary Endpoints Analysis

6.7.2.1 Number of Investigator-confirmed Angioedema Attacks

The number of investigator-confirmed angioedema attacks during the treatment period (Day 0 through Day 182) expressed as a monthly angioedema attack rate, will be analyzed using the SFAS and the RD-SFAS. For the SFAS, the number of investigator-confirmed angioedema attacks will be presented by actual treatment in the Study TAK-743-3001 and previous treatment assignment in the Study SHP643-303. Similarly, subgroup analysis will be conducted for this

efficacy endpoint based on the three levels of baseline subtype (with known mutations, with family history, and with idiopathic non-histaminergic angioedema) from the Study SHP643-303. For the RD-SFAS, the number of investigator-confirmed angioedema attacks will be presented by the actual treatment a subject receives, 300 mg every 2 weeks and 300 mg every 4 weeks.

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

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

The baseline, treatment period, and treatment period change from baseline in the investigator-confirmed angioedema attack rate will be summarized along with 95% CI for SFAS and without 95% CI for RD-SFAS. *The summary will include the total number of investigator-confirmed angioedema attacks reported during the treatment period and subject-time in months that each subject contributed to the treatment period. Figures will be created for each analysis* set *plotting the on-study investigator-confirmed angioedema attacks reported during the treatment period relative to Day 0 for each subject.*

In addition, the number of investigator-confirmed angioedema attacks per month (defined as 28 days) will be summarized descriptively by month (per 28-day interval) for SFAS without 95% CI. *The summary will include the number, change from baseline, and percent change from baseline of investigator-confirmed angioedema attacks. Investigator-confirmed angioedema attacks will be grouped into 28-day intervals using the start date of the angioedema attack. The date of the first exposure to study drug in this study will be used as the start of the first interval and end of the interval will be the date of first exposure to study drug in this study plus 27 days. Each successive interval will start the last day of the prior interval plus 1 day and end 28 days later.*

Similar summary tables will be presented for the following efficacy endpoints for each analysis set (SFAS and the RD-SFAS without 95% CI)*:*

- *Number of moderate or severe investigator-confirmed angioedema attacks during the treatment period.*

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

The analysis will also be repeated for the efficacy evaluation period, Day 70 to Day 182 for subjects who were on placebo in the Study SHP643-303.

6.8 Analyses of Other Efficacy Endpoints

6.8.1 Time to First Angioedema Attack

The time to the first investigator-confirmed angioedema attack (days) after Day 0 for the treatment period will be analyzed for the SFAS only and will be calculated from the date and time of the first dose of lanadelumab to the date and time of the first investigator-confirmed angioedema attack. The summary will only be presented by prior treatment group in the Study SHP643-303.

Subjects who do not experience any attacks during the treatment period will be censored at the date and time of the end of the period, i.e., visit date of Day 182 visit and time of 23:59. Subjects who discontinue the study during the treatment period prior to experiencing their first on-study investigator-confirmed angioedema attack will be censored at the date of study discontinuation and time of 23:59.

Time to the first investigator-confirmed angioedema attack will be summarized using Kaplan-Meier (KM) estimates of the 25th, 50th (median), and 75th percentiles with associated two-sided 95% CI, as well as percentage of events and censored observations.

In addition, KM plots detailing each subject's contribution to the analysis will be provided.

A sample SAS code for KM estimates is provided in Appendix 10.5.

6.8.2 Time to First Angioedema Attack After Day 70

The time to the first investigator-confirmed angioedema attack (days) after Day 70 for the treatment period will be analyzed for the subjects who were on placebo in the Study SHP643-303 and in the SFAS only. The summary will only be presented for all subjects together irrespective of prior treatment group in the Study SHP643-303 and actual treatment regimen in the Study TAK-743-3001.

The time to first angioedema attack (days) after Day 70 will be calculated as the earliest of the date of the angioedema attack after Day 70 as defined in Section 10.2.6.2, date of study discontinuation or completion, or date of Day 182 visit minus the date of Day 70 visit plus 1.

Subjects with attacks occurring after Day 70 will be considered events at the time of the angioedema attack. Subjects who discontinue/complete the study prior to having an angioedema attack will be censored at the time of discontinuation/completion.

6.8.3 Characteristics of Investigator-confirmed Angioedema Attacks

For the SFAS and RD-SFAS, characteristics of investigator-confirmed angioedema attacks will be summarized for the observation period, the treatment period (Day 0 through Day 182), and presumed steady state (Day 70 through Day 182) for subjects who were on placebo in the Study SHP643-303 at both the subject level and event-level. The calculations described below will be conducted for each efficacy evaluation period. For the SFAS, the number of investigator-confirmed angioedema attacks will be presented by actual treatment in the Study TAK-743-3001 and previous treatment assignment in the Study SHP643-303. For the RD-SFAS, the number of investigator-confirmed angioedema attacks will be presented by the actual treatment a subject receives, 300 mg every 2 weeks and 300 mg every 4 weeks.

6.8.3.1 Subject Level angioedema Attack Characteristics

6.8.3.1.1 Angioedema Attack Duration

For each subject, the mean duration of all investigator-confirmed angioedema attacks will be calculated in hours and summarized. See Section 10.2.5.1 for details on handling angioedema attack duration and Section 10.2.9 for handling of missing date/time of angioedema attacks

The subject-level average attack duration will be categorized into 12-hour intervals and tabulated by category (<12 hours, 12-24 hours, >24-48 hours, and >48 hours).

6.8.3.1.2 Angioedema Attack Severity

For each subject, the mean and maximum severity (based on BAARP) of all investigator-confirmed angioedema attacks will be summarized for the treatment period. See Section 10.2.5.1 for details on handling angioedema attack severity.

The average attack severity will be calculated per subject by attributing a numeric value to each severity as follows: 0=No attack, 1=Mild, 2=Moderate, and 3=Severe. Higher values will indicate more severe attacks, while lower values will indicate less severe attacks. The mean attack severity will be summarized for all subjects as well as only subjects with angioedema attacks.

The number and percentage of subjects will be tabulated by maximum attack severity (no attacks, mild, moderate, and severe).

6.8.3.2 Event Level Angioedema Attack Characteristics

6.8.3.2.1 Angioedema Attack Location

The number and percentage of subjects with attacks, as well as the number of events, will be tabulated by the primary attack location (peripheral, abdominal, and laryngeal) as determined by the investigator. See Section 10.2.5.1 for details on handling angioedema primary attack location.

Additionally, the attack location will be re-classified and summarized with an emphasis on the laryngeal attack. In this summary, an attack with either the primary or secondary location(s) identified as laryngeal will be considered as a laryngeal attack; otherwise, attacks will be classified by their reported primary attack location.

6.8.3.2.2 Rescue Medication Use

The number and percentage of subjects with rescue medication use for an angioedema attack, as well as the number of events (number of rescue medications used), will be tabulated by type of rescue medication (icatibant, plasma-derived C1-INH, and other) as reported in the Angioedema Acute Attack CRF.

See Section 10.2.5.1 for details on handling angioedema attack rescue medication use.

6.8.3.2.3 Supportive Treatment Use

The number and percentage of subjects with supportive treatment use for an angioedema attack, as well as the number of events, will be tabulated by type of supportive treatment (IV fluids, pain medication, oxygen, anti-emetic, and other) as reported in the angioedema Acute Attack CRF.

See Section 10.2.5.1 for details on handling angioedema attack supportive treatment use.

6.8.4 Achievement of at Least a 50%, 70% ,90%, and 100% Reduction in the Investigator-confirmed NNA per 4 weeks during each of the efficacy evaluation periods Relative to the Observation Period

There will be four classes of responders based on pre-specified percentage reduction in the investigator-confirmed NNA per 4 weeks (i.e., monthly investigator-confirmed angioedema attack rate defined in Section 10.6.7.2.1) from the observation period in the Study SHP643-303: 50% or more reduction, 70% or more reduction, 90% or more, and 100% reduction for the SFAS only for each efficacy evaluation period. The summary will only be presented by actual treatment groups in the TAK-743-3001 study (lanadelumab 300 mg every 2 weeks and lanadelumab 300 mg every 4 weeks).

For the SFAS, the percentage reduction will be calculated as the Study SHP643-303 observation period angioedema attack rate minus the treatment period angioedema attack rate divided by the observation period angioedema attack rate. Number and percentage of subjects achieving each of the four predefined thresholds will be summarized for the treatment period. The three classes of responders are nested within each other and not mutually exclusive.

6.8.5 Achievement of Treatment Period NNA per 4 weeks <1.0, during each of the efficacy evaluation periods

For the SFAS only, there will be one class of responder based on pre-specified investigator-confirmed NNA per 4 weeks (i.e., monthly investigator-confirmed angioedema attack rate defined in Section 6.7.2.1 for each efficacy evaluation period: <1.0 per 4 weeks).

The number and percentage of subjects achieving the predefined threshold will be summarized for the SFAS.

6.8.6 Achievement of Attack-free Status for the treatment period

An attack-free day is defined as a calendar day with no investigator-confirmed angioedema attack.

For the SFAS, the number and percentage of subjects achieving attack-free for the treatment period will be summarized. A two-sided 95% CI for the proportion of subjects achieving attack-free will be derived using the exact method.

For subjects who discontinue during the treatment period, the evaluation period will end at the date of study discontinuation with time 23:59 and attack-free status will be evaluated for the period of time that the subject was in the evaluation period. For subjects who switch dosing regimens, the evaluation period will end at the date/time of the initial dose of the new dosing regimen as specified in Section 10.2.17.

6.8.7 Percentage of Attack-Free Days

An attack-free day is defined as a calendar day with no investigator-confirmed angioedema attack.

For the SFAS, the percentage of angioedema attack free days during the treatment period will be calculated by counting the number of days in the treatment period without an angioedema attack and dividing by the number of days the subject was in the treatment period.

Descriptive statistics for the percentage of angioedema attack free days will be summarized for the treatment period.

6.8.8 Efficacy Listings for the Reduced-dose Safety Analysis Set

Listings will present the following information separately for q2wks and q4wks dosing periods for subjects who had a dose frequency modification from q2wks to q4wks:

- Number of days on treatment, treatment compliance, number and rate of investigator-confirmed angioedema attacks, angioedema attacks requiring acute treatment, moderate or severe angioedema attacks, high morbidity angioedema attacks, maximum severity angioedema attacks and the achievement of at least a 50%, 70% and 90% reduction in angioedema attack rate relative to the observation period in the Study SHP643-303.

6.8.9 Sensitivity Analyses of Other Secondary Efficacy Endpoints

All secondary efficacy analyses will be repeated using all subject-reported angioedema attacks instead of limiting the analysis to those attacks that were investigator-confirmed.

For the analysis for the achievement of attack-free period in Section 6.8.6, the analysis will be repeated with patients who drop out early counted as not attack-free regardless of attack-free status while on the study.

6.8.10 Summary of analyses presented for the Safety Analysis Set and Reduced-Dose Safety Analysis Set

Table presents the analyses that will be presented by the Safety Analysis Set and Reduced-Dose Safety Analysis Set.

Table 2 Efficacy Analyses for the Safety Analysis Set and Reduced-Dose Safety Analysis Set

Endpoint	Safety Analysis Set	Reduced Dose Safety Analysis Set
Number of Investigator-confirmed Angioedema Attacks	X	X
Number of Investigator-confirmed Angioedema Attacks by Month	X	X
Number of Moderate or Severe Investigator-confirmed Angioedema Attacks	X	X
Number of Moderate or Severe Investigator-confirmed Angioedema Attacks by Month	X	X

Number of High Morbidity Angioedema Attacks	X	X
Number of High Morbidity Angioedema Attacks by Month	X	X
Time to First Angioedema Attack	X	
Subject Level Characteristics of Investigator-confirmed Angioedema Attacks during the Treatment Period	X	X
Event Level Characteristics of Investigator-confirmed Angioedema Attacks during the Treatment Period	X	X
Achievement of at least 50%, 70%, 90%, and 100% reduction in the investigator-confirmed NNA per 4 weeks relative to observation period	X	
Achievement of a Treatment Period NNA per 4 weeks <1.0	X	
Achievement of attack-free status for the treatment period	X	
Percentage of attack-free days	X	
Efficacy Listings	X	X

7.0 SAFETY ANALYSIS

No statistical hypothesis testing will be performed. All safety summaries will be based on the Safety Analysis Set (SFAS) and specified summaries will be based on the Reduced-Dose Safety Analysis Set (RD-SFAS). Safety endpoints include AEs, clinical laboratory variables, vital signs, and ECG variables.

The definition of baseline is provided in Section 10.2.2.

All safety data, including derived data, will be presented in subject data listings.

7.1.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. AEs will be coded using MedDRA Version 24.0 or newer. WHO Drug Global B3 version 01Mar2020 or newer will be used.

Treatment-emergent AEs (TEAEs) are defined as AEs with onset at the time of or following the first exposure to lanadelumab in this study, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. For AEs with partial onset times, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date as to when the AE occurred relative to study drug administration, then the AE will be classified as treatment-emergent. Partial date imputation for AE is described in Section 10.2.11.

The analyses described in this section will be based on TEAEs only; plainly referred to as AEs in this section for brevity. All AEs (TEAEs and non-TEAEs) will be provided in the AE subject listing.

Related AEs are AEs classified as related to study drug by the investigator. Missing relationship to study drug imputation is described in Section 10.2.13.

Severe AEs are AEs classified as severe (grade 3) or life threatening (grade 4) by the investigator. Missing severity imputation is described in Section 10.2.12.

The collection of tabulations described in this section (with the exception of the analyses of AESI and injection site reaction [ISR]) will be produced for 2 mutually exclusive subgroups of AEs based on whether the AE was identified in EDC as a subject-reported angioedema attack or not, and defined as follows:

- Non-angioedema attack reported AEs will include the subset of AEs identified in EDC as not a reported angioedema attack. Essentially, this will be all AEs excluding angioedema attack reported events.
- Angioedema attack reported AEs will include the subset of AEs identified in EDC as a reported angioedema attack. Note that this includes investigator-confirmed angioedema attacks; all investigator-confirmed angioedema attacks will be coded to the PT of angioedema.

For AE summaries, AEs will be classified to one of two analysis periods:

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

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 the treatment 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 the treatment period. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, related severe AEs, and investigator-reported

AESI for each analysis period. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency.

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

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

7.1.2 Adverse Events of Special Interest

AESI for this study are hypersensitivity reactions. Adverse events of special interest (AESI) for this study are hypersensitivity reactions. Investigators are required to document any potential AESI AEs on the AE CRF page, and to notify the sponsor within the timeline specified in the protocol. These AESI AEs are collectively referred to as investigator-reported AESI. In addition to investigator-reported AESI, the preferred terms from MedDRA 24.0 or newer. *Standardized MedDRA Queries (SMQ) will be used to identify an SMQ-defined AESI.* The SMQ 'Hypersensitivity' will be used to identify SMQ-defined AESI, and will include both narrow and broad search terms. Table 3 shows the SMQs used to identify AESI of hypersensitivity.

Table 3 SMQ Terms Used to Identify AESI

AESI	SMQ
Hypersensitivity	Hypersensitivity

Investigator-reported AESI and SMQ-defined AESI will be summarized separately, as shown below:

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

- AESI by SOC and PT: The number and percentage of subjects with an AESI, as well as the total number of AESIs, will be summarized for each treatment group by SOC and PT for

each analysis period. This tabulation will be repeated for related AESI for the treatment period and follow-up period AEs. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency.

- Related AESI by SOC and PT: The number and percentage of subjects with a related AESI, as well as the total number of related AESIs, will be summarized by SOC and PT for the treatment period and follow-up period. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency.

  A listing of investigator-reported AESI will be provided.

7.1.3 Injection Site Reaction AEs

ISR AEs will be identified by adverse events with the preferred terms starting with 'Injection site', 'Application site', or 'Administration site'.

The number and percentage of subjects with any ISR AE, any related ISR AE, any serious ISR AE, any related serious ISR AE, any severe ISR AE, and any related severe ISR AE, as well as the total number of events for each category will be summarized for the treatment period. The number of deaths due to an ISR AE, hospitalization due to an ISR AE and study discontinuation due to an ISR AE will be summarized for the treatment period.

The number and percentage of subjects with an ISR AE, as well as the total number of ISR AEs, will be summarized by SOC, and PT for the treatment period.

The number and percentage of subjects with an ISR AE will be summarized by SOC, PT and maximum severity for the treatment period. Tabulations will be presented by SOC in alphabetical order and by PT within each SOC by descending frequency.

The number of ISR events and the percentage of ISR events calculated based on total number of injections, will be summarized by PT and overall for the treatment period. Descriptive statistics (n, mean, SD, minimum, median, and maximum) will be presented to describe the ISR duration (hours). ISR duration will also be summarized by category (0-0.5 hour, >0.5 - 1 hour, >1 – 12 hour, >12 – 24 hour, <= 1 Day - Unclear, > 1 Day: >1-14 Days, >14 Days).

Refer to Section 10.2.16 for algorithm to derive duration of injection site reaction AEs. A listing of ISR AEs will be provided.

7.1.4 AE Tabulations

Table 4 provides a summary of the AE tabulations by analysis period and analysis set as described in this section.

Table 4 Adverse Event Tabulations by Analysis Period and Analysis Set

AE Tabulation	Treatment Period	Follow-up Period	Safety Analysis Set	Reduced-Dose Safety
AE summary	X	X	X	X
AE by SOC and PT	X	X	X	
Related AE by SOC and PT	X	X	X	
SAE by SOC and PT	X		X	
Related SAE by SOC and PT	X		X	
Severe AE by SOC and PT	X		X	
Related severe AE by SOC and PT	X	X	X	
Investigator-reported AESIs by SOC and PT	X	X	X	X
AEs by PT	X		X	X
Related AEs by PT	X		X	X
Severe AE by PT	X		X	
Investigator reported AESI summary	X	X	X	X
Investigator reported AESI by SOC and PT	X	X	X	X
Related Investigator reported AESI by SOC and	X	X	X	X
SMQ-Defined AESI summary	X[a]	X	X	X
SMQ-Defined AESI by SOC and PT	X[a]	X	X	X
Related SMQ-Defined AESI by SOC and PT	X[a]	X	X	X
Summary of ISR AEs	X		X	
ISR AEs by SOC and PT	X		X	
ISR AEs by SOC, PT, and Max Severity	X		X	
Number and duration of ISR AEs	X		X	
Summary of angioedema attack reported AE	X		X	X
TEAE angioedema attack reported by SOC and PT	X		X	X
Related TEAE attack reported by SOC and PT	X		X	
Related TEAE attack reported by PT	X		X	X
Severe TEAE attack reported by SOC and PT	X		X	

Severe TEAE attack reported by PT	X		X	X
Related Severe TEAE attack reported by SOC and PT	X		X	
Serious TEAE attack reported by SOC and PT	X		X	
Related Serious TEAE attack reported by SOC	X		X	

[a]For SMQ-defined hypersensitivity AESI during the treatment period, two sets of summary tables will be provided for the AEs including or excluding injection site reactions

7.1.5 Extent of Exposure and Compliance

7.1.5.1 Exposure to Investigational Product (IP)

Exposure to IP for each analysis set will be summarized for the treatment period in terms of time on treatment (month) and total dose received (mg).

Time on treatment (month) will be calculated as (number of days from the date of the first dose to the earlier of early discontinuation date, or the date of the end of the treatment period, inclusively)/28.

Total dose received (mg) will be calculated as the sum of subject's dose (mg) received at each visit, i.e., 150 mg/mL*study drug volume (mL) administered at the visit.

For the SFAS and RD-SFAS, these quantities will be calculated by the actual treatment received (either 300 mg every 2 weeks (q2wks) or 300 mg every 4 weeks), and the SFAS will be calculated by prior treatment in the Study SHP643-303 as well. See Section 10.2.17 for the definition of the actual treatment groups.

Descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum) will be presented for time on treatment and total dose received. In addition, time on treatment will be summarized by category (<1 Month, 1 –< 3 Months, 3 –< 6 Months, >= 6 Months) for the Treatment Period. Summaries will also be provided for the Safety Analysis Set of the total number of doses received, percentage of injections that were self-administered at home, self-administered in the clinic, and administered by the study staff in-clinic. Listings of study administrations by subject will also be provided.

A listing of dose frequency modifications will be provided.

7.1.5.2 Measurements of Treatment Compliance

Treatment compliance is defined as the percentage of planned doses received by the subject and will be calculated as follows:

Treatment compliance (%) = (number of doses received / number of planned doses) * 100.

The number of planned doses is the number of doses planned to be administered up to study completion or early termination, i.e., the number of records entered using the study drug administration CRF regardless of whether the study drug was indicated to be administered or not except in the case of a dose withheld due to assigned dosing frequency reduction.

Descriptive statistics (n, mean, SD, minimum, median, and maximum) of total number of doses received by the subject, treatment compliance, and the number and percentage of subjects that received at least 80% of planned doses will be presented for the SFAS and RD-SFAS.

7.2 Clinical Laboratory Data

Laboratory evaluations that are done at study site visits will be collected and processed via a central laboratory and presented in conventional units. Clinical laboratory data will be summarized by the SFAS and by the treatment group in the parent Study SHP643-303 and overall.

Clinical laboratory parameters to be evaluated include the following:

Chemistry

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

Hematology

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

Coagulation

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

Urinalysis

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

Hematology, Chemistry, Coagulation, and Urinalysis results will be summarized as described below.

Actual values and change from baseline in clinical laboratory tests will be summarized by study visit. If more than one laboratory result is reported per study visit per parameter, the last non-missing result will be selected for analysis. A post-baseline analysis will summarize all last non-missing post-baseline results per parameter for scheduled visits, unscheduled visits, and all visits. Detailed definition of baseline is given in Section 10.2.2.

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

will summarize on non-missing post-baseline most severe results per subject and per parameter for scheduled, unscheduled, and all post-baseline visits.

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. See Section 10.2.14 for details on handling clinical significance attribution for lab values. *The number of subjects with a non-missing result, and the number and percentage of subjects with a clinically significant result less than the lower limit of normal (LLN), non-clinically significant result less than the LLN, within the normal range, non-clinically significant result more than the upper limit of normal (ULN), and clinically significant result more than the ULN will be summarized by study visit. If more than one laboratory result is reported per study visit per parameter, the result yielding the most severe classification will be selected for analysis.*

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable (e.g., "<X"), a coded value will be used in the analysis instead as specified in Section 10.2.15. However, the actual values as reported in the database will be presented in data listings.

All laboratory test results will be presented in subject listings. Subjects with clinically significant abnormal laboratory test results will be listed. This listing will include all results of the laboratory parameter that was abnormal and determined to be clinically significant by the investigator for a subject across study visit to identify any trends.

7.3 Vital Signs

Vital signs will be summarized by the SFAS and by the overall only.

The following vital signs will be measured:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- HR (beats per minute)
- Body temperature (C)
- RR (breaths per minute)

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

Detailed definition of baseline is given in Section 10.2.2. *Actual values and changes from baseline in vital signs will be summarized by study visit and study time point. If more than one vital sign result is reported per study visit and study time point per parameter, the last non-missing result will be selected for analysis.* A post-baseline analysis will summarize all last non-missing post-baseline results per parameter for scheduled visits, unscheduled visits, and all visits.

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

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

7.4 Electrocardiogram (ECG)

ECG data will be summarized by the SFAS and by overall only.

The following ECG variables will be measured:

- HR (beats per minute)
- RR duration (millisecond [msec])
- PR duration (msec)
- QRS duration (msec)
- QT duration (msec)

Actual values and changes from baseline in ECG variables will be summarized by study visit. Detailed definition of baseline is given in Section 10.2.2. If more than one ECG result is reported per study visit and study time point per parameter, the last non-missing result will be selected for analysis. A post-baseline analysis will summarize all last non-missing post-baseline results per parameter for scheduled visits, unscheduled visits, and all visits.

ECG overall assessments will be classified according to clinical significance of ECG findings and abnormality as determined by the investigator. *The number of subjects with a non-missing result, and the number and percentage of subjects with a normal overall assessment, subjects with an abnormal overall assessment and all ECG findings not clinically significant, and subjects with an abnormal overall assessment and at least one clinically significant ECG finding will be summarized by study visit* including ECG not performed. If more than one ECG result is reported per study visit per parameter, the result yielding the most severe classification will be selected for analysis. Post-baseline analysis will summarize on non-missing post-baseline most severe results per subject and per parameter for scheduled, unscheduled, and all post-baseline visits.

All ECG data will be presented in subject listings. Subjects with clinically significant abnormal ECG findings will be listed. This listing will include all ECG findings that were abnormal and determined to be clinically significant by the investigator for a subject across study time points to identify any trends. An additional listing will include all clinically significant ECG results.

7.5 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

7.5.1 Pharmacokinetic Analysis

All summaries and analyses of the pharmacokinetic data will be based on the PK Set defined in Section 5.4 by actual treatment.

7.5.1.1 Drug Concentration

The plasma concentrations of lanadelumab will be summarized for the protocol scheduled sampling visit.

7.5.1.2 Statistical Analysis of Pharmacokinetic Data

No formal statistical hypothesis will be tested.

The plasma lanadelumab concentration data will be provided in subject data listings 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) for each sampling visit.

Figures of mean (± SD) concentration-time profiles plasma lanadelumab will be generated.

7.5.1.3 Handling Below Limit of Quantitation (BLQ) Values

For PK data, the plasma concentration below the lower limit of quantitation (LLOQ) will be set to zero.

The BLQ plasma concentrations will not be imputed in the subject data listings.

7.5.2 Pharmacodynamic Analysis

No formal statistical hypothesis will be tested.

The plasma kallikrein activity will be measured by cHMWK level (i.e., cHMWK levels) and fluorogenic pKal assay with FXIIa activation.

Plasma kallikrein activity will be summarized by nominal PD sampling time.; cHMWK levels and fluorogenic pKal assay will be summarized for the protocol scheduled sampling visits by actual treatment.

cHMWK levels and fluorogenic pKal assay will be provided in subject data listing(s) and summarized using descriptive statistics (number of subjects, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and CV% of geometric mean) for each sampling visit.

Figures of mean (± SD) concentration-time profiles cHMWK will be generated.

The BLQ plasma concentrations will not be imputed in the subject data listings.

7.5.3 Biomarker Analysis

C1 esterase inhibitor (C1-INH), complement component 4 (C4), and complement component 1q (C1q) assays will be obtained at screening for eligibility assessment.

The C1-INH, C1q, and C4 testing results at screening will be listed for all subjects. The corresponding reference ranges will be provided in the same listing.

7.6 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

7.6.1 PRO Analysis

7.7 Health-related Quality of Life Analyses

Health-related quality of life will be assessed using the angioedema quality of life (AE-QoL) questionnaire (Weller et al., 2012). The AE-QoL will be summarized for the SFAS overall.

The AE-QoL consists of 17 disease-specific quality-of-life items, each of the 17 items has a five-point response scale ranging from 0 (Never) to 4 (Very Often). The questionnaire is scored to produce a total score and four domain scores (functioning [item 1 – 4]. fatigue/mood [item 6 – 10], fear/shame [item 12 – 17], and nutrition [item 5, 11]). Raw domain scores (mean of the item scores within each domain) and raw total score (mean of all item scores) will be rescaled using

linear transformations into final percentage scores ranging 0 to 100, based on the maximum possible score.

The AE-QoL domain scores and total score will be calculated by using the following formula:

(Sum of all completed items) / (maximum sum of all possible items) * 100.

The minimal and highest possible domain and total scores are 0 and 100, respectively. Only answered items are included in the computation. An AE-QoL domain score should not be calculated if more than one item is left unanswered in that domain. The AE-QoL total score should not be calculated if more than 25% of items (>4 items) are left unanswered.

- Computation of AE-QoL Total Score

  Example 1: All items were completed (maximum possible sum: 68 points)

  Sum of all 17 completed items: 41 points.

  Total score = 100*(41/68) = 60 (out of a possible 100 points)

  Example 2: 2 items were not completed (maximum possible sum: 60 points).

  Sum of all 15 completed items: 41 points.

  Total score = 100*(41/60) = 68 (out of a possible 100 points)

- Computation of Domain Scores (Example: Fears/Shame)

  Example: Sum of all 6 completed items: 14 points

  Maximum possible sum: 24 points

  Domain Score = 100*(14/24) = 58 (out of a possible 100 points)

For the Safety Analysis Set, the AE-QoL total score and domain scores will be summarized using descriptive statistics by study visit.

Change in total scores and 4 domain scores from baseline (Day 0 of Study TAK-743-3001) to end of treatment period will be summarized for subjects previously received placebo in the Study SHP643-303. Change in total scores and 4 domain scores from baseline (Day 0 of Study SHP-643-303) to end of treatment period will be summarized for subjects previously exposed to lanadelumab from Study SHP-643-303. Overall change in total scores and 4 domain scores from baseline will also be summarized.

The AE-QoL questionnaire responses will be listed for each subject by study visit.

7.7.1 Health Care Utilization Analysis

There are no health care utilization analyses planned for this study.

7.8 Other Analyses

7.8.1 Immunogenicity Analyses

Immunogenicity will be measured based on the presence or absence of neutralizing or non-neutralizing ADA in plasma and will be analyzed using the Safety Analysis Set and overall.

Antibody testing is a 3-step process. If a sample tests ADA negative for the screening test, no further testing will be done; if a sample tests ADA positive for the screening test, confirmatory test will be done. ADA result is defined as positive if both the screening test result and confirmatory test result are positive; negative if either the screening test result or confirmatory test result is negative; otherwise, the ADA result is considered not evaluable.

If ADA result is positive, ADA titer result will be derived, and neutralizing ADA testing will be done. Neutralizing ADA results that are neither reactive nor non-reactive is defined as not evaluable.

The ADA result (positive/negative/not evaluable) and neutralizing ADA result (reactive/non-reactive/not evaluable) will be summarized using descriptive statistics by study visit.

The ADA result, ADA titer result immunogenicity analyses are planned for this study.

7.9 Interim Analyses

No Interim analysis is planned for this study.

7.10 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

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

8.0 REFERENCES

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

9.0 CHANGES TO PROTOCOL PLANNED ANALYSES

In order to be consistent with the analysis sets listed in the Study SHP643-303 the following changes were made:

The Safety Population in the protocol has been renamed to be the Safety Analysis Set.

The Reduced-Dose Safety Population in the protocol has been renamed to be the Reduced-Dose Safety Analysis Set.

The Pharmacokinetic Population in the protocol has been renamed to be the Pharmacokinetic Set.

The Pharmacodynamic Population in the protocol has been renamed to be the Pharmacodynamic Set.

The Screened Set was added to the list of analysis sets.

The protocol states separate summaries of adverse events will be presented for each analysis population, in the SAP we specify which summaries will be presented for each analysis set. The protocol states that the time period for the RD-SFAS will be the time while the subjects are on 300 mg every 4 weeks. However, the RD-SFAS will be presented during the time the subjects are on 300 mg every 2 weeks and 300 mg every 4 weeks.

10.0 APPENDIX

10.1 Changes From the Previous Version of the SAP

A summary of the changes for SAP version 2.0 is provided in page 2 of Revision History. Any minor revisions in grammar, spelling, punctuation, and format are not reflected in the summary of changes.

10.2 Data Handling Conventions

10.2.1 General Data Reporting Conventions

Outputs will be presented according to Takeda Standard TFL Shells.

For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, SD, minimum, and maximum values will be presented.

For the summary statistics of all numerical variables, unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. SD will be displayed to two levels of precision greater than the data collected.

Percentages shall be reported to 1 decimal place, except when the percentage equals exactly 100 where it shall be displayed as an integer (100). For zero, only count and no percentage will be displayed. This rule also applies to CV%. The denominator for all percentages will be the number of subjects within the population of interest, unless otherwise specified.

BMI and AE-QoL domain/total scores will be rounded to 1 decimal place and normalized number of angioedema attacks will be rounded to 2 decimal places for reporting.

Listings will be sorted by subject ID, visit (when available), assessment/event start date (when available), assessment/event end date (when available) and alphabetically by preferred term/name (when available), unless otherwise specified.

10.2.2 Definition of Baseline

For safety analyses, baseline is defined as the last non-missing value prior to first exposure to study drug (based on date or date/time). For rollover subjects previously exposed to lanadelumab, baseline is the last non-missing value prior to first exposure to study drug in the parent Study SHP643-303. For rollover subjects previously on placebo in the Study SHP643-303, baseline is the last non-missing value prior to first exposure to TAK-743-3001 study drug.

For efficacy analyses, the baseline angioedema attack rate will be presented as the normalized number of attacks per month (4 weeks) and calculated for each subject as number of angioedema attacks occurring during the observation period of Study SHP643-303 divided by the number of days the subject contributed to the observation period of Study SHP643-303 multiplied by 28 days.

For pharmacokinetic and pharmacodynamic analyses, baseline is defined as the Day 0 (Visit 1) non-missing value which is carried over from the last study visit (Day 182) of Study SHP643-303 prior to first exposure to TAK-743-3001 study drug (based on date or date/time).

10.2.3 Definition of Visit Windows

Although there is a visit window of ± 3 days around the expected visit date, nominal visits will be used for the per-visit analyses. Therefore, no windowing of visits by study day will be done for data obtained at the scheduled visits.

For the analysis, study day will be calculated as follows:

If the assessment date is on or after the date of first dose of IP:

Study day = assessment date – first dosing date + 1

If the assessment date is before the date of first dose of IP:

Study day = assessment date – first dosing date

10.2.4 Analysis Periods

The treatment period (Day 0 to Day 182) is defined as the interval of time:

[*date/time of first exposure to study drug*, *date of Day 182 visit at 23:59*]

The presumed steady state period of Day 70 through Day 182 is defined as the interval of time:

[*date/time of first dose of IP + 70 days*, *date of Day 182 visit at 23:59*]

The follow-up period for AEs is defined as the interval of time:

[*date of Day 182 visit + 1 day at 0:00*, *date of Day 196 visit at 23:59*]

For subjects in the Reduced-Dose Safety Analysis Set, the 300 mg q2wks treatment period is defined as the interval of time:

[*date of first dose of q2wks dosing*, the earlier of (*date of Day 182 visit at 23:59)* ***or*** *(date of the first q4wks dosing after the q2wks dosing – 1 day at 23:59)* ***or*** *(date of study discontinuation at 23:59)*]

For subjects in the Reduced-Dose Safety Analysis Set, the 300 mg q4wks treatment period is defined as the interval of time:

[*date of first dose of q4wks dosing*, the earlier of (*date of Day 182 visit at 23:59)* ***or*** *(date of the first q2wks dosing after the q4wks dosing – 1 day at 23:59)* ***or*** *(date of study discontinuation at 23:59)*]

10.2.5 Derived Efficacy Endpoints

10.2.5.1 Unique Angioedema Attacks

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.

Specifically, there must be at least 24 hours between the stop date/time of the first event and the start date/time of the next event, for the attacks to be considered distinct. If there is less than 24 hours between the stop date/time of the first event and the start date/time of the next event, the events will be counted as one attack.

When two or more attacks are combined for efficacy analysis, the parameters of the attacks will be conservatively chosen. The start date and time of the combined attack will take the earliest start date and time from the individual attacks; and the end date and time of the combined attack will take the latest end date and time of the individual attacks. If there are two attacks within 24 hours, but the start date of the later attack occurs after the end of the efficacy evaluation period, the attacks will be combined and counted as one attack that occurs within the efficacy evaluation period of the start time. The severity of the combined attack will take the highest severity from the individual attacks. The primary location of the combined attack will be determined by the primary location of the individual attacks, and by following the hierarchy of laryngeal attack, abdominal attack, and peripheral attack. One primary location will be taken; and all the other primary location(s) and secondary locations will be considered as secondary location for the

combined attack. The rescue medications and supportive treatment for the combined attack will include all the records from individual attacks. Also, the combined attack will be considered as an investigator-confirmed attack if any of the individual attack being combined is an investigator-confirmed attack.

The duration of an angioedema attack is calculated as stop date/time – start date/time.

The imputation rules for partial start or end date and time for angioedema attacks date/time is described in Section 10.2.9.

10.2.6 Time to First Angioedema Attack

10.2.6.1 Time to First Angioedema Attack After Day 0

The time to first angioedema attack (days) after Day 0 will be calculated as the earliest of the date of the angioedema attack after Day 0, date of study discontinuation or completion, or date of Day 182 visit minus the date of Day 0 visit plus 1.

Subjects with attacks occurring will be events. Subjects who discontinue/complete the study prior to having an angioedema attack will be censored.

10.2.6.2 Time to first Angioedema Attack After Day 70

The time to first angioedema attack (days) after Day 70 will be calculated as the earliest of the date of the angioedema attack after Day 70, date of study discontinuation or completion, or date of Day 182 visit minus the date of Day 70 visit plus 1.

Subjects with attacks occurring will be events. Subjects who discontinue/complete the study prior to having an angioedema attack will be censored.

10.2.7 Repeated or Unscheduled assessments of Safety Parameters

Unscheduled measurements will not be included in by-visit summaries, however if a subject has repeated assessments before the start of IP, then the results from the final assessment made prior to the start of IP will be used as baseline. If EOS/ET assessments are repeated or unscheduled, the last post-baseline assessment will be used as the EOS/ET assessment for generating descriptive statistics. All post-baseline assessments will be presented in the data listings.

10.2.8 Handling of Missing, Unused, and Spurious Data

All subjects in the analysis sets defined in Section 5.0 will be included in the associated analyses.

No imputation for missing data (e.g., last observation carried forward) will be applied except for the missing date/time for angioedema attacks, the partial dates for AEs and prior/concomitant medications, the missing severity for AEs and the missing relationship to IP for AEs.

Imputed dates will not be presented in the listings. The original missing date/time will be presented in the listings.

10.2.9 Missing Start or End Date and Time for Angioedema Attacks

The following rules apply to the handling of angioedema attack data for efficacy analyses only.

In general, missing start date/time and end date/time will be imputed as described in Section 10.2.11 However, the following rules will be applied for the attacks satisfying the corresponding conditions, in order to conservatively classify the attacks as separate, distinct attacks with at least 24 hours in-between:

- For angioedema attacks with a missing start time and a non-missing start date one calendar day after the end date of the previous attack, the start time will be imputed using the end time of the previous angioedema attack to ensure there are 24 hours in between the two attacks.
- For angioedema attacks with a missing start time and a non-missing end date/time within 24 hours from the end date/time of the previous attack, the attack should be considered as one attack with the previous attack (see Section 10.2.5.1 for details on combining angioedema attacks)
- For angioedema attacks with missing end time and a non-missing end date one calendar day before the start date of the next attack, the end time will be imputed as the start time of the next angioedema attack to ensure there are 24 hours in between the two attacks.
- For angioedema attacks with a missing end time and non-missing start date/time within 24 hours from the start date/time of the next attack, the attack should be considered as one attack with the next attack (see Section 10.2.5.1 for details on combining angioedema attacks)

For angioedema attacks with a non-missing start date and time and a missing stop date and time:

- If the event is not indicated as ongoing, the stop date and time will be imputed as start date and time + 48 hours or 24 hours before the start date and time of the next attack, whichever is earlier.
- If the event is indicated as ongoing, the stop date and time will be imputed as the earliest of the following two date and time:
    - Start date and time + 48 hours or study completion date and the stop time of 23:59, whichever is later.
    - 24 hours before the start date and time of the next attack.

10.2.10 Missing Date/Time Information for Prior or Concomitant Medications/Therapies/Procedures

For prior or concomitant medications (and/or therapies/procedures), including rescue medications, incomplete (i.e., partially missing) start date/time will be used to determine if the medication/therapy/procedure is concomitant or prior. If a determination cannot be made using the non-missing date parts as to when the medication/therapy/procedure occurred relative to study drug administration, then the medication/therapy/procedure will be classified as concomitant.

10.2.11 Missing Date/Time Information for Adverse Events

For AEs with partial start date/time, non-missing date/time 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/time parts as to when the AE occurred relative to study drug administration, e.g. AE start year and month are the same as the year and month of the first dose of IP, then the AE will be classified as treatment-emergent.

10.2.12 Missing Severity assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of IP, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of IP, then the worst severity will be assigned, i.e., "life threatening (grade 4)". The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

This rule applies also to BAARP severity for angioedema attacks for which the worst severity is "Severe".

10.2.13 Missing Relationship to IP for Adverse Events

If the relationship to IP is missing for an AE starting on or after the date of the first dose of IP, a causality of "Related" will be assigned. The imputed values for relationship to double-blind IP will be used for incidence summaries, while the actual values will be presented in data listings.

10.2.14 Clinical Significance Attributions for Laboratory Results

Lab results will be classified as Normal, CS Low, NCS Low, NCS High, or CS High using a combination of the CS/NCS classification by the investigator and the Low/High classification based on the central lab reference range.

10.2.15 Character Values of Clinical Laboratory Variables

The non-standard laboratory results will be converted to numeric values using the rules shown in Table 4Table 5.

Table 5 Convention for Converting Non-Standard Laboratory Results

Non-Standard Lab Values	Standardized Numeric Values
<0.2	Deduct 0.01 from the reference value. i.e., 0.19
<0.1	Deduct 0.01 from the reference value. i.e., 0.09
>1.045	Add 0.001 to the reference value. i.e., 1.046
<3	Deduct 0.1 from the reference value, i.e., 2.9
<2	Deduct 0.1 from the reference value, i.e., 1.9

10.2.16 Duration of Injection Site Reaction AEs

Duration of ISR AEs is calculated as 'stop date/time – start date/time' for the ISR AEs with non-missing start and stop date/time.

The missing start or stop date/time for ISR AEs will not be imputed. ISR AEs with missing start or stop date/time will be excluded from the summary statistics analysis and reported as number missing in the continuous analysis of ISR AE duration. For the categorical analyses on ISR AE duration, the following rules will be applied:

- ISR AE with non-missing start and stop date/time: duration of the AE will be calculated as 'stop date/time – start date/time' and mapped to a duration category.

- ISR AE with non-missing start and stop dates and missing time: duration of the AE will be calculated as 'stop date – start date +1'. If the calculated duration is 1 day, then the duration category for this AE is <= 1 day - unclear. If the calculated duration is greater than 1 day, then it will be mapped to a >1 day category.

- ISR AE with missing start or stop date: The ISR AE will be excluded from the categorical analyses on duration and will be listed in the missing category.

10.2.17Definition of actual dosing regimens for the Safety Analysis Set (SFAS) and Reduced Dose Safety Analysis Set (RD-SFAS)

The following two dosing regimen periods will be investigated for the Safety Analysis Set and Reduced Dose Safety Analysis Set, the subgroup of subjects who had a dose frequency modification from 300 mg q2wks to 300 mg q4wks, as recorded on the Dose Frequency Modification eCRF. These dosing regimen periods will be applied below:

- Q2W dosing period: Any period during which a subject receives q2wks regimen, i.e., all intervals of time defined as:

  First interval:

  [date/time of first exposure to study drug, start date/time of q4wks regimen minus 1 minute]

  Subsequent intervals, if any:

[start date/time of next q2wks regimen, start date/time of next q4wks regimen minus 1 minute] if there is another modification to q4wks regimen or

[start date/time of next q2wks regimen, date of Day 364 visit at 23:59] otherwise.

- Q4W dosing period: Any period during which a subject receives q4wks regimen, i.e., all intervals of time defined as:

[start date/time of q4wks regimen, start date/time of next q2wks regimen minus 1 minute] if there is another modification to q2wks regimen or

[start date/time of q4wks regimen, date of Day 364 visit at 23:59] otherwise.

Start date/time of q4wks regimen is defined as the date/time of the dose received prior to the date captured in the field "Initial date study drug was administered under modified dosing frequency" of eCRF corresponding to new dose regimen of 300 mg q4wks.

Start date/time of subsequent q2wks regimen is defined as the date/time of the dose received prior to the date captured in the field "Initial date study drug was administered under modified dosing frequency" of eCRF corresponding to new dose regimen of 300 mg q2wks unless the date/time of prior dose received is more than 2 weeks + 4 days before the "Initial date study drug was administered under modified dosing frequency"; if the prior date captured is more than two weeks before the "Initial date study drug was administered under modified dosing frequency", then the "Initial date study drug was administered under modified dosing frequency" will be used as the start date/time of subsequent q2wks regimen.

Additionally, for subjects with a dose frequency modification, the baseline investigator-confirmed attack rate, as well as the treatment period investigator-confirmed attack rate, change from baseline, and percent change from baseline will be summarized using descriptive statistics while the subject is on lanadelumab 300 mg q2wks regimen and lanadelumab 300 mg q4wks regimen for efficacy evaluation periods. The summaries will also be provided during Treatment Period B only when dose modifications occurred.

Similarly, for subjects who had a dose frequency modification from q2wks to q4wks, adverse events will be flagged as starting either during the Q2W or Q4W dosing period. This categorization of adverse events will only occur in the analysis datasets.

10.3 Analysis Software

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

10.4 Schedule of Activities

Table 6 Schedule of Activities - Day 0 to Day 196

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10.5 Sample SAS code

Sample SAS Code for Time to Event Analysis

The analysis of time to first angioedema attack (see Section 6.8.1) is based on the KM method. First angioedema attack is the event of interest. The following SAS code is proposed for analyses of time to first angioedema attack.

Consider the subject level dataset HAEDATA which contains the variables HAETIME and STATUS. HAETIME is the time from first IP administration to the first investigator-confirmed HAE attack or censored time. STATUS=1 if the subject is censored and STATUS=0 if investigator-confirmed angioedema attack happens before the date and time of the end of the period. Details of censoring is provided in Section 6.8.1.

PROC LIFETEST can be used as follows to obtain the KM plot.

```
ods graphics on;
ods output Quartiles=Quarts CENSOREDSUMMARY=Summary;
proc lifetest data=HAEDATA method=km plots=survival;
   time HAETIME*STATUS(1);
run;
```

Dataset QUARTS contains KM estimates of the 25th, 50th (median), and 75th percentiles with associated two-sided 95% CI.

Dataset SUMMARY contains the number of events of interest, number and percentage of censored observations in Variable FAILED, CENSORED and PCTCENS, respectively.