STATISTICAL ANALYSIS PLAN

Protocol Title:	HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 for Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)
Protocol Number:	DX-2930-03
Protocol Version/Date:	Amendment 2.0 21 April 2016
Indication:	Prevention of angioedema attacks in subjects with HAE
Study Phase	III
SAP Author	PPD, MPH (Rho, Inc.)
SAP Analysis Type	Final Analysis
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1. LIST OF ABBREVIATIONS

AE	Adverse event
AE-QoL	Angioedema Quality of Life Questionnaire
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic chemical
BLQ	Below the limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C1-INH	C1-inhibitor
CI	Confidence interval
CO2	Carbon dioxide
CPK	Creatine phosphokinase
CSR	Clinical study report
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data Safety Monitoring Board
EC	Ethics committee
ECG	Electrocardiogram
EQ5D	EuroQoL Group 5-Dimension
eCRF	Electronic case report form
EDC	Electronic data capture
FWER	Family-wise type I error rate
GEE	Generalized estimating equations
GLM	Generalized linear model
HAARP	HAE Attack Assessment and Reporting Procedures
HAE	Hereditary angioedema
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
ITT	Intent-to-treat
IWRS	Interactive web-based randomization system
KM	Kaplan-Meier

LS	Least squares
LTP	Long-term prophylaxis
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Prothrombin time
PT	Preferred term
QOL	Quality of life
RBC	Red blood cell
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SMQ	Standardized MedDRA Queries
SOC	System organ class
TEAE	Treatment-emergent adverse event
VAS	Visual analog scale
WBC	White blood cell
WHO-DD	World Health Organization-Drug Dictionary

2. INTRODUCTION

2.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is being developed after review of DX-2930-03 protocol, but before database lock and unblinding of treatment assignment. This SAP contains detailed information to aid in the implementation of the statistical analysis and reporting of the study data for use in the clinical study report (CSR). This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline, entitled Guidance for Industry: Statistical Principles for Clinical Trials, and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the analysis sets that will be used for analysis, as well as subject characteristics, efficacy, safety, pharmacokinetic (PK), pharmacodynamic (PD), and quality of life (QoL) parameters. The details of the specific statistical methods as stated in the protocol will be provided and any changes from the protocol-specified analyses will be documented in the SAP prior to database lock. If additional analyses are required to supplement the planned analyses described in this SAP after the database lock, they may be completed and will be described in the CSR. Table, figure, and listing specifications are provided in separate documents.

2.2 Background

DX-2390-03 is a Phase 3, randomized, double-blind, placebo-controlled, multicenter clinical study evaluating the safety and efficacy of DX-2930 as a treatment for the prevention of hereditary angioedema (HAE) attacks. Details of the study design, rationale, and procedures are documented in Protocol DX-2390-03 Amendment 2.0.

2.3 Study Rationale

DX-2930 is a fully human IgG1 recombinant monoclonal antibody that binds specifically to active plasma kallikrein. DX-2930 is being developed for prophylactic treatment of angioedema attacks in patients with HAE, a serious and life-threatening disease.

3. STUDY OBJECTIVES

3.1 Primary Objectives

To evaluate the efficacy of DX-2930 in preventing HAE attacks.

3.2 Secondary Objectives

To evaluate the safety of repeated subcutaneous administrations of DX-2930.

3.3 Tertiary Objectives

- To evaluate the pharmacodynamic (PD) effects of chronically administered DX-2930
- To assess the immunogenicity of chronically administered DX-2930
- To evaluate the pharmacokinetics (PK) of chronically administered DX-2930
- To evaluate the effect of DX-2930 on health related quality of life (QoL)

4. STUDY DESIGN

4.1 General Description

This study is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of DX-2930 in preventing acute angioedema attacks in subjects with Type I and Type II HAE. This double-blind study is planned to be followed by an open-label extension (OLE) that is described in a separate protocol (Protocol DX-2930-04).

A figure showing dosing is in Appendix 10.3. A table showing the Study Activities Schedule for the study is provided in Appendix 10.4.

Long-Term Prophylactic (LTP) Therapy Washout:

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2-week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm the subject has successfully completed the 2-week washout period before they can enter the run-in period.

Run-In Period:

Screened subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period, will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. Only subjects meeting a minimum baseline rate of at least 1 investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 investigator-confirmed attacks to proceed to enrollment and randomization. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered screen failures. Subjects who fail screening will not be allowed to rescreen into the study.

Treatment Period:

After verification of eligibility, subjects will be randomized 2:1 to receive repeated subcutaneous (SC) administrations of DX-2930 or placebo in a double-blind fashion. Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to 1 of 3 dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks, or 150 mg every 4 weeks. Randomization into all treatment groups will be stratified by the baseline attack rate observed during the run-in period into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks.

Each subject will undergo a treatment period consisting of 13 doses of blinded Investigational Medicinal Product (IMP), for a period of 26 weeks from the date of first dose on Day 0 through

two weeks after the final dose. Subjects randomized to one of the 4 treatment arms will either receive a DX-2930 or placebo dose according to the dosing schedule in Appendix 10.3.

Open-Label Extension (OLE) Study:

Subjects who complete the treatment period will be offered the option of enrolling in an open-label extension (OLE) study that will be described in a separate protocol (DX-2930-04).

Follow-up Period:

Subjects who do not participate in the OLE will undergo safety and additional evaluations (i.e., PK and PD) during an 8 week follow-up period. Subjects (or caregivers) will be instructed to inform the site of any HAE attacks they experience for up to 30 days after the final follow-up visit.

4.2 Discussion of Study Design, Including the Choice of Control Group

This study is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of DX-2930 in preventing acute angioedema attacks in subjects with Type I and Type II HAE. The following is a discussion of the rationale behind the design of the trial.

- **Primary endpoint selection**: The objective of this study is to evaluate the efficacy of DX-2930 in preventing HAE attacks. The number of HAE attacks is a direct way to evaluate efficacy.

- **Dose selection:** The dose rationale is based on the pharmacodynamic bioactivity, PK, safety, and efficacy of DX-2930 from the Phase 1 clinical studies and nonclinical studies. Together, these attributes provide the rationale for the selected doses and regimens to achieve drug levels likely to prevent a majority of HAE attacks. Based on these considerations, 300 mg every 2 weeks, 300 mg every 4 weeks, and 150 mg every 4 weeks were identified as the dosing regimens for evaluation. The 3 proposed dose-regimen combinations provide a 6-fold range of steady-state trough concentrations and leverage both the biomarker and efficacy data generated in study DX-2930-02. Evaluation of the DX-2930 plasma concentrations at the time of attacks reported by DX-2930-treated subjects in DX-2930-02 suggests that the 3 planned dosing regimens will provide a meaningful range of clinical response.

- **Control group selection:** This trial incorporates a placebo comparator to evaluate and interpret the efficacy of DX-2930. The use of placebo is justified because 1) placebo does not represent a reduction in current standard of care for subjects due to the availability of acute attack treatments and 2) none of the therapies currently used for the prevention of HAE attacks are suitable for use as an active comparator.

- **Study population:** Subjects 12 years of age and older with a confirmed diagnosis of HAE (Type I or II) who experience at least 1 investigator-confirmed attack per 4 weeks during the run-in period. HAE diagnosis will be confirmed through documented clinical history consistent with HAE and diagnostic testing conducted during the screening visit.

- **Baseline symptom severity:** To be eligible to participate in the study, subjects had to meet a minimum baseline HAE attack rate of at least 1 investigator-confirmed HAE attack per 4 weeks during the run-in period.

- **Stratified randomization:** Randomization to treatment is stratified by the baseline HAE attack rate observed during the run-in period. The three levels of HAE attack rate strata are 1-<2 attacks per 4 weeks, 2-<3 attacks per 4 weeks and 3 or more attacks per 4 weeks.

- **Safety monitoring:** Adverse events (AE), clinical laboratories and vital signs will be monitored throughout the study.

4.3 Method of Assigning Subjects to Treatment Regimens

Subjects will be randomized after confirmation of study eligibility in a 2:1 ratio to receive repeated SC administrations of DX-2930 or placebo in a double-blind fashion via an Interactive Web-based Randomization System (IWRS). Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to 1 of 3 dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks, or 150 mg every 4 weeks. Randomization into all treatment groups will be stratified by the baseline attack rate observed during the run-in period into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks.

4.4 Blinding

Subjects will be randomized to receive 300 mg DX-2930 every 2 weeks, 300 mg DX-2930 every 4 weeks, 150 mg DX-2930 every 4 weeks or placebo every 2 weeks in a double-blind fashion. The appearance of the placebo will be indistinguishable from DX-2390. Subjects, caregivers for subjects under 18 years of age, Investigators and site personnel will be blinded to the treatment administered until the study is complete. The Sponsor will be blinded to the treatment administered until all subject involvement in the treatment period is complete, the database has locked, and primary statistical analyses have been conducted.

An Unblinded Data Team Charter will be developed to document which roles will have access to which data and their responsibilities. The Unblinded Data Team is independent from the blinded study team and is not involved in the day-to-day conduct of the study.

4.5 Sample Size Determination

Power analysis and sample size estimation was based on 1000 computer simulations using a generalized linear model for count data assuming a Poisson distribution with Pearson chi-square scaling of standard errors to account for potential overdispersion. The active treatment dose in each active treatment arm to placebo ratio was set at 1:1.5. A 10% missing data/dropout rate for both active treatment and placebo was also built into the empirical sample size simulations.

For a treatment effect of 60% reduction in attacks as compared to placebo, assuming a placebo attack rate of 0.3 attacks per week over a 26 week period for an average total of 7.8 attacks during the treatment period, a sample size of 24 actively treated subjects for the primary active treatment arm and 36 placebo subjects would provide at least 95% power (at alpha=0.025, one-sided). A 60% reduction is well below the smallest expected reduction in attacks, for in the DX-2930-02 study, we observed reductions of attacks of near 100%. These sample sizes will also provide adequately sized safety population for evaluation. Up to 120 subjects (approximately 80 subjects in the 3 active treatment groups and 40 in the placebo group) may be enrolled to account for potential early drop-outs during the study.

5. EFFICACY AND SAFETY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoint

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

5.1.2 Secondary Efficacy Endpoints

- Number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period.
- Number of moderate or severe investigator-confirmed HAE attacks during the treatment period.

5.1.3 Exploratory Efficacy Endpoints

- Time to first HAE attack after Day 14.
- Number of high-morbidity investigator-confirmed HAE attacks during the treatment period.
- Number of investigator-confirmed HAE attacks resulting in an emergency department visit and/or admission to hospital during the Treatment Period.
- Achievement of a reduction from the baseline in the investigator-confirmed HAE attack rate (i.e., responder analysis).
- Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, location, and medication use.
- Percentage of attack free days.

5.2 Safety Endpoints

The safety and tolerability of DX-2390 will be evaluated through the assessment of adverse events, clinical laboratory testing, vital sign measurements, electrocardiogram (ECG) recordings, concomitant medications and physical examination findings.

5.3 Other Endpoints

Additional endpoints of interest in this study are the plasma concentration of DX-2930, pharmacodynamic biomarker assays, anti-drug antibodies and quality of life data as collected with the EuroQoL Group 5-Dimension (EQ5D) Questionnaire and the Angioedema Quality of Life (AE-QoL) Questionnaire.

6. EFFICACY AND SAFETY VARIABLES

6.1 Study Activities Schedule

Please refer to Appendix 10.4 for details of assessments performed at each visit.

6.2 Efficacy Assessments

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

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

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

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

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

Sites personal will also record the severity of the attack, if the attack required acute treatment, if the attack resulted in an emergency department visit or hospitalization, if the attack was hemodynamically significant (systolic blood pressure < 90, requires IV hydration, or associated with syncope or near-syncope) and whether the attack was peripheral, abdominal or laryngeal.

In this study HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to study drug, will be recorded on the AE page of the eCRF. Any AE reported to the site meeting criteria for a serious adverse event must be reported to the Sponsor using the SAE Reporting Form in the electronic data capture (EDC) system within 24 hours of becoming aware of the event. For all serious adverse events that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. For all non-serious AEs that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 3 days of initial notification and, in accordance with

HAARP, evaluate if it represented a confirmed HAE attack. If necessary for the evaluation, the Investigator or designee may contact the subject for additional information. Any subject-reported attack not confirmed by the Investigator must have an alternate AE diagnosis recorded. All subject-reported and investigator-confirmed HAE attacks will be recorded in the eCRF.

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

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

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

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

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

6.3 Safety Assessments

6.3.1 Adverse Events

Adverse events will be collected from signing of the informed consent through the last study visit. For a detailed definition on AEs, Serious AEs (SAEs), severity of AEs, and relatedness of AEs and SAEs, please refer to the protocol.

An AE is treatment-emergent if the onset time is after first administration of IMP or, in the event that onset time precedes first IMP administration, the AE increases in severity after first administration of IMP.

In this study, the severity of AEs will be assessed according to Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases) and the Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Table, Draft, November 2007 (US National Institutes of Health: National Institute of Allergy and Infectious Diseases). For abnormalities not specifically found in the Toxicity Tables, the following general scale will be used to estimate grade of severity:

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

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

The causal relationship between the study IMP and the AE will be assessed as Not Related or Related.

6.3.1.1 Adverse Events of Special Interest

Adverse events of special interest (AESI) will be captured and monitored during this study. AESI include hypersensitivity reactions and events of disordered coagulation.

Hypersensitivity Reactions

As hypersensitivity reactions have been observed for monoclonal antibodies as a class, these events are considered AESI for this study. Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with hypersensitivity reactions, regardless of causality, within 24 hours from the time of study drug administration. Investigators will report hypersensitivity reactions that occur after 24 hours, only if the reactions are suspected to be related to study drug.

Events of Disordered Coagulation

Bleeding AESI

Although aPTT prolongation due to plasma kallikrein inhibition is an artifactual *in vitro* phenomenon, as a precautionary measure in evaluating the safety of DX-2930, bleeding events will be reported as AESI for this study. Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with a clinical event of bleeding. Coagulation testing (aPTT, PT, INR) should be performed when possible, and when temporally reasonable, with any reports of bleeding or for clinical conditions possibly indicative of bleeding.

Hypercoagulable AESI

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

6.3.2 Vital Signs

Vital signs will be assessed by the Investigator or his/her qualified designee according to the Study Activities Schedule (Appendix 10.4). Routine vital sign assessments will be taken with the subject in the sitting or supine position after 5 minutes at rest and will include body temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR). BP should be determined using the same arm and the same equipment for each assessment. There is a ±15 minute window for all vital signs.

At study visits in which IMP is administered, vital signs will be obtained prior to dosing, 1 hour after dosing, and 2 hours after dosing for the first 4 doses with the ability to eliminate the 2 hour vitals for the remaining doses based on the discretion of the Investigator and the absence of safety signals.

6.3.3 Physical Examination

A physical examination including height, weight and calculation of Body Mass Index (BMI) will be performed by the Investigator or his/her qualified designee according to the Study Activities Schedule (Appendix 10.4). Height and weight will be collected at the screening visit only.

6.3.4 Electrocardiogram (ECG)

A standard 12-lead ECG (single recording) will be performed at screening, baseline prior to Dose 1, Day 56, and Day 144±1 day (to capture the estimated C_{max}), and Day 182. The ECG assessment at C_{max} on Day 144±1 day may be performed via at-home nurse or technician in lieu of a subject visit to the study site. For subjects that do not rollover into OLE (DX-2930-04), an ECG will be performed on Day 238. The date and time of each ECG and its results will be documented in the source documents and eCRF. Electrocardiograms will be sent to a central reading vendor for assessment.

6.3.5 Clinical Laboratories

Laboratory testing will be performed according to the Study Activities Schedule (Appendix 10.4).

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

6.3.5.1 Hematology

- Hemoglobin
- Hematocrit
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Absolute platelet count

6.3.5.2 Coagulation

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

6.3.5.3 Chemistry

- Albumin
- Alkaline phosphatase
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Bilirubin (total and direct)
- Blood urea nitrogen (BUN)
- Calcium
- Carbon dioxide (CO2)
- Chloride
- Creatinine
- Creatine phosphokinase (CPK)
- Glucose
- Phosphate
- Magnesium
- Potassium
- Sodium
- Total protein
- Uric acid

6.3.5.4 Urinalysis

- Bilirubin
- Glucose
- Ketones
- Blood

- Nitrite
- pH
- Protein
- Specific gravity
- Microscopy (if indicated by macroscopic findings)

6.3.6 Concomitant Therapies

The Sponsor representatives and Investigator at the site conducting the trial will review and evaluate prior and concomitant medication usage on an ongoing basis. All prescription, over-the-counter medications, herbals, and supplements that are being taken or have been taken by subjects from the time of screening through the duration of the study will be regarded as concomitant medications and must be documented in the source documents and eCRF.

6.4 Other Assessments

6.4.1 Pharmacokinetic Assessment

Blood samples for the measurement of plasma DX-2930 concentration will be obtained at pre-dose on Days 0, 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3 and 238±3 during the follow-up period for any subjects not entering OLE.

6.4.2 Pharmacodynamic Assessment

To evaluate the PD effects of DX-2930 upon plasma kallikrein activity, blood samples will be obtained at pre-dose on Days 0, 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3 and 238±3 during the follow-up period for any subjects not entering OLE.

6.4.3 Plasma Anti-Drug Antibody Testing

Plasma samples for testing for formation of antibodies to DX-2930 will be obtained at pre-dose on Days 0, 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 238±3 during the follow-up period for any subjects not entering OLE.

6.4.4 Quality of Life Assessments

Quality of life data will be obtained using the EuroQoL Group 5-Dimension (EQ5D) Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using Angioedema Quality of Life (AE-QoL) Questionnaire at pre-dose on Days 0, 28 ±3, 56 ±3, 98±3, 126 ±3, 154 ±3, and 182±3. An additional quality of life assessment will be conducted on Day 238±3 for subjects not entering OLE.

ED-5D-5L

The EQ-5D-5L consists of 2 parts: descriptive questions and a visual analog scale (VAS). The descriptive questions comprise 5 dimensions: Mobility, Self-care, Usual activities, Pain/discomfort, and Anxiety/depression. Each dimension is divided into 5 levels of perceived problems: no problems, slight problems, moderate problems, severe problems, and extreme problems. The VAS records the subject's self-rated health on a 20-cm vertical VAS with endpoints labelled "the best health you can imagine" and "the worst health you can imagine".

AE-QoL

The AE-QoL consists of 4 domains (functioning, fatigue/mood, fears/shame and nutrition) and 17 questions. Details of how to compute scores for the domains and the total score are included in Appendix 10.2.14.

7. STATISTICAL ANALYSIS

7.1 General Methodology

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, PPD, PPD, USA).

Unless otherwise specified, summary tabulations will be presented by treatment group (DX-2930 300 mg every 2 weeks, DX-2930 300 mg every 4 weeks, DX-2930 150 mg every 4 weeks, and Placebo). All data listings will be sorted by treatment group, site, and subject number, and will include the subject's age, sex, and race.

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, standard deviation (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.

Formal statistical hypothesis testing will be performed on the primary and rank ordered secondary efficacy endpoints with the global family-wise type I error rate (FWER) strongly controlled at two-sided 0.05 using a Bonferroni-based general gatekeeping procedure as described in Section 9.5.

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.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. The denominator for all percentages will be the number of subjects for that treatment group within the population of interest, unless otherwise specified.

See Section 10.2 for detailed descriptions of analysis definitions and programming conventions.

7.2 Analysis Populations

The analysis populations will be defined as follows:

7.2.1 Intent-to-treat (ITT) Population

The ITT Population will include all randomized subjects who received any study drug. The primary efficacy analyses will be carried out with the ITT Population. Subjects will be analyzed according to their randomized treatment assignment regardless of the treatment actually received.

7.2.2 Safety Population

The Safety Population will include all subjects who received any study drug. All safety analyses will use the Safety Population. Subjects will be analyzed according to the treatment actually received, regardless of the treatment assigned.

7.3 Subject Disposition

The number of subjects screened, randomized, treated with study drug, completed the study and discontinued prematurely by reason will be summarized overall and by randomized treatment assignment for all subjects. For each analysis population, the number of subjects included in the population, completing the study and those that discontinued prematurely by reason, will be summarized by treatment group, overall DX-2930, and overall. Listings of all disposition data will be provided.

7.4 Protocol Deviations

Protocol deviations will be collected at both the site and subject level.

Deviations at the site level will be applied to all subjects who were enrolled at that site at the time of the deviation. Deviation types for site level deviations are: Use of incorrect equipment, use of incorrect forms, use of expired laboratory samples, use of equipment with expired maintenance, study procedure completed by non-authorized personnel, site personnel did not complete training prior to completing study procedure, amendment implementation without approval/notification or IRB/EC, temperature excursion for IP and other.

Deviation types for subject level deviations are: eligibility criteria, informed consent/assent/HIPAA, concomitant medication, investigational product, study visit (missed/out of window), study procedure (missed/out of window), site personnel/assessor error, randomization, safety reporting, IRB/EC reporting, EQ-5D, Angioedema Quality of Life, lab collection, and other (not otherwise defined).

Summary tables of protocol deviation type by treatment group, overall DX-2930, and overall will be provided for the ITT Population. All protocol deviations will be included in a subject listing.

7.5 Demographic and Other Baseline Characteristics

Baseline and demographic variables will be descriptively summarized by treatment group, overall DX-2930, and overall for each analysis population.

Demographic variables to be presented include age (years), age category (<18, 18 to <40, 40 to <65, ≥65 years), sex (male, female), ethnicity (Hispanic, Non-Hispanic), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White and Other), race group (White, Other) geographical region (US, Canada, Europe and Jordan), height (cm), weight (kg), weight group (<50, 50 to <75, 75 to <100, ≥100 kg), BMI (kg/m^2) and BMI group (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2).

A separate table will be created for baseline characteristics and will include age at onset of angioedema symptoms, HAE type (Type I, Type II, Unspecified), history of laryngeal attacks, primary attack locations, number of attacks in the last 1, 3, and 12 months, baseline HAE attack rate (attacks/4 weeks) and baseline HAE attack rate strata (1 to <2, 2 to <3, ≥3 attacks/4 weeks). All baseline and demographic data will be presented in subject listings.

7.6 Medical History

Medical history will be coded using Medical Dictionary for regulatory Activities (MedDRA) version 18.1 and summarized by system organ class (SOC) and preferred term (PT) by treatment group, overall DX-2930 and overall for each analysis population. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency. All medical history will be presented in subject listings.

7.7 Treatment Compliance and Extent of Exposure

All planned study drug administrations will be recorded in the case report form, including whether a full, partial, or no dose was given; date and time of dose; and location of the injection. Regardless of treatment assignment, all subjects are to receive two injections of blinded study drug given in the same upper arm, with at least 2 cm separation between each injection site.

It is anticipated that all subjects will be compliant with treatment because the study drug will be administered by qualified site personnel. Treatment compliance and the extent of exposure 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 that received at least 80% of planned doses, summarized by treatment group for each analysis population. Listings of study administrations by subject will also be provided.

7.8 Analysis of Efficacy

All efficacy analyses will be performed on the ITT Population.

7.8.1 Primary Efficacy Analysis

The primary efficacy endpoint, number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182), will be compared for each active treatment group

(DX-2930) to the placebo group 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) and the normalized baseline attack rate (continuous), and 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 10.2.9.1 for the calculation of the normalized baseline attack rate.

From this model, the least squares mean rate and standard error for each treatment group as well as, the mean rate ratios relative to the placebo group and corresponding 95% confidence intervals for each active treatment group will be estimated. These estimates will be reported as mean event rates per unit of time (week and monthly) 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:

$$H_0: \lambda_{DX\text{-}2930} / \lambda_{placebo} = 1 \text{ versus } H_1: \lambda_{DX\text{-}2930} / \lambda_{placebo} \neq 1$$

$\lambda_{DX\text{-}2930}$ refers to the mean investigator-confirmed HAE attack rate in the DX-2930 group and $\lambda_{Placebo}$ refers to the mean investigator-confirmed HAE attack rate in the placebo group. The null hypothesis is that the mean investigator-confirmed HAE attack rate ratio is 1 (no difference between treatment groups), versus the alternative hypothesis that the HAE attack rate ratio is not 1. Estimated attack rate ratios less than one would indicate that subjects treated with DX-2930, on average, have a lower incidence of investigator-confirmed HAE attacks during the treatment period. The hypothesis will be tested using the model-based least squares means estimate of the treatment difference using a Wald-based chi-square test.

The percentage difference in mean investigator-confirmed HAE attack rate of each active treatment group 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 ratios and corresponding 95% confidence intervals will be estimated from the generalized linear model as described previously.

In order to maintain the overall Type I error at 0.05, a conservative Bonferroni-based procedure will be used for the comparisons of each of the active treatment groups with the placebo group with equal weights for each test set at 1.67% significance level ($\alpha/3$). See Section 9.5 for more information.

Unadjusted monthly investigator-confirmed HAE attack rates will be calculated for the pretreatment, run-in and treatment periods. See Section 10.2.9 for details. The pretreatment period, run-in period, treatment period, treatment period change from baseline, and treatment period change from run-in period in the monthly investigator-confirmed HAE attack rate will be summarized by treatment group. This summary will include the total number of investigator-confirmed HAE attacks reported and the subject-time in months each subject contributed to the pretreatment, run-in period, and treatment period. Figures by treatment group (one for each

treatment group) plotting the on-study investigator-confirmed HAE attacks reported during the treatment period relative to randomization for each subject will be created.

In addition to the data summaries for the primary analysis of the primary efficacy endpoint described above, the number of investigator-confirmed HAE 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 number, change from pretreatment, and percent change from pretreatment of investigator-confirmed HAE attacks. Investigator-confirmed HAE attacks will be grouped into 28-day intervals using the start date of the HAE 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 10.2.6.1 for the definition of the pretreatment period.

All HAE attacks will be presented in listings.

7.8.2 Secondary Efficacy Analyses

The rank ordered secondary efficacy endpoints are as follows:

1. Number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period.
2. Number of moderate or severe investigator-confirmed HAE attacks during the treatment period.

The secondary endpoints 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.

To adjust for the potential of inflated overall type-I error rate, the rank ordered secondary endpoints will be tested in a fixed sequence for each active treatment group to placebo group comparison 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 for that active treatment group to placebo group comparison is found to be statistically significant. See Section 9.5 for more information.

7.8.3 Exploratory Efficacy Analyses

Exploratory analyses will include data summaries for the following:

- Time to first HAE attack after Day 14, i.e., duration that a subject is attack free after Day 14
- Number of high-morbidity investigator-confirmed HAE attacks during the treatment period.
- Number of investigator-confirmed HAE attacks resulting in an emergency department visit or admission to the hospital.
- Number of investigator-confirmed HAE attacks resulting in an emergency department visit.
- Number of investigator-confirmed HAE attacks resulting in admission to the hospital.

- Achievement of a reduction from pretreatment in the investigator-confirmed HAE attack rate (i.e., responder analysis).
- Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, and rescue mediation use.
- Percentage of attack free days

The exploratory efficacy 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.

Time to first HAE attack after Day 14

The time to first HAE attack (days) will be calculated from the date of Day 14 visit to the date of the first attack after Day 14 visit. Subjects who do not have an attack will be censored at the date of discontinuation or completion of the study (Day 182 for subjects who do not roll-over into the OLE). Time to the first HAE attack after Day 14 will be summarized using Kaplan-Meier methods. A log-rank test comparing each active treatment group to the placebo group will be included.

Number of high-morbidity investigator-confirmed HAE attacks

A high-morbidity HAE 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 HAE attacks during the treatment period 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 HAE attacks resulting in an emergency department visit or admission to the hospital

For each HAE 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 HAE attacks resulting in an emergency department visit or admission to the hospital during the treatment period 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 HAE attacks resulting in an emergency department visit

For each HAE attack, the site records if the attack resulted in a visit to the emergency department. The number of investigator-confirmed HAE attacks resulting in an emergency department visit during the treatment period 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 HAE attacks resulting in admission to the hospital

For each HAE attack, the site records if the attack resulted in hospitalization. The number of investigator-confirmed HAE attacks resulting in admission to the hospital during the treatment period 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.

Achievement of reduction from pretreatment in the investigator-confirmed HAE attack rate (i.e., responder analysis)

There will be five classes of responders based on percent reduction in the investigator-confirmed HAE attack rate from the pretreatment attack rate: 50% or more reduction, 60% or more reduction, 70% or more reduction, 80% or more reduction and 90% or more reduction. For each subject, a treatment period HAE attack rate and pretreatment HAE attack rate will be calculated. See Section 10.2.9 for details. The percentage reduction will be calculated as the pretreatment HAE attack rate minus the treatment period HAE attack rate divided by the pretreatment HAE attack rate. Summary statistics will be presented for each of the five classes of responders by treatment. The five classes of responders are nested and not mutually exclusive.

Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, location and mediation use

Attack characteristics, as described below, will be summarized by treatment group and overall DX-2930 for the pretreatment period and treatment period.

HAE Attack Duration

For each subject, the mean, minimum and maximum duration of all investigator-confirmed HAE attacks will be calculated in hours and summarized. See Section 10.2.7.1 for details. 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).

HAE Attack Severity

For each subject, the mean and maximum severity of all investigator-confirmed HAE attacks will be calculated using a numerical rating and summarized. See Section 10.2.7.2 for details. The number and percentage of subjects, as well as the number of events, will be tabulated by attack severity (mild, moderate, and severe).

HAE Attack Location

The number and percentage of subjects with attacks, as well as the number of events, will be tabulated by attack location (peripheral, abdominal, and laryngeal).

Rescue Medication Use

The number and percentage of subjects with rescue medication use for an HAE attack, as well as the number of events, will be tabulated by rescue medication by type (ecallantide, icatibant, nano-filtered C1-INH, plasma-derived C1-INH, recombinant C1-INH, fresh frozen plasma, and other).

Supportive Treatment Use

The number and percentage of subjects with supportive treatment use for an HAE 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).

Percentage of HAE attack free days

The percentage of HAE attack free days will be calculated by counting the number of days in the treatment period without an HAE attack and dividing by the number of days the subject was in the treatment period. If an HAE attack was 8 hours or less on a particular day that day will be considered attack-free. Summaries of the percentage of HAE attack free days will be provided by treatment group.

7.9 Analysis of Safety

All safety analyses will be performed on the Safety Population. No inferential statistics are planned.

7.9.1 Adverse Events

Adverse events (AEs) will be coded using the MedDRA coding dictionary version 18.1.

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

The analyses described in this section will be based on treatment-emergent AEs; plainly referred to as AEs in this section for brevity.

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

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).

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, and any related severe AE will 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 and overall DX-2930. This tabulation will be repeated for each of the analysis periods.

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized for each treatment group and overall DX-2930 by SOC, and PT for each analysis period. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, and related severe AEs for treatment period and follow-up period AEs. This tabulation will be repeated for SAEs for pretreatment period. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the overall DX-2930 group and then the placebo group.

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized for each treatment group and overall DX-2930 by PT for treatment period AEs only. This tabulation will be repeated for related AEs and serious AEs for treatment period AEs. Tabulations will be presented sorted by PT by descending frequency in the overall DX-2930 group and then the placebo group.

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

Adverse events of special interest (AESI) for this study are hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events). Standardized MedDRA Queries (SMQ) for each AESI will be performed using the study data. The number and percentage of subjects with an AESI, as well as the total number of AESIs, will be summarized for each treatment group and overall DX-2930 by SOC and PT. Separate summary tables will be created for each AESI and for those events with the SMQs classified as related, serious, related serious, severe, and related severe. A listing detailing the PT within the SMQ will be provided.

7.9.2 Clinical Laboratory Evaluation

Laboratory test results will be presented in conventional units.

Baseline is defined as the last non-missing value prior to the first exposure to study drug.

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

Actual values and changes from baseline in clinical laboratory tests for hematology, coagulation, chemistries, and urinalysis will be summarized for each treatment group and overall DX-2930 by study visit. If more than one laboratory result is reported per study visit per parameter, the last non-missing result will be selected for analysis. All laboratory results will be presented in subject listings.

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. The number of subjects with a non-missing result, and the number and percentage of subjects with a clinically significant result less than the lower limit of normal, non-clinically significant result less than the lower limit of normal, within the normal range, non-clinically significant result more than the upper limit of normal, and clinically significant result more than the upper limit of normal will be summarized for each treatment group and overall DX-2930 by study visit. If more than one laboratory result is reported per study visit per parameter, the result yielding the most severe classification will be selected for analysis.

Categorical laboratory test results (urinalysis excluding pH) will be summarized for treatment group and overall DX-2930 by study visit. If more than one laboratory result is reported per study visit per parameter, the result yielding the most severe classification will be selected for analysis.

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

7.9.3 Vital Signs

Baseline is defined as the last non-missing value prior to the first exposure to study drug.

Actual values and changes from baseline in vital signs will be summarized for each treatment group and DX-2930 overall by study visit and study time point. All vital sign data will be presented in subject listings.

Vital sign values will be classified according to clinical significance as determined by the investigator. The number of subjects with a non-missing result, and the number and percentage of subjects with a non-clinically significant result and clinically significant result will be summarized for each treatment group and overall DX-2930 by study visit and study time point. If more than one vital sign result is reported per study visit and study time point per parameter, the result yielding the most severe classification will be selected for analysis. Subjects with clinically significant vital sign values will be listed. This listing will include all results of the vital sign parameter that was determined by the investigator to be clinically significant for a subject across study time points to identify any trends.

7.9.4 Electrocardiography

The number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECG results, or ECG not performed, will be summarized for each treatment group and overall DX-2930 by study visit. Subjects with clinically significant ECG results will be listed. This listing will include all results for a subject across study time points to identify any trends.

All ECG data will be provided in subject listings.

7.9.5 Physical Examinations

Physical examination findings by body system will be classified as normal, abnormal not clinically significant, abnormal clinically significant or not performed by the investigator and will be summarized for each treatment group and DX-2930 overall by study visit. Subjects with clinically significant abnormal physical examination findings will be listed. This listing will include all results of the body system that was determined by the investigator to be clinically significant for a subject across study time points to identify any trends.

All physical examination findings will be provided in subject listings.

7.9.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) Version 2015 Q3.

Prior medications are defined as medications with start and stop times at or prior to the time of study drug administration.

Concomitant medications are defined as medications with a start times after the time of study drug administration or medications with a start times prior to study drug administration but continuing after treatment.

For medications with partial onset times, non-missing date parts will be used to determine if the medication is concomitant or prior medication. If a determination cannot be made using the non-missing date parts as to when the medication occurred relative to study drug administration then the medication will be classified as concomitant medication.

The number and percentage of subjects with prior or concomitant medications will be summarized for each treatment group and overall DX-2930 by therapeutic class and preferred term. Therapeutic class will be based on the Therapeutic Subgroup corresponding to level 2 of the Anatomic Therapeutic Chemical (ATC) classification system. Tabulations will be presented sorted by therapeutic class in alphabetical order and by PT within each therapeutic class by descending frequency in the overall DX-2930 group and then the placebo group. A separate similar table will be provided for rescue medications. All medications will be presented in subject listings.

7.10 Other Analyses

Additional analyses of pharmacokinetic (PK) and pharmacodynamic (PD) data will be described in a separate PK/PD report.

Additional analysis of quality of life (QoL) data will be described in a separate QoL report.

7.10.1 Analysis of Pharmacokinetic Data

Plasma concentrations of DX-2930 will be summarized for each treatment group by nominal PK sampling time and listed by subject using the Safety Population.

Plasma concentrations reported as BLQ (below the limit of quantification) of the assay will be reported as zero in the data listings, and BLQ concentrations are treated as zero in the calculation of summary statistics.

7.10.2 Analysis of Pharmacodynamic Data

Plasma kallikrein activity will be summarized for each treatment group by nominal PD sampling time and listed by subject using the Safety Population.

7.10.3 Analysis of Immunogenicity Data

The number and percentage of positive antibodies will be summarized for each treatment group and DX-2930 overall by study visit and overall and listed by subject using the Safety Population.

7.10.4 Analysis of Quality of Life Data

The number and percentage of subjects at each level of the EQ-5D-5L dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) for each treatment group and DX-2930 overall by study visit using the Safety Population. In addition, the VAS score for the subject's self-rated health will be summarized for each treatment group and DX-2930 overall by study visit using the Safety Population.

The responses to the AE-QoL for each item will be tabulated for each treatment group and DX-2930 overall by study visit using the Safety Population. In addition, the domain scores (functioning, fatigue/mood, fears/shame, nutrition) and total score will be summarized for each treatment group and DX-2930 overall by study visit using the Safety Population.

All QoL data will be provided in subject listings.

8. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

8.1 Changes in the Conduct of the Study

There was no change in the conduct of the study.

8.2 Change from the Analyses Planned in the Protocol

8.2.1 Efficacy Evaluation Period

The phase "Efficacy Evaluation Period" was used in the protocol to describe the time interval for which efficacy would be evaluated and was defined as Day 0 through Day 182. This phase was changed to treatment period for consistency with the Study Activities Schedule. The definition of the duration of the interval remains Day 0 through Day 182.

8.2.2 ITT and Safety Population Definitions

The definition of the ITT Population specified in the protocol stated that the population will include all randomized subjects who are administered at least 1 dose of active IMP or placebo. The definition in the SAP was modified from "at least 1 dose of active IMP or placebo" to "any exposure to study drug". This change was made to clarify that a subject did not need to receive the full dose to be included in this analysis population, but that subjects receiving partial doses would be included.

A similar modification was applied to the definition of the Safety Population.

8.2.3 Adverse Events

The protocol stated that incidence of AEs and rate of study discontinuation among the four treatments arms would be compared, the SAP clarified that this comparison would be based on descriptive statistics.

Additionally, the analysis of the incidence of AEs by month from start of study drug was omitted. Because subjects are repeatedly exposed to study drug on at least a monthly basis, it is not expected that the type or frequency of AE would vary by month.

8.2.4 Laboratory Parameters

The protocol specified that for laboratory parameters the change from screening would be summarized. Instead, a change from baseline will be summarized and a definition of baseline was included in the SAP.

The protocol specified that laboratory parameters would be summarized using shift tables. This summary was omitted and replaced with a summary of results based on reference ranges and clinical significance as determined by the investigator.

8.2.5 Vital Sign Parameters

The protocol specified that for vital sign parameters the change from screening would be summarized. Instead, a change from baseline will be summarized and a definition of baseline was included in the SAP.

9. STATISTICAL/ANALYTIC ISSUES

9.1 Adjustment for covariates

The analysis of the primary and secondary efficacy adjusts for the normalized pretreatment HAE attack rate. No additional covariate adjustment is planned.

9.2 Handling of Dropouts or Missing Data

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

9.3 Interim Analysis and Data Monitoring

No interim analyses are planned. However, an independent Data Safety Monitoring Board (DSMB) 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 DSMB review will be conducted according to the DSMB Charter and DSMB SAP. Because no formal hypothesis testing for safety assessments is planned, multiplicity concerns regarding repeated analyses are not an issue.

9.4 Multicenter Studies

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

9.5 Multiple Comparisons/Multiplicity

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 7.8.2) will be controlled at 0.05. To strongly control the global FWER at this level, a general gatekeeping approach with branches for each active treatment group to placebo group comparison will be utilized in which each family of statistical tests will be conducted in a sequential manner. Specifically, a three-branch general gatekeeping procedure with three families of hypotheses will be defined as follows:

Family 1 (F_1): Hypothesis tests for the primary efficacy endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{11}, H_{12}, and H_{13}).

Family 2 (F_2): Hypothesis tests for the first ranked secondary endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{21}, H_{22}, and H_{23}).

Family 3 (F_3): Hypothesis tests for the second ranked secondary endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{31}, H_{32}, and H_{33}).

The 3 sets of hypotheses in F1, F2, and F3 will be tested in a fixed sequence within each active treatment group to placebo group comparison or branch. Testing within a branch 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 within the branch.

Within a family, hypotheses will be tested using a conservative Bonferroni-based procedure with equal weights for each test set at 1.67% significance level (α/3). If the null hypothesis for a test is rejected, α will be propagated entirely to the next test in the sequence, which will then be tested at the 1.67% significance level.

To further illustrate this approach, the test for the primary endpoint will be conducted first at the 1.67% significance level for each active treatment group compared with the placebo group and, if significant, the first secondary endpoint will be similarly tested at the 1.67% significance level. The testing sequence will continue in order through the remaining secondary endpoints for each active treatment group to placebo comparison or branch as long as the null hypothesis is rejected at the 1.67% significance level.

Testing within the last family (F3) will utilize the remaining α by applying the Holm-Bonferroni procedure.

9.6 Examination of Subgroups

Subgroup analyses are planned for the primary efficacy endpoint and adverse events. 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/m2)
- Run-in Period HAE Attack Rate (1 to <2, 2 to <3, ≥3 attacks/month)
- Pretreatment Period HAE Attack Rate (1 to <2, 2 to <3, ≥3 attacks/month)
- HAE Type (Type I, Type II, Unspecified)
- Geographic Region (US, Canada, Jordan, Europe)
- Type of Long-term Prophylactic Therapy Prior to Study Randomization (C1-INH, Androgens, Anti-fibrinolytics, Not on LTP)

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

9.7 Sensitivity Analyses

The following sensitivity analyses will be performed on the primary efficacy endpoint to evaluate the robustness of the results. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

1. The primary analysis will be repeated using the Safety Population. Subjects will be analyzed according to the treatment actually received. This analysis will only be presented if the Safety Population is different from the ITT Population or if subjects did not receive treatment as randomized.

2. The primary analysis will be repeated counting HAE attacks occurring on Day 14 after administration of study drug through Day 182, instead of Day 0 to Day 182.

3. The primary analysis will be repeated counting HAE attacks occurring on Day 7 after administration of study drug through Day 182, instead of Day 0 to Day 182.

4. The primary analysis will be repeated using all subject reported HAE attacks instead of limiting the analysis to those attacks that were investigator-confirmed.

5. The primary analysis will be repeated using a generalized estimating equations (GEE) analysis method counting HAE attacks occurring on Day 14 after administration of study drug through Day 182 in order to descriptively compare the results from this study with those from DX-2930-02 study. The methods for this analysis are listed below.

   HAE attack rates for each active treatment group will be compared to the placebo group using a mixed-model repeated measures (MMRM) analysis of covariance (ANCOVA) for count data (assuming a Poisson distribution with log link function) using GEE. The model will include a fixed effect for treatment (categorical), pretreatment period attack rate (continuous), and a random effect for subject.

   Repeated measurement analysis will be employed, with a 7-day time period (i.e., 168 hours) serving as the discrete unit of measurement. Subject weeks for which completed observation is less than the full 168 hours within a week will be treated as a full week if at least 3 or more days of data were recorded during the week. Weeks with fewer than 3 days will not be included.

   In the event that there are 0 events in one of the treatment groups, a small value of 0.000001 will be added in order to calculate event rates.

Additionally, as applicable, the following sensitivity analyses will be performed on secondary and exploratory efficacy endpoints as detailed in Table 1. Data summaries will parallel those described for the each of the endpoints.

Table 1: Sensitivity Analysis for Secondary and Exploratory Efficacy Endpoints

Secondary and Exploratory Efficacy Endpoint	Sensitivity Analysis Item				
	1	**2**	**3**	**4**	**5**
Number of HAE attacks requiring acute treatment	x	x	x	x	
Number of moderate or severe HAE attacks	x	x	x	x	
Time to first HAE attack	x		x	x	
Number of high-morbidity HAE attacks	x	x	x	x	
Number of HAE attacks resulting in visit to emergency department or admission to the hospital	x	x	x	x	
Number of HAE attacks resulting in visit to emergency department	x	x	x	x	
Number of HAE attacks resulting in admission to the hospital	x	x	x	x	
Responder Analysis	x	x	x	x	
Characteristics of HAE attacks	x	x	x	x	
Percentage of attack-free days	x	x	x	x	

10. APPENDICIES

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14.2.1.5	Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group and Age Group – ITT Population
14.2.1.6	Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group and Sex – ITT Population
14.2.1.7	Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group and Race Group – ITT Population
14.2.1.8	Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group and Weight Group – ITT Population
14.2.1.9	Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group and BMI Group – ITT Population
14.2.1.10	Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group and Run-in Period HAE Attack Rate Group – ITT Population
14.2.1.10	Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group and Pretreatment Period HAE Attack Rate Group – ITT Population
14.2.1.11	Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group and HAE Type – ITT Population
14.2.1.12	Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group and Geographic Region – ITT Population
14.2.1.12	Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group and Type of Long-term Prophylactic Therapy Prior to Study Randomization – ITT Population
14.2.2.1	Investigator-confirmed HAE Attacks Requiring Acute Treatment during the Treatment Period (Day 0 to Day 182) by Treatment Group – ITT Population
14.2.3.1	Moderate and Severe Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group – ITT Population
14.2.4.1	Time to First HAE Attack After Day 14 by Treatment Group – ITT Population
14.2.5.1	High-morbidity Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group – ITT Population
14.2.6.1	Investigator-confirmed HAE Attacks Requiring an Emergency Department Visit or Admission to the Hospital during the Treatment Period (Day 0 to Day 182) by Treatment Group – ITT Population
14.2.7.1	Investigator-confirmed HAE Attacks Requiring an Emergency Department Visit during the Treatment Period (Day 0 to Day 182) by Treatment Group – ITT Population
14.2.8.1	Investigator-confirmed HAE Attacks Requiring Admission to the Hospital during the Treatment Period (Day 0 to Day 182) by Treatment Group – ITT Population

14.2.9.1	Plot of Mean DX-2930 Concentration Over Time – PK Population

10.1.3 List of Planned Listings

Listing No.	Title
16.2.1	Disposition
16.2.2	Protocol Deviations
16.2.3.1	Analysis Populations
16.2.3.2	Inclusion and Exclusion Criteria
16.2.4.1	Demographics
16.2.4.2	Baseline Disease Characteristics
16.2.4.3	Medical History
16.2.4.4	Prior and Concomitant Medications
16.2.5.1	Study Drug Administration
16.2.5.2	Treatment Compliance and Exposure
16.2.6.1	HAE Attacks
16.2.6.2	Plasma Concentration of DX-2930
16.2.6.3	Kallikrein Activity
16.2.6.4	EQ5D
16.2.6.5	Angioedema Quality of Life
16.2.7	Adverse Events
16.2.8.1	Hematology Values
16.2.8.2	Coagulation Values
16.2.8.3	Chemistry Values
16.2.8.4	Urinalysis Values
16.2.8.5	Vital Signs
16.2.8.6	ECGs
16.2.8.7	Immunogenicity
16.2.8.8	Physical Examinations

10.2 Definitions and Programming Conventions

10.2.1 Age

Age will be calculated as the date of birth minus the date of informed consent, truncated to years.

10.2.2 BMI

BMI will be calculated as:

$$BMI = \frac{mass\ (kg)}{height(m)^2}$$

10.2.3 Study Day

The study day is calculated as start or stop date – date of randomization + 1 for dates on or after randomization, or start or stop date – date of randomization for dates prior to randomization.

10.2.4 Durations of Events

The duration of an event is calculated as stop date/time – start date/time if time is not missing, and stop date – start date + 1 if either the start or stop time is missing.

10.2.5 Baseline

Baseline is defined as the last non-missing value prior to first exposure to study drug.

10.2.6 Analysis Periods

10.2.6.1 Pretreatment Period

The pretreatment period is defined as the interval of time that starts at the date/time informed consent is signed and ends prior to the date/time of first exposure to study drug (Day 0 visit).

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

10.2.6.2 Run-in Period

The run-in period is defined as the interval of time that starts at the start date for the run-in period and ends on the end date for the run-in period.

[*start date of run-in period*, *end date of run-in period*)

10.2.6.3 Treatment Period

The treatment period is defined as the interval of time that starts on the date/time of first exposure to study drug (Day 0 visit) and ends on the date of Day 182 visit.

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

10.2.6.4 Follow-up Period

The follow-up period is defined as the interval of time that starts on the date of the Day 182 visit + 1 and ends on the date of the subject's last date of contact for the study.

[*date of Day 182 visit + 1*, *date of last study contact*]

10.2.7 HAE Attack Characteristics

10.2.7.1 HAE Attack Duration

The duration of an HAE attack is calculated as stop date/time – start date/time if time is not missing, and stop date – start date + 1 if both the start and stop time is missing. If the attack stop time is not missing but the start time is missing, start time will be imputed as 0:00. If start time is not missing but the end time is missing it will be imputed as 23:59.

10.2.7.2 HAE Attack Severity

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

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

To calculate the average attack severity per subject, a numeric value will be attributed to each severity as follows: 1=Mild, 2=Moderate, and 3=Severe. Higher values will indicate more severe attacks, while lower values will indicate less severe attacks.

10.2.8 Unique HAE 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.

That is 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 attacks to be considered distinct from the previous attack. 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.

10.2.9 HAE Attack Rate

10.2.9.1 Pretreatment HAE Attack Rate

The pretreatment HAE attack rate will be presented as the normalized number of attacks per month and calculated for each subject as the number of HAE attacks occurring during the pretreatment period divided by the number of days the subject contributed to the pretreatment period multiplied by 28 days.

10.2.9.2 Run-in Period HAE Attack Rate

The run-in period HAE attack rate will be presented as the normalized number of attacks per month and calculated for each subject as number of HAE attacks occurring during the run-in period divided by the number of days the subject contributed to the run-in period multiplied by 28 days.

10.2.9.3 Treatment Period HAE Attack Rate

The treatment period HAE attack rate will be presented as the normalized number of attacks per month and calculated for each subject as the number of HAE attacks occurring during the treatment period divided by number of days the subject contributed to the treatment period multiplied by 28 days.

10.2.10 Time to First HAE Attack

The time to first HAE attack (days) will be calculated as the earliest of the date of the HAE attack after the Day 14, date of study discontinuation or completion, or date of Day 182 visit for subjects who do not roll-over into the OLE visit minus the date of Day 14 visit plus 1.

Subjects with attacks occurring first will be events. Subjects who discontinue/complete the study or roll-over into the OLE prior to having a post-Day 14 visit HAE attack will be censored.

10.2.11 Adverse Events

10.2.11.1 Treatment-emergent Adverse Events

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

10.2.11.2 Related Adverse Events

Related AEs are AEs classified as related to study drug by the investigator.

10.2.11.3 Severe Adverse Events

Severe AEs are AEs classified as severe (grade 3) or life threatening (grade 4) by the investigator.

10.2.12 GLM Model Sample SAS Code

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

```
PROC GENMOD DATA=eff_data;
  CLASS trtgrp;
  MODEL no_attks = trtgrp bl_rate / DIST=poisson LINK=log OFFSET=logdays PSCALE;
  LSMEANS trt / DIFF CL EXP ILINK;
  ESTIMATE '300mg every 2 wk vs pbo' trtgrp 1 0 0 -1 / EXP;
  ESTIMATE '300mg every 4 wk vs pbo' trtgrp 0 1 0 -1 / EXP;
  ESTIMATE '150mg every 4 wk vs pbo' trtgrp 0 0 1 -1 / EXP;
RUN;
```

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

10.2.13 GEE Model Sample SAS Code

Sample code for a sensitivity analysis of the primary endpoint.

```
PROC GENMOD DATA=eff_data;
  CLASS trtgrp subject;
  MODEL no_attks = trtgrp bl_rate / DIST=poisson LINK=log;
  REPEATED SUBJECT=subject / CORR=IND;
  LSMEANS trtgrp / DIFF CL EXP ILINK;
  ESTIMATE '300mg every 2 wk vs pbo' trtgrp 1 0 0 -1 / EXP;
  ESTIMATE '300mg every 4 wk vs pbo' trtgrp 0 1 0 -1 / EXP;
  ESTIMATE '150mg every 4 wk vs pbo' trtgrp 0 0 1 -1 / EXP;
RUN;
```

Where:
eff_data = efficacy analysis dataset
trtgrp = treatment group (categorical)
no_attks = number of HAE attacks per week
bl_rate = normalized pretreatment HAE attack rate (continuous)

10.2.14 Angioedema Quality of Life

Below are instructions for how to calculate AE-QoL domain scores and total score.

AE-QoL is meant to be evaluated by determining its four individual domain scores (profile instrument), but it may also be used to determine a total score (index instrument).

Each item answered by the subject scores between 0 and 4 points depending on the answer option chosen by the subject. The first answer option gets 0 points, the second option 1 point, the

third option 2 points, etc. The AE-QoL domain scores and total score are calculated by using the following formula:

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

Computation of AE-QoL Total Score
Example 1: All items were completed (maximum possible sum: 68 points)
Sum of all 17 completed items: 41 points.
Total score = 100*(41/68) = 60 (out of a possible 100 points)

Example 2: 2 items were not completed (maximum possible sum: 60 points).
Sum of all 15 completed items: 41 points.
Total score = 100*(41/60) = 68 (out of a possible 100 points)

Computation of Domain Scores (Example: Fears/Shame)
Example: Sum of all 6 completed items: 14 points
Maximum possible sum: 24 points
Domain Score = 100*(14/24) = 58 (out of a possible 100 points)

Remarks
Since only answered items are included in the computation (and the calculated domain and total scores are not raw scores but linear transformations to a 0-to-100 scale), the calculated scores are not or only little influenced by missing items.

An AE-QoL domain score should not be calculated if more than one item is left unanswered in that domain. The AE-QoL total score should not be calculated if more than 25% of items (>4 items) are left unanswered.

The minimal and highest possible domain and total scores are 0 and 100, respectively.

References
Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, Metz M, Staubach P, Maurer M. Development and construct validation of the angioedema quality of life questionnaire. Allergy. 2012; 67(10): 1289-98.

10.3 Treatment Period Dosing Schedule

Treatment Period		Treatment Arms: DX-2930 or Placebo			
Dose Number	**Dose Day/ Week**	**300 mg every 2 weeks**	**300 mg every 4 weeks**	**150 mg every 4 weeks**	**Placebo**
1	Day 0/ Week 0	DX-2930	DX-2930	DX-2930	Placebo
2	Day 14/ Week 2	DX-2930	Placebo	Placebo	Placebo
3	Day 28/ Week 4	DX-2930	DX-2930	DX-2930	Placebo
4	Day 42/ Week 6	DX-2930	Placebo	Placebo	Placebo
5	Day 56/ Week 8	DX-2930	DX-2930	DX-2930	Placebo
6	Day 70/ Week 10	DX-2930	Placebo	Placebo	Placebo
7	Day 84/ Week 12	DX-2930	DX-2930	DX-2930	Placebo
8	Day 98/ Week 14	DX-2930	Placebo	Placebo	Placebo
9	Day 112/ Week 16	DX-2930	DX-2930	DX-2930	Placebo
10	Day 126/ Week 18	DX-2930	Placebo	Placebo	Placebo
11	Day 140/ Week 20	DX-2930	DX-2930	DX-2930	Placebo
12	Day 154/ Week 22	DX-2930	Placebo	Placebo	Placebo
13	Day 168/ Week 24	DX-2930	DX-2930	DX-2930	Placebo
--	Day 182/ Week 26	No Dose	No Dose	No Dose	No Dose

10.4 Study Activity Schedule

Study Activities Schedule																	
	Screening Visit	Run-in Period [1]	Treatment Period[2]													Follow-up Period[3]	
Tests and Assessments			**Visit 1 Dose 1 Day 0**	**Site Check-in[4]**	**Visit 2 Dose 2 Day 14**	**Visit 3 Dose 3 Day 28**	**Visit 4 Dose 4 Day 42**	**Visit 5 Dose 5 Day 56**	**Visits 6 and 7 Doses 6 and 7 Days 70 and 84**	**Visit 8 Dose 8 Day 98**	**Visits 9 and 10 Doses 9 and 10 Days 112 and 126**	**Visit 11 Dose 11 Day 140**	**Day 144±1**	**Visits 12 and 13 Doses 12 and 13 Days 154 and 168**	**Visit 14 Day 182**	**Visit 15 Day 210**	**Visit 16 Day 238**
Informed Consent	X																
Eligibility Review	X		X														
Long-term prophylactic therapy washout[5]	X																
Randomization			X														
Blinded IMP Treatment			X		X	X	X	X	X	X	X	X		X			
Demographic and Medical History	X																
C1-INH, C1q and C4 Testing[6]	X																
Pregnancy Test[7] (females)	X		X			X		X		X	X			X	X		X
Vital Signs[8]	X		X		X	X	X	X	X	X	X	X		X	X	X	X
Physical Examination[9]	X		X			X		X		X		X			X		X
12-Lead ECG[10]	X		X					X					X		X		
Clinical Laboratory Testing[11]	X		X			X		X		X		X			X		X
Serologies: HBsAg, HCV, and HIV	X																
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X

Study Activities Schedule

	Screening Visit	Run-in Period [1]	Treatment Period[2]													Follow-up Period[3]	
Tests and Assessments			**Visit 1 Dose 1 Day 0**	**Site Check-in[4]**	**Visit 2 Dose 2 Day 14**	**Visit 3 Dose 3 Day 28**	**Visit 4 Dose 4 Day 42**	**Visit 5 Dose 5 Day 56**	**Visits 6 and 7 Doses 6 and 7 Days 70 and 84**	**Visit 8 Dose 8 Day 98**	**Visits 9 and 10 Doses 9 and 10 Days 112 and 126**	**Visit 11 Dose 11 Day 140**	**Day 144±1**	**Visits 12 and 13 Doses 12 and 13 Days 154 and 168**	**Visit 14 Day 182**	**Visit 15 Day 210**	**Visit 16 Day 238**
HAE Attack Data[12]	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Quality of Life Assessments[13]			X			X		X		X	X			X	X		X
PK Blood Sampling			X					X		X		X			X	X	X
PD Sample Collection			X					X		X		X			X	X	X
Plasma Anti-Drug Antibody Testing			X					X		X		X			X		X
Discharge from Study[14,15]															X		X

ECG = Electrocardiogram; PK = Pharmacokinetic; PD = Pharmacodynamic; IMP = Investigational Medicinal Product

1. Subjects will undergo a run-in period to determine their baseline HAE attack rate. Only subjects with a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 Investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 Investigator-confirmed attacks to proceed to enrollment and randomization. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered a screen fail.
2. Treatment Period visits have a ±3 day window, with a maximum of 17 days or a minimum of 11 days between any two doses, starting with Dose 2, Day 14 through Day 182.
3. For subjects who do not rollover into OLE (DX-2930-04). Follow-up visits have a ±3 day window
4. Site personnel contact the subject to solicit for any attacks not already reported by the subject once between scheduled site visits or approximately 7 days after last contact with subject.
5. Subjects who are on long-term prophylactic (LTP) therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm that the subject has successfully completed the 2 week washout period before they can enter the run-in period.
6. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment.
7. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 and Day 182 must be urine-based. Tests performed at screening, Days 28, 56, 98, 126, 154, and Day 238 can be serum or urine-based.
8. There is a ± 15 minute window for all vital signs. At study visits in which IMP is administered, vital signs including sitting or supine BP, HR, body temperature, and RR, will be obtained prior to dosing, 1 hour after dosing, and 2 hours after dosing for the first 4 doses with the ability to eliminate the 2 hour vitals for the remaining doses based on the discretion of the Investigator and the absence of safety signals.

9. Height and weight will be collected at the Screening visit only.
10. ECGs (single recordings) are collected at screening, baseline prior to Dose 1, Day 56, Day 144±1 day to capture the estimated C_{max} and Day 182. The ECG assessment at C_{max} on Day 144±1 day may be performed via at-home nurse or technician in lieu of a subject visit to the study site.
11. Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis.
12. Historical attack information will be collected at screening. During the study subjects (or caregivers, in the event the subject is < 18 years old or is incapacitated) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. Site personnel will also contact the subject once a week or at approximately 7 days after last contact with the subject during the run-in period and once between study visits or approximately 7 days after last contact with the subject during the treatment period in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not given through prior subject contact with the site.
13. Quality of life data will be obtained using the EuroQoL Group 5-Dimension (EQ5D) Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using the Angioedema-Quality of Life (AE-QoL) Questionnaire at pre-dose on Days 0, 28 ±3, 56 ±3, 98±3, 126 ±3, 154 ±3, and 182±3. An additional quality of life assessment (EQ5D and AE-QoL) will be conducted on Day 238±3 for subjects not entering OLE.
14. Subjects who rollover into the Open-Label Extension protocol (DX-2930-04) will provide consent by Day 182 and receive their first open-label dose following the completion of all DX-2930-03 assessments scheduled on Day 182. At the completion of these assessments, the subject will be discharged from DX-2930-03 and roll into the DX-2930-04 study.
15. Subjects who terminate from the study early will undergo (if possible) all of the assessments and procedures as Day 182 at their final study visit.