Statistical Analysis Plan

NCT Number: NCT04206605

Title: A Phase 3, Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Efficacy and Safety of Lanadelumab for Prevention Against Acute Attacks of Non-histaminergic Angioedema with Normal C1-Inhibitor (C1-INH)

Study Number: SHP643-303

Document Version and Date: Version 2.0 (10-November-2022)

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

Statistical Analysis Plan

Lanadelumab; TAK-743 (formerly SHP643, DX-2930)

Phase 3

A Phase 3, Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Efficacy and Safety of Lanadelumab for Prevention Against Acute Attacks of Non-histaminergic Angioedema with Normal C1-Inhibitor (C1-INH)

Protocol Identifier: SHP643-303

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Confidentiality Statement

REVISION HISTORY

Version	Issue Date	Summary of Changes
2.0	10 Nov 2022	Added modified full analysis set and modified steady state full analysis set to include subjects who were eligible for the study and received study drug. The example of pKal is removed from the example as an exploratory endpoint. Added randomization listing that includes strata. Baseline attack rate strata removed from summary table but added to randomization listing. Added CMH analysis approach if CMH test with Newcombe CI does not produce estimates due to imbalance in stratification. Added duration category >1 -<5 days and 5 - <14 days for injections site AE duration. Added analysis for all post-baseline results for lab values (hematology, coagulation, chemistry, urinalysis, vital signs). Added highest and shift tables for chemistry lab parameters. Included sensitivity analysis to exclude subjects who were enrolled and received study drug and they did not meet all eligibility criteria. Added tabulation of AE-QoL scores per visit per function and addition of patient reported

		outcomes (PRO) SAP to address the AE-QoL endpoints. Protocol deviations section updated to detail the handling of the site level deviations and important protocol deviations. Included HAE attack rate responder threshold categories <0.75 attacks per month, <0.5 attacks per month, <0.25 attacks per month.
1.0	18 Nov 2020	Not applicable. Final version of document.

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ABBREVIATIONS

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
BAARP	Non-histaminergic bradykinin-mediated angioedema attack assessment and reporting procedures
BLQ	Below Limit of Quantitation
BMI	Body Mass Index
BP	Blood Pressure
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
CMH	Cochran-Mantel-Haenszel
CO_2	Carbon Dioxide
CPK	Creatine Phosphokinase
CRF	Case Report Form
CSR	Clinical Study Report
CS	Clinically Significant
CTMS	Clinical Trial Management System
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
ET	Early Termination
FAS	Full Analysis Set
FWER	Family-wise type I error rate
GLM	Generalized linear model
HAE	Hereditary Angioedema

HR	Heart Rate
HRQoL	Health-Related Quality of Life
INR	International Normalized Ratio
IP	Investigational Product
ISR	Injection Site Reaction
IV	Intravenous
KM	Kaplan-Meier
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantitation
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
NCS	Non Clinically Significant
NNA	Normalized Number of Attacks
OLE	Open-Label Extension
PD	Pharmacodynamic
pH	Potential Hydrogen
PK	Pharmacokinetic
pKal	Plasma Kallikrein
PT	Preferred Term (MedDRA®)
QoL	Quality of Life
RBC	Red Blood Cells
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SMQ	Standardized MedDRA® Query
SOC	System Organ Class
SS-FAS	Steady State Full Analysis Set
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety, health-related quality of life, pharmacokinetic (PK)/pharmacodynamic (PD), biomarker and immunogenicity data as described in the protocol amendment 3 dated 19 April 2021. Specifications for tables, figures, and listings are contained in a separate document.

The PK and PD properties of lanadelumab (including PK parameters, cHMWK, C1-INH, C4, and additional biomarkers as appropriate) will be evaluated by a population modeling and a simulation approach using data from this study and from all other studies in the lanadelumab clinical development program. A separate clinical pharmacology SAP will support the population PK and PD analysis modeling and the analysis results will be reported separately. The effect on ADA and neutralizing antibodies on PK of lanadelumab, PD (cHMWK), and the number of investigator-confirmed angioedema attacks during the efficacy evaluation periods will be assessed and results will be provided in the separate PK/PD TLF and population PK and PD analysis reports. The effect of lanadelumab on health-related quality of life (HR-QoL) will be evaluated based on the AE-QoL questionnaire. A separate QoL SAP will describe the HR-QoL analysis, and the results will be reported separately.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock and unblinding of treatment assignment. If additional analyses are required to supplement the planned analysis described in this SAP after database lock, they may be completed and will be described in the clinical study report (CSR).

2. OBJECTIVES, ESTIMAND(S), AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objective(s)

The secondary objectives of the study are:

- To evaluate the safety of repeated SC administrations of lanadelumab in preventing angioedema attacks.

- To evaluate the PK of repeated SC administrations of lanadelumab in preventing angioedema attacks.

- To evaluate the PD of repeated SC administrations of lanadelumab in preventing angioedema attacks.

- To evaluate the immunogenicity of repeated SC administrations of lanadelumab in preventing angioedema attacks.

- To evaluate the effect of lanadelumab on health-related quality of life (HR-QoL) assessment.

2.1.3 Exploratory Objective(s)

The exploratory objective is to evaluate the effect of lanadelumab on exploratory biomarker(s) of angioedema disease-state bioactivity.

2.2 Estimands

The primary and secondary estimands are described in Table 1.

Table 1. List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable (or endpoint)**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Primary	The primary estimand is the effect of lanadelumab on the rate of angioedema attacks during the treatment period (Day 0 through Day 182).	Adolescents (12 to <18 years of age) and adults with non-histaminergic angioedema with normal C1-INH defined through inclusion and exclusion criteria as stated in the protocol and who received any exposure to the investigational product during the treatment period.	Number of investigator-confirmed angioedema attacks during the treatment period (Day 0 through Day 182).	1/ Rescue medication: treatment policy (Regardless of whether or not rescue medication/supportive treatment use had occurred.) 2/ Premature study discontinuation before the end of the treatment period: while on treatment (The logarithm of time in days each subject was observed during the treatment period will be used as an offset variable in the model.)	Least square mean of attack rate during the treatment period, adjusting for baseline attack rate. Mean rate ratio of lanadelumab relative to placebo and corresponding 95% confidence interval (CI).

Table 1. List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable (or endpoint)**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Key Secondary (Rank 1)	A supportive estimand is the effect of lanadelumab on achieving attack-free status during the treatment period (Day 0 through Day 182).	Adolescents (12 to <18 years of age) and adults with non-histaminergic angioedema with normal C1-INH defined through inclusion and exclusion criteria as stated in the protocol and who received any exposure to the investigational product during the treatment period.	Achievement of attack-free status for the treatment period (Day 0 through Day 182).	1/ Rescue medication: treatment policy (Regardless of whether or not rescue medication/supportive treatment use had occurred.) 2/ Premature study discontinuation before the end of the treatment period: while on treatment (Attack-free is evaluated up to study discontinuation.)	Proportion of subjects achieving attack-free status for the treatment period of Day 0 through Day 182 and corresponding exact 95% confidence interval (CI).

Table 1. List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable (or endpoint)**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Key Secondary (Rank 2)	A supportive estimand is the effect of lanadelumab on the rate of moderate or severe angioedema attacks during the treatment period (Day 0 through Day 182).	Adolescents (12 to <18 years of age) and adults with non-histaminergic angioedema with normal C1-INH defined through inclusion and exclusion criteria as stated in the protocol and who received any exposure to the investigational product during the treatment period.	Number of investigator-confirmed moderate or severe angioedema attacks during the treatment period (Day 0 through Day 182).	1/ Rescue medication: treatment policy (Regardless of whether or not rescue medication/supportive treatment use had occurred.) 2/ Premature study discontinuation before the end of the treatment period: while on treatment (The logarithm of time in days each subject was observed during the treatment period will be used as an offset variable in the model.)	Least square mean of attack rate during the treatment period, adjusting for baseline attack rate. Mean rate ratio of lanadelumab relative to placebo and corresponding 95% confidence interval (CI).

Table 1. List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	B: Variable (or endpoint)	C: Strategy for addressing intercurrent event	D: Population-level summary
Key Secondary (Rank 3)	A supportive estimand is the effect of lanadelumab on the rate of angioedema attacks during the presumed steady state period (Day 70 through Day 182).	Adolescents (12 to <18 years of age) and adults with non-histaminergic angioedema with normal C1-INH defined through inclusion and exclusion criteria as stated in the protocol and who received any exposure to the investigational product during the presumed steady state period.	Number of investigator-confirmed angioedema attacks during the presumed steady state period (Day 70 through Day 182).	1/ Rescue medication: treatment policy (Regardless of whether or not rescue medication/supportive treatment use had occurred.) 2/ Premature study discontinuation before the end of the treatment period: while on treatment (The logarithm of time in days each subject was observed during the presumed steady state period will be used as an offset variable in the model.)	Least square mean of attack rate during the presumed steady state period, adjusting for baseline attack rate. Mean rate ratio of lanadelumab relative to placebo and corresponding 95% confidence interval (CI).

Table 1. List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable (or endpoint)**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Key Secondary (Rank 4)	A supportive estimand is the effect of lanadelumab on achieving attack-free status during the presumed steady state period (Day 70 through Day 182).	Adolescents (12 to <18 years of age) and adults with non-histaminergic angioedema with normal C1-INH defined through inclusion and exclusion criteria as stated in the protocol and who received any exposure to the investigational product during the presumed steady state period.	Achievement of attack-free status for the presumed steady state period (Day 70 through Day 182).	1/ Rescue medication: treatment policy (Regardless of whether or not rescue medication/supportive treatment use had occurred.) 2/ Premature study discontinuation before the end of the treatment period: while on treatment (Attack-free is evaluated up to study discontinuation.)	Proportion of subjects achieving attack-free status for the presumed steady state period of Day 70 through Day 182 and corresponding exact 95% confidence interval (CI).

Table 1. List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable (or endpoint)**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Key Secondary (Rank 5)	A supportive estimand is the effect of lanadelumab on the rate of moderate or severe angioedema attacks during the presumed steady state period (Day 70 through Day 182).	Adolescents (12 to <18 years of age) and adults with non-histaminergic angioedema with normal C1-INH defined through inclusion and exclusion criteria as stated in the protocol and who received any exposure to the investigational product during the presumed steady state period.	Number of investigator-confirmed moderate or severe angioedema attacks during the presumed steady state period (Day 70 through Day 182).	1/ Rescue medication: treatment policy Regardless of whether or not rescue medication/supportive treatment use had occurred. 2/ Premature study discontinuation before the end of the treatment period: while on treatment (The logarithm of time in days each subject was observed during the presumed steady state period will be used as an offset variable in the model.)	Least square mean of attack rate during the presumed steady state period, adjusting for baseline attack rate. Mean rate ratio of lanadelumab relative to placebo and corresponding 95% confidence interval (CI).

2.3 Endpoints

2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the number of investigator-confirmed angioedema attacks during the treatment period (Day 0 through Day 182).

2.3.2 Key Secondary Efficacy Endpoints

The following are the rank-ordered secondary efficacy endpoints:

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

2.3.3 Other Secondary Efficacy Endpoints

Additional secondary efficacy endpoints include:

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

2.3.4 Exploratory Efficacy Endpoints

The following endpoints will also be analyzed:

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

- Number of investigator-confirmed angioedema attacks resulting in an emergency department visit and/or admission to hospital during the treatment period (Day 0 through Day 182)

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

- Characteristics of investigator-confirmed angioedema attacks, including attack duration, severity, location, and medication use during the observation period, treatment period (Day 0 through Day 182), and presumed steady state period (Day 70 through Day 182)

- Percentage of attack free days during the treatment period (Day 0 through Day 182) and during the presumed steady state period (Day 70 through Day 182)

- Achievement of investigator-confirmed angioedema attack-free interval of 1 month or 3 months during the treatment period (Day 0 through Day 182)

- Achievement of investigator-confirmed angioedema attack-free interval of 1 month or 3 months during the presumed steady state period (Day 70 through Day 182)

2.3.5 Exploratory Endpoint

The exploratory endpoint include exploratory biomarker(s) of angioedema-disease state bioactivity () in blood and plasma.

2.3.6 Safety Endpoints

Safety endpoints are as follows:

- TEAEs, including AESIs and SAEs
- Clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis)
- Vital signs including blood pressure, heart rate, body temperature, and respiratory rate

2.3.7 Pharmacokinetic Endpoint

The PK endpoint is plasma concentrations of lanadelumab.

2.3.8 Pharmacodynamics Endpoint

The PD endpoint is plasma cHMWK and pKal activity.

2.3.9 Health-related Quality of Life (QoL) Endpoint

The health-related QoL endpoint will be measured by the AE-QoL questionnaire, which consists of 17 disease-specific quality-of-life items, to produce a total AE-QoL score and 4 domain scores (functioning, fatigue/mood, fear/shame, and nutrition). The responses to the AE-QoL for each item will be tabulated for each treatment group by study visit using the full analysis set.

The health-related QoL endpoints are as follows and will be included in as separate patient reported outcomes (PRO) report:

- Change in total AE-QoL scores from baseline (Day 0) to Day 182
- Change in domain AE-QoL scores from baseline (Day 0) to Day 182

2.3.10 Immunogenicity Endpoint

The immunogenicity endpoint is the presence or absence of anti-drug antibody (ADA) in plasma (neutralizing or non-neutralizing antibody in plasma).

3. STUDY DESIGN

3.1 General Description

This randomized, placebo-controlled, double-blind, Phase 3 study will enroll approximately 75 subjects (12 years of age and above) with normal C1-INH angioedema. The study is composed of the following periods:

- Screening Period and Washout Period

All subjects will undergo screening assessments during a screening period of up to 8 weeks.

Screened subjects who have been on any long-term prophylaxis (LTP) (e.g., C1-INH, androgens, or antifibrinolytics) are required to undergo a minimum 2-week washout period prior to entering the observation period. The washout period is included in the screening period.

- Observation Period

Enrolled subjects meeting all eligibility criteria at screening will enter an observation period of 8 weeks to determine the baseline angioedema attack rate and confirm their eligibility.

Only subjects meeting a minimum baseline attack rate of at least 1 investigator-confirmed attack per 4 weeks, along with being treated with icatibant for at least 2 angioedema

attacks or at least one moderate or severe attack, will be eligible for randomization and will enter the treatment period. Subjects who experience 3 or more investigator-confirmed attacks within the first 4 weeks will be allowed to exit the observation period early at 4 weeks and proceed to randomization. Subjects who do not meet the minimum attack rate during the observation period will be considered screen failures; subjects who screen fail will not be allowed to rescreen for the study.

- Double-blind Treatment Period

Subjects who enter the double-blind treatment period will receive SC administration of investigational product q2wks for 26 weeks.

- Open-Label Extension (OLE) Study

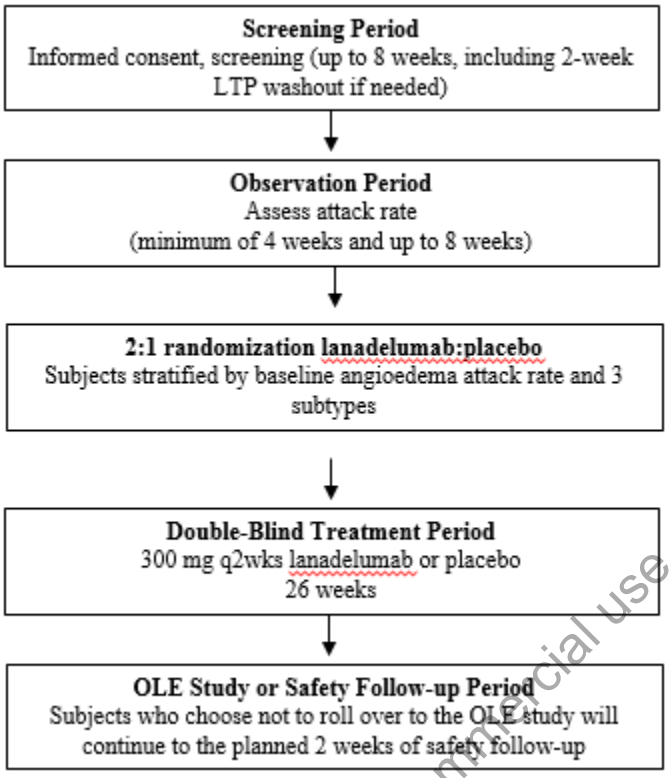
Subjects may roll over into a 26-week long OLE study, TAK-743-3001, upon completion of all assessments scheduled on Day 182.

- Safety Follow-up Period

Subjects who choose not to roll over to the OLE study will continue to the planned 2 weeks of safety follow-up at the completion of all study assessments scheduled on Day 182.

A schematic representation of the study design is displayed in Figure 1. The study schedule of events can be found in Appendix 1 Table 5 and Table 6 .

Figure 1 Study Design



3.2 Randomization

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

Randomization will be stratified by the baseline angioedema attack rate observed during the observation period and by subtype. The two levels of angioedema attack rate strata are 1-<2 attacks per 4 weeks and 2 or more attacks per 4 weeks. The three levels of subtype are 1) with known mutations (FXII, PLG, ANGPT1, or KNG1 genes, or other predefined mutations associated with normal C1-INH angioedema); 2) with family history (a first-degree relative) and unknown mutations; and 3) with idiopathic non-histaminergic angioedema (INHA).

3.3 Blinding

This is a double-blind study. Blinding was achieved by means of identical appearance for lanadelumab and placebo. To ensure the blind is maintained, data which is unblinding such as treatment, or potentially unblinding such as post-baseline attack data, and PK and

PD data, will be restricted as outlined in the Clinical Trial Integrity Document. Unblinding of the overall dataset will occur after the database has been locked.

3.4 Sample Size and Power Considerations

Approximately 75 subjects with non-histaminergic normal C1-INH angioedema are planned to be randomized. Power analyses were based on 10,000 simulations from a negative binomial distribution with dispersion parameter of 2 and 0.5 for lanadelumab and placebo-treated subjects, respectively, a 10% dropout with exponential loss-to-follow-up, and will be analyzed using a general linear model for count data assuming a Poisson distribution with Pearson chi-square scaling of standard errors to account for potential overdispersion. The randomization ratio was set at 2:1 for lanadelumab: placebo.

The dispersion parameters chosen for the power analysis were estimated from the results observed in the pivotal lanadelumab study in subjects with HAE (Study DX2930-03). In Study DX2930-03, the dispersion parameter was estimated at 0.5 and 2.1, for the placebo arm and the lanadelumab 300 mg q2wks arm, respectively. Because the primary endpoint, number of angioedema attacks during the treatment period, is expected to behave in a similar fashion as was observed in pivotal study for HAE, Study DX2930-03, similar dispersion parameters were assumed for the sample size calculation. The effect size of 60% reduction compared to placebo were also based on the results observed in the pivotal study. In Study DX-2930-03, the lower 95% confidence limit for attack rate reduction (lanadelumab 300 mg q2wks group versus placebo) was 76.2%. Due to higher disease variability compared with HAE, a conservative effect size assumption of 60% was assumed for subjects with non-histaminergic angioedema with normal C1-INH. .

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

4. STATISTICAL ANALYSIS SETS

The analysis sets are defined as:

4.1 Screened Set

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

4.2 Enrolled Set

The Enrolled Set consists of all subjects who have signed informed consent and also passed inclusion/exclusion criteria.

4.3 Treatment Period Full Analysis Set (FAS)

The Treatment Period Full Analysis Set (FAS) will include all randomized subjects who receive any exposure to the investigational product (IP) during the treatment period (Day 0 through Day 182). Subjects will be analyzed according to their randomized treatment assignment regardless of the treatment actually received.

4.3.1 Treatment Period Modified Full Analysis Set (mFAS)

The Treatment Period Modified Full Analysis Set (mFAS) will include all randomized subjects who receive any exposure to the investigational product (IP) during the treatment period (Day 0 through Day 182) and met all study eligibility criteria. Subjects will be analyzed according to their randomized treatment assignment regardless of the treatment actually received.

4.4 Steady State Period Full Analysis Set (SS-FAS)

The Steady State Period FAS (SS-FAS) will include all randomized subjects who receive any exposure to the IP during the presumed steady state period (Day 70 through Day 182). Subjects will be analyzed according to their randomized treatment assignment regardless of the treatment actually received.

4.4.1 Modified Steady State Full Analysis Set (mSS-FAS)

The Steady State Period FAS (SS-FAS) will include all randomized subjects who receive any exposure to the IP during the presumed steady state period (Day 70 through Day 182) and met all study eligibility criteria. Subjects will be analyzed according to their randomized treatment assignment regardless of the treatment actually received.

4.5 Safety Analysis Set (SAS)

The Safety Analysis Set (SAS) will include all subjects who receive any exposure to the IP. Subjects will be analyzed according to the treatment actually received regardless of randomized treatment assignment. In the event a subject receives both the correct and incorrect treatments during the study, the treatment used most often will be selected.

4.6 Pharmacokinetic Set (PK Set)

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

4.7 Pharmacodynamic Set (PD Set)

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

5. STUDY SUBJECTS

5.1 Disposition of Subjects

The number of subjects who were included in each defined analysis set (i.e., Screened, Enrolled, FAS, SS-FAS, SAS, PK and PD) will be summarized by randomized treatment assignment and overall for the Screened Set. The number of subjects included in each analysis population will be summarized by study site and country as well.

The number and percentage of subjects who completed the treatment period (by either rolling over to the open-label long term extension study or continuing to the planned 2 weeks of safety follow-up), completed the follow-up period, and prematurely discontinued, along with reasons for premature discontinuation, from the study will be summarized for the FAS population.

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. A Kaplan-Meier (KM) plot showing the time to withdrawal will be presented by treatment group for the FAS population. Time to withdrawal will start with the date of randomization; subjects will be censored based on their completion date (either the end of the treatment period visit, Day 182, for subjects rolling over to the OLE study, or the end of the follow-up period for subjects not rolling over to the OLE study).

A listing of subjects' randomization assignments and stratification factors will be included.

5.2 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group and overall for the SAS, FAS and SS-FAS populations.

The following demographic and baseline characteristics will be summarized:

- Age at informed consent date (years),
- Age category (<18, 18 to <40, 40 to <65, ≥65 years),
- 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, and Other),
- Weight (kg),
- Weight group (<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), and
- 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.

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),
- Number of attacks of different severity (mild, moderate, severe) in the last 3 months prior to screening,
- 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,
- Observation period angioedema attack rate (attacks/4 weeks),
- Observation period angioedema attack rate categories (1-<2 attacks/4 weeks, ≥2 attacks/4 weeks),
- Observation period angioedema attack rate strata (1-<2 attacks/4 weeks, ≥2 attacks/4 weeks), and
- Type of LTP therapy before entering the observation period (C1-INH, Androgens, Anti-fibrinolytics, or not on LTP).

The LTP (C1-INH, Androgens, or Anti-fibrinolytics) treatment a subject was on prior to the observation period will be 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 12.6.2) 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')

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). See Section 12.4.7.1 for the calculation of the observation period angioedema attack rate.

All baseline and demographic data will be presented in subject listings for the Screened Set.

5.3 Medical History

Medical history will be collected at the Screening Visit and will be coded using MedDRA Version 22.1 or newer.

The medical history will be summarized by system organ class (SOC) and preferred term (PT) by treatment group and overall for the SAS population. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the lanadelumab group and then the placebo group.

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

5.4 Prior Therapies, Procedures and Medication

Prior medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) dated 01 Sep 2019. Prior therapies and procedures will be coded using MedDRA Version 22.1 or newer.

Prior medication/therapy/procedure is defined as any medication/therapy/procedure with the start date and time prior to the date and time of the first dose of investigational product (IP).

Partial date imputation for medications is described in Section 12.6.2.

Prior medications will be summarized by the number and proportion of subjects within each Anatomical Therapeutic Chemical (ATC) Level 2 therapeutic class and PT for the SAS population. Tabulations will be presented sorted by therapeutic class in alphabetical order and by PT within each therapeutic class by descending frequency in the lanadelumab group and then the placebo group. Multiple medication usage by a subject in the same category (i.e., therapeutic class or preferred name) will be counted only once. All prior medications will be summarized, and a separate summary of prior medications taken during the observation period will be generated.

All prior therapies, procedures and medication will be listed for the Screened Set. High-dose antihistamines will be flagged in listings.

5.5 Concomitant Therapies, Procedures and Medications

Concomitant medications will be coded using the WHO Drug Dictionary dated 01 Sep 2019. Concomitant therapies and procedures will be coded using MedDRA Version 22.1 or newer.

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 treatment period, inclusive. Concomitant procedure is defined as any procedure with a start date and time between the dates and times of the first dose of IP and end of the treatment period, inclusive.

Any medication/therapy/procedure with a start date after the end of the treatment period will not be considered a concomitant medication/therapy/procedure. Partial date imputation for medications is described in Section 12.6.2.

Concomitant medications will be summarized by the number and proportion of subjects within each ATC Level 2 therapeutic class and PT for the SAS population. Tabulations will be presented sorted by therapeutic class in alphabetical order and by PT within each therapeutic class by descending frequency in the lanadelumab group and then the placebo group. Multiple medication usage by a subject in the same category (i.e., therapeutic class or preferred name) will be counted only once.

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

5.6 Exposure to Investigational Product

Exposure to IP will be summarized by treatment group and overall in terms of treatment duration (month) and total dose received (mg) for the SAS and FAS populations.

Treatment duration (month) will be calculated as (number of days from the date of the first dose to the earliest of the early discontinuation date or the date corresponding to 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.

Descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum) will be presented for treatment duration and total dose received. In addition, treatment duration will be summarized by category (<1 Month, 1 –< 3 Months, 3 –< 6 Months, >= 6 Months).

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

5.7 Measurements of Treatment Compliance

Treatment compliance will be described by the percentage of planned doses received by the subject, total number of doses received by the subject, and the number and percentage of subjects who received at least 80% of planned doses.

The percentage of planned doses received will be calculated as the number of doses received / number of planned doses while on treatment * 100.

The number of planned doses is the number of doses planned to be administered up to the date of study completion or early termination, based upon the q2wks dosing schedule.

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

A listing of measurements of treatment compliance will be provided.

5.8 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 programmatically applied to all subjects who were enrolled at that site at the time of the deviation for deviations recorded before 30Jun2022. These deviations will be included in the tabular summary and protocol deviation listings. Due to an update in the CRO system of collecting PDs, site-level protocol deviations recorded after 30Jun2022 will be tracked as non-compliance in CTMS and a separate report will be transferred to Biostatistics which will be used to create a separate summary table and non-compliance listing.

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. Due to an update in the CRO system of collecting PDs, deviations occurring after 14JUL2022 were classified as important or not. These deviations will be identified with a flag in the listings, and a table with the summary of important protocol deviations will be summarized.

Protocol deviations will be summarized by deviation type and severity by treatment group and overall for the FAS, and separately for protocol deviations specific to Covid-19. Protocol deviations will be summarized according to the old protocol deviation categories as summarized prior to the update in the CRO system of collecting PDs and all new categories will be mapped to the old categories to facilitate output summaries (Please see Table 2: Old and New PD Categories) . All protocol deviations will be included in a subject listing.

Table 2: Old and New PD Categories

Old PD Categories	New PD Categories	Categories presented in tables and listings (Old PD Categories)
Informed Consent Criteria	Informed Consent and Process	Informed Consent Criteria
Eligibility and Entry Criteria	Inclusion Criteria	Eligibility and Entry Criteria
Eligibility and Entry Criteria	Exclusion criteria	Eligibility and Entry Criteria
Concomitant Medication Criteria	Concomitant Medication	Concomitant Medication Criteria
Laboratory Assessment Criteria	Laboratory Assessment	Laboratory Assessment Criteria
Study Procedures Criteria	Study Procedures	Study Procedures Criteria
Serious Adverse Event Criteria	Safety	Serious Adverse Event Criteria
Randomization Criteria	Randomization	Randomization Criteria

Visit Schedule Criteria	Visit Schedule	Visit Schedule Criteria
Investigational Product (IP) Compliance	IP conditions	Investigational Product (IP) Compliance
Investigational Product (IP) Compliance	IP preparation	Investigational Product (IP) Compliance
Investigational Product (IP) Compliance	IP administration	Investigational Product (IP) Compliance
Investigational Product (IP) Compliance	Subject IP compliance	Investigational Product (IP) Compliance
Efficacy Criteria	Efficacy	Efficacy Criteria
Other Criteria	Subject Discontinuation	Other Criteria
Administrative Criteria	Administrative	Administrative Criteria
Other Criteria	Blinding	Other Criteria
Other Criteria	Patient Reported Outcomes	Other Criteria
Other Criteria	PK/PD	Other Criteria
Other Criteria	Other	Other Criteria
Source Documents Criteria	Not applicable in the new categorisation as these are non-compliances rather than PDs.	Not applicable in the new categorisation as these are non-compliances rather than PDs.

Regulatory or Ethics Approvals Criteria	Not applicable in the new categorisation as these are non-compliances rather than PDs.	Not applicable in the new categorisation as these are non-compliances rather than PDs.

6. EFFICACY ANALYSES

All efficacy analyses will be based on the FAS unless stated otherwise and will be conducted according to the treatment assigned. Data from all study sites that participate in this protocol will be combined so that an adequate number of subjects will be available for analyses.

For all efficacy analyses, unique angioedema attacks, as defined in Section 12.4.1, will be used. Handling of missing start or end date and time for angioedema attacks is described in Section 12.6.1. Additional details for deriving efficacy endpoints can be found in Section 12.

All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise. Control of Type I error is discussed in Section 6.4 in detail.

Efficacy data, including derived efficacy parameters defined in the subsections below, will be presented in subject data listings.

6.1 Analyses of Primary Efficacy Endpoint

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

The primary efficacy endpoint will be analyzed using a generalized linear model (GLM) for count data assuming a Poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential overdispersion. The model will include fixed effects for treatment group (categorical), normalized baseline attack rate (continuous), and the stratification factor of subtype (categorical). The logarithm of time in days each subject was observed during the treatment period will be used as an offset variable in the model. See Section 12.4.7.1 for the calculation of the normalized baseline

(observation period) attack rate. From this model, the least squares mean rate and standard error for each treatment group as well as the mean rate ratio relative to the placebo group and corresponding 95% confidence interval will be estimated. These estimates will be reported as mean event rates per 4 weeks by transforming the estimates using the exponential function and scaling by the unit of time.

The primary endpoint will be tested by the following hypothesis:

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

Where $\lambda_{lanadelumab}$ refers to the mean investigator-confirmed angioedema attack rate in the lanadelumab group and $\lambda_{Placebo}$ refers to the mean investigator-confirmed angioedema attack rate in the placebo group. The null hypothesis is that the mean investigator-confirmed angioedema attack rate ratio is 1 (no difference between treatment groups), versus the alternative hypothesis that the angioedema attack rate ratio is not 1. Estimated attack rate ratios less than 1 would indicate that subjects treated with lanadelumab, on average, have a lower incidence of investigator-confirmed angioedema attacks during the presumed treatment period. The hypothesis will be tested using the model-based least squares means estimate of the treatment difference (expressed as rate ratio relative to placebo) using a Wald-based chi-square test with Type I error set at 5%. See Section 12.4.7.2 for the calculation of the treatment period attack rate.

The percentage difference in mean investigator-confirmed angioedema attack rate of lanadelumab from the attack rate of placebo will be calculated as 100% * (mean rate ratio – 1). Similarly, the estimated upper and lower confidence limits for the mean rate ratio can be transformed by subtracting 1 and multiplying by 100% to calculate 95% confidence intervals for the percentage change. The mean rate ratio and corresponding 95% confidence interval will be estimated from the generalized linear model as described previously.

Unadjusted monthly investigator-confirmed angioedema attack rates will be calculated for the observation and treatment periods. See Section 12.4.7.1 and Section 12.4.7.2 for details. The observation period, treatment period, and treatment period change from observation period in the monthly investigator-confirmed angioedema attack rate will be summarized by treatment group. This summary will include the total number of investigator-confirmed angioedema attacks reported and the subject-time in months subjects contributed to the observation and treatment periods. Figures by treatment group plotting the on-study investigator-confirmed angioedema attacks reported during the

treatment period with timing relative to randomization for each subject will be created (i.e., "birds on a wire" plots).

In addition to the data summaries for the primary analysis of the primary efficacy endpoint described above, the number of investigator-confirmed angioedema attacks per month (defined as 28 days) will be summarized descriptively by month (per 28 day interval) and treatment group. The summary will include the monthly investigator-confirmed angioedema attack rate, change from observation period, and percent change from observation period of investigator-confirmed angioedema attack rate. 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 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 plus 28 days. Each successive interval will start the last day of the prior interval plus 1 day and end 28 days later. See Section 12.3.1 for the definition of the observation period.

6.1.1 Sensitivity Analyses of Primary Efficacy Endpoint

The following sensitivity analyses will be performed on the primary efficacy endpoint to evaluate the robustness of the results.

1. The primary analysis will be repeated using the SAS population (subjects will be analyzed according to the treatment actually received regardless of randomized treatment assignment).
2. The primary analysis will be repeated using all subject-reported angioedema attacks instead of limiting the analysis to those attacks that were investigator-confirmed.
3. The primary analysis will be repeated using a generalized linear model assuming a negative binomial distribution.
4. The impact of missing data on the primary analysis will be explored using a tipping point analysis.

   Subjects who do not complete the treatment period (Day 0 through Day 182) but who were dosed and have contributed any amount of time to the treatment period will be included in the primary analysis. These subjects will have some portion of the treatment period observed and the remainder of the treatment period, after study discontinuation, will be unobserved. The model used for the primary analysis assumes that events occur at a constant rate within an individual, and uses only the number of events in the observed portion of the treatment period with an offset

parameter to account for the length of time in which those events were observed to derive the event rate for that individual.

To better understand the impact of unobserved portion of the treatment period generated by subjects who discontinue early on the results of our primary analysis, a tipping point analysis will be conducted. In this analysis, a range of progressively more conservative assumptions about the number of events occurring in the unobserved portion of the treatment period will be explored in order to find the assumption which will reverse the conclusion (i.e., yield a non-significant p-value) of the primary analysis. The assumption that will reverse the conclusion is referred to as the tipping point. Once the tipping point is identified, the clinical plausibility of the assumption can be assessed.

The tipping point analysis will employ the same model as specified for the primary analysis including progressively conservative assumptions about the unobserved portion of time generated by subjects who discontinue early. The exact range of assumptions will be determined after treatment unblinding to ensure an appropriate range is explored based on the magnitude of treatment effect and pattern of missing data. The results of the various assumptions will be summarized with attack rate ratios, corresponding 95% confidence intervals and p-values in both tabular and graphical presentations. The details of this method are described in Appendix 2.

The primary efficacy analysis will be repeated for subjects in the modified full analysis set (mFAS) that were randomized and received study drug but did not meet study eligibility criteria.

6.1.2 Supplementary Analyses of Primary Efficacy Endpoint

No supplementary analyses are planned for the primary efficacy endpoint.

6.2 Analyses of Key Secondary Efficacy Endpoints

The rank ordered secondary efficacy endpoints are as follows:

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

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

Detailed definition of these periods is given in Section 12.3.1. An angioedema attack will be counted for a specific efficacy evaluation period only if that angioedema attack started during that period. For example, if an angioedema 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. Moderate and severe angioedema attacks are defined in Section 12.4.5.

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

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

The number and percentage of subjects who are attack-free for the specified analysis period, as well as the difference between treatment groups and corresponding exact 95% Clopper-Pearson confidence interval (CI) will be summarized. A subject is considered as attack free during a time period if the subject has no investigator-confirmed angioedema attacks during that time period. For subjects who discontinue the study prior to completion of the analysis period of interest, subjects will be classified as attack-free or not based on the observed contribution to the analysis period.

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

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

Where $p_{lanadelumab}$ refers to the proportion of subjects that are attack-free during the specified analysis period in the lanadelumab group and $p_{placebo}$ refers to the proportion of subjects that are attack-free during the specified analysis period in the placebo group. The null hypothesis is that the proportion of attack-free subjects in the lanadelumab treatment group is equal to that in the placebo group, versus the alternative hypothesis that the proportions are not equal. A Cochran-Mantel-Haenszel (CMH) test, adjusting for baseline

stratification factor(s) (categorical), will be used to test the null hypothesis, with Type I error set at 5%. A Mantel-Haenszel estimate for the common risk difference and corresponding stratified Newcombe confidence limits will be presented. If either the adjusted CMH test or common risk difference cannot be estimated because of an imbalance in the stratification factors, then the unadjusted CHM test or unadjusted risk difference and corresponding confidence limits will be presented. In this case, the potential bias in the unstratified analysis will be examined on an unblinded basis.

To adjust for the potential of inflated overall Type I error rate, the rank ordered secondary endpoints will be tested in a fixed sequence using a general gatekeeping approach consistent with the logical restrictions of the rank ordering of the endpoints. Secondary endpoints will not be declared statistically significant unless the primary endpoint is found to be statistically significant. Lower ranked secondary endpoints will not be declared statistically significant unless the primary and all of the higher ranked secondary endpoints are found to be statistically significant. The multiple testing procedure is detailed in Section 6.4.

6.2.1 Sensitivity Analyses of Key Secondary Efficacy Endpoints

The following sensitivity analyses will be performed on the key secondary endpoints to evaluate the robustness of the results. See Table 2 for details.

1. The primary analysis of the endpoint will be repeated using the SAS population (only if the SAS population is different from the FAS population).
2. The primary analysis of the endpoint will be repeated using all subject-reported angioedema attacks instead of limiting the analysis to those attacks that were investigator-confirmed.
3. The primary analysis of the endpoint will be repeated using an alternative approach for deriving attack-free status, where subjects who discontinue during a time period are considered as non-responders for that time period.

Table 2: Sensitivity Analysis for Efficacy Endpoints

	Sensitivity Analysis Item		
Secondary Efficacy Endpoint	1	2	3
Rank 1: Subjects that are attack free during the treatment period	x	x	x
Rank 2: Number of moderate or severe angioedema attacks during the treatment period	x	x	
Rank 3: Number of angioedema attacks during the presumed steady state period	x	x	
Rank 4: Subjects that are attack free during the presumed steady state period	x	x	x
Rank 5: Number of moderate or severe angioedema attacks during the presumed steady state period	x	x	

Note that for analysis of endpoints based on the presumed steady state period using the SAS population, 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.

Analyses for the key secondary endpoints will be repeated mFAS which excludes subjects that were randomized and received study drug but did not meet study entry criteria.

6.2.2 Supplementary Analyses of Key Secondary Efficacy Endpoints

No supplementary analyses are planned for the key secondary efficacy endpoints.

6.3 Analyses of Other Secondary Efficacy Endpoints

Additional secondary efficacy endpoints are as follows:

- Maximum attack severity during presumed steady state period (Day 70 through Day 182) and treatment period (Day 0 through Day 182)
- Time to first angioedema attack after Day 0
- Time to first angioedema attack after Day 70
- Achievement of at least a 50%, 70%, 90% and 100% reduction in the investigator-confirmed normalized number of attacks (NNA) per 4 weeks during each of the efficacy evaluation periods relative to the observation period NNA
- Achievement of an efficacy evaluation period NNA <1.0 attacks per 4 weeks, <0.75 attacks per 4 weeks, <0.50 attacks per 4 weeks, and <0.25 attacks per 4 weeks during each of the efficacy evaluation periods

Maximum attack severity during presumed steady state period and treatment period

For each subject, the mean and maximum severity (based on BAARP) of all investigator-confirmed angioedema attacks will be summarized for each efficacy evaluation period. See Section 12.4.6 for details on handling angioedema attack severity.

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).

Time to first angioedema attack after Day 0

The time to first angioedema attack (days) will be calculated from the date of Day 0 visit to the date of the first attack after Day 0 visit. Subjects who do not have an attack will be censored at the date of discontinuation (if prior to completion of the treatment period) or the date of the Day 182 visit. Time to the first angioedema attack after Day 0 will be summarized using Kaplan-Meier methods, stratified by baseline strata. A stratified log-rank test comparing lanadelumab to placebo will be included.

Time to first angioedema attack after Day 70

The time to first angioedema attack (days) will be calculated from the date of Day 70 visit to the date of the first attack after Day 70 visit. Subjects who do not have an attack will be censored at the date of discontinuation (if prior to completion of the treatment period) or the date of the Day 182 visit. Time to the first angioedema attack after Day 70 will be summarized using Kaplan-Meier methods, stratified by baseline strata. A stratified log-rank test comparing lanadelumab to placebo will be included.

Achievement of a pre-specified reduction in the investigator-confirmed normalized number of attacks (NNA) per 4 weeks during each of the efficacy evaluation periods relative to the observation period NNA

The investigator-confirmed normalized number of attacks (NNA) per 4 weeks during observation period and each of the efficacy evaluation periods will be expressed as a monthly (4 weeks, i.e., 28 days) angioedema attack rate for each subject. In what follows, for conciseness, angioedema attack rate refers to NNA per 4 weeks.

There will be four classes of responders based on pre-specified percentage reduction in the investigator-confirmed angioedema attack rate from the observation period attack rate: 50% or more reduction, 70% or more reduction, 90% or more reduction, and 100% reduction. For each subject, a treatment period angioedema attack rate and observation period angioedema attack rate will be calculated, as described in Section 12.4.7. The percentage reduction will be calculated as the observation period angioedema attack rate minus the treatment period angioedema attack rate divided by the observation period angioedema attack rate. Summary statistics will be presented for each of the five classes of responders by treatment. The five classes of responders are nested within each other and not mutually exclusive.

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

There will be a class of responders based on achieving the pre-specified investigator-confirmed NNA per 4 weeks of <1.0 for each of the efficacy evaluation periods. The

number and percentage of subjects achieving the predefined threshold will be summarized for each efficacy evaluation period.

6.3.1 Sensitivity Analyses of Other Secondary Efficacy Endpoints

No sensitivity analyses are planned for other secondary efficacy endpoints.

6.3.2 Supplementary Analyses of Other Secondary Efficacy Endpoints

No supplementary analyses are planned for other secondary efficacy endpoints.

6.4 Multiplicity Adjustment

The global family-wise Type I error rate (FWER) for the statistical tests of the primary and rank ordered secondary efficacy endpoints (rank specified in Section 6.2) will be controlled at 0.05. To strongly control the global FWER at this level, a general gatekeeping approach will be utilized in which the statistical tests will be conducted in a sequential manner. Testing will continue in sequence until the first test that the null hypothesis cannot be rejected; statistical significance cannot be declared for that test or for any of the remaining tests. To further illustrate this approach, the test for the primary endpoint will be conducted first at the 5% significance level for the active treatment group compared with the placebo group and, if significant, the first secondary endpoint will be similarly tested at the 5% significance level. The testing sequence will continue in order through the remaining secondary endpoints for active treatment group to placebo comparison as long as the null hypothesis is rejected at the 5% significance level.

6.5 Analyses of Exploratory Endpoints

Additional endpoints to be explored include those listed below. These endpoints are considered supportive and any statistical tests comparing treatments will be made without adjustment for multiplicity. The resulting p-values from these supportive analyses will be interpreted descriptively as summarizing the weight of evidence for a treatment effect. In the event of model non-convergence, descriptive results will be presented without p-values.

- Number of high-morbidity investigator-confirmed angioedema attacks during the treatment period (Day 0 through Day 182)
- Number of investigator-confirmed angioedema attacks resulting in an emergency department visit and/or admission to hospital during the treatment period (Day 0 through Day 182)

- Number of investigator-confirmed laryngeal angioedema attacks during the treatment period (Day 0 through Day 182)
- Characteristics of investigator-confirmed angioedema attacks, including attack duration, severity, location, and medication use during the observation period, treatment period (Day 0 through Day 182), and steady state period (Day 70 through Day 182)
- Percentage of attack free days during the treatment period (Day 0 through Day 182) and during the presumed steady state period (Day 70 through Day 182)
- Achievement of investigator-confirmed angioedema attack-free interval of 1 month or 3 months during the treatment period (Day 0 through Day 182)
- Achievement of investigator-confirmed angioedema attack-free interval of 1 month or 3 months during the presumed steady state period (Day 70 through Day 182)

Number of high-morbidity investigator-confirmed angioedema attacks during the treatment period

A high-morbidity angioedema attack is defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation < 24 hours), hemodynamically significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) or laryngeal. If the length of hospitalization can't be determined due to missing dates and times, then that hospitalization will be conservatively counted as being greater than 24 hours. The number of high-morbidity investigator-confirmed angioedema attacks during the treatment period (Day 0 through Day 182) will be analyzed using the same method as for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

Number of investigator-confirmed angioedema attacks resulting in an emergency department visit or admission to the hospital during the treatment period

For each angioedema attack, the site records if the attack resulted in a visit to the emergency department or admission to the hospital. The number of investigator-confirmed angioedema attacks resulting in an emergency department visit or admission to the hospital during the treatment period (Day 0 through Day 182) will be analyzed using the same method as for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

Number of investigator-confirmed angioedema attacks resulting in an emergency department visit during the treatment period

For each angioedema attack, the site records if the attack resulted in a visit to the emergency department. The number of investigator-confirmed angioedema attacks resulting in an emergency department visit during the treatment period (Day 0 through Day 182) will be analyzed using the same method as for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

Number of investigator-confirmed angioedema attacks resulting in admission to the hospital during the treatment period

For each angioedema attack, the site records if the attack resulted in hospitalization. The number of investigator-confirmed angioedema attacks resulting in admission to the hospital during the treatment period (Day 0 through Day 182) will be analyzed using the same method as for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

Number of investigator-confirmed laryngeal angioedema attacks during the treatment period

For each angioedema attack, the investigator records a primary location and up to 3 secondary location(s). In this analysis, a laryngeal angioedema attack will be defined as an attack with either the primary or secondary location indicated as laryngeal.

The number of investigator-confirmed laryngeal angioedema attacks during the treatment period (Day 0 through Day 182) will be analyzed using the same method as for the primary efficacy endpoint, with an addition of the history of laryngeal angioedema attacks (categorical) as a fixed effect in the model. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

Characteristics of investigator-confirmed angioedema attacks, including attack duration, severity, location and medication use during the observation, treatment, and presumed steady state periods

Attack characteristics at subject level and event level, as described below, will be summarized by treatment group for the observation period, the treatment period (Day 0 through Day 182) and the presumed steady state period (Day 70 through Day 182).

Subject level angioedema attack characteristics

Angioedema Attack Duration

For each subject, the mean duration of all investigator-confirmed angioedema attacks will be calculated in hours and summarized. See Section 12.4 for details on handling angioedema attack data. 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).

Angioedema Attack Severity

For each subject, the mean and maximum severity of all investigator-confirmed angioedema attacks will be calculated using a numerical rating and summarized. See Section 12.4.6 for details. The number and percentage of subjects will be tabulated by maximum attack severity (no attacks, mild, moderate, and severe).

Event level angioedema attack characteristics

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. 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.

Rescue Medication Use

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

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 supportive treatment by type (IV fluids, pain medication, oxygen, anti-emetic, and other) as reported in the Angioedema Acute Attack CRF.

Percentage of angioedema attack free days during the treatment period

The percentage of angioedema attack free days during the treatment period (Day 0 through Day 182) 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. An attack-free day is defined as a calendar day with no investigator-confirmed angioedema attack.

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

Percentage of angioedema attack free days during the presumed steady state period

The percentage of angioedema attack free days during the presumed steady state period (Day 70 through Day 182) will be calculated by counting the number of days in the presumed steady state period without an angioedema attack and dividing by the number of days the subject was in the treatment period. An attack-free day is defined as a calendar day with no investigator-confirmed angioedema attack.

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

Achievement of investigator-confirmed angioedema attack-free interval of 1 month or 3 months during the treatment period

A subject is considered as attack free during a time period if the subject has no investigator-confirmed angioedema attacks during that time period. For subjects who discontinue the study prior to completion of the analysis period of interest, subjects will be classified as attack-free or not based on the observed contribution to the analysis period.

The number and percentage of subjects who achieve investigator-confirmed angioedema attack free intervals of 1 month (4 weeks; 'Day 0 to one day before Day 28 visit') or 3 months (12 weeks; 'Day 0 to one day before Day 84 visit') during the treatment period will be tabulated by treatment group. Risk difference comparing lanadelumab to placebo, and corresponding exact 95% confidence interval (Santner, 1980) will be provided.

Achievement of investigator-confirmed angioedema attack-free interval of 1 month, 3 months, or until the Day 182 Visit during the presumed steady state period

The number and percentage of subjects who achieve investigator-confirmed angioedema attack free intervals of 1 month (4 weeks; 'Day 70 to one day before Day 98 visit') or 3 months (12 weeks; 'Day 70 to one day before Day 154 visit') during the presumed steady state period will be tabulated by treatment group. Risk difference comparing lanadelumab to placebo, and corresponding exact 95% confidence interval (Santner, 1980) will be provided.

6.6 Subgroup Analyses

Subgroup analyses are planned to be conducted for the primary efficacy endpoint. Any p-values that are presented will be descriptive.

The following subgroups will be used:

- Age group (<18, 18 to <40, 40 to <65, ≥65 years)
- Sex (Male, Female)
- Race group (White, Other)
- Weight group (<50, 50 to <75, 75 to <100, ≥100 kg)
- BMI Group (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2)
- Observation period angioedema attack rate group (1 to <2, ≥2 attacks/4 weeks)
- Subtype
    - with known mutations (FXII, PLG, ANGPT1, or KNG1 genes, or other predefined mutations associated with normal C1-INH angioedema)
    - with family history (a first-degree relative) and unknown mutations; and
    - with idiopathic non-histaminergic angioedema (INHA)
- Geographical region (North America, Europe, and Other)
- History of laryngeal angioedema attack (history laryngeal attack, no history of laryngeal attack)

The subgroups will be analyzed using the same method as described for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint. For the subgroup analyses conducted for the primary efficacy endpoint, a forest plot depicting the rate ratio and corresponding 95% CI estimated from the Poisson generalized linear model will be provided for lanadelumab versus placebo within each subgroup.

7. SAFETY ANALYSIS

All safety analyses will be performed using the SAS population. Analyses will be summarized by treatment group.

The definition of baseline is provided in Section 12.2.

7.1 Adverse Events (AE)

AEs are reported on the Adverse Events (Drug Only) CRF and the Angioedema Acute Attack CRF and will be coded using MedDRA Version 22.1 or newer.

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 12.6.3.

The analyses described in this section will be based on TEAEs only; plainly referred to as AEs in this section for brevity.

Related AEs are AEs classified as related to study drug by the investigator. Missing relationship to study drug imputation is described in Section 12.6.5.

Severe AEs are AEs classified as severe (grade 3) or life threatening (grade 4) by the investigator. Missing severity imputation is described in Section 12.6.4.

In this study, the primary endpoint is based on an AE. If lanadelumab is efficacious, it will result in a systematic difference in the incidence of AEs by treatment group which will complicate the interpretation of the safety. Thus, the collection of tabulations described in this section (with the exception of the analyses of AEs of special interest (AESI) and injection site reaction (ISR)) will be produced for 2 mutually exclusive subgroups of AEs based on if the AE was reported as an angioedema attack or not, and defined as follows:

- Non-Angioedema Attack Reported AEs will include the subset of AEs identified on the AE CRF page (events not reported as an angioedema attack). Angioedema attack reported AEs are reported on a separate CRF page.
- Angioedema Attack Reported AEs will include the subset of AEs identified on the Angioedema Acute Attack CRF page as a reported angioedema attack. Note that this includes investigator-confirmed and non-confirmed angioedema attacks.

For this analysis, AEs will be classified to one of three analysis periods:

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

Detailed definition of these analysis periods is given in Section 12.3.1. For AEs with partial onset times, non-missing date parts will be used to determine if the AE falls within the period. If a determination cannot be made using the non-missing date parts as to if the AE falls within the period, the AE will be conservatively counted as a treatment-period AE.

The number and percentage of subjects with any AE, any related AE, any SAE, any related SAE, any severe AE, any related severe AE, and any investigator-reported AESI, as well as the total number of events for each category, will be summarized by treatment group. The number of deaths due to an AE, hospitalization due to an AE and study discontinuation due to an AE will be summarized by treatment group. This tabulation will be repeated for each of the analysis periods. For serious AEs and investigator-reported AESI during the treatment period, relative risks and risk differences, and their associated exact 95% CI (Santner, 1980) will be provided for the comparison between lanadelumab and placebo. If the relative risk cannot be calculated the risk difference will be provided.

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized for each treatment group by SOC and PT for each analysis period. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, related severe AEs, and investigator-reported AESI for the treatment period and follow-up period AEs. This tabulation will be repeated for SAEs and severe AEs for pretreatment period. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the lanadelumab group and then the placebo group. For serious AEs during the treatment period and follow-up period, risk difference and corresponding exact 95% CI (Santner, 1980) will be provided for the comparison between lanadelumab and placebo by SOC and PT. If the relative risk cannot be calculated the risk difference will be provided.

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized for each treatment group by PT for treatment period AEs only. This tabulation will be repeated for related AEs and severe AEs, as well as for frequently occurring (≥5%) AEs for treatment period AEs. Tabulations will be presented sorted by PT by descending frequency in the lanadelumab group and then the placebo group.

Subgroup analyses are planned to be conducted for non-angioedema attack treatment period AEs, related AEs, and severe AEs for the subgroups identified in Section 6.6. This will include an overall summary table for non-angioedema attack treatment period AEs, and summaries by SOC and PT for these subsets of AEs.

All AEs (TEAEs and non-TEAEs) will be provided in subject listings. In addition, subject listings of AEs causing discontinuation of study medication, AEs leading to death, and SAEs will be produced.

7.1.1 Adverse Events of Special Interest (AESI)

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 23.1 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.

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 by treatment group 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. Risk difference and corresponding exact 95% CI (Santner, 1980) will be provided for the comparisons between lanadelumab and placebo. 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 in the lanadelumab group and then the placebo group.
- 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 for each treatment group 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 in the lanadelumab group and then the placebo group.

A listing of investigator-reported AESI will be provided.

7.1.2 Injection Site Reaction AEs (ISR)

Injection site reaction (ISR) AEs will be identified by adverse events with the preferred terms starting with 'Injection site', 'Application site', or 'Administration site', and will be analyzed for the treatment period only.

The number and percentage of subjects with any ISR AE, any related ISR AE, any severe ISR AE, any related severe ISR AE, any ISR SAE, and any related ISR 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 ISR AE, hospitalization due to an ISR AE and study discontinuation due to an ISR AE will be summarized by treatment group.

The number and percentage of subjects with an ISR AE, as well as the total number of ISR AEs, will be summarized for each treatment group by SOC and PT for the treatment period. The number and percentage of subjects with an ISR AE will be summarized for each treatment group by SOC, PT, and maximum severity for the treatment period. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the lanadelumab group and then the placebo group.

The duration of ISR AEs overall and by PT will be summarized numerically (in hours, using summary statistics) and categorically (0 - 0.5 hour, >0.5 - 1 hour, >1- 12 hours, >12 – 24 hours, ≤1 day - unclear, >1 – <5 days, 5- ≤14 days, and >14 days). The definition of the duration of ISR AEs is provided in Section 12.6.3.3.

7.1.3 AE Tabulations

Table 3 provides a summary of the AE tabulations by analysis period as described in this section.

Table 3: Adverse Event Tabulations by Analysis Period

	Pretreatment Period	Treatment Period	Follow-up Period
AE summary	x	x	x
AE by SOC and PT	x	x	x
AE by PT		x	
Related AE by SOC and PT		x	x
Related AE by PT		x	
Severe AE by SOC and PT	x	x	x
Severe AE by PT		x	
Related Severe AE by SOC and PT		x	x
SAE by SOC and PT	x	x	x
Related SAE by SOC and PT		x	x
Frequently Occurring AE		x	
Summary of Investigator-reported AESI	x	x	x
Investigator-reported AESI by SOC and PT	x	x	x
Related Investigator-reported AESI by SOC and PT		x	x
Summary of SMQ-defined AESI	x	x[a]	x
SMQ-defined AESI by SOC and PT	x	x[a]	x
Related SMQ-defined AESI by SOC and PT		x[a]	x
Summary of ISR AEs		x	
ISR AEs by SOC and PT		x	
ISR AEs by SOC, PT, and Severity		x	
Number and duration of ISR AEs		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

7.2 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 parameters to be evaluated include the following:

Hematology	Hemoglobin, hematocrit, red blood cells (RBC), white blood cells (WBC) count total and differential - neutrophils, lymphocytes, monocytes, eosinophils, basophils, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), absolute platelet count.
Chemistry	Albumin, alkaline phosphatase, alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), bilirubin (total and direct), blood urea nitrogen (BUN), calcium, carbon dioxide (CO_2), chloride, creatinine, creatine phosphokinase (CPK), glucose, phosphate, magnesium, potassium, sodium, total protein.
Coagulation	Prothrombin time, activated partial thromboplastin time (aPTT), international normalized ratio (INR)
Urinalysis	Bilirubin, glucose, ketones, blood, nitrite, potential hydrogen (pH), protein, specific gravity, microscopy (if indicated by macroscopic findings).
Virology	Hepatitis B Surface Antigen (HbsAg); Hepatitis C Virus (HCV); Human Immunodeficiency Virus (HIV)

Hematology, Chemistry, Coagulation, and Urinalysis results will be summarized as described below. Virology will be provided in SDTM datasets only.

Continuous laboratory test results (hematology, chemistry, coagulation, and urine pH) will be summarized as described below.

Actual values and change from baseline in clinical laboratory tests will be summarized for each treatment group by study visit. Additionally, all post-baseline scheduled visits, unscheduled visits, and all post-baseline visit actual values and change from baseline will be summarized for each treatment group. If more than one laboratory result is reported per study visit per parameter, the last non-missing result will be selected for analysis.

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. See Section 12.6.6 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 for each treatment group 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 is summarized on non-missing post-baseline most severe results per subject and per parameter.

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 12.6.7. However, the actual values as reported in the database will be presented in data listings.

Categorical laboratory test results (urinalysis excluding pH) will be summarized for each treatment group 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.

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.

Among chemistry parameters, additional analyses in Table 3 will be conducted on liver function tests for the Full Analysis Set using the highest pre-treatment and highest overall treatment period and follow-up period measurements. The number and percentage of subjects with highest results falling into the categories of normal (<=1 x ULN), >1 – <=3 x ULN, >3 – <=5 x ULN, and greater than >5 x ULN on the liver function tests for ALT, AST will be summarized for all pre-treatment measurements and overall treatment period and follow-up period measurements. Total bilirubin (BILI) will be summarized by the number and percentage of subjects with highest results falling into the categories of <=2 x ULN and >2 x ULN for all pre-treatment measurements and overall treatment period and follow-up period measurements. Additionally, for the Full Analysis Set, a shift table summarizing the shift in categories from highest pre-treatment measurements to the highest overall treatment period and follow-up period measurements will be created for the liver function tests including ALT, AST and BILI.

Table 3. Lab Parameter Criteria Categories

Parameter	Criteria Categories			
Liver Function Tests				
Alanine transaminase (U/L)	Normal (<=1 x ULN)	>1 – <=3 x ULN	>3 – <=5 x ULN	>5 x ULN
Aspartate transaminase (U/L)	Normal (<=1 x ULN)	>1 – <=3 x ULN	>3 – <=5 x ULN	>5 x ULN
Bilirubin (umol/L)	-	<=2.0 x ULN	>2 x ULN	-

7.3 Vital Signs

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)

Actual values and changes from baseline in vital signs will be summarized for each treatment group 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.

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 for each treatment group 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.

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)

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 for each treatment group by study visit. 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.

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 for each treatment group by study visit. 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.

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.

7.5 Other Safety Data

7.5.1 Biomarker Test

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

A descriptive summary analysis (n, mean, standard deviation [SD], minimum, median, and maximum) will be performed for these results. Results will be listed for all subjects which will include the corresponding reference ranges.

7.5.2 Pregnancy Test

Pregnancy test results will be listed by study visit.

7.5.3 Physical Examination

Adverse events emerging from any physical examination will be recorded on eCRFs and reported with adverse events. Physical examination will be listed by study visit.

8. PHARMACOKINETIC ANALYSIS

All summaries and analyses of the pharmacokinetic data will be based on the PK Set defined in Section 4.6.

8.1 Drug Concentration

The plasma concentrations of lanadelumab will be 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

treatment group by the protocol scheduled sampling visit, and provided in subject data listings.

8.2 Handling Below Limit of Quantitation (BLQ) Values

Plasma concentrations below the lower limit of quantitation (LLOQ) will be set to zero in the calculation of summary statistics; they will not be imputed in the subject data listings.

8.3 Statistical Analysis of Pharmacokinetic Data

No formal statistical hypothesis will be tested.

9. PHARMACODYNAMIC ANALYSIS

All summaries and analyses of the pharmacodynamic data will be based on the PD Set defined in Section 4.7.

9.1 Pharmacodynamic Data

The plasma kallikrein activity will be measured by cHMWK and pKal levels. Results will be provided in subject data listings and summarized by treatment group using descriptive statistics (number of subjects, arithmetic mean, SD, CV%, median, minimum, maximum,, geometric mean, and CV% of geometric mean) for each sampling visit.

10. OTHER ANALYSES

Health-related quality of life analyses and immunogenicity analyses are planned for this study.

10.1 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), at the study visits specified in Appendix 1 Table 5 and Table 6 for the SAS population.

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 responses to the AE-QoL for each item will be tabulated for each treatment group by study visit. The AE-QoL questionnaire responses will be listed for each subject by study visit.

10.2 Immunogenicity Analyses

Immunogenicity will be measured based on the presence or absence of neutralizing or non-neutralizing ADA in plasma.

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

The ADA result, ADA titer result (quantitative) and neutralizing ADA result will be listed for each subject by study visit.

11. INTERIM ANALYSIS/ DATA MONITORING (REVIEW) COMMITTEE

No interim analysis or adaptive design is planned for this study. However, an independent DMC will be established to provide ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating subjects in the study. Analysis of the data for DMC review will be conducted according to the DMC Charter. Because no formal hypothesis testing for safety assessments is planned, multiplicity concerns regarding repeated analyses are not an issue.

12. DATA HANDLING CONVENTIONS

12.1 General Data Reporting Conventions

Outputs will be presented according to Shire TFLs Library V9.0.

Unless otherwise specified, summary tabulations will be presented by treatment group (lanadelumab 300 mg every 2 weeks and Placebo).

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

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. Standard deviation will be displayed to two levels of precision greater than the data collected. P-values will be rounded to 3 decimal places, p-values <0.0005 will be displayed as <0.001.

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. The denominator for all percentages will be the number of subjects within the population of interest, unless otherwise specified.

BMI will be rounded to 1 decimal place and normalized number of angioedema attacks will be rounded to 2 decimal places for reporting.

All data listings will be sorted by treatment group, site, subject number, visit (when available), assessment/event start date (when available), assessment/event end date (when available) and alphabetically by preferred term/name (when available), and will include the subject's age, sex, and race.

12.2 Definition of Baseline and EOS/ET

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 efficacy analyses, refer to observation period attack rate defined in Section 12.4.7.1.

For safety analyses, EOS/ET will be defined as the last post-baseline assessment for generating descriptive statistics.

12.3 Definition of Visit Windows

Although there is a visit window of ± 4 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:

$$\text{Study day} = \text{assessment date} - \text{first dosing date} + 1$$

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

$$\text{Study day} = \text{assessment date} - \text{first dosing date}$$

Note that Day 0 will be equivalent to study day 1.

12.3.1 Analysis Periods

The pretreatment period is defined as the interval of time:

[*date/time of informed consent, date/time prior of first exposure to study drug*]

The observation period is defined as the interval of time:

- If the observation period end date < date of first dose of IP:

[*start date of observation period at 0:00*, *end date of observation period at 23:59*]

- If the observation period end date = date of first dose of IP:

[*start date of observation period at 0:00*, *date/time of first dose of IP – 1 minute*]

The treatment period of Day 0 through 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 is defined as the interval of time:

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

12.4 Derived Efficacy Endpoints

The following rules apply to the handling of angioedema attack data for efficacy analyses only. Angioedema attacks starting prior to the observation period are not processed by these rules.

12.4.1 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.

12.4.2 Angioedema Attack Duration

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

12.4.3 Investigator-Confirmed Angioedema Attacks

Investigator-confirmed angioedema attacks are those that the PI confirmed as meeting the BAARP criteria (as indicated on the Angioedema Acute Attack CRF) for an angioedema attack.

12.4.4 Investigator-Confirmed Angioedema Attacks Requiring Acute Therapy

Investigator-confirmed angioedema attacks requiring acute therapy are those attacks where it was indicated on the CRF that the subject received acute angioedema therapy treatment for the attack.

12.4.5 Moderate and Severe Investigator-Confirmed Angioedema Attacks

Moderate and severe investigator-confirmed angioedema attacks are those attacks that were classified as of moderate or severe according to the BAARP defined severity and reported as such on the Angioedema Acute Attack CRF.

12.4.6 Angioedema Attack Severity

The overall severity of the subject's attack was to be determined by the investigator using the following definitions provided as part of BAARP:

- Mild: Transient or mild discomfort
- Moderate: Mild to moderate limitation in activity - some assistance may be needed

- Severe: Marked limitation in activity, assistance required

The 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.

12.4.7 Angioedema Attack Rate

12.4.7.1 Observation Period Angioedema Attack Rate

The observation period 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 divided by the number of days the subject contributed to the observation period multiplied by 28 days.

12.4.7.2 Treatment Period Angioedema Attack Rate

The treatment period angioedema attack rate will be presented as the normalized number of attacks per month and calculated for each subject as the number of angioedema attacks occurring during the treatment period divided by number of days the subject contributed to the treatment period multiplied by 28 days. No assessment of treatment compliance will be considered for this calculation.

12.4.7.3 Presumed Steady State Period Angioedema Attack Rate

The presumed steady state period angioedema attack rate will be presented as the normalized number of attacks per month and calculated for each subject as the number of angioedema attacks occurring during the presumed steady state period divided by number of days the subject contributed to the presumed steady state period multiplied by 28 days. If the subject did not contribute to the presumed steady state period this rate will be missing. No assessment of treatment compliance will be considered for this calculation.

12.4.8 Time to First Angioedema Attack

12.4.8.1 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.

12.4.8.2 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.

12.5 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. However, all assessments will be presented in the data listings.

12.6 Handling of Missing, Unused, and Spurious Data

All subjects in the analysis sets defined in Section 4 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. Imputation of missing date/time for angioedema attack data as described in Section 12.6.1 apply to efficacy analyses only. Angioedema attacks starting prior to the observation period are not processed by these rules. For safety analyses, angioedema attacks will be analyzed as reported, and missing date information will be handled as described for adverse events in Section 12.6.3.

12.6.1 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 time will be imputed as described in Section 12.6.3. 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 12.4.1 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 12.4.1 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.

12.6.2 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.

12.6.3 Missing Date 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.

To facilitate categorization of AEs as treatment emergent, imputation of start date/time will be used. Stop date/time will not be imputed. The handling of missing dates for ISRs is described in Section 12.6.3.3.

12.6.3.1 Incomplete Start Date/Time

Follow the same rules as in Section 12.6.2.1.

12.6.3.2 Incomplete Stop Date/Time

Not applicable.

12.6.3.3 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.

12.6.4 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 a severity of "Life threatening (grade 4)" will be

assigned. 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".

12.6.5 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.

12.6.6 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.

12.6.7 Character Values of Clinical Laboratory Variables

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

Table 4. 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

*Note this logic should be applied to all other possible values recorded in the database.

Gonzalez, Justo L. *The Story of Christianity.: (The Early Church to the Reformation)*. Vol. 1. The Story of Christianity. HarperOne, 2014.

13. ANALYSIS SOFTWARE

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

14. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

The pKal was removed as an example of an exploratory endpoint and only included as a secondary endpoint.

15. REFERENCES

Rubin, D. B. (1976). Inference and Missing Data. *Biometrika;* 63: 581–592.

Rubin, D. B. (1987). *Multiple Imputation for Nonresponse in Surveys.* New York: John Wiley & Sons.

Santner, T. S. (1980). Small-sample confidence intervals for p1 − p2 and p1/p2 in 2 × 2 contingency tables. *J. Amer. Statist. Assoc;* 75: 386–394.

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.

16. APPENDICES

16.1 Appendix 1 – Schedule of Activities

Table 5: Schedule of Activities – Screening and Observation Period

Procedures	Screening[a] (up to 8 weeks)	OBSERVATION PERIOD (BY STUDY WEEK)[m]									See protocol section below for details
		Start of Observation Period	1	2	3	4	5	6	7	8	
Informed consent (written permission and assent)	X										8.3.1
Eligibility review	X	X									8.3.2
Demographics and medical/angioedema history	X										8.3.3 and 8.3.4.1
Prior/current medications, therapies, and procedures[b]	X		X----------							----------X	6.6
Telephone contact[c]				X		X		X		X	8.2.1.3
Angioedema attack monitoring[b]	X	X----------								----------X	8.2.1
Antihistamine treatment[d]			X----------							----------X	8.2.1.3
Distribute icatibant and antihistamine treatment		X									8.2.1.2
Genotype testing[e]	X										8.3.6.5
C1-INH, C4, and C1q testing[f]	X										8.2.1.1
LTP washout[g]	X										8.2.1.1
Vital signs[h]	X										8.3.5.4
Physical exam[i]	X										8.3.5.1
12-lead ECG	X										8.3.5.7
Pregnancy test[j]	X										8.3.5.6
Clinical laboratory testing[k]	X										8.3.5.5
Virology testing: HBsAg, HCV, and HIV (serologies)[l]	X										8.3.5.5
Adverse events	X	X----------								----------X	8.3.5.2

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

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

[b] All angioedema attacks will be reported after signing the ICF and assessed in accordance with BAARP (Appendix 5). From the start of the observation period, all subjects or parents/caregivers will use a diary to record symptoms and occurrences of angioedema attacks and any medications taken by the subject for the management of attacks. Angioedema attacks will be monitored daily and recorded as they occur. Subjects or parents/caregivers are instructed to notify and report details of an attack to the study site within 72 hours of the onset of an angioedema attack, in accordance with BAARP (Appendix 5).

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

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

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

[f] C1-INH, C4, and C1q testing is required at screening from the sponsor-approved central laboratory. If C1-INH therapy is used, the drug needs to be washed out for at least 5 half-lives before the testing sample is collected.

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

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

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

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

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

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

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

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

Table 6: Schedule of Activities – Treatment Period and Follow-up Period

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

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

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

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

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

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

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

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

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

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

[i] During the treatment and follow-up period, subjects or parents/caregivers will use a diary to record symptoms and occurrences of angioedema attacks and any medications taken by the subject for the management of attacks. Angioedema attacks will be monitored daily and recorded as they occur. Subjects or parents/caregivers are instructed to notify and report details of an attack to the study site within 72 hours of the onset of an angioedema attack, in accordance with BAARP (Appendix 5). Any subject-reported or parent/caregiver-reported attack not confirmed by the investigator must have an alternate AE diagnosis recorded in the source documents and electronic case report form.

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

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

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

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

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

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

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

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

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

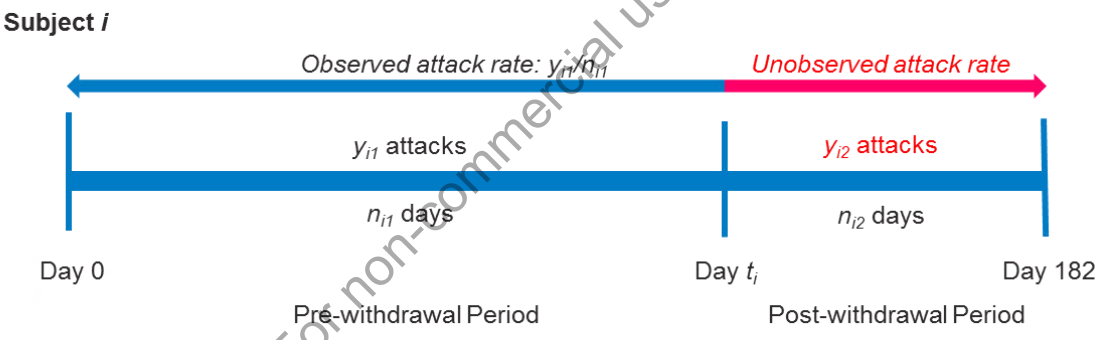
[s] To extend flexibility to patients during the COVID-19 public health emergency, an in-person visit may be substituted with a remote visit. The type of remote visit (e.g., telehealth visit or home health care visit) will be documented in the study records and eCRF. See Section 8.1 of the protocol for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

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

16.2 Appendix 2 – Details of Tipping Point Analysis

Figure 2 illustrates the missing data pattern generated from subjects who discontinue early from the treatment period of the SHP643-303 study. Subject *i* receives first dose of the study drug at Day 0 and discontinues the study at Day t_i prior to the end of the treatment period at Day 182. The pre-withdrawal period for Subject *i* is defined as Day 0 through Day t_i and the post-withdrawal period is defined as Day t_i + 1 through Day 182. In the pre-withdrawal period, we know both the length of the period (n_{i1}) and the number of investigator-confirmed angioedema attacks during the period (y_{i1}), and can calculate the observed attack rate (y_{i1}/n_{i1}) for the period. In the post-withdrawal period, we know only the length of the period (n_{i2}), however, both the number of investigator-confirmed angioedema attacks during the period (y_{i2}) and the unobserved attack rate (y_{i2}/n_{i2}) for the period are unknown.

Figure 2 Missing Data Pattern for Subjects who Discontinue Early from the Treatment Period of Study SHP643-303



To assess the impact of the unobserved portion of the treatment period generated by subjects who discontinue the study prior to completing the treatment period on the results of our primary analysis, a tipping point analysis will be conducted. In this analysis, a range of progressively more conservative assumptions about the number of events occurring in the post-withdrawal period will be explored in order to find the assumption which will reverse the conclusion (i.e., yield a non-significant p-value) of the primary analysis. The assumption that will reverse the conclusion is referred to as the tipping point. Once the tipping point is identified, the clinical plausibility of the assumption can be assessed.

The tipping point analysis will employ the same model as specified for the primary analysis including progressively conservative assumptions about the unobserved attack

rate during the post-withdrawal period. This is achieved by assuming that subjects in the active treatment arm who discontinue the study prior to completing the treatment period would have, on average, their unobserved attack rate worse by some amount (δ) compared with the observed attack rates of subjects that completed the study. Subjects who discontinue the study prior to completing the treatment period from the placebo arm would have the same unobserved attack rate as those who completed the study. In contrast, the model used for the primary analysis assumes that events occur at a constant rate within an individual, and uses only the number of events in the observed portion of the treatment period with an offset parameter to account for the length of time in which those events were observed to derive the event rate for that individual (i.e., the observed attack rate).

The tipping point analysis will be conducted as follows:

Step 1: Multiple Imputation (MI)

MI will be used to impute 1000 samples of the unobserved attack rate (y_{i2}/n_{i2}) for each subject who discontinued the study prior to completing the treatment period conditional on the observed data. Multiple imputation is used to incorporate variance that accounts for the uncertainty associated with the imputed values (Rubin, 1976) (Rubin, 1987). The imputed unobserved attack rate will be used to generate 1000 imputed values of the total number of attacks over the entire treatment period for each subject who discontinued the study prior to completing the treatment period.

Steps 1a – 1c detail the multiple imputation approach to generate complete data for subjects who discontinued the study prior to completing the treatment period:

Step 1a: 1000 independent samples are drawn from the posterior distribution of model parameters fit using a Bayesian analysis of the model defined for the primary analysis. The sampled set of values of the model parameters are then used to generate a set of values for the expected unobserved attack rate (y_{i2}/n_{i2}) for each subject who discontinued the study prior to completing the treatment period using each subject's covariate values. This will result in 1000 imputed values for the unobserved attack rate for each discontinued subject.

Step 1b: The expected unobserved attack rate (y_{i2}/n_{i2}) for each subject who discontinued the study prior to completing the treatment period is then multiplied by the length of the post-withdrawal period (n_{i2}) for that subject to get the expected number of attacks for the post-withdrawal period (y_{i2}).

Step 1c: The expected number of attacks for the post-withdrawal period (y_{i2}) is added to the observed number of attacks in the pre-withdrawal period (y_{i1}) to get the total number of attacks over the entire treatment period ($y_{i1} + y_{i2}$) for subjects who discontinued the study prior to completing the treatment period.

Step 2: Analyze the MI Datasets with Primary Analysis Model

The primary regression model will be run using each of the 1000 multiply imputed complete data sets. The primary regression model is the Poisson regression generalized linear model with covariates for observation period attack rate, treatment group, and an offset variable for the log number of days observed.

Step 3: Combine Estimates using Rubin's Rules

From each of 1000 runs of the primary analysis model, the estimates will be combined using Rubin's rules (Rubin, 1987) to get one estimate for each of the rate ratios comparing the active treatment groups to placebo and corresponding 95% confidence intervals and p-values. These values will be summarized in both a tabular and graphical form.

Step 4: Pattern Imputation with Delta Adjustment

Steps 1 through 3 will be repeated with a slight modification at Step 1b to explore the impact of progressively worse assumptions (defined by δ) on the unobserved attack rate for subjects who discontinue early from the active treatment arm. In this study, δ represents a rate ratio comparing the rate of investigator-confirmed angioedema attacks in the active treatment group to the rate of investigator-confirmed angioedema attacks in the placebo group.

Modified Step 1b: For subjects that discontinue the study prior to completing the treatment period from the active treatment arm, the expected unobserved attack rate (y_{i2}/n_{i2}) for each discontinued subject is first multiplied by a specific rate ratio δ, then multiplied by the length of post-withdrawal period (n_{i2}) for that subject to get the expected number of attacks for the post-withdrawal period (y_{i2}). For subjects that discontinue the study prior to completing the treatment period from the placebo arm, Step 1b is followed without modification.

Steps 1 through 4 are repeated for values of δ that represent progressively worse assumptions on the unobserved attack rate for subjects who discontinue the study prior to completing the treatment period from the active treatment arm until the tipping point is

identified (value of δ that yields a non-significant p-value). As the value of δ increases, the overall attack rate imputed for subjects in the active treatment arm increases. Values of $\delta > 1$ will be determined post-hoc in order to define reasonable increments for which to increase δ given the magnitude of treatment effect and the pattern of missing data.

Note that the imputed results generated following Steps 1 through 3 without modification represent the case when $\delta=1$, corresponding to missing at random (MAR) imputation. The estimates generated from the case when $\delta=1$, should be very similar if not exactly the same as the estimates generated from the primary analysis model.

If the value of δ which causes the study results to be reversed is plausible, then the missing data assumptions used are questionable. However, if the value of δ is not plausible, then the missing data assumptions are reasonable.

In the SHP643-303 study, the protocol specifies that there must be 24 hours in between each investigator-confirmed angioedema attack. Therefore, the total number of attacks during the treatment period is restricted to about 1 attack per day. If δ allows for more attacks than 1 per day, then the value of δ is not plausible under the study specifications and the missing data assumptions will be declared reasonable.

16.3 Appendix 3 – Sample SAS Code

16.3.1 GLM Model Sample SAS Code

Sample code for the primary efficacy analysis of the primary endpoint.

```
PROC GENMOD DATA=eff_data;
CLASS trtgrp subtype;
MODEL no_attks = trtgrp bl_rate subtype / DIST=poisson LINK=log
OFFSET=logdays PSCALE;
LSMEANS trt / DIFF CL EXP ILINK;
ESTIMATE '300mg every 2 wk vs pbo' trtgrp 1  -1 / EXP;
RUN;
```

Where:
eff_data = efficacy analysis dataset
trtgrp = treatment group (categorical)
no_attks = number of angioedema attacks during the analysis period
bl_rate = normalized pretreatment angioedema attack rate (continuous)
subtype = genetic subtype of subject
logdays = logarithm of time in days each subject was observed during the analysis period

For the sensitivity analysis using a generalized linear model assuming a negative binomial distribution, replace DIST=poisson with DIST=negbin.

16.3.2 Tipping Point Analysis Sample SAS Code

Step 1: Use multiple imputation to impute the unobserved rate of attacks by completing the following process:

1a. Sample code that draws 1000 independent samples from the posterior distribution of model parameters which are fit using a Bayesian analysis.

```
proc genmod data = prim_eff_all order = data;
   class trtpn; *treatment group;
   model NUM_ATTKS = trtpn runbase /DIST= poisson LINK = log OFFSET
= LNUMDAYS ;
   bayes outpost=bayes_prim thin=1 nmc=1000 nbi=200;
 run;
```

Sample code for the sampled set of values being used to generate values for the unobserved attack rate for subjects who discontinued the study prior to completing the treatment period. The values are generated using the model parameter estimates from Step 1a and each subject's covariate values. There should be 1000 imputed values for each discontinued subject.

The variable miss_treat is an indicator for not completing the treatment period and attk_rate is the unobserved attack rate for the post-withdrawal period.

```
%macro mi_data;
%do i = 1 %to 1000;
*estimate lambda for poisson distribution;
data prim_eff_all&i;
   set prim_eff_all;

   *calculate the rate for each sample of coefficients from the
model in Step 1a using each subject's covariate values;
   if TRTPN = 1 then lambda = exp(&&INTERCEPT&i + &&RUNBASE&i +
&&TRTPN1&i);
   if TRTPN = 2 then lambda = exp(&&INTERCEPT&i + &&RUNBASE&i +
&&TRTPN2&i);

*calculate the attack rate;
 if miss_treat = 1 then attk_rate = RAND('POISSON', lambda);
run;
%end;
%mend mi_data;
```

1b. The expected unobserved attack rate (from step 1b) for each subject who discontinued early is then multiplied by the length of the post-withdrawal period for that subject to get the expected number of attacks for the post-withdrawal period.

1c. The expected number of attacks for the post-withdrawal period is added to the observed number of attacks in the pre-withdrawal period to get the total number of attacks over the entire treatment period.

Step 2: The sample code shows the for primary regression model being run using each of the 1000 multiply imputed complete data sets. The imputation variable is the indicator for the which imputation dataset is being analyzed and prim_ efficacy is the dataset that includes the 1000 datasets that have been imputed using step 1.

```
proc genmod data = prim_efficacy order = data;
   by imputation;
   class trtpn; *treatment group;
   model num_attks_final = trtpn runbase /DIST= poisson LINK = log
PSCALE; *model;
  lsmeans trtpn/ diff cl exp ilink;
run;
```

Step 3: Combine the results from the multiply imputed datasets using Rubin's rules (then exponentiate the estimate and the 95% confidence interval for the estimate of the rate ratios). Below is the code used to combine the results across imputations (note: the estimates and the 95% CI of the estimates need to be exponentiated).

```
proc mianalyze data = Diffs;
   by trtpn;
   where _trtpn = 1;
   modeleffects estimate;
   stderr stderr;
run;
```


16.3.3 Sample Code to Derive Relative Risk and Risk Difference

```
proc freq data=adae;
   tables trt*SAE / riskdiff relrisk;
   exact relrisk riskdiff;
run;
```

16.3.4 Sample SAS Code for Time to Event Analysis

The analysis of time to first angioedema attack after Day 0 (see Section 6.3) 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 ANEDATA which contains the variables ANETIME and STATUS. ANETIME is the time from first IP administration to the first investigator-confirmed angioedema 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 6.3.

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

```
ods graphics on;
ods output Quartiles=Quarts CENSOREDSUMMARY=Summary;
proc lifetest data=ANEDATA method=km plots=survival;
   time ANETIME*STATUS(1);
   strata trt01p/ diff = control('Placebo')  test = (logrank);
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.

Similar code will apply to the analysis of time to first angioedema attack after Day 70.

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