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 3.0 09 January 2017
Indication:	Prevention of angioedema attacks in subjects with HAE
Study Phase	III
SAP Analysis Type	Final Analysis
SAP Version/Date	Original SAP 24 May 2016 Amendment 1.0 03 May 2017

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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
cHMWK	Cleaved High Molecular Weight Kininnogen
CO2	Carbon dioxide
CPK	Creatine phosphokinase
CSR	Clinical study report
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data Safety Monitoring Board
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
MI	Multiple Imputation
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 3.0.

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 table showing dosing is in Appendix 10.4. A table showing the Study Activities Schedule for the study is provided in Appendix 10.5.

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 10.4.

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

Primary and secondary efficacy endpoints will be based on the treatment period spanning Day 0 (after study drug administration) through Day 182, unless otherwise specified.

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 (Day 0 through Day 182)
- Number of moderate or severe investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182)
- Number of Investigator-confirmed HAE attacks occurring on Day 14 after administration of study drug through Day 182 (Day 14 through Day 182)

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 (Day 0 through Day 182)
- Number of investigator-confirmed HAE attacks resulting in an emergency department visit and/or admission to hospital during the treatment period (Day 0 through Day 182)
- Number of investigator-confirmed laryngeal HAE attacks during the treatment period (Day 0 through Day 182)
- Achievement of a pre-specified reduction from the run-in period in the investigator-confirmed HAE attack rate (i.e., responder analysis) during the treatment period (Day 0 through Day 182).
- Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, location, and medication use during the run-in period and treatment period (Day 0 through Day 182)
- Percentage of attack free days during the treatment period (Day 0 through Day 182)
- Achievement of investigator-confirmed HAE attack-free interval of 1 month, 3 months, or until the Day 182 visit during the treatment period (Day 0 through Day 182)

- Achievement of investigator-confirmed HAE attack-free interval of 1 month, 3 months, or until the Day 182 visit after Day 14 (Day 14 through Day 182)

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 10.5 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.

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.
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 10.5). 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 10.5). 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 10.5).

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 Section 10.3.21.

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 10.3 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, treated as randomized, and included in each analysis population will be summarized by randomized treatment assignment, overall DX-2930, and overall for all subjects. This summary will be provided by study site as well. See Section 10.2 for a list of study sites.

For each analysis population, the number of subjects included in the population, completing the study, completing the treatment period (by roll-over status to the long term extension DX-2930-04 study), completing the follow-up period, and those that discontinued prematurely by reason, will be summarized by treatment group, overall DX-2930, and overall for all subjects.

Listings of all disposition data will be provided. A Kaplan-Meier (KM) plot showing the time to withdrawal will be presented by treatment group for the ITT population.

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 (IP), 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 and baseline characteristic 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), BMI group for subjects ≥ 18 years of age (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2), BMI percentile group for subjects < 18 years of age (Underweight: <5^{th} percentile, Healthy or Overweight: 5^{th} to <95^{th} percentile, Obese: >=95^{th} percentile), long term prophylactic (LTP) therapy use prior to study randomization (C1-INH, Androgens, Anti-fibrinolytics, or not on LTP), and type of LTP therapy prior to study randomization (C1-INH, Oral Therapy, C1-INH and Oral Therapy, Not on LTP).

A separate table will be created for baseline HAE 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, run-in period HAE attack rate (attacks/4 weeks), run-in period HAE attack rate group (1 to <2, 2 to <3, ≥3 attacks/4 weeks) and run-in period 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 20.0 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 10.3.10.1 for the calculation of the normalized run-in period 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 (α/3). See Section 9.5 for more information.

Unadjusted monthly investigator-confirmed HAE attack rates will be calculated for the run-in and treatment periods. See Section 10.3.10 for details. The run-in period, treatment period, 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 run-in and treatment periods. Figures by treatment group plotting the on-study investigator-confirmed HAE attacks reported during the treatment period with timing relative to randomization for each subject will be created (i.e., "birds on a wire" plots).

In addition to the data summaries for the primary analysis of the primary efficacy endpoint described above, the number of investigator-confirmed 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 monthly investigator-confirmed HAE attack rate, change from run-in period, and percent change from run-in period of investigator-confirmed HAE attack rate. 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 10.3.7.2 for the definition of the run-in 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 (Day 0 through Day 182)
2. Number of moderate or severe investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182)
3. Number of Investigator-confirmed HAE attacks occurring on Day 14 after administration of study drug through Day 182 (Day 14 through Day 182)

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. A summary table will be provided to tabulate the statistical testing results for the primary and secondary endpoints, including the rate ratio and its 95% CI,

unadjusted p-value estimated from the Poisson GLM model, and adjusted p-value corrected for multiple comparisons, for each endpoint and each comparison between a DX-2930 treatment group and the placebo group in the multiple testing hierarchy. See Section 9.5 for more information on the multiple testing strategy.

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 (Day 0 through Day 182)
- Number of investigator-confirmed HAE attacks resulting in an emergency department visit or admission to the hospital during the treatment period (Day 0 through Day 182)
- Number of investigator-confirmed HAE attacks resulting in an emergency department visit during the treatment period (Day 0 through Day 182)
- Number of investigator-confirmed HAE attacks resulting in admission to the hospital during the treatment period (Day 0 through Day 182)
- Number of investigator-confirmed laryngeal HAE attacks during the treatment period (Day 0 through Day 182)
- Achievement of a pre-specified reduction from the run-in period in the investigator-confirmed HAE attack rate (i.e., responder analysis) during the treatment period (Day 0 through Day 182)
- Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, and rescue mediation use during the run-in period and treatment period (Day 0 through Day 182)
- Percentage of attack free days during the treatment period (Day 0 through Day 182)
- Achievement of investigator-confirmed HAE attack-free period of 1 month , 3 months, or until the Day 182 visit during the treatment period (Day 0 through Day 182)
- Achievement of investigator-confirmed HAE attack-free period of 1 month, 3 months, or until the Day 182 visit after Day 14 (Day 14 through Day 182)

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 (if prior to completion of the treatment period) or the date of the Day 182 visit. 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 during the treatment period

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 (Day 0 through Day 182) will be analyzed using the same method as for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

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

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 (Day 0 through Day 182) will be analyzed using the same method as for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

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

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 (Day 0 through Day 182) will be analyzed using the same method as for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

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

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 (Day 0 through Day 182) will be analyzed using the same method as for the primary efficacy endpoint. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

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

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

The number of investigator-confirmed laryngeal HAE attacks during the treatment period (Day 0 through Day 182) will be analyzed using the same method as for the primary efficacy endpoint,

with an addition of the history of laryngeal HAE attacks (categorical) as a fixed effect in the model. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

Achievement of a pre-specified reduction from run-in period in the investigator-confirmed HAE attack rate (i.e., responder analysis)

There will be five classes of responders based on pre-specified percentage reduction in the investigator-confirmed HAE attack rate from the run-in period 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 run-in period HAE attack rate will be calculated. See Section 10.3.10 for details. The percentage reduction will be calculated as the run-in period HAE attack rate minus the treatment period HAE attack rate divided by the run-in period 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 within each other and not mutually exclusive.

Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, location and mediation use during the run-in and treatment periods

Attack characteristics at subject level and event level, as described below, will be summarized by treatment group and overall DX-2930 for the run-in period and treatment period.

Subject level HAE attack characteristics

HAE Attack Duration

For each subject, the mean duration of all investigator-confirmed HAE attacks will be calculated in hours and summarized. See Section 10.3.9 for details on handling HAE attack data. The subject-level average attack duration will be categorized into 12 hour intervals and tabulated by category (<12 hours, 12-24 hours, >24-48 hours, and >48 hours).

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

Event level HAE attack characteristics

HAE Attack Location

The number and percentage of subjects with attacks, as well as the number of events, will be tabulated by the primary attack location (peripheral, abdominal, and laryngeal) as determined by the investigator. Additionally, the attack location will be re-classified and summarized with an emphasis on the laryngeal attack. In this summary, an attack with either the primary or secondary location(s) identified as laryngeal will be considered as a laryngeal attack; otherwise attacks will be classified by their reported primary attack location.

Rescue Medication Use

The number and percentage of subjects with rescue medication use for an 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) as reported in the AE CRF.

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) as reported in the AE CRF.

Percentage of HAE attack free days during the treatment period

The percentage of HAE attack free days during the treatment period (Day 0 through Day 182) will be calculated by counting the number of days in the treatment period without an HAE attack and dividing by the number of days the subject was in the treatment period. An attack-free day is defined as a calendar day with no investigator-confirmed HAE attack.

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

Achievement of investigator-confirmed HAE attack-free interval of 1 month, 3 months, or until the Day 182 Visit during the treatment period

A subject is considered as attack free during a time period if the subject has no investigator-confirmed HAE attacks during that time period. Subjects who discontinued during a time period are considered as non-responders for that time period.

The number and percentage of subjects who achieve investigator-confirmed HAE attack free intervals of 1 month (4 weeks; 'Day 0 to one day before Day 28 visit'), 3 months (12 weeks; 'Day 0 to one day before Day 70 visit'), or until the Day 182 visit (approximately 6 months or 24 weeks; 'Day 0 to Day 182 visit') during the treatment period will be tabulated by treatment group. Risk difference comparing each active DX-2930 treatment group to the placebo treatment group, and corresponding exact 95% confidence interval (Santner, 1980) will be provided.

Achievement of investigator-confirmed HAE attack-free interval of 1 month, 3 months, or until the Day 182 Visit after Day 14 during the treatment period

A subject is considered as attack free during a time period if this subject has no investigator-confirmed HAE attacks during that time period. Subjects who discontinued during a time period are considered as a non-responder for that time period.

The number and percentage of subjects who achieve investigator-confirmed HAE attack free intervals of 1 month (4 weeks; 'Day 14 visit to one day before Day 42 visit'), 3 months (12 weeks; 'Day 14 visit to one day before Day 84 visit'), or until the Day 182 visit (approximately 6 months or 24 weeks; 'Day 14 visit to Day 182 visit') after Day 14 during the treatment period will be tabulated by treatment group. Risk differences comparing each active DX-2930 treatment

group to the placebo treatment group, and corresponding exact 95% confidence intervals (Santner, 1980) will be provided.

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 20.0.

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.

In this study, the primary endpoint is based on an AE. If DX2930 is efficacious, it will result in a systematic difference in the incidence of AEs by treatment group which will complicate the interpretation of the safety. Thus, the collection of tabulations described in this section (with the exception of the analyses of AEs of special interest (AESI) and injection site reaction (ISR)) will be produced for 2 mutually exclusive subgroups of AEs based on if the AE was identified in EDC as a subject-reported HAE attack or not, and defined as follows:

- Non-HAE Attack Reported AEs will include the subset of AEs identified in EDC as not a reported HAE attack. Essentially, this will be all AEs excluding HAE attack reported events.

- HAE Attack Reported AEs will include the subset of AEs identified in EDC as a reported HAE attack. Note that this includes investigator-confirmed HAE attacks; all investigator-confirmed HAE attacks will be coded to the PT of HAE.

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 severe AE, any related severe AE, any SAE, and any related SAE, as well as the total number of events for each category, will be summarized by treatment group. The number of deaths due to an 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. For serious AEs and investigator-reported AESI during the treatment period and follow-up period, relative risks and risk differences, and their associated exact 95% CI (Santner, 1980) will be provided for the comparison between each active DX-2930 dose group and the placebo group, and overall DX-2930 group and 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 SOC, and PT for each analysis period. This tabulation will be repeated for related AEs, severe AEs, related severe AEs, SAEs, and related SAEs, 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. For serious AEs during the treatment period and follow-up period, risk difference and corresponding exact 95% CI (Santner, 1980) will be provided for the comparison between each active DX-2930 dose group and the placebo group, and overall DX-2930 group and the placebo group, by SOC and PT.

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 severe 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, and severe AEs will be produced.

Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) for this study are hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events). Investigators are required to document any potential AESI AEs on the CRF page, and notify the sponsor within 24 hours. These AESI AEs are collectively referred to as investigator-reported AESI.

In addition to investigator-reported AESI, standardized MedDRA Queries (SMQ) for each AESI will be performed using the study data. The algorithm to define SMQ-defined AESI is provided

in Section 10.3.13.5. For SMQ-defined AESI, separate summary tables will be created for AESI categories of hypersensitivity events, hypercoagulable events, and bleeding events.

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

- Summary of AESI: The number and percentage of subjects with any AESI AE, any related AESI AE, any severe AESI AE, any related severe AESI AE, any AESI SAE, and any related AESI SAE, as well as the total number of events for each category, will be summarized by treatment group. The number of deaths due to an AESI AE, hospitalization due to an AESI AE and study discontinuation due to an AESI AE will be summarized by treatment group and overall DX-2930 for each analysis period.

- AESI by SOC and PT: The number and percentage of subjects with an AESI, as well as the total number of AESIs, will be summarized for each treatment group and overall DX-2930 by SOC and PT for each analysis period. Risk difference and corresponding exact 95% CI (Santner, 1980) will be provided for the comparisons between each active DX-2930 dose group and the placebo group, and overall DX-2930 group and the placebo group. This tabulation will be repeated for related AESI for the treatment period and follow-up period AEs. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the overall DX-2930 group and then the placebo group.

- Related AESI by SOC and PT: The number and percentage of subjects with a related AESI, as well as the total number of related AESIs, will be summarized for each treatment group and overall DX-2930 by SOC and PT for the treatment period and follow-up period. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the overall DX-2930 group and then the placebo group.

SMQ-defined hypersensitivity AESI during the treatment period include some terms of injection site reactions. It was considered by the Data Safety Monitoring Board (DSMB) that including these terms in the tabulation would take away focus on systemic AESIs. Therefore, tables on SMQ-defined hypersensitivity AESI during the treatment period will be summarized in two ways: a display with all injection site reaction terms (PTs containing ‘Injection site’, ‘Administration site’, or ‘Application site’) included, and a display with all injection site reaction terms excluded.

A listing of investigator-reported AESI will be provided.

Injection Site Reactions (ISR)

ISR AEs were not predefined in the protocol, but instead are identified using the algorithm detailed in Section 10.3.13.6 based on the spontaneous reporting of adverse events.

The number and percentage of subjects with any ISR AE, any related ISR AE, any severe ISR AE, any related severe ISR AE, any ISR SAE, and any related ISR SAE, as well as the total

number of events for each category, will be summarized by treatment group. The number of deaths due to an ISR AE, hospitalization due to an ISR AE and study discontinuation due to an ISR AE will be summarized by treatment group and overall DX-2930. This tabulation will be performed for the treatment period only.

The number and percentage of subjects with an ISR AE, as well as the total number of ISR AEs, will be summarized for each treatment group and overall DX-2930 by SOC, and PT for the treatment period. The number and percentage of subjects with an ISR AE will be summarized for each treatment group and overall DX-2930 by SOC, PT, and maximum severity for the treatment period. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency in the overall DX-2930 group and then the placebo group.

The duration of ISR AEs overall and by PT will be summarized numerically (summary statistics) and categorically (0 - 0.5 hour, >0.5 - 1 hour, >1- 12 hours, >12 – 24 hours, ≤1 day - unclear, >1 – 14 days, and >14 days). The definition of the duration of ISR is provided in Section 10.3.13.7.

A Listing of ISR AEs during the treatment period will be provided.

Table 1 provides a summary of the AE tabulations by analysis period as described in this section.

Table 1: Adverse Event Tabulations by Analysis Period

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

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

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. See Section 10.3.20 for details on handling clinical significance attribution for lab values. The number of subjects with a non-missing result, and the number and percentage of subjects with a clinically significant result less than the lower limit of normal, 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 abnormal 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 2017 Q1.

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 excluding medications taken for an HAE attack 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 concomitant medications taken for an HAE attack. 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 measured by percentage of cleaved high molecular weight kininnogen (%cHMWK) 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 subjects with neutralizing antibody, positive, negative, or not evaluable antibody results will be summarized for each treatment group and DX-2930 overall by study visit and overall and all immunogenicity data for subjects with any positive immunogenicity result will be 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.

The protocol stated that an AE is treatment-emergent if the onset time is after first administration of IMP; the SAP clarified that an AE is treatment-emergent if the onset time is on or after first administration of study drug.

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}).

Family 4 (F_4): Hypothesis tests for the third ranked secondary endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{41}, H_{42}, and H_{43}).

The 4 sets of hypotheses in F1, F2, F3, and F4 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 (F4) will utilize the remaining α by applying the Holm-Bonferroni procedure.

9.6 Examination of Subgroups

Subgroup analyses are planned to be conducted for the primary efficacy endpoint and adverse events (non-HAE attack treatment period AEs, related AEs, and severe AEs). In addition, a subgroup analysis by history of laryngeal attacks will be performed for the exploratory efficacy endpoint, number of investigator-confirmed laryngeal HAE attacks during the treatment period. 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 Group (1 to <2, 2 to <3, ≥3 attacks/4 weeks)
- 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, Oral Therapy, C1-INH and Oral Therapy, Not on LTP)
- History of laryngeal HAE attack (history laryngeal attack, no history of laryngeal attack)

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

conducted for the primary efficacy endpoint, a forest plot depicting the rate ratio and corresponding 95% CI estimated from the Poisson generalized linear model will be provided for each active treatment group versus placebo group comparison within each subgroup.

9.7 Sensitivity Analyses

The following sensitivity analyses will be performed on the primary efficacy endpoint and/or secondary and exploratory endpoints to evaluate the robustness of the results. See Table 2 for details.

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 7 after administration of study drug through Day 182, instead of Day 0 to Day 182.

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

4. 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.

5. The impact of missing data on the primary analysis will be explored using a tipping point analysis.

   Subjects who do not complete the treatment period (Day 0 through Day 182) but who were dosed and have contributed any amount of time to the treatment period will be included in the primary analysis. These subjects will have some portion of the treatment period observed

and the remainder of the treatment period, after study discontinuation, will be unobserved. The model used for the primary analysis assumes that events occur at a constant rate within an individual, and uses only the number of events in the observed portion of the treatment period with an offset parameter to account for the length of time in which those events were observed to derive the event rate for that individual.

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

The tipping point analysis will employ the same model as specified for the primary analysis including progressively conservative assumptions about the unobserved portion of time generated by subjects who discontinue early. The exact range of assumptions will be determined after treatment unblinding to ensure an appropriate range is explored based on the magnitude of treatment effect and pattern of missing data. The results of the various assumptions will be summarized with attack rate ratios, corresponding 95% confidence intervals and p-values in both tabular and graphical presentations. The details of this method are described in Section 10.3.12.

6. 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.

Table 2 details which sensitivity analyses will be performed for each efficacy endpoint. Data summaries will parallel those described for the each of the endpoints.

Table 2: Sensitivity Analysis for Efficacy Endpoints

	Sensitivity Analysis Item					
Efficacy Endpoint	**1**	**2**	**3**	**4**	**5**	**6**
Number of HAE attacks	x	x	x	x	x	x
Number of HAE attacks requiring acute treatment	x	x	x			x
Number of moderate or severe HAE attacks	x	x	x			x
Number of Investigator confirmed HAE attacks occurring on Day 14 after administration of study drug through Day 182	x	-	x			-
Time to first HAE attack after Day 14	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
Number of investigator-confirmed laryngeal HAE attacks	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
Achievement of attack-free during treatment period or after Day 14	x					-

10. APPENDICIES

10.1 Appendix I List of Statistical Outputs

10.1.1 List of Planned Tables

Table No.	Title
14.1.1.1	Analysis Population by Treatment Group – All Subjects
14.1.1.2	Analysis Populations by Treatment Group and Site – All Subjects
14.1.2.1	Subject Disposition by Treatment Group – ITT Population
14.1.2.2	Subject Disposition by Treatment Group – Safety Population
14.1.3.1	Demographics and Baseline Characteristics by Treatment Group – ITT Population
14.1.3.2	Demographics and Baseline Characteristics by Treatment Group – Safety Population
14.1.4.1	HAE Attack History by Treatment Group – ITT Population
14.1.4.2	HAE Attack History by Treatment Group – Safety Population
14.1.5.1	Medical History by System Organ class, Preferred Term, and Treatment Group – ITT Population
14.1.5.2	Medical History by System Organ class, Preferred Term, and Treatment Group – Safety Population
14.1.6.1	Prior Medications by Treatment Group – Safety Population
14.1.6.2	Concomitant Medications and Therapies (Excluding Medications taken for an HAE Attack) by Treatment Group – Safety Population
14.1.6.3	Concomitant Medications taken for an HAE Attack by Treatment Group – Safety Population
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14.2.2.5	GEE Poisson Regression of Investigator-confirmed HAE Attacks during the Treatment Period (Day 14 to Day 182) by Treatment Group – ITT Population
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14.2.2.10	Poisson Regression of Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Weight Group and Treatment Group – ITT Population
14.2.2.11	Poisson Regression of Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by BMI Group and Treatment Group – ITT Population
14.2.2.12	Poisson Regression of Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Run-in Period HAE Attack Rate Group and Treatment Group – ITT Population
14.2.2.13	Poisson Regression of Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by HAE Type and Treatment Group – ITT Population
14.2.2.14	Poisson Regression of Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Geographic Region and Treatment Group – ITT Population
14.2.2.15	Poisson Regression of Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Type of Long-term Prophylactic Therapy Prior to Study Randomization and Treatment Group – ITT Population
14.2.2.16	Poisson Regression of Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by History of Laryngeal HAE Attack and Treatment Group – ITT Population
14.2.2.17	Summary of Investigator-confirmed HAE Attacks by Treatment Group – ITT Population
14.2.2.18	Investigator-Confirmed HAE Attacks per Month by Study Month and Treatment Group – ITT Population
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14.2.3.6	Summary of Investigator-confirmed HAE Attacks Requiring Acute Treatment by Treatment Group – ITT Population
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14.2.4.4	Poisson Regression of Moderate and Severe Investigator-confirmed HAE Attacks during Day 8 to Day 182 by Treatment Group – ITT Population
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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
14.2.1.11	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
14.2.1.13	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
14.2.1.14	Investigator-confirmed HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group and History of Laryngeal Attack – ITT Population
14.2.1.15	Forest Plot of Rate Ratio on Number of Investigator-Confirmed HAE Attacks by Subject Subgroups – 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

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 List of Clinical Study Sites

Site #	State/Province	Country	PI Last Name
PPD	AL	US	Anderson
	MA	US	Banerji
	OH	US	Bernstein
	NY	US	Busse
	PA	US	Craig
	NY	US	Davis-Lorton
	WA	US	Gower
	CA	US	Jacobs
	MD	US	Li
	FL	US	Lockey
	TX	US	Lumry
	OH	US	McNeil
	MO	US	Wedner
	KS	US	Gierer
	NC	US	Johnston
	AR	US	Manning
	OH	US	Radojicic
	CO	US	Soteres
	MN	US	Shapiro
	NJ	US	Weinstein
	TX	US	Otto
	MI	US	Baptist
	CO	US	Melamed
	PA	US	Petrov
	OH	US	Rehman
		Puerto Rico	Zaragoza
	CA	US	Riedl
	LA	US	Boggs
	VA	US	Schwartz
	UT	US	Harris
	NC	US	Lugar
	NJ	US	Sher
	CA	US	Tachdijian
	OK	US	Nickel
	WI	US	Zafra
	MA	US	Hong
	UT	US	Smith

PPD

UK	US	Longhurst
	Germany	Magerl
	Germany	Staubach
	Italy	Cicardi
	Germany	Martinez-Saguer
Ontario	Canada	Sussman
Quebec	Canada	Hébert
Alberta	Canada	Ritchie
Ontario	Canada	Yang
Québec	Canada	Chapdelaine
	Jordan	Shennak

10.3 Definitions and Programming Conventions

10.3.1 Age

Age will be calculated as the date of birth minus the date of informed consent, divided by 365.25, and truncated to years.

10.3.2 BMI

BMI will be calculated as:

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

The mass and height collected at the screening visit will be used to calculate baseline BMI.

10.3.3 LTP Prior to Study Randomization

The LTP (C1-INH, Androgens, or Anti-fibrinolytics) treatment a subject was on prior to study randomization will be determined by applying the algorithm presented in Table 3 to prior medications (i.e., medications with start and stop date prior to study enrollment) reported for that subject that lasted for ≥4 days.

Table 3 LTP Prior to Study Randomization

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

Subjects will be further classified into four LTP subgroup, based on the LTP use prior to study randomization. Table 4 provides the algorithm to classify subjects by type of LTP use prior to study randomization.

Table 4 LTP Subgroup

LTP Subgroup	Subject
C1-INH	Subjects who took only C1-INH as LTP
Oral Therapy	Subjects who took either Androgens and/or Anti-fibrinolytics as LTP but not C1-INH
C1-INH and Oral Therapy	Subjects who took C1-INH and androgens and/or anti-fibrinolytics as LTP
Not on LTP	Subjects who didn't take any LTP medications prior to study randomization

10.3.4 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.

10.3.5 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.

10.3.6 Baseline

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

10.3.7 Analysis Periods

10.3.7.1 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*)

10.3.7.2 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*]

10.3.7.3 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*]

10.3.7.4 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*]

10.3.8 Handling of Data for Subjects who Rolled-Over to the DX-2930-04 Early

Two subjects (subject ID 107007 and 108001) rolled-over to DX-2930-04 (long-term extension study) prior to the Day 182 visit due to study site error. These two subjects were considered to have completed the DX-2930-03 study as the early discontinuation of the treatment period was in error. For these two subjects, the following data handling conventions were employed:

- The planned number of doses used in the compliance and extent of exposure calculations will be based on the planned number of doses at their last visit instead of the Day 182 visit.

- For the tipping point analysis these subjects will be treated as study completers. No imputation will be performed for these subjects. The shorten duration of observation will be accounted for in the model with the use of the offset parameter.

10.3.9 Handling of HAE Attack Data

The following rules apply to the handling of HAE attack data for efficacy analyses only. HAE attacks starting prior to the run-in period are not processed by these rules. For safety analyses, HAE attacks will be analyzed as reported.

10.3.9.1 Imputing Missing Start or End Date and Time for HAE Attacks

In general, missing start time will be imputed as 0:00 and missing end time will be imputed as 23:59. However, the following rules will be applied for the attacks satisfying the corresponding conditions, in order to conservatively classify the attacks as separate, distinct attacks with at least 24 hours in-between:

- For HAE attacks with a missing start time and a non-missing start date one calendar day after the end date of the previous attack, the start time will be imputed using the end time of the previous HAE attack to ensure there are 24 hours in between the two attacks.

- For HAE attacks with a missing start time and a non-missing end date/time within 24 hours from the end date/time of the previous attack, the attack should be considered as one attack with the previous attack (see Section 10.3.9.2 for details on combining HAE attacks)

- For HAE attacks with missing end time and a non-missing end date one calendar day before the start date of the next attack, the end time will be imputed as the start time of the next HAE attack to ensure there are 24 hours in between the two attacks.

- For HAE attacks with a missing end time and non-missing start date/time within 24 hours from the start date/time of the next attack, the attack should be considered as one attack with the next attack (see Section 10.3.9.2 for details on combining HAE attacks)

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

- If the event is not indicated as ongoing, the stop date and time will be imputed as start date and time + 48 hours or 24 hours before the start date and time of the next attack, whichever is earlier.

- If the event is indicated as ongoing, the stop date and time will be imputed as the earlier of the following two date and time:

    - Start date and time + 48 hours or study completion date and the stop time of 23:59, whichever is later.

    - 24 hours before the start date and time of the next attack.

10.3.9.2 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.

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

When two or more attacks are combined for efficacy analysis, the parameters of the attacks will be conservatively chosen. The start date and time of the combined attack will take the earliest start date and time from the individual attacks; and the end date and time of the combined attack will take the latest end date and time of the individual attacks. The severity of the combined attack will take the highest severity from the individual attacks. The primary location of the combined attack will be determined by the primary location of the individual attacks, and by following the hierarchy of laryngeal attack, abdominal attack, and peripheral attack. One primary location will be taken; and all the other primary location(s) and secondary locations will be considered as secondary location for the combined attack. The rescue medications and supportive treatment for the combined attack will include all the records from individual attacks. Also, the combined attack will be considered as an investigator-confirmed attack if any of the individual attack being combined is an investigator-confirmed attack.

10.3.9.3 HAE Attack Duration

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

10.3.9.4 Investigator-confirmed HAE Attacks Requiring Acute Therapy

Investigator-confirmed HAE attacks requiring acute therapy are those attacks identified as 'treated for HAE attack with acute therapy' on the CRF.

10.3.9.5 Moderate and Severe Investigator-confirmed HAE Attacks

Moderate and severe investigator-confirmed HAE attacks are those attacks that were classified as of moderate or severe according to the HARRP defined severity and reported as such on the CRF.

10.3.9.6 HAE Attack Severity

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

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

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

10.3.10 HAE Attack Rate

10.3.10.1 Run-in Period HAE Attack Rate

The run-in period HAE attack rate will be presented as the normalized number of attacks per month (4 weeks) 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.

Due to a slightly longer than planned run-in period, four of the randomized subjects had a calculated run-in period HAE attack rate that is lower than 1 (0.97). The actual value of the calculated run-in period attack rate will be used as the run-in period attack rate for these subjects. However, these subjects will be included in the 1-2 attacks/month group in the run-in period HAE attack rate group categorization.

10.3.10.2 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.

10.3.11 Time to First HAE Attack

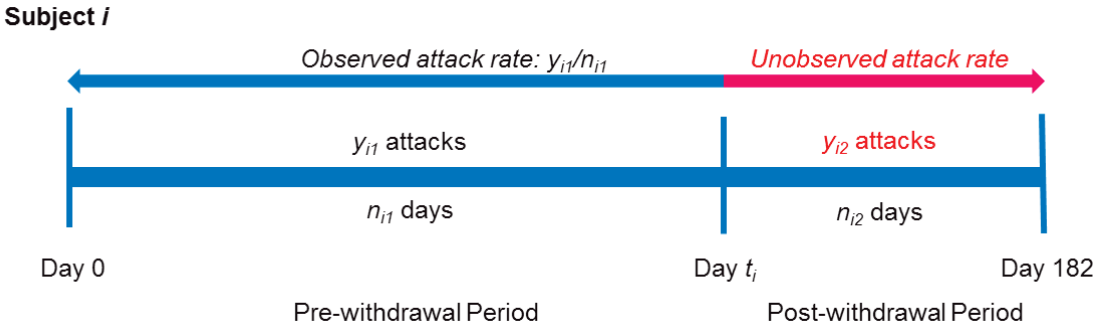
The time to first HAE attack (days) will be calculated as the earliest of the date of the HAE attack after the Day 14, date of study discontinuation or completion, or date of Day 182 visit for subjects who do not roll-over into the OLE visit minus the date of Day 14 visit plus 1.

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.

10.3.12 Details of the Tipping Point Analyses

Figure 1 illustrates the missing data pattern generated from subjects who discontinue early from the treatment period of the DX-2930-03 study. Subject i receives first dose of the study drug at Day 0 and discontinues the study at Day t_i prior to the end of the treatment period at Day 182. The pre-withdrawal period for Subject i is defined as Day 0 through Day t_i and the post-withdrawal period is defined as Day $t_i + 1$ through Day 182. In the pre-withdrawal period, we know both the length of the period (n_{i1}) and the number of investigator-confirmed HAE attacks during the period (y_{i1}), and can calculate the observed attack rate (y_{i1}/n_{i1}) for the period. In the post-withdrawal period, we know only the length of the period (n_{i2}), however, both the number of investigator-confirmed HAE attacks during the period (y_{i2}) and the unobserved attack rate (y_{i2}/n_{i2}) for the period are unknown.

Figure 1 Missing Data Pattern for Subjects who Discontinue Early from the Treatment Period of Study DX-2930-03



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

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

The tipping point analysis will be conducted as follows:

Step 1: Multiple Imputation (MI)

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

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

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

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

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

Step 2: Analyze the MI Datasets with Primary Analysis Model

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

Step 3: Combine Estimates using Rubin's Rules

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

Step 4: Pattern Imputation with Delta Adjustment

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

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

Steps 1 through 4 are repeated for values of δ that represent progressively worse assumptions on the unobserved attack rate for subjects who discontinue the study prior to completing the treatment period from the active treatment arms until the tipping point is identified (value of δ that yields a non-significant p-value). As the value of δ increases, the overall attack rate imputed for subjects in the active treatment arm increases. Values of $\delta > 1$ will be determined post-hoc in order to define reasonable increments for which to increase δ given the magnitude of treatment effect and the pattern of missing data.

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

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

In the DX-2930-03 study, the protocol specifies that there must be 24 hours in between each investigator-confirmed HAE attack. Therefore, the total number of attacks during the treatment period is restricted to about 1 attack per day. If δ allows for more attacks than 1 per day, then the value of δ is not plausible under the study specifications and the missing data assumptions will be declared reasonable.

10.3.13 Adverse Events

10.3.13.1 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.

10.3.13.2 Related Adverse Events

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

10.3.13.3 Severe Adverse Events

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

10.3.13.4 Investigator-reported AESI

An investigator-reported AESI is an adverse event identified by the investigator on the CRF as an adverse event of special interest.

10.3.13.5 SMQ-Defined AESI

The broad terms from MedDRA 20.0 SMQ will be used to identify an SMQ-defined AESI. Table 5 shows the SMQ's used to identify AESI of hypersensitivity, hypercoagulable, and bleeding.

Table 5 SMQs Used to Identify AESI

AESI	SMQ
Hypersensitivity	Hypersensitivity
Hypercoagulable	Embolic and thrombotic events, arterial Embolic and thrombotic events, venous Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous
Bleeding	Haemorrhage laboratory terms Haemorrhage terms (excl laboratory terms)

10.3.13.6 Injection Site Reaction AEs

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

10.3.13.7 Duration of Injection Site Reaction AEs

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

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

- ISR AE with non-missing start and stop date/time: duration of the AE will be calculated as 'stop date/time – start date/time' and mapped to a duration category.
- ISR AE with non-missing start and stop dates and missing time: duration of the AE will be calculated as 'stop date – start date +1'. If the calculated duration is 1 day, then the duration category for this AE is ≤ 1 day - unclear. If the calculated duration is greater than 1 day, then it will be mapped to a >1 Day category.
- ISR AE with missing start or stop date: The ISR AE will be excluded from the categorical analyses on duration.

10.3.14 Non-standard Laboratory Results

The non-standard laboratory results will be converted to numeric values using the rules shown in Table 6.

Table 6 Convention for Converting Non-Standard Laboratory Results

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

10.3.15 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

10.3.16 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)

10.3.17 Tipping Point Analysis Sample SAS Code

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

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

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

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

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

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

  *calculate the rate for each sample of coefficients from the model in Step 1a using each
subjects covariate values;
  if TRTPN = 1 then lambda = exp(&&INTERCEPT&i + &&RUNBASE&i +
&&TRTPN1&i);
  if TRTPN = 2 then lambda = exp(&&INTERCEPT&i + &&RUNBASE&i +
&&TRTPN2&i);
  if TRTPN = 3 then lambda = exp(&&INTERCEPT&i + &&RUNBASE&i +
&&TRTPN3&i);
  if TRTPN = 4 then lambda = exp(&&INTERCEPT&i + &&RUNBASE&i +
&&TRTPN4&i);
*calculate the attack rate;
 if miss_treat = 1 then attk_rate = RAND('POISSON', lambda);
run;
%end;
%mend mi_data;
```

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

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

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

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

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

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

10.3.18 Sample Code to Derive Relative Risk and Risk Difference

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

10.3.19 Sample Code on Time-to-Event Analyses

```
proc lifetest data = time_attk;
  time attk14*cnsr(0);
  strata trt01p/ diff = control('Placebo')  test = (logrank);
run;
```

where attk14 is the time to the first attack after day 14
cnsor is the indicator for being an event

10.3.20 Clinical Significance Attributions for Laboratory Results

The EDC system design permitted attribution of clinical significance for all laboratory values, not just those that are outside of the reference range. Therefore, many data points have an attribution of clinical significance when none is expected.

The laboratory results will be programmatically classified for analysis due to the database limitation using the following algorithm:

1. Lab results within the reference range will be classified as Normal.
2. Lab results outside of the reference range will be classified as a) CS Low, b) NCS Low, c) NCS High, or d) CS High using a combination of the CS/NCS classification by the investigator and the Low/High classification based on the central lab reference range.

10.3.21 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

<u>Computation of AE-QoL Total Score</u>
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)

<u>Computation of Domain Scores (Example: Fears/Shame)</u>
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)

<u>Remarks</u>
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.

10.4 Treatment Period Dosing Schedule

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

10.5 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		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

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**
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
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

BP = blood Pressure; C1-INH = C1 Inhibitor; C_{max} = Maximum plasma drug concentration; ECG = Electrocardiogram; HAE = hereditary Angioedema; HbsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency virus; HR = Heart Rate; IMP = Investigational Medicinal Product; LTP = Long-term Prophylactic; OLe = Open-label Extension; PD = Pharmacodynamic; PK = Pharmacokinetic; RR = Resting Rate

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

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**

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) Self-Report Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using the Angioedema Quality of Life Questionnaire (AE-QoL) 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.

11. REFERENCES

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