CLINICAL STUDY PROTOCOL

NCT Number: NCT02741596

Study Title: HELP Study Extension™: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)

Study Number: DX-2930-04

Protocol Version and Date:

Original Protocol: 14 December 2015
Amendment 1.0: 27 June 2016
Amendment 2.0: 20 January 2017
Amendment 3.0: 29 June 2017

Clinical Trial Protocol: DX-2930-04

Study Title:	HELP Study Extension™: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number:	DX-2930-04
Study Phase:	Phase 3
Product Name:	DX-2930
IND Number:	116647
EudraCT Number:	2015-005255-27
Indication:	Prevention of angioedema attacks in patients with HAE
Investigators:	Multicenter
Sponsor:	Dyax Corp. 55 Network Drive, Burlington, MA 01803 USA
Sponsor Contact:	[redacted], Clinical Development 55 Network Drive, Burlington, MA 01803 USA Phone: [redacted]
Medical Monitor US and Canada:	[redacted], M.D. Rho, Inc. 6330 Quadrangle Drive, Chapel Hill, NC 27517 USA Phone: [redacted]
Medical Monitor Europe and Jordan:	[redacted], M.D. Voisin Consulting 3, rue des Longs Prés 92100 Boulogne, France Phone: [redacted]

	Date:
Original Protocol	14 December 2015

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

Study Title: HELP Study Extension™: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)

Study Number: DX-2930-04

Final Date: 14 December 2015

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The signature of the Sponsor representative indicates that the Sponsor will comply with all Sponsor obligations detailed in applicable regulations and guidelines and will ensure the Investigator is informed of all relevant information that becomes available.

Signed:_____ Date:_____

[redacted], Clinical Development
55 Network Drive, Burlington, MA 01803

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP), and all applicable regulatory requirements and guidelines as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use only the informed consent form approved by Dyax Corp. and my Institutional Review Board (IRB), Research Ethics Board (REB) or Ethics Committee (EC) and will fulfill all responsibilities for submitting pertinent information to the IRB/REB/EC responsible for this study.

I further agree that Dyax Corp. or their designees shall have access to any source documents from which eCRF information may have been generated.

By signing this protocol, I agree to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP to which it conforms.

Signed:_____ Date:_____
Investigator
Address: _____

_____

SYNOPSIS

Sponsor: Dyax Corp.
Name of Finished Product: DX-2930 Drug Product (DP)
Name of Active Ingredient: DX-2930 is a recombinant, Chinese hamster ovary (CHO) cell-expressed, fully human immunoglobulin G subclass 1 (IgG1), kappa light chain, monoclonal antibody.
Names of Inactive Ingredients: Sodium phosphate dibasic dihydrate, citric acid monohydrate, L-histidine, sodium chloride, and Polysorbate 80
Study Title: HELP Study Extension™: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number: DX-2930-04
Study Phase: Phase 3
Study Location: Approximately 60 study sites planned across the United States, Italy, United Kingdom, Germany, Canada and Jordan
Primary Objective: To evaluate the long-term safety of repeated subcutaneous administrations of DX-2930
Secondary Objectives: • To evaluate the long-term efficacy of DX-2930 in preventing HAE attacks • To characterize the outer bounds of dosing frequency for DX-2930
Tertiary Objectives: • To assess the immunogenicity of chronically administered DX-2930 • To evaluate the effect of DX-2930 upon quality of life (QOL) assessments • To evaluate Pharmacodynamic (PD) and Pharmacokinetic (PK) data following open-label DX-2930 dosing

Study Design:
This study is an open-label, long term safety and efficacy study to evaluate DX-2930 in preventing acute angioedema attacks in patients with Type I and Type II HAE. There are two types of subjects who will be enrolled into this study:

1. Subjects who rollover from the DX-2930-03 study
2. Subjects who were not participants in DX-2930-03.

Roll-over Subjects:
Rollover subjects are subjects who complete the double-blind treatment period at Day 182 of the DX-2930-03 study and consent to enter DX-2930-04. Subjects who discontinue from DX-2930-03 after enrollment are not eligible to enroll in DX-2930-04. Willing subjects must sign informed consent for DX-2930-04 no later than the DX-2930-03 Day 182 treatment period study visit.

The first DX-2930-04 visit for rollover subjects (Day 0) will occur on the same day as the DX-2930-03 Day 182 study visit. Rollover subjects will complete all DX-2930-03 final study assessments at which time they will be discharged from that study. No assessments conducted between the DX-2930-03 Day 182 study visit and the first DX-2930-04 visit (Day 0) will be duplicated. Results of the final DX-2930-03 assessments will be used as the pre-dose results for Day 0 Dose 1 of DX-2930-04.

Subjects who are eligible to roll over into DX-2930-04 but elect not to may not enroll in DX-2930-04 at a later time.

All subjects, caregivers, Investigators and site personnel will remain blinded to the DX-2930-03 treatment assignment until the conclusion of the DX-2930-04 study.

Non-rollover subjects:
Up to 50 subjects who were not participants in the DX-2930-03 study will be permitted to enroll if they meet the eligibility requirements. Subjects who screen fail out of DX-2930-03 for not meeting the minimum attack requirements during the run-in period must wait until enrollment for the double-blind study has ended before they can screen for DX-2930-04. The Sponsor may ease this restriction based on the enrollment rate observed in DX-2930-03.

Screening Period:
There is no screening period for rollover subjects.

Non-rollover subjects must provide informed consent and have screening assessments completed within 4 weeks prior to their first open-label dose. Screened non-rollover 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 treatment 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 and have no ongoing adverse events related to the washout before they can receive their first open-label

dose.

Treatment Period:

Rollover Subjects: Following informed consent and pre-dose assessments, rollover subjects will receive a single open-label dose of 300 mg DX-2930 administered subcutaneously (SC). Subjects will not receive any additional DX-2930 doses until their first reported HAE attack.

The duration of time between the first open-label dose and first reported HAE attack will vary by rollover subject. All rollover subjects must adhere to the Study Activities Schedule, for the entire duration of the study. However, until a rollover subject reports their first HAE attack, only scheduled study visits where the following tests and assessments are performed must be conducted at the investigative site: pregnancy testing, clinical laboratory testing, physical examination, 12-Lead ECG, QOL, PK, PD and anti-drug antibody sample collection. All other scheduled study visits may be conducted via site check-in calls to collect information on adverse events, concomitant therapy, and HAE attack data. Refer to the Appendix 1 Study Activities Schedule.

Once a rollover subject reports their first HAE attack they will present to the investigative site for their second open-label dose of DX-2930 as quickly as subject and site schedules allow. If the second dose is to be administered within the accepted ±4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit unless that scheduled visit has already occurred.

> For example, if the second dose is to be administered on Day 52, all of the tests and assessments scheduled for the Day 56 visit will be conducted. This Day 52 visit to receive the second dose will count as the Day 56 visit.
>
> As another example, if the second dose is to be administered on Day 46, the subject can have this study visit count as their Day 42 visit if they have not already attended the Day 42 visit. If they have already attended the Day 42 visit, then this Day 46 visit will be considered an acceptable, extra study visit.

In the scenario that the second dose is to be administered outside of the accepted ±4 day window around a scheduled visit, this visit will not replace any scheduled visit and will thus represent an acceptable, extra study visit.

> For example, if the second dose is to be administered on Day 63, this visit will represent an acceptable, extra study visit.

Regardless of the study day, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical examination, clinical laboratory testing, PK, PD, and anti-drug antibody. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data.

Subsequent doses after dose 2 require a minimum of 10 days and maximum of 18 days between administrations, and should fall within the accepted ±4 day window around study

visits.

For example, if the second dose is to be administered on Day 37, the third dose should be administered between Day 52 and Day 55, which would ensure both a dosing interval within 10 to 18 days from the second dose and a visit within the ±4 day window around the Day 56 study visit. The fourth dose should then be administered between Day 66 and Day 73, which would ensure both a dosing interval within 10 to 18 days from the third dose and a visit within the ±4 day window around the Day 70 study visit.

Regardless of when a subject's first HAE attack occurs, there will be a minimum of 10 days between their first open-label dose and their second open-label dose. Following their second dose, rollover subjects will continue to receive repeated SC administrations of open-label 300 mg DX-2930 every 2 weeks for the remaining duration of the treatment period. The treatment period will last 26 weeks from the date of the first open-label dose. The number of doses administered during this period will vary by subject based on the date of each subject's second dose, but will not exceed 13 doses. The Day 168 study visit is the last visit at which a dose may be administered.

Non-rollover Subjects: Once all screening assessments have been completed, eligibility confirmed and LTP washout completed (if applicable), non-rollover subjects will arrive at the study site and, following pre-dose assessments, receive an open-label dose of 300 mg DX-2930 administered SC. Non-rollover subjects will continue to receive SC administrations of open-label 300 mg DX-2930 every 2 weeks throughout the duration of the treatment period. A total of 13 doses will be administered with the last dose administered at the Day 168 study visit.

Follow-up Period:
After completion of the 26-week treatment period, all subjects will undergo safety evaluations during an 8-week follow-up period unless rolling over into another ongoing DX-2930 clinical study or access program that permits such a rollover.

Modifications to Open-Label Dosing:
If, at any time, an important dose-related safety signal is identified either from this study or DX-2930-03, the Sponsor may decide to switch the enrolled subjects who have not yet completed the treatment period, and any subsequent subjects, to receive a different open-label DX-2930 dose and/or frequency.

In addition, based on the results of the DX-2930-03 study, the Sponsor may switch to a different dose and/or frequency.

Study Population:
The study is expected to enroll subjects from the DX-2930-03 study, as well as up to 50 additional subjects who were not enrolled in DX-2930-03. The total enrollment is expected to be approximately 150 HAE Type I or II subjects. Subjects will be 12 years of age or older who experience at least 1 attack per 12 weeks. HAE diagnosis will be confirmed through documented clinical history and diagnostic testing conducted either during screening or during prior participation in study DX-2930-02 or DX-2930-03. The study will aim to enroll

at least 10 subjects who are 12 to 17 years of age, inclusive of subjects 12 to 17 years old who roll over from the DX-2930-03 study.

Criteria for Inclusion:

Subjects must meet the following criteria to be enrolled in this study:

1. Male and female HAE subjects who are 12 years of age or older at the time of screening.
2. Documented diagnosis of HAE (Type I or II) based on all of the following:
    - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).
    - Diagnostic testing results obtained during screening (or a prior DX-2930 study) that confirm HAE Type I or II: C1 inhibitor (C1-INH) functional level < 40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.
    - At least one of the following: Age at reported onset of first angioedema symptoms ≤ 30 years, a family history consistent with HAE Type I or II, or C1q within normal range.
3. A historical baseline HAE attack rate of at least 1 attack per 12 weeks
4. Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects age 12 to 17, whose caregiver has provided informed consent, are willing and able to read, understand and sign an assent form.
5. Males and females who are fertile and sexually active must adhere to contraception requirements for the duration of the study as follows:
    - Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception from the screening period through 30 days after the final study visit: progestin-only oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD, all types). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.
    - Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
    - Males, including males who are surgically sterile (post vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study visit.

Criteria for Exclusion:

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

1. Discontinued from DX-2930-03 after enrollment for any reason.
2. If rolling over from DX-2930-03, presence of important safety concerns that would preclude participation in this study.
3. Concomitant diagnosis of another form of chronic, recurrent angioedema such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.
4. Dosing with an investigational drug (not including DX-2930) or exposure to an investigational device within 4 weeks prior to screening.
5. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
6. Use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to the start of the treatment period (Day 0).
7. Use of short-term prophylaxis for HAE by non-rollover subjects within 7 days prior to the start of the treatment period (Day 0). Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.
8. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's Syndrome).
9. Pregnancy or breastfeeding.
10. Subject has any condition that, in the opinion of the Investigator or Sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., history of substance abuse or dependence, a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of study results).

Test Product; Dose; and Mode of Administration:

DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated using the following compendial components: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Polysorbate 80. Each open-label vial contains a nominal concentration of 150 mg DX-2930 active ingredient in 1 mL solution.

For each 300 mg dose of DX-2930, each subject will receive a total of 2 mL, which will be administered in a single 2 mL SC injection. The injection will be given in the upper arm, thigh or abdomen.

Duration of Treatment:

All subjects will receive open-label DX-2930 during a 26-week treatment period. The number of doses that rollover subjects receive during this period will vary by subject but will not exceed 13 doses. The last dose of open-label DX-2930 administered to these subjects

may be given at the Day 168 study visit. Non-rollover subjects will receive 300 mg DX-2930 every 2 weeks for a total of 13 doses, with the first dose administered on Day 0 and the final dose administered at the Day 168 study visit.

There will be a ±4-day window around each study visit. There will be a minimum of 10 days between any two doses. Excluding the interval between the first and second open-label doses for rollover subjects, there will be a maximum of 18 days between any two doses. Subjects will be monitored at the study site through 1 hour post-dose.

Duration of Study for Individual Subjects:

Following informed consent, subjects will either rollover from DX-2930-03 or undergo screening assessments (non-rollover subjects). Screening assessments for non-rollover subjects must occur within 4 weeks prior to the first open-label dose. Eligible subjects will be enrolled and undergo a 26-week treatment period. At the conclusion of the 26-week treatment period, subjects will be followed for an additional 8 weeks unless rolling over into another ongoing DX-2930 clinical study or access program that permits such a rollover.

Prohibited Concomitant Treatments:

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

- Long-term prophylaxis for HAE (e.g., use of C1-INH for long-term prophylaxis, attenuated androgens, or anti-fibrinolytics).
- Angiotensin-converting enzyme (ACE) inhibitors.
- Estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy).
- Androgens (e.g., stanozolol, danazol, oxandrolone, methyltestosterone, testosterone).
- Any other investigational drug or device.

The use of short-term prophylactic treatment for HAE will be permitted if medically indicated. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.

Management of Acute Attacks:

Acute HAE attacks during the study are to be managed in accord with the Investigator's usual care of their patients, including use of acute attack therapies that the Investigator deems as medically appropriate. Use of C1-INH will be permitted as an acute attack therapy but not as a long-term prophylactic therapy.

Safety Assessments:

Safety assessments will include the following:

- Adverse events (AEs), including serious adverse events (SAEs) and adverse events of special interest (AESI). SAEs and AESI will be reported to the Sponsor within 24 hours of becoming aware of the event.
- Vital signs, including sitting or supine blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR)
- Physical examination

- Clinical laboratory testing (hematology, serum chemistry, coagulation and urinalysis)
- 12-Lead electrocardiogram (ECG)

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

Pharmacokinetic (PK) Assessments:
Blood samples will be collected for the measurement of plasma DX-2930 concentrations.

Pharmacodynamic (PD) Assessments:
Blood samples will be collected to evaluate the pharmacodynamic effects of DX-2930 through biomarker assays.

Immunogenicity Assessments:
Blood samples will be collected to assay for the presence of anti-drug antibodies, including evaluation of neutralizing antibodies (if any confirmed positive anti-drug antibodies are detected).

C1-INH, C1q and C4 Assessments:
Samples will be obtained for C1-INH, C4, and C1q assays at screening for non-rollover subject eligibility assessment.

Quality of Life Assessments:
Quality of life (QOL) assessments will be conducted using the EQ5D, SF-36 and the Angioedema Quality of Life Questionnaire (AEQoL).

Collection of HAE Attack Data:
The collection, reporting and assessment of attacks in this study will be done in accordance with the HAE Attack Assessment and Reporting Procedures (HAARP). Refer to Appendix 4. Site personnel will be trained on HAARP prior to screening and enrolling subjects at their site.

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

At screening, HAE attack history will be collected for non-rollover subjects. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant attack location(s), average duration, acute attack therapy use and history of long-term prophylaxis.

During the study, subjects (or caregivers) will be instructed to notify and report details to the study site within 72 hours of the onset of an attack. This includes the first attack experienced by rollover subjects following their first open-label dose. In the situation 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 experienced.

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.

Site personnel will contact rollover subjects approximately every 7 days following the first dose of open-label DX-2930 to solicit for any HAE attacks not already reported. Site check-ins will continue until the subject has received their second open-label dose.

During each study visit, site personnel will solicit for any new HAE attack information that was not already provided to the site.

In this study, HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to DX-2930, 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 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 to receive additional information. Any subject-reported attack not confirmed by the Investigator or physician designee must have an alternate AE diagnosis recorded. All subject-reported and Investigator/ physician designee-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 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 or physician designee may still clinically determine that the event did not represent an 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 (e.g., greater than 7 days), 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.

Study Stopping Rules:
Safety data, including SAEs and AESI, will be monitored regularly throughout the duration of the study. If any potential safety signal is identified as a result of monitoring in this study, or from any safety findings from the DX-2930-03 study, the Sponsor may take actions as deemed appropriate, including suspending further dosing, while the potential risk is evaluated and a course of action has been determined.

Individual Stopping Rules:
Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or a DX-2930-related, clinically significant non-serious AE) that, in the assessment of the Investigator, warrants discontinuation from further dosing for that subject's well-being. The Investigator has the ability to contact and consult with the Medical Monitor on such matters. Subjects will continue to be followed through the completion of all scheduled non-dosing visits, unless they request to be discontinued from the study.

Criteria for Evaluation:
Safety Measures:

- AEs including SAEs and AESI
- Clinical Laboratory testing (hematology, clinical chemistry, coagulation and urinalysis)
- Vitals signs including blood pressure, heart rate, oral body temperature and respiratory rate
- Physical Examination
- 12-lead ECG

Efficacy Endpoints:

- Time to first HAE attack for rollover subjects (based upon time from first open label study dose until first HAE attack)
- Mean rate of HAE attacks for all subjects (14 days post-second dose to Day 182 for rollover subjects; Day 14 to Day 182 for non-rollover subjects)

- Mean rate of acute therapy usage for all subjects (14 days post-second dose to Day 182 for rollover subjects; Day 14 to Day 182 for non-rollover subjects)
- Mean rate of moderate or severe attacks for all subjects (14 days post-second dose to Day 182 for rollover subjects; Day 14 to Day 182 for non-rollover subjects)
- Mean rate of high-morbidity attacks for all subjects (14 days post-second dose to Day 182 for rollover subjects; Day 14 to Day 182 for non-rollover subjects); 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.

Additional Measures:

- Anti-drug antibody development
- Pharmacokinetics (PK)
- Pharmacodynamic (PD) effects
- Quality of Life Assessments

Analysis Populations:
The analysis population will be based on subjects who receive at least one dose of DX-2930 after entering the study.

Sample Size Determination:
No formal sample size calculation was performed. The sample size is not based on any statistical considerations. This study is designed to evaluate the safety and efficacy of open-label treatment with DX-2930 in subjects who participated in DX-2930-03 and individuals who were not otherwise able to participate in DX-2930-03.

Statistical Methodology:
The distribution of time from first open-label dose to first HAE attack will be determined for rollover subjects. The estimation will be based on a standard Cox proportional hazards model where several baseline covariates will be tested including baseline attack rate prior to entering DX-2930-03, the treatment arm in DX-2930-03, the time since the last dose given in DX-2930-03, the time since the last HAE attack, and the rate of attacks during DX-2930-03. The distribution of time to first attack will be adjusted for any significant baseline ($p < 0.05$) covariates, and by examining the distribution separately by the treatment arm the patient was in during DX-2930-03. In this survival analysis, one observation (time to first attack) per subject will be generated.

For other efficacy endpoints, mean event rates will be assessed for all subjects (14 days post-second dose to Day 182 for rollover subjects; Day 14 to Day 182 for non-rollover subjects).

In addition, for rollover subjects, the mean change from the documented values in DX-2930-03 at baseline (last measurement prior to randomization into DX-2930-03) and entry (last measurement in DX-2930-03 prior to enrollment into DX-2930-04) will be compared to the values assessed at DX-2930-04 time points from 14 days after the second

dose in DX-2930-04 through Day 182 (i.e., 2 weeks after the final scheduled dose on Day 168). Changes will be calculated and presented as descriptive statistics for each DX-2930-03 treatment group (300 mg DX-2930 every 2 weeks, 300 mg DX-2930 every 4 weeks, 150 mg DX-2930 every 4 weeks). For each time period, graphs will be constructed for mean changes in efficacy variables from baseline. Time periods will be defined as relative time from the DX-2930-03 baseline for those who participated.

For non-rollover subjects, efficacy variables will be presented as descriptive statistics only.

For disposition, demographic and safety analyses, subjects will be represented in the reporting as follows:

- Subjects who received 26 weeks of 300 mg DX-2930 every 2 weeks in DX-2930-03 and up to 26 weeks of DX-2930 treatment in DX-2930-04.
- Subjects who received 26 weeks of 300 mg DX-2930 every 4 weeks in DX-2930-03 and up to 26 weeks of DX-2930 treatment in DX-2930-04.
- Subjects who received 26 weeks of 150 mg DX-2930 every 4 weeks in DX-2930-03 and up to 26 weeks of DX-2930 treatment in DX-2930-04.
- Subjects who received 26 weeks of placebo in DX-2930-03 and up to 26 weeks of DX-2930 treatment in DX-2930-04.
- Subjects who received up to 26 weeks of DX-2930 treatment in DX-2930-04.

Data from the start of DX-2930 treatment through the final treatment period study visit (up to 52 weeks for subjects whose treatment with DX-2930 was initiated in DX-2930-03) will be combined for safety evaluation of the overall DX-2930 exposure.

Safety Analysis:

All Subjects:

Safety measures include AEs, concomitant medications, clinical laboratory tests, vital signs (blood pressure, heart rate, respiratory rate, and body temperature), physical examination findings, and ECGs.

Treatment-emergent AEs (TEAEs) are defined as AEs with onset at the time of or following the start of treatment with DX-2930, 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. The number and percentage of subjects with TEAEs will be displayed by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries in terms of severity and relationship to DX-2930 will also be provided. SAEs will be summarized separately in a similar fashion. Patient listings of AEs causing discontinuation of DX-2930 treatment, AEs resulting in death, SAEs and AESI will be produced.

AESI will be analyzed according to primary System Organ Classes (SOCs) and Preferred Terms (PTs) determined by the search of relevant Standardized MedDRA Queries (SMQs). Summary tables with SOCs and PTs, from the SMQ searches, will be generated presenting the number and percentage of subjects by AE, severity, seriousness, and relationship to study medication.

Usage of concomitant medications (other than rescue medications) will be summarized descriptively.

Actual values and change from Day 0 in vital signs and clinical laboratory tests will be summarized with descriptive statistics at each assessment obtained. For all laboratory tests, a shift table will be produced summarizing changes from normal to abnormal and vice-versa.

The number and percentage of subjects with normal, abnormal-not clinically significant, and abnormal-clinically significant ECG findings will be displayed. Other safety parameters, such as subject withdrawals will be summarized.

Rollover Subjects: Adverse events that started during subject participation in DX-2930-03 and were ongoing at the time of first open-label dose in DX-2930-04 will not be counted as an AE in DX-2930-04 unless that event has worsened in severity or frequency following the first open-label dose. Adverse events that started during subject participation in DX-2930-03 and resolved following the first open-label dose in DX-2930-04 and then subsequently reappeared in DX-2930-04 will be counted as a new TEAE in DX-2930-04.

The incidence of AEs in DX-2930-04 from each DX-2930-03 treatment group (300 mg DX-2930 every 2 weeks vs. 300 mg DX-2930 every 4 weeks vs. 150mg DX-2930 every 4 weeks vs placebo) as well as evaluation of overall AEs in the combined group of all rollover subjects will be assessed. Changes from baseline (last measurement prior to the first dose of DX-2930 received, regardless of if it occurred in DX-2930-03 or DX-2930-04) to the DX-2930-04 time points for physical examination results, vital sign parameters, and clinical laboratory parameters will be summarized by DX-2930-03 treatment group and for the combined group of all rollover subjects.

Non-rollover Subjects: Adverse events will be captured from the time of informed consent through the final study visit. Adverse event tabular summaries will be based on all treatment-emergent AEs

Date of Original Protocol: 14 December 2015

Study Activities Schedule

Study Activities Schedule																		
	Screening Visit[1]	Treatment Period ± 4 days for each visit															Follow-up Period[2] ± 4 days for each visit	
Tests and Assessments		Visit 1 Dose 1 Day 0	Site Check-in[3]	Visit 2 Dose 2[4] Day 14	Visit 3 Dose 3 Day 28	Visit 4 Dose 4 Day 42	Visit 5 Dose 5 Day 56	Visit 6 Dose 6 Day 70	Visit 7 Dose 7 Day 84	Visit 8 Dose 8 Day 98	Visit 9 Dose 9 Day 112	Visit 10 Dose 10 Day 126	Visit 11 Dose 11 Day 140	Visit 12 Dose 12 Day 154	Visit 13 Dose 13 Day168	Visit 14 Day 182	Visit 15 Day 210[5]	Visit 16 Day 238
Informed Consent[6]	X																	
Eligibility Review	X	X																
Long-term prophylactic therapy washout[7]	X																	
DX-2930 Administration		X		X	X	X	X	X	X	X	X	X	X	X	X			
Demographic and Medical History	X																	
C1-INH, C1q and C4 Testing[8]	X																	
Pregnancy Test[9] (females)	X	X								X						X		X
Vital Signs[10]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical Examination[11]	X	X					X			X			X			X		X
Clinical Laboratory Testing[12]	X	X					X			X			X			X		X
12-Lead ECG	X	X								X						X		X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAE Attack Data[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessments[14]		X								X						X		X

Study Activities Schedule

	Screening Visit[1]	Treatment Period ± 4 days for each visit															Follow-up Period[2] ± 4 days for each visit	
Tests and Assessments		**Visit 1 Dose 1 Day 0**	**Site Check -in[3]**	**Visit 2 Dose 2[4] Day 14**	**Visit 3 Dose 3 Day 28**	**Visit 4 Dose 4 Day 42**	**Visit 5 Dose 5 Day 56**	**Visit 6 Dose 6 Day 70**	**Visit 7 Dose 7 Day 84**	**Visit 8 Dose 8 Day 98**	**Visit 9 Dose 9 Day 112**	**Visit 10 Dose 10 Day 126**	**Visit 11 Dose 11 Day 140**	**Visit 12 Dose 12 Day 154**	**Visit 13 Dose 13 Day168**	**Visit 14 Day 182**	**Visit 15 Day 210[5]**	**Visit 16 Day 238**
PK Blood Sampling[15]		X								X						X		X
PD Sample Collection[15]		X								X						X		X
Plasma Anti-Drug Antibody Testing[15]		X								X						X		X
Discharge from Study[16]																		X

ECG = Electrocardiogram; PK = Pharmacokinetic; PD = Pharmacodynamic

1. Screening visit is for non-rollover subjects only. Screening visit can occur up to 28 days prior to first open-label dose.
2. The Follow-up Period is not required for subjects who choose to roll over into an ongoing DX-2930 clinical study or access program that permits such a rollover.
3. Site personnel will contact rollover subjects approximately every 7 days following the first dose of open-label DX-2930 to solicit for any HAE attacks not already reported. Site check-in with rollover subjects will continue until the subject receives their second open label dose.
4. For rollover subjects, the timing of Dose 2 for will vary by subject based on when their first HAE attack occurs following Dose 1. Following the first reported attack, subjects will begin receiving regular SC administrations of 300 mg DX-2930 every 2 weeks. A minimum of 10 days between the first and second open-label doses is required. If the second dose is to be administered within the accepted ±4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit unless that scheduled visit has already occurred. If that scheduled visit has already occurred, or if the second dose is to be administered outside of the accepted ± 4 day window around a scheduled visit, this visit will not replace any scheduled visit and will thus represent an acceptable, extra study visit. Regardless, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical examination, clinical laboratory testing, PK, PD, and anti-drug antibody. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data.
5. The Day 210 Visit is a site check-in for all rollover and non-rollover subjects.
6. Rollover subjects will provide consent no later than the Day 182 DX-2930-03 study visit.
7. Non-rollover 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 treatment period.
8. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment unless already collected as part of protocol DX-2930-02 or DX-2930-03.
9. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 must be urine-based to confirm eligibility prior to first dose. Tests performed at screening, Day 98, Day 182, and Day 238 can be serum or urine-based.
10. There is a ± 15 minute window for all vital signs. Vital signs will be obtained prior to dosing and 1 hour after dosing.
11. Height and weight will be collected at the Screening visit only. Physical examinations will be conducted for all rollover and non-rollover subjects according to the study activities schedule. In addition to the physical examinations specified in the study activities schedule, an additional physical examination will be conducted for these subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs.

[12] Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis. Clinical laboratory testing will be conducted for all rollover and non-rollover subjects according to the study activities schedule. In addition to the testing specified in the study activities schedule, additional testing will be conducted for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs.

[13] Historical attack information will be collected at screening. During the study subjects (or caregivers) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. During study visits, site personnel will solicit for any new HAE attack information that was not given through prior subject contact with the site.

[14] Quality of life data will be obtained using the EQ5D, SF-36 and Angioedema Quality of Life Questionnaire (AE-QoL).

[15] PK, PD and Anti-drug Antibody PD samples will be drawn for all rollover and non-rollover subjects according to the study activities schedule. In addition to the samples specified in the study activities schedule, an additional PK, PD and Anti-drug Antibody sample will be drawn for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs.

[16] 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.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAE	Acquired angioedema
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{0-t}	AUC from time zero to the last quantifiable concentration in plasma at time t
$AUC_{0-\infty}$	AUC from time 0 to infinity
AUC_{last}	AUC from time 0 to the last measurable concentration
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C1-INH	C1 inhibitor
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
C_{max}	Maximum plasma drug concentration
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRO	Clinical Research Organization
DMID	Division of Microbiology and Infectious Diseases
DP	Drug product
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EQ-5D	A standardized instrument for use as a measure of health outcome
ET	Early termination
FDA	Food and Drug Administration

GCP	Good Clinical Practice
HAE	Hereditary angioedema
HIPAA	Health Information Portability and Accountability Act
HMWK	High molecular weight kininogen
HR	Heart rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgG1	Immunoglobulin G subclass 1
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
K_i	inhibition constant
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Prothrombin time
REB	Research ethics board
RBC	Red blood cell (count)
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous

SD	Standard deviation
SF-36	A multi-purpose short form healthy survey with 36 questions
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SOC	System Organ Class
SOP	Standard operating procedure
$t_{½}$	Terminal elimination half-life
t_{max}	Time to maximum plasma concentration
TEAE	Treatment-Emergent Adverse Event
TT	Thrombin time
US	United States
Vd/F	Apparent volume of distribution during terminal phase after extravascular administration
WBC	White blood cell (count)
WHO	World Health Organization

1 INTRODUCTION

1.1 DX-2930

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 hereditary angioedema (HAE), a serious and life-threatening disease.

1.2 Hereditary Angioedema

HAE is a long-term, debilitating, and life-threatening disease caused by mutations in the C1-inhibitor (C1-INH) gene, resulting in deficiency or dysfunction of C1-INH protein. HAE manifests clinically as unpredictable, intermittent attacks of subcutaneous or submucosal edema of the face, larynx, gastrointestinal tract, limbs and/or genitalia (Zuraw, 2008). Swelling may last up to five or more days; most patients suffer multiple attacks per year. HAE is an orphan disorder. The exact prevalence of HAE is unknown, but current estimates range from 1 per 10,000 to 1 per 150,000 persons, with many authors agreeing that 1 per 50,000 is likely the closest estimate (Bygum, 2009; Goring et al., 1998; Lei et al., 2011; Nordenfelt et al., 2014; Roche et al., 2005).

Swelling in the larynx can obstruct the airways and cause death from asphyxiation (Bork et al., 2012; Bork et al., 2000). Approximately 50% of all HAE patients will experience a laryngeal attack in their lifetime, and there is no way to predict which patients are at risk of a laryngeal attack (Bork et al., 2003; Bork et al., 2006).

Abdominal attacks are often associated with nausea, vomiting, and severe pain; intestinal symptoms resembling abdominal emergencies may lead to unnecessary surgery (Zuraw, 2008).

Approximately 85% of patients have Type I HAE, characterized by very low production of functionally normal C1-INH protein, while the remaining approximately 15% of patients have Type II HAE and produce normal or elevated levels of a functionally impaired C1-INH (Zuraw, 2008). In patients with Types I and II HAE, uncontrolled plasma kallikrein generation results in excess bradykinin release from high-molecular weight kininogen (HMWK) and vascular leak mediated by bradykinin binding to the B2 receptor (B2-R) on the surface of endothelial cells (Zuraw, 2008). Clinical suspicion of Types I and II HAE can be confirmed by available blood tests. In addition to abnormalities in C1-INH level and function, plasma C4 levels are markedly reduced at all times in blood from most patients.

1.3 Therapeutic Rationale for DX-2930

Plasma kallikrein plays a critical role in the pathogenesis of HAE attacks (Davis, 2006; Kaplan and Joseph, 2010). In normal physiology, C1-INH regulates the activity of plasma kallikrein as well as a variety of other proteases, such as C1r, C1s, factor XIa, and factor XIIa. Plasma kallikrein regulates the release of bradykinin from HMWK. Due to a deficiency

of C1-INH in HAE, uncontrolled plasma kallikrein activity occurs and leads to the excessive generation of bradykinin. Bradykinin is a vasodilator which is thought to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain (Craig et al., 2012; Zuraw et al., 2013). Intervening at the level of bradykinin production with a plasma kallikrein inhibitor therefore represents an attractive and rational therapeutic strategy for HAE. Indeed, the importance of plasma kallikrein as a drug target in HAE has been validated through the observed effectiveness of Kalbitor® (ecallantide), a peptide that specifically targets plasma kallikrein, which was approved by the FDA for the treatment of acute HAE attacks (Kalbitor® Package Insert, 2015).

DX-2930 is a highly potent and specific inhibitor of plasma kallikrein (K_i = 125 pM). X-ray crystallography of DX-2930 combined with plasma kallikrein demonstrates DX-2930 binding to the active site of kallikrein (Kenniston et al., 2014).

1.4 Safety Rationale for DX-2930

Safety data from the Phase 1a clinical study, a first-in-human study with DX-2930 in healthy subjects did not identify any safety concerns. Single doses up to 3 mg/kg of DX-2930 were well-tolerated. There were no dose-limiting toxicities, serious adverse events, or any other safety concerns identified.

Pharmacokinetic (PK) data from the Phase 1a (DX-2930-01) and Phase 1b (DX-2930-02) clinical studies in conjunction with data from the nonclinical toxicity studies support a wide safety margin. The mean C_{max} for human subjects treated at a dose of 300 mg on Days 1 and 15 was approximately 27 µg/ mL. As comparison, a mean C_{max} of 744 µg/ mL was observed following dosing of monkeys with 50 mg/kg DX-2930 subcutaneous (SC) weekly for 6 months resulting in a safety margin of approximately 28-fold. No toxicologically significant findings were observed in these treated animals or in any other nonclinical toxicity study to date for systemically administered DX-2930.

Safety data is also available from the Phase 1b study (DX-2930-02), a multiple-ascending dose study in HAE patients. In this study, two doses of DX-2930 up to 400 mg administered 14 days apart were well-tolerated. There were no dose-limiting toxicities, serious adverse events in any DX-2930 treated subjects, or any other safety concerns identified in this study of HAE patients. Pharmacokinetic data from the 1b study found that the drug exposure following two administrations of DX-2930 (up to a maximum of 400 mg) was substantially less than that attained and evaluated in the nonclinical toxicity studies.

For additional detail regarding the safety rationale for DX-2930, please refer to the DX-2930 Investigator's Brochure.

1.5 DX-2930 Non-Clinical Pharmacology and Toxicology

For more detail regarding the nonclinical findings, please refer to the DX-2930 Investigator's Brochure.

1.6 DX-2930 Clinical Data

The clinical development program to date for DX-2930 consists of 2 studies to evaluate the safety, tolerability, and PK of DX-2930, including one completed Phase 1a single-ascending dose study in healthy subjects and a Phase 1b multiple-ascending dose study in HAE patients. These studies are summarized in the following sections.

1.6.1 Single-Ascending Dose Study in Healthy Subjects (DX-2930-01)

DX-2930-01 was a Phase 1a randomized, double-blind, placebo-controlled study in healthy subjects to evaluate the safety, tolerability, and PK following a single, SC dose of DX-2930. Participating subjects were randomized to receive placebo or active study drug within one of the following sequential, ascending dose cohorts: 0.1, 0.3, 1.0, or 3.0 mg/kg. For each dosing cohort, 6 subjects were randomized to receive active drug and 2 subjects to receive placebo.

A total of 32 subjects enrolled in the study and were randomized. The treatment groups were well balanced for demographic characteristics. The actual dose of DX-2930 administered to subjects ranged from 6.2 mg (in the 0.1 mg/kg group) to 300 mg (in the 3.0 mg/kg group) across all cohorts.

Based on the safety analysis, a single administration of DX-2930 was well tolerated up to doses of 3.0 mg/kg without evidence of dose-limiting toxicity. There were no deaths, SAEs, or subject discontinuations due to adverse events (AEs) during the study. Furthermore, there was no significant imbalance between placebo and DX-2930 for any particular treatment-emergent adverse event (TEAE). The most commonly reported TEAE was headache, which occurred at a rate of 25% for both DX-2930 and placebo.

The PK profile demonstrated linear, dose-dependent drug exposure with a mean half-life of approximately 17 to 21 days across dose groups. Results from two exploratory biomarker assays provide evidence for an important pharmacodynamic effect of DX-2930 in humans.

For additional detail regarding the single dose, clinical study in healthy subjects, please refer to the DX-2930 Investigator's Brochure.

1.6.2 Multiple-Ascending Dose Study in HAE Patients (DX-2930-02)

DX-2930-02 was a Phase 1b randomized, double-blind, placebo-controlled, multiple ascending-dose study in patients with HAE to evaluate safety, tolerability, and PK of SC DX-2930. Participating subjects were randomized 2:1 to receive either active study drug or placebo within one of the following sequential, ascending dose cohorts: 30, 100, 300, or 400 mg (nominal 6 subjects per cohort). Each subject received 2 doses of study drug separated by 14 days.

A total of 37 subjects were randomized and treated with DX-2930 or placebo. One subject in the 400 mg dose group received a single dose of DX-2930 and, following several unsuccessful attempts to schedule their second dose, was replaced. This subject returned for a single follow-up visit before being lost to follow-up for reasons not related to the study.

Routine C1-INH testing revealed that one other subject did not have HAE Type I or II, despite a historical lab test indicating otherwise.

Subject demographics were balanced in terms of age, race, ethnicity and BMI. There were slightly more females in the DX-2930 group than in the placebo group (66.7% versus 53.8%).

The most common AEs reported were HAE attacks, injection site pain, and headache. The rates were not appreciably higher in the DX-2930 subjects compared to placebo. Two subjects were reported to have 3 related severe TEAEs. One of these was a DX-2930 subject (30 mg) with injection site pain lasting 1 minute and one was a DX-2930 subject (400 mg) with worsening headache lasting 1 minute and night sweats.

No safety signals were identified for vital signs, physical examinations, clinical laboratory tests, or electrocardiograms (ECG). Results suggested DX-2930 was well tolerated in this study with no evidence of dose-limiting toxicity at doses up to 400 mg.

A total of 3 out of 92 post-dose samples (3.3%), obtained from 2 out of 23 subjects (8.7%), were confirmed to be anti-drug antibody-positive. No samples were positive for neutralizing activity.

The pharmacokinetic analysis for all subjects in the 30, 100, 300 and 400 mg doses showed drug levels in HAE subjects were dose-dependent and exhibited a prolonged half-life of approximately 2 weeks, typical of a human monoclonal antibody. C_{max} drug levels increased with increasing dose, as expected. These parameters were consistent with values obtained in healthy subjects in study DX-2930-01.

A Western blot assay showed pre-dose baseline levels of mean 2-chain HMWK in unactivated plasma collected from HAE patients was approximately 50%. A statistically significant reduction in 2-chain HMWK levels was observed on study days 8 and 22 in the 300 and 400 mg dose groups compared to pre-dose levels, and approached levels similar to that observed in healthy subjects. This outcome demonstrated the pharmacodynamic activity of DX-2930 and its ability to effectively normalize the instability of HAE plasma in this assay.

Primary efficacy analyses were based on subjects in the 300 mg, 400 mg, and placebo dose groups who reported having at least 2 attacks in the 3 months prior to study entry (0.15 attacks/week). Of those subjects treated with 300 or 400 mg DX-2930, 15 of 16 subjects met these criteria. Of the placebo treated subjects, 11 of 13 subjects met these criteria.

The baseline HAE attack rates (attacks/week) were 0.39 attacks per week in the placebo group, 0.33 attacks per week in the 300 mg group, 0.55 attacks per week in the 400 mg group and 0.49 attacks per week in the 300 and 400 mg combined group. During the pre-specified, primary efficacy interval of 6 weeks (from days 8 to 50; corresponding to a period of notable drug exposure), the HAE attack rate, adjusted for baseline attack rate, was 0 in the 300 mg group and 0.045 attacks per week in the 400 mg group, compared to 0.37 attacks per week in

the placebo group. This resulted in a 100% reduction vs placebo for the 300 mg DX-2930 group ($P < 0.0001$) and an 88% reduction vs placebo for 400 mg DX-2930 ($P = 0.005$). During this primary efficacy interval, 100% of subjects in the 300 mg group ($P = 0.026$) and 82% of subjects in the 400 mg group ($P = 0.03$) were attack-free compared with 27% of subjects in the placebo group.

The data from this study demonstrated proof of concept of the ability of DX-2930 to prevent acute attacks of HAE. A statistically significant finding of HAE attack prevention by DX-2930 was observed. DX-2930 was well tolerated in HAE subjects up to 400 mg. Drug exposure appeared to be dose-proportional and consistent with the results obtained in healthy subjects in study DX-2930-01. Pharmacodynamic effect assays provided evidence that DX-2930 has a direct effect on plasma kallikrein activity in patient plasma.

For additional detail regarding the multiple dose, clinical study in HAE subjects, please refer to the DX-2930 Investigator's Brochure.

1.7 Rationale for Open-Label Extension Study DX-2930-04

The open-label DX-2930 extension study will be preceded by the initiation of a pivotal, multi-center, double-blind, randomized, placebo-controlled parallel-arm study (DX-2930-03) evaluating the efficacy of DX-2930 in preventing acute angioedema attacks in patients with Type I or Type II HAE. Further information on the DX-2930-03 study design can be found in Appendix 5.

Subjects who complete the DX-2930-03 treatment period will be offered the option of rolling into the open-label extension study, DX-2930-04. A limited number of individuals with HAE Type I or Type II who were not enrolled in DX-2930-03 (up to 50) will be also enrolled.

The rationale for this open-label extension study is to evaluate the long term safety and efficacy of repeated treatment with DX-2930. For subjects rolling over from DX-2930 who were randomized to one of the active study arms, the duration of exposure will cover 1 full year. For rollover subjects randomized to placebo in DX-2930-03, and for non-rollover subjects, the duration of exposure will cover 6 months. Combined, the overall exposure between DX-2930-03 and DX-2930-04 provide a sizable dataset to evaluate DX-2930 as a life-long, chronic treatment for preventing acute attacks of HAE.

This study also seeks to characterize the outer bounds of DX-2930 dosing frequency (possibly beyond 2 to 4 weeks) by assessing the duration of time between rollover subject's first open-label dose and their first reported HAE attack. Additionally, this study will assess the immunogenicity of DX-2930 administered chronically as well as evaluate PK, PD and subject quality of life data following repeated administrations.

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objectives

- To evaluate the long-term efficacy of DX-2930 in preventing HAE attacks.
- To characterize the outer bounds of dosing frequency for DX-2930.

2.3 Tertiary Objectives

- To assess the immunogenicity of chronically administered DX-2930.
- To evaluate the effect of DX-2930 upon quality of life assessments.
- To evaluate Pharmacodynamic (PD) and Pharmacokinetic (PK) data following open-label DX-2930 dosing

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Overview

This study is an open-label, long term safety and efficacy study to evaluate DX-2930 in preventing acute angioedema attacks in patients with Type I and Type II HAE. There are two types of subjects who will be enrolled into this study:

1. Subjects who rollover from the DX-2930-03 study.
2. Subjects who were not participants in DX-2930-03.

Roll-over Subjects:
Rollover subjects are subjects who complete the double-blind treatment period at Day 182 of the DX-2930-03 study and consent to enter DX-2930-04. Subjects who discontinue from DX-2930-03 after enrollment are not eligible to enroll in DX-2930-04. Willing subjects must sign informed consent for DX-2930-04 no later than the DX-2930-03 Day 182 treatment period study visit.

The first DX-2930-04 visit for rollover subjects (Day 0) will occur on the same day as the DX-2930-03 Day 182 study visit. Rollover subjects will complete all DX-2930-03 final study assessments at which time they will be discharged from that study. No assessments conducted between the DX-2930-03 Day 182 study visit and the first DX-2930-04 visit (Day 0) will be duplicated. Results of the final DX-2930-03 assessments will be used as the pre-dose results for Day 0 Dose 1 of DX-2930-04.

Subjects who are eligible to roll over into DX-2930-04 but elect not to may not enroll in DX-2930-04 at a later time.

All subjects, caregivers, Investigators and site personnel will remain blinded to the DX-2930-03 treatment assignment until the conclusion of the DX-2930-04 study.

Non-rollover subjects:
Up to 50 subjects who were not participants in the DX-2930-03 study will be permitted to enroll if they meet the eligibility requirements. Subjects who screen fail out of DX-2930-03 for not meeting the minimum attack requirements during the run-in period must wait until enrollment for the double-blind study has ended before they can screen for DX-2930-04. The Sponsor may ease this restriction based on the enrollment rate observed in DX-2930-03.

Screening Period:
There is no screening period for rollover subjects.

Non-rollover subjects must provide informed consent and have screening assessments completed within 4 weeks prior to their first open-label dose. Screened non-rollover 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 treatment 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 and have no ongoing adverse events related to the washout before they can receive their first open-label dose.

Treatment Period:

Rollover Subjects: Following informed consent and pre-dose assessments, rollover subjects will receive a single open-label dose of 300 mg DX-2930 administered subcutaneously (SC). Subjects will not receive any additional DX-2930 doses until their first reported HAE attack.

The duration of time between the first open-label dose and first reported HAE attack will vary by rollover subject. All rollover subjects must adhere to the Study Activities Schedule, for the entire duration of the study. However, until a rollover subject reports their first HAE attack, only scheduled study visits where the following tests and assessments are performed must be conducted at the investigative site: pregnancy testing, clinical laboratory testing, physical examination, 12-Lead ECG, QOL, PK, PD and anti-drug antibody sample collection. All other scheduled study visits may be conducted via site check-in calls to collect information on adverse events, concomitant therapy, and HAE attack data. Refer to Appendix 1 Study Activities Schedule.

Once a rollover subject reports their first HAE attack they will present to the investigative site for their second open-label dose of DX-2930 as quickly as subject and site schedules allow. If the second dose is to be administered within the accepted ± 4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit unless that scheduled visit has already occurred.

> For example, if the second dose is to be administered on Day 52, all of the tests and assessments scheduled for the Day 56 visit will be conducted. This Day 52 visit to receive the second dose will count as the Day 56 visit.
>
> As another example, if the second dose is to be administered on Day 46, the subject can have this study visit count as their Day 42 visit if they have not already attended the Day 42 visit. If they have already attended the Day 42 visit, then this Day 46 visit will be considered an acceptable, extra study visit.

In the scenario that the second dose is to be administered outside of the accepted ±4 day window around a scheduled visit, this visit will not replace any scheduled visit and will thus represent an acceptable, extra study visit.

> For example, if the second dose is to be administered on Day 63, this visit will represent an acceptable, extra study visit.

Regardless of the study day, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical

examination, clinical laboratory testing, PK, PD, and anti-drug antibody. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data.

Subsequent doses after dose 2 require a minimum of 10 days and maximum of 18 days between administrations, and should fall within the accepted ± 4 day window around study visits.

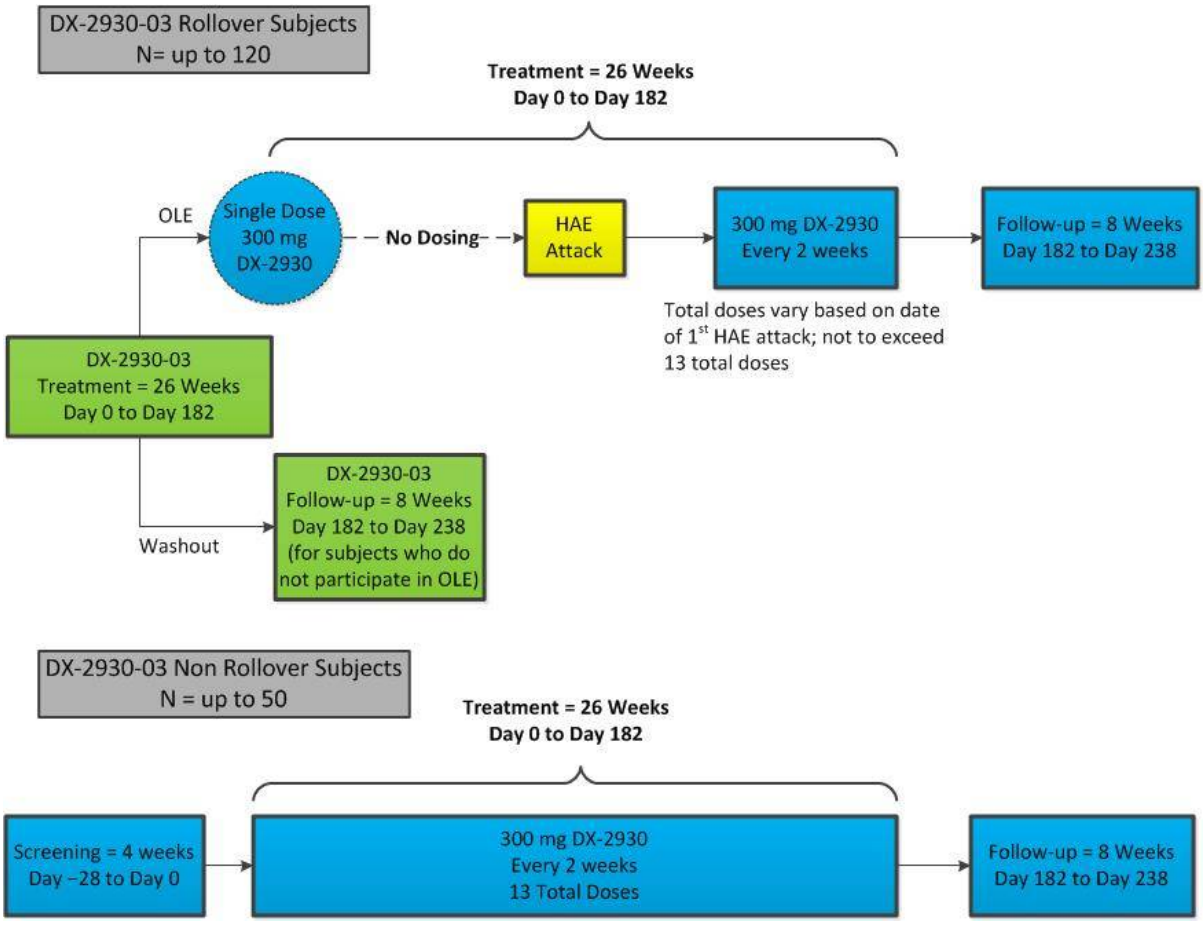
> For example, if the second dose is to be administered on Day 37, the third dose should be administered between Day 52 and Day 55, which would ensure both a dosing interval within 10 to 18 days from the second dose and a visit within the ±4 day window around the Day 56 study visit. The fourth dose should then be administered between Day 66 and Day 73, which would ensure both a dosing interval within 10 to 18 days from the third dose and a visit within the ±4 day window around the Day 70 study visit.

Regardless of when a subject's first HAE attack occurs, there will be a minimum of 10 days between their first open-label dose and their second open-label dose. Following their second open-label dose, subjects will continue to receive repeated SC administrations of open-label 300 mg DX-2930 every 2 weeks for the remaining duration of the treatment period. The treatment period will last 26 weeks from the date of the first open-label dose. The number of doses administered during this period will vary by subject based on the date of each subject's second dose, but will not exceed 13 doses. The Day 168 study visit is the last visit at which a dose may be administered.

Non-rollover Subjects: Once all screening assessments have been completed, eligibility confirmed and LTP washout completed (if applicable), non-rollover subjects will arrive at the study site and, following pre-dose assessments, receive an open-label dose of 300 mg DX-2930 administered SC. Non-rollover subjects will continue to receive SC administrations of open-label 300 mg DX-2930 every 2 weeks throughout the duration of the treatment period. A total of 13 doses will be administered with the last dose administered at the Day 168 study visit.

Follow-up Period:
After completion of the 26-week treatment period, all subjects will undergo safety evaluations during an 8-week follow-up period unless rolling over into another ongoing DX-2930 clinical study or access program that permits such a rollover. Figure 1 shows a schematic of the open-label extension study.

Figure 1. Schematic of the Open-Label Extension Study



Modifications to Open-Label Dosing:
If at any time an important dose-related safety signal is identified either from this study or DX-2930-03, the Sponsor may decide to switch the enrolled subjects who have not yet completed the treatment period, and any subsequent subjects, to receive a different open-label DX-2930 dose and/or frequency.

In addition, based on the results of the DX-2930-03 study, the Sponsor may switch to a different dose and/or frequency.

3.1.2 Stopping Rules

3.1.2.1 Study Level Stopping Rules

Safety data, including SAEs and AESI, will be monitored regularly throughout the duration of the study. If any potential safety signal is identified as a result of monitoring in this study, or from any safety findings from the DX-2930-03 study, the Sponsor may take actions as

deemed appropriate, including suspending dosing in the study, while the potential risk is evaluated and a course of action has been determined.

3.1.2.2 Individual Stopping Rules

Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or a DX-2930-related, clinically significant non-serious AE) that, in the assessment of the Investigator, warrants discontinuation from further dosing for that subject's well-being. The Investigator has the ability to contact and consult with the Medical Monitor on such matters. Subjects will continue to be followed through the completion of all scheduled non-dosing visits, unless they request to be discontinued from the study.

3.1.3 Follow-up for Subjects Meeting Stopping Criteria

Subjects that develop either an SAE or other toxicity considered clinically relevant (AE, laboratory, physical examination, vital sign, or ECG finding) will be carefully monitored until resolution, which may include the following:

- Additional clinical laboratory tests and/or other clinical investigations
- Additional visits or extended duration of follow-up
- Obtaining a specialist consultation

3.2 Rationale for Open-Label Extension Dose Selection

The dose selected for the open-label extension (300 mg every 2 weeks) is anticipated to be effective and safe as determined in the pivotal, double-blind DX-2930-03 trial. If at any time an important dose-related safety signal is identified either from this study or DX-2930-03, the Sponsor may decide to switch the enrolled subjects who have not yet completed the treatment period, and any subsequent subjects, to receive a different open-label DX-2930 dose and/or frequency.

Additionally, based on the efficacy results of the DX-2930-03 study, the Sponsor may switch to a different dose and/or frequency.

3.3 Individual Subject Dosing and Follow-Up

All subjects will receive open-label DX-2930 during a 26-week treatment period. The number of doses that rollover subjects receive during this period will vary by subject but will not exceed 13 doses. The last dose of open-label DX-2930 administered to these subjects may be given at the Day 168 study visit. Non-rollover subjects will receive 300 mg DX-2930 every 2 weeks for a total of 13 doses, with the first dose administered on Day 0 and the final dose administered at the Day 168 study visit.

There will be a ±4 day window around each study visit. There will be a minimum of 10 days between any two doses. Excluding the time interval between the first and second open-label doses for rollover subjects, there will be a maximum of 18 days between any two doses. Subjects will be monitored at the study site through 1 hour post-dose.

3.4 Study Duration for Individual Subjects

Following informed consent, subjects will either rollover from DX-2930-03 or undergo screening assessments (non-rollover subjects). Screening assessments for non-rollover subjects must occur within 4 weeks prior to the first open-label dose. Eligible subjects will be enrolled and undergo a 26-week treatment period. At the conclusion of the 26-week treatment period, subjects will be followed for an additional 8 weeks unless rolling over into another ongoing DX-2930 clinical study or access program that permits such a rollover.

4 STUDY POPULATION SELECTION

4.1 Study Population

The study is expected to enroll subjects from the DX-2930-03 study, as well as up to 50 additional subjects who were not enrolled in DX-2930-03. The total enrollment is expected to be approximately 150 HAE Type I or II subjects. Subjects will be 12 years of age or older who experience at least 1 attack per 12 weeks. HAE diagnosis will be confirmed through documented clinical history and diagnostic testing conducted either during screening or during participation in study DX-2930-02 or DX-2930-03.

The subject population includes subjects who are 12 to 17 years old. Like adults, children with HAE can suffer from recurrent and debilitating attacks. Symptoms may present very early in childhood, and upper airway angioedema has been reported in HAE patients as young as the age of 3 (Bork et al., 2003). In one case series of 49 pediatric HAE patients, 23 had suffered at least one episode of airway angioedema by the age of 18 (Farkas, 2010). An important unmet medical need exists among children with HAE, especially adolescents, since the disease commonly worsens after puberty (Bennett and Craig, 2015; Zuraw, 2008). The study will aim to enroll at least 10 subjects who are 12 to 17 years of age, inclusive of subjects 12 to 17 years old who roll over from the DX-2930-03 study.

4.2 Inclusion Criteria

Subjects must meet the following criteria to be enrolled in this study:

1. Male and female HAE subjects who are 12 years of age or older at the time of screening.

2. Documented diagnosis of disease HAE (Type I or II) based on all of the following:

    - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).

    - Diagnostic testing results obtained during screening (or a prior DX-2930 study) that confirm HAE Type I or II: C1 inhibitor (C1-INH) functional level < 40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by LPT use.

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

3. A historical baseline HAE attack rate of at least 1 attack per 12 weeks.

4. Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects age 12 to 17, whose caregiver

has provided informed consent, are willing and able to read, understand and sign an assent form.

5. Males and females who are fertile and sexually active must adhere to contraception requirements for the duration of the study as follows:

   - Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception from the screening period through 30 days after the final study visit: progestin-only oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD, all types). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.

   - Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.

   - Males, including males who are surgically sterile (post vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study visit.

4.3 Exclusion Criteria

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

1. Discontinued from DX-2930-03 after enrollment for any reason.

2. If rolling over from DX-2930-03, presence of important safety concerns that would preclude participation in this study.

3. Concomitant diagnosis of another form of chronic, recurrent angioedema such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.

4. Dosing with an investigational drug (not including DX-2930) or exposure to an investigational device within 4 weeks prior screening.

5. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.

6. Use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to the start of the treatment period (Day 0).

7. Use of short-term prophylaxis for HAE by non-rollover subjects within 7 days prior to the start of the treatment period (Day 0). Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.

8. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's Syndrome).

9. Pregnancy or breastfeeding.

10. Subject has any condition that, in the opinion of the Investigator or Sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., history of substance abuse or dependence, a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of study results).

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

For detailed information regarding open-label DX-2930 administration, refer to the Pharmacy Manual.

DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated using the following compendial components: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Polysorbate 80. Each open label vial contains a nominal concentration of 150 mg DX-2930 active ingredient in 1 mL solution.

For each 300 mg dose of DX-2930, each subject will receive a total of 2 mL, which will be administered in a single 2.0 mL SC injection. The injection will be given in the upper arm, thigh or abdomen.

5.2 Dosing and Follow-Up Scheme

Details of subject dosing and follow-up are outlined in Section 3.1.1 and included in the Study Activities Schedule, Appendix 1.

Rollover subjects will receive their first open label SC dose of 300 mg DX-2930 on Day 0. Subjects will not receive any additional DX-2930 doses until their first reported HAE attack. Following this attack subjects will receive open label SC doses of 300 mg DX-2930 every 2 weeks until the end of the treatment period.

The treatment period will last 26 weeks from the date of the first open-label dose. The number of doses administered during this period will vary by subject based on the date of each subject's second dose, but will not exceed 13 doses. The Day 168 study visit is the last visit at which a dose may be administered.

Non-rollover subjects will receive their first open-label dose SC dose of 300 mg DX-2930 on Day 0 and will continue to receive SC administrations of open-label 300 mg DX-2930 every 2 weeks throughout the duration of the treatment period. A total of 13 doses will be administered with the last dose administered at the Day 168 study visit.

After completion of the 26-week treatment period, all subjects will undergo safety evaluations during an 8-week follow-up period unless rolling over into another ongoing DX-2930 clinical study or access program that permits such a rollover.

5.3 Method of Identifying Subjects

Subjects meeting all eligibility criteria will be enrolled in the study and sequentially assigned a unique site-based identification number.

5.4 Prior and Concomitant Therapy

For subjects not rolling over from DX-2930-03, reasonable efforts will be made to determine all relevant treatments received by the subject from the time of screening through the final study visit. For subjects rolling over from DX-2930-03, concomitant therapy use will be carried forward from that study and will continue to be collected through the final study visit.

All information on concomitant therapy (including all prescription/non-prescription medications, herbal medications and vitamin supplements) must be recorded on the subject's eCRF and should include the name of the procedure or drug and duration of the treatment (start and stop dates). Concomitant treatments (non-pharmacological treatments) include any surgical or diagnostic procedures.

5.4.1 Allowed Therapies

The following therapies are allowed during the study:

- Therapies for co-existing conditions, including those for acute attacks of HAE, are permitted if not excluded in Section 5.4.2.
- The use of short-term prophylactic treatment for HAE will be permitted if medically indicated. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.
- Therapies to treat any AEs the subject experiences during the study are permitted.

5.4.2 Excluded Concomitant Therapies

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

- Long-term prophylaxis for HAE (e.g., use of C1-INH for long-term prophylaxis, attenuated androgens, or anti-fibrinolytics).
- Angiotensin-converting enzyme (ACE) inhibitors.
- Estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy).
- Androgens (e.g., stanozolol, danazol, oxandrolone, methyltestosterone, testosterone).
- Any other investigational drug or device.

5.5 Restrictions

5.5.1 Medical Interventions

Medical interventions deemed necessary by the Principal Investigator for the health and well-being of the subject will not be excluded during this study.

5.5.2 Fluid and Food Intake

There are no restrictions on fluid and food intake. Subjects may continue their usual dietary regimens.

5.5.3 Activity

There are no activity restrictions. Subjects may continue their usual activity regimens.

5.6 Treatment Compliance

All doses of open-label DX-2930 will be administered during clinic visits under the direct supervision of the Investigator or qualified site personnel designated by the Investigator.

5.7 Packaging and Labeling

The open-label DX-2930 will be supplied by Dyax Corp. and packaged and labeled according to applicable local and regulatory requirements for investigational studies.

5.8 Storage and Accountability

All of the DX-2930 must be stored refrigerated (2ºC to 8ºC/36ºF to 46ºF) in the carton and protected from light, in a securely locked area, accessible to authorized persons only, until needed for dose preparation. Qualified site personnel will inventory the DX-2930 received and will maintain records of disposition of the drug, including dates, quantity and use.

5.9 Investigational Medicinal Product Retention at Study Site

The Investigator (or designee) is responsible for maintaining accurate accountability records of DX-2930 throughout the clinical study. All DX-2930 received at the site must be inventoried and accounted for in an accountability log provided by the Sponsor. All dispensing and accountability records will be available for Sponsor review. Drug accountability will be verified during on-site monitoring visits.

Upon the completion or termination of the study, and upon written authorization from the Sponsor, or its representative, all unused and/or partially used DX-2930 should be returned or destroyed at the investigational site, as specified by Sponsor. It is the Investigator's responsibility to ensure that the Sponsor, or its representative, has provided written authorization that procedures for proper disposal of the DX-2930 have been established, and that appropriate records of the disposal are documented and maintained. No unused DX-2930 may be disposed until fully accounted for by the Sponsor monitor (or designee).

6 STUDY PROCEDURES

Please refer to the Study Activities Schedule, Appendix 1.

6.1 Informed Consent

The ICF must be executed prior to performing any study related activities and must be approved by the reviewing institutional review board (IRB), research ethics board (REB) or independent ethics committee (IEC). Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the Investigator.

Subjects who are not rolling over from the double-blind DX-2930-03 study will provide informed consent at Screening. Subjects who are rolling over from the double-blind DX-2930-03 study will provide consent no later than the DX-2930-03 Day 182 study visit. Upon completion of the final assessments, the subjects will be discharged from the double-blind study and will start participation in the OLE study and receive their first open-label dose.

6.2 Eligibility Review

The Investigator or qualified site personnel will confirm that all Inclusion and Exclusion criteria have been met.

6.3 Demographics and Medical History

Demographics: date of birth (alternately age or year of birth, if full date is not allowed to be collected for legal reasons), sex, race and ethnicity (where locally permitted) and medical history will be obtained at Screening from subjects not rolling over from DX-2930-03 and will be recorded on the source document and eCRF. Medical history will capture the subject's current medical status (current disease processes), past medical status (past disease processes), history of surgery, allergies and concomitant medications. For subjects rolling over from DX-2930-03, these data will be carried forward from that study.

6.4 HAE Attack Information Collection

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 and enrolling subjects at their site.

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

At screening, HAE attack history will be collected for non-rollover subjects. Information collected will include any prior history of laryngeal attacks, attack frequency, average

severity, predominant attack location(s), average duration, acute attack therapy use and history of long-term prophylaxis.

During the study, subjects (or caregivers) will be instructed to notify and report details to the study site within 72 hours of the onset of an attack. This includes the first attack experienced by rollover subjects following their first open-label dose. In the situation 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 experienced.

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.

Site personnel will contact rollover subjects approximately every 7 days following the first dose of open-label DX-2930 to solicit for any HAE attacks not already reported. Site check-ins will continue until the subject has received their second open-label dose.

During each study visit, site personnel will solicit for any new HAE attack information that was not already provided to the site.

In this study, HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to DX-2930, 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 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 to receive additional information. Any subject-reported attack not confirmed by the Investigator or

physician designee must have an alternate AE diagnosis recorded. All subject-reported and Investigator/ physician designee-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 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 or physician designee may still clinically determine that the event did not represent an 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 (e.g., greater than 7 days), 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.

6.5 Vital Signs

Vital signs will be assessed by the Investigator or his/her qualified designee according to the Study Activities Schedule (Appendix 1). 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. For subjects who rollover from DX-2930-03, vital signs taken during the final study visit in DX-2930-03 will serve as the Day 0 pre-dose vital signs in this study and will not be duplicated.

6.6 Physical Examination

A complete 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 1). The physical examination will include the following body systems:

- Height and weight (at Screening visit only for non-rollover subjects)
- General appearance

- Ears, nose, and throat
- Head and neck
- Ophthalmological
- Respiratory
- Cardiovascular
- Abdomen
- Neurological
- Extremities
- Dermatological
- Lymphatic

For subjects who rollover from DX-2930-03, physical exam taken during the final study visit in DX-2930-03 will serve as the Day 0 pre-dose physical exam in this study and will not be duplicated.

6.7 Electrocardiography (ECG)

A standard 12-lead ECG (single recording) will be performed according to the Study Activities Schedule (Appendix 1). 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. For subjects who rollover from DX-2930-03, the ECG taken during the final study visit in DX-2930-03 will serve as the Day 0 pre-dose ECG in this study and will not be duplicated.

6.8 Clinical Laboratory Tests

6.8.1 Laboratory Parameters

Laboratory testing will be performed according to the Study Activities Schedule (Appendix 1).

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

When multiple sample collection types are performed at the same assessment time point, the samples will be drawn in the following order (depending on what sample types are to be collected at that time point): laboratory safety samples (hematology, coagulation, serum chemistry), C1-INH, C4, C1q, PK, anti-drug antibodies, PD. Aliquots from the PK, PD and anti-drug antibody samples may be retained as back-up for additional parameter testing if necessary. Subjects will be in a seated or supine position during blood collection. The total blood draw for each roll-over subject will be approximately 144 mL. The total blood draw

for each non roll-over subject will be approximately 157 mL. For subjects who rollover from DX-2930-03, testing performed during the final study visit in DX-2930-03 will serve as the Day 0 pre-dose laboratory testing in this study and will not be duplicated.

6.8.1.1 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

6.8.1.2 Coagulation

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

6.8.1.3 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

6.8.1.4 Urinalysis

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

6.8.1.5 Pregnancy Test

Pregnancy tests will be either serum or urine based.

6.8.1.6 C1-INH Functional Assay

Results of a C1-INH functional assay are required for eligibility assessment. Samples will be drawn at the Screening visit unless they were previously drawn in study DX-2930-02 or DX-2930-03. Results of the C1-INH functional assay from DX-2930-02 or DX-2930-03 may be used to confirm diagnosis in this study. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.

6.8.1.7 C4 Assay

Results of a C4 assay may be required for eligibility assessment. The C4 sample will be drawn at the same time as the C1-INH sample is drawn during the Screening visit unless previously drawn in study DX-2930-02 or DX-2930-03. Results of the C4 assay from DX-2930-02 or DX-2930-03 may be used to confirm diagnosis in this study. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.

6.8.1.8 C1q Assay

Results of a C1q assay may be required for eligibility assessment. Any subject who requires C1-INH and C4 assay results for diagnostic confirmation in this study will have C1q assay results obtained as well. The C1q sample will be drawn at the same time as the C1 and C4 sample is drawn during the Screening visit.

6.8.1.9 PK Sample Collection

As outlined in Section 6.9.

6.8.1.10 PD Sample Collection

As outlined in Section 6.10.

6.8.1.11 Plasma Anti-Drug Antibody Testing

As outlined in Section 6.11.

6.8.2 Sample Collection, Storage, and Shipping

Blood samples for laboratory assessments will be collected at the site by a trained phlebotomist designated and/or approved by the study Investigator. Details for the collection, processing, storage and shipment of samples for all laboratory determinations will be provided in the Laboratory Manual.

Biological material will be stored and secured in a manner that assures that unauthorized access is prohibited and the samples are not lost, allowed to deteriorate, or accidentally or illegally destroyed.

6.9 Pharmacokinetic Assessments

Blood samples for the measurement of plasma DX-2930 concentration will be obtained as specified in the Study Activities Schedule (Appendix 1).

6.10 Pharmacodynamic Assessments

To evaluate the PD effects of DX-2930 upon plasma kallikrein activity, blood samples will be obtained as specified in the Study Activities Schedule (Appendix 1).

6.11 Plasma Anti-Drug Antibody Testing

Plasma samples for testing for formation of antibodies to DX-2930 will be obtained as specified in the Study Activities Schedule (Appendix 1).

6.12 Prior and Concomitant Therapy

The Sponsor representatives and Investigator at the site conducting the trial will review and evaluate prior and concomitant medication usage on an ongoing basis. For subjects not rolling over from DX-2930-03, 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 on the source document and eCRF following informed consent. For subjects rolling over from DX-2930-03, concomitant therapy use will be carried forward from that study and will continue to be collected through the duration of the study.

6.13 Investigational Medicinal Product Treatment

Instructions for safe handling of DX-2930, preparation of each subcutaneous dose and administration of DX-2930, are provided in the Pharmacy Manual. Preparation and dispensing of DX-2930 will be handled by qualified site personnel as directed by the Principal Investigator at the study site. The requirements for maintaining DX-2930 accountability are provided in Section 5.8 of this protocol.

6.14 Quality of Life Assessments

Quality of life data will be collected using the EQ5D, SF-36 and the Angioedema Quality of Life Questionnaire (AEQoL), as specified in the Study Activities Schedule (Appendix 1). For subjects who rollover from DX-2930-03, quality of life assessments obtained during the final study visit in DX-2930-03 will serve as the Day 0 pre-dose quality of life assessments in this study and will not be duplicated.

6.15 Adverse Event Reporting

Adverse events will be collected from signing of the informed consent through the last study visit.

6.15.1 Definitions

6.15.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical trial subject whether or not it appears to have a causal relationship with the treatment administered.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or participation in a clinical study, whether or not directly related to the medicinal product or study participation.

- AEs may be new events or may be pre-existing conditions that have become aggravated or have worsened in severity or frequency during the course of the study.
- AEs may be clinically significant changes from baseline in physical examination, laboratory tests, or other diagnostic investigation (e.g., laboratory results, x-ray findings).

Laboratory abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. A clinically significant laboratory abnormality that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to DX-2930 interruption or discontinuation, will in itself, be considered an AE. Laboratory or diagnostic testing abnormalities that reflect or are part of a known underlying medical condition are not, in themselves, AEs; rather, the underlying medical condition leading to the abnormalities would be reported as the AE.

Pregnancy is not an AE; however, if a female subject becomes pregnant during the conduct of the study, the Investigator must notify the Sponsor according to the procedures provided in Section 6.15.5.2.

6.15.1.2 Serious Adverse Event

A SAE is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening experience; Note: "Life-threatening" refers to a situation in which the subject was at risk of death at the time of the event; it does not refer to an event that might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization; Note: Does not include hospitalization for observation with release within 24 hours. A scheduled hospitalization for a pre-existing condition that has not worsened during participation in the study does not meet this criterion. Pre-planned hospitalizations for an elective medical/surgical procedure or routine check-ups do not meet this criterion.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is considered to be an important medical event defined as those that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

6.15.1.3 Overdose

An overdose is defined as a significant variation from the recommended/scheduled dosage for a product. The dosing for this study will be conducted in a controlled clinical setting and an overdose is not anticipated. However, in the event of an accident, for this study, an overdose of DX-2930 is considered a dose that is two-fold higher than the intended dose for the subject.

6.15.1.4 Planned Hospitalization

A hospitalization planned by the subject prior to the first dose of open-label DX-2930 is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the trial, it must be reported as an AE.

6.15.1.5 Treatment-Emergent Adverse Events (TEAE)

An AE is treatment-emergent if the onset time is after first administration of open-label DX-2930 through the final follow-up visit or, in the event that onset time precedes first DX-2930 administration, the AE increases in severity during the open-label treatment period.

For rollover subjects, any adverse event that started during the subject's participation in DX-2930-03 and was ongoing at the time of the first open-label dose in DX-2930-04 will not be counted as an AE in DX-2930-04 unless that event has worsened in severity or frequency following the first open-label dose. Adverse events that started during subject participation in DX-2930-03, resolved following the first open-label dose in DX-2930-04, and then subsequently reappeared in DX-2930-04 will be counted as a new TEAE in DX-2930-04.

6.15.1.6 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) will be captured and monitored during this study. **Investigators will report all AESI to Dyax, regardless of causality, using the same timelines as described for SAE reporting.** The following describe the AESI and the criteria for reporting AESI.

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

Athough 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.

6.15.2 Monitoring

6.15.2.1 Monitoring of Adverse Events

Each subject will be monitored for the occurrence of AEs, including SAEs and AESI, from signing of the ICF through the final follow-up visit.

- Subjects will be questioned and/or examined by the Investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.
- Subjects having TEAEs will be monitored until resolution with relevant clinical assessments and laboratory tests, as determined by the Investigator.
- AEs, actions taken as a result of AEs, and follow-up results must be recorded in the eCRF as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For any SAEs or AEs that require the subject to be discontinued from dosing, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s). Subjects will continue to be followed through completion of all scheduled visits.

6.15.2.2 Monitoring of Safety Laboratory Assessments

All safety laboratory assessments will be performed at a central laboratory. The clinical laboratory values will be reported to the Investigator who will review them for clinical significance and consideration of abnormal values as potential AEs.

6.15.3 Assessment of Adverse Events

6.15.3.1 Assessment of Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

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) (Appendix 2) 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) (Appendix 3). For abnormalities not specifically found in the Toxicity Tables, the following general scale will be used to estimate grade of severity:

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

- GRADE 4 (Life-threatening): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

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

6.15.3.2 Assessment of Causality

A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of DX-2930, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
- The temporal association between DX-2930 exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of DX-2930.
- The AE resolved or improved with decreasing the dose or stopping use of DX-2930 (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between DX-2930 and the AE will be assessed using one of the following categories:

Not Related: Factors consistent with an assessment of Not Related include:

- Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of DX-2930); or
- Other causative factors more likely explain the event (e.g., a pre-existing condition, other concomitant treatments).

Related: Factors consistent with an assessment of Related include:

- There is a positive temporal relationship (e.g., the event occurred within a reasonable time frame following administration of DX-2930); or
- The AE is more likely explained by administration of DX-2930 than by another cause (i.e., the AE shows a pattern consistent with previous knowledge of DX-2930 or the class of DX-2930).

6.15.3.3 Assessment of Clinical Significance

Clinical significance of individual AEs will be determined by the Investigator, with discussion with the Medical Monitor as appropriate.

6.15.4 Clinical Laboratory Adverse Events

Laboratory abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. A clinically significant laboratory abnormality that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to DX-2930 treatment interruption or discontinuation, will be considered an AE.

When laboratory abnormalities are considered to be AEs, the DMID Adult Toxicity Table (Appendix 2) or DMID Pediatric Toxicity Tables (Appendix 3) will be used to assess severity. Where discrepancies in the upper limit of normal (ULN) and lower limit of normal (LLN) of laboratory ranges occur between those included in the DMID tables and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade. Clinical significance of individual laboratory AEs will be determined by the Investigator with input from the Medical Monitor as needed.

Following is an exception to defining clinically significant, abnormal laboratory values as AEs:

- APTT prolongation in the absence of any associated bleeding or other evidence of clinical relevance will not be considered a clinically significant laboratory abnormality or AE. In the appropriate physiologic setting, such as IV heparin therapy, aPTT can be used to monitor bleeding risk. However, as noted in the Investigators Brochure, aPTT prolongation due to plasma kallikrein inhibition is an artifactual *in vitro* phenomenon. Although plasma kallikrein drives fibrin formation in the aPTT assay, plasma kallikrein-driven coagulation does not appear to have hemostatic or other physiologically important functions *in vivo*. It is well documented that, in humans, deficiency of factor XII or prekallikrein (and thus plasma kallikrein) is not associated with abnormal bleeding, either spontaneous or during surgical procedures (Renne and Gruber, 2012). Despite the lack of clinical effect, deficiency of either protein is associated with marked prolongation of the aPTT.

6.15.5 Reporting Investigator Safety Observations to the Sponsor

6.15.5.1 Reporting Non-serious Adverse Events

All AEs, regardless of seriousness, severity, or causal relationship to DX-2930, will be recorded on the AE page of the eCRF. In this study all HAE attacks reported by the subject, regardless of whether or not they are confirmed by the Investigator, will be captured as AEs.

6.15.5.2 Reporting Pregnancies

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, the Investigator must report the pregnancy to the Dyax Pharmacovigilance Department using the **Pregnancy Reporting Form** within **24 hours** of becoming aware of the event. The Investigator must obtain consent to collect pregnancy information (including the status of the newborn, if applicable).

If some of the information required for completion of the Pregnancy Reporting Form is unavailable at the time of the initial report, follow-up reports will be completed and submitted within 24 hours of becoming aware of the new information. The Investigator is required to follow the pregnancy through delivery. The outcome of the pregnancy and the status of the newborn (if applicable) will be reported on the Pregnancy Reporting Form within 24 hours of becoming aware.

6.15.5.3 Safety Observations Requiring Expedited Reporting by the Investigator to Dyax

Any occurrence of the following events or outcomes in a subject in the trial must be reported expeditiously by the Investigator or qualified designee to the Dyax Pharmacovigilance Department:

- SAE
- AESI
- Overdose
- Cancer

The Investigator is to report any expedited safety observations from the list above to Dyax using the **SAE Reporting Form in the EDC system** within 24 hours of becoming aware of the event.

Any SAE reported to the Dyax Pharmacovigilance Department using the SAE Reporting Form in the EDC system is to be recorded in the eCRF, as well as in the subject's source documentation along with any actions taken. If all required information on the form is not available at the time of the initial report, follow-up information will be completed in the EDC system.

The Investigator is required to follow SAEs until resolution regardless of whether the subjects are still participating in the study. SAE resolution is defined as:

- Resolved with or without residual effects.
- A return to baseline for a pre-existing condition.
- Laboratory values have returned to baseline or stabilized.
- The Investigator does not expect any further improvement or worsening of the event.
- Fatal outcome—if an autopsy is performed; the autopsy report is requested to be provided to the sponsor as soon as it is available.

6.15.5.4 Expedited Reporting by the Sponsor to a Regulatory Health Authority

The Sponsor or designee will report relevant safety information to concerned health authorities in accordance with local laws and regulations.

6.15.5.5 Safety Contact Information

24-Hour Medical Safety Contact for US and Canada
[redacted], M.D.
[redacted]
Phone (US): [redacted]
Email: [redacted]
Calls or emails received weekends, holidays, or weekdays between 8:00 pm and 8:00 am Eastern (US) time will be responded to the morning of the following business day

24-Hour Medical Safety Contact for Europe and Middle East
[redacted], M.D.
[redacted]
Phone: [redacted]
Email: [redacted]

Dyax Pharmacovigilance Department
Contacts: [redacted] **or** [redacted]
Email: [redacted]
Phone (US): [redacted]

6.15.5.6 Safety Notifications by the Sponsor to the Investigator

Investigators will receive prompt notification of any adverse experience related to DX-2930 that is both serious and unexpected, or any finding that suggests a significant risk for subjects. The Investigator will promptly inform his / her IRB/REB/IEC of the notification and insert the notification in the Investigator's Regulatory Binder in accordance with local regulations.

6.16 Subject Withdrawal

The Investigator may withdraw a subject from DX-2930 treatment for any of the following reasons:

- In the opinion of the Investigator, the subject is unable to comply with the requirements of the protocol for satisfactory completion or interpretation of study results (including use of prohibitive medications),
- A serious or intolerable AE occurs,
- A clinically significant change in a laboratory parameter occurs,
- The Sponsor or Investigator terminates the study, or
- The subject requests to be discontinued from the study.

Subjects will continue to be followed through completion of all scheduled visits, unless the subject requests to be discontinued from the study.

6.17 Appropriateness of Measurements

This is a Phase 3 open-label extension study that is designed to evaluate the long-term safety and efficacy of DX-2930 in prophylactic therapy for angioedema attacks in subjects with HAE. DX-2930 is a recombinant, fully human IgG1, kappa light chain, monoclonal antibody. The open-label, non-controlled study design is a standard approach for extension studies that follow double-blind pivotal trials. Measures employed in this protocol are standard measures routinely used for the evaluation of the efficacy, safety and tolerability of an investigational product. Measures employed for rollover subjects between the first and second open-label doses are appropriate to characterize the outer bounds of dosing frequency for DX-2930.

7 STUDY ACTIVITIES

Study activities are summarized by study visit in Appendix 1 (Study Activities Schedule).

7.1 Screening Visit (Up to Day −28) For Non-Rollover Subjects

The following procedures and assessments are to be performed during the Screening Visit for subjects not rolling over from the DX-2930-03 study:

- Informed consent (Section 6.1)
- Eligibility review (Section 6.2)
- Demographics and medical history (Section 6.3)
- C1-INH functional assay, C4 and C1q sample collection (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6); documentation of height and weight
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.15); pre-existing signs and symptoms
- Subjects who are on LTP for HAE must complete a minimum 2 week washout period, as confirmed by the Investigator, before entering the treatment period

For subjects rolling over from the double-blind DX-2930-03 study, no Screening visit is required as subjects will enter the OLE on the same day that their last DX-2930-03 study visit is completed. Diagnostic test results and demographic and medical history for these subjects will be carried forward from that study.

7.2 Start of Treatment Period: Visit 1, Dose 1 (Day 0)

The following procedures and assessments are to be performed on Day 0 prior to the first dose of DX-2930. For subjects who rollover from DX-2930-03, all final assessments taken during the final study visit in DX-2930-03 will be used as the pre-dose results on Day 0 and will not be duplicated.

- Informed consent (for subjects rolling over from the double-blind DX-2930-03 study) (Section 6.1)
- Eligibility review (Section 6.2)
- Urine pregnancy test (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)

- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK baseline sample collection (Section 6.9)
- PD baseline sample collection (Section 6.10)
- Baseline anti-drug antibody sample collection (Section 6.11)
- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.15)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- First dose of open-label DX-2930 (Section 5.1)

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.15)

7.3 Interval between Dose 1 and Dose 2 for Rollover Subjects

Rollover subjects must adhere to the Study Activities Schedule for the entire duration of the study. Until a rollover subject reports their first HAE attack, study visits may be conducted via site check in calls, except for the following study visits which must be conducted at the investigative site:

- Day 56
- Day 98
- Day 140
- Day 182

The tests and assessments required at these visits are specified in the sections below.

Site check in calls may serve as any of the following study visits until the subject receives their second open-label dose:

- Day 14
- Day 28

- Day 42
- Day 70
- Day 84
- Day 112
- Day 126
- Day 154
- Day 168

Site personnel will also contact rollover subjects approximately 7 days after each study visit (both site visits and check-in calls) until the subject receives their second open-label dose.

The following assessments are performed during all site calls:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.15)

7.4 Dose 2 of DX-2930 for Rollover Subjects

The duration of time between Dose 1 and Dose 2 will vary by subject based on when their first HAE attack occurs following Dose 1. As a result, rollover subjects may not receive DX-2930 treatment at every dosing visit as outlined in the Study Activities Schedule.

Once a rollover subject reports their first HAE attack they will present to the investigative site for their second open-label dose of DX-2930 as quickly as subject and site schedules allow. This treatment visit may be counted as a scheduled study visit, or as an acceptable extra study visit. For details on determining whether the second dose is counted as a scheduled or extra study visit, refer to Section 3.1.1. Regardless of when the second dose is administered, the following tests and assessments will be conducted pre-dose on the day it is administered:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.15)

The following tests and assessments will also be performed if the second dose occurs on a scheduled study visit for which they are required:

- Urine pregnancy test (females) (Section 6.8)
- 12-Lead ECG (Section 6.7)
- Quality of life assessments (Section 6.14)

After the required pre-dose tests and assessments are completed:

- Second dose of open-label DX-2930 (Section 5.1)

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.15)

7.5 Visit 2 (Day 14 ±4 days); Dose 2 of DX-2930 for Non-Rollover Subjects

On Day 14 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1)

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.15)

7.6 Continuation of Treatment Period: Visits 3 and 4 (Days 28 and 42, All ±4 Days)

On Days 28 and 42 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects these doses represent Dose 3 and Dose 4.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.15)

7.7 Continuation of Treatment Period: Visit 5 (Day 56 ±4 Days)

On Day 56 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 5.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.15)

7.8 Continuation of Treatment Period: Visits 6 and 7 (Days 70 and 84, All ±4 Days)

On Days 70 and 84 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects these doses represent Dose 6 and Dose 7.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.15)

7.9 Continuation of Treatment Period: Visit 8 (Day 98 ±4 Days)

On Day 98 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Urine pregnancy test (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.15)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 8.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.15)

7.10 Continuation of Treatment Period: Visits 9 and 10 (Days 112 and 126, All ±4 Days)

On Days 112 and 126 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects these doses represent Dose 9 and Dose 10.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.15)

7.11 Continuation of Treatment Period: Visit 11 (Day 140 ±4 Days)

On Day 140 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 11.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.15)

7.12 Continuation of Treatment Period: Visits 12 and 13 (Days 154 and 168 All ±4 Days)

On Days 154 and 168 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects these doses represent Dose 12 and Dose 13.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.15)

7.13 Completion of Treatment Period: Visit 14 (Day 182 ±4 Days)

On Day 182, the following procedures and assessments will be performed:

- Urine pregnancy test (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.15)
- Quality of life assessments (Section 6.14)
- Study Discharge: Subjects may have an opportunity to roll into an ongoing DX-2930 clinical study or access program that permits such rollover. Subjects who choose to do this will be discharged at this study visit.

7.14 Follow-up Period: Visit 15 (Day 210 ±4 Days)

On Day 210 all rollover and non-rollover subjects who do not choose to roll over into another ongoing DX-2930 clinical study or access program that permits such a rollover will receive a site check-in call. During this call site personnel will collect information regarding the following:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.15)

7.15 Final Follow-up Visit: Visit 16 (Day 238 ±4 Days)

On Day 238 all rollover and non-rollover subjects who do not choose to roll over into another ongoing DX-2930 clinical study or access program that permits such a rollover will complete a final study visit at the investigative site.

- Urine pregnancy test (females) (Section 6.8)

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Complete physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.15)
- Quality of life assessments (Section 6.14)

7.16 Early Termination

Subjects that terminate early from the study will undergo (if possible) all of the assessments and procedures scheduled for Day 182.

8 QUALITY CONTROL AND ASSURANCE

The Sponsor (Dyax) and the Contract Research Organization (CRO) conducting trial management services, Rho, Inc., will implement a system of quality assurance that includes all elements described in this protocol. Within this system, SOPs from the Sponsor and CRO will be implemented to ensure that the clinical trial is conducted in compliance with regulatory requirements and Good Clinical Practices (GCP). Quality control will be applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The site staff should assist in all aspects of audit/inspection.

9 DATA ANALYSIS / STATISTICAL METHODS

9.1 Sample Size Determination

The study is expected to enroll subjects from the DX-2930-03 study, as well as up to 50 additional subjects who were not enrolled in DX-2930-03. The total enrollment is expected to be approximately 150 HAE Type I or II subjects. No formal sample size calculation was performed. The sample size is not based on any statistical considerations. This study is designed to evaluate the safety and efficacy of open-label treatment with DX-2930 in subjects who participated in DX-2930-03 and individuals who were not otherwise able to participate in DX-2930-03.

9.2 Analysis Populations

The analysis population will be based on subjects who receive at least one dose of DX-2930 after entering the study.

9.3 Comparison of Interest

Because this study consists of a non-randomized, pre-selected population of subjects all receiving DX-2930, hypothesis testing will not be performed. The exception will be the secondary efficacy endpoint of time to first HAE attack for rollover subjects, as described in Section 9.7.

For disposition, demographic and safety analyses, subjects will be represented in the reporting of DX-2930-04 as follows:

- Subjects who received 26 weeks of 300 mg DX-2930 every 2 weeks in DX-2930-03 and up to 26 weeks of DX-2930 treatment in DX-2930-04.
- Subjects who received 26 weeks of 300 mg DX-2930 every 4 week in DX-2930-03 and up to 26 weeks of DX-2930 treatment in DX-2930-04.
- Subjects who received 26 weeks of 150 mg DX-2930 every 4 weeks in DX-2930-03 and up to 26 weeks of DX-2930 treatment in DX-2930-04.
- Subjects received 26 weeks of placebo in DX-2930-03 and up to 26 weeks of DX-2930 treatment in DX-2930-04.
- Subjects who received up to 26 weeks of DX-2930 treatment in DX-2930-04.

Data from the start of DX-2930 treatment through the final treatment period study visit (up to 52 weeks for subjects whose treatment with DX-2930 was initiated in DX-2930-03) will be combined for safety evaluation of the overall DX-2930 exposure.

9.4 Analysis of Disposition

The numbers of subjects completing or withdrawing, along with reasons for withdrawal, will be tabulated by treatment group as indicated in Section 9.3.

9.5 Demographics and Baseline Characteristics Analyses

Baseline and demographic variables will be descriptively summarized by treatment group as indicated in Section 9.3.

9.6 Analysis of Pharmacokinetic and Pharmacodynamic Endpoints

9.6.1 Pharmacokinetic Assessments:

Blood samples will be collected for the measurement of plasma DX-2930 concentrations prior to study drug administration on Day 0 and on Days 98 ±3, 182 ±3, as well as prior to Dose 2 for rollover subjects at whatever study visit that second dose occurs. An additional sample will be collected on Day 238 ±3 for subjects who complete the Follow-up Period.

Plasma concentrations of DX-2930 will be summarized with descriptive statistics by nominal PK sampling time.

9.6.2 Pharmacodynamic Assessments:

Blood samples will be collected to evaluate the pharmacodynamic effects of DX-2930 through biomarker assays prior to study drug administration on Day 0 and on Days 98 ±3 and 182 ±3, as well as prior to Dose 2 for rollover subjects at whatever study visit that second dose occurs. An additional sample will be collected on Day 238 ±3 for subjects who complete the Follow-up Period.

Plasma kallikrein activity will be summarized with descriptive statistics by nominal PD sampling time.

9.6.3 Immunogenicity Assessments:

Blood samples will be collected to assay for the presence of anti-drug antibodies, including evaluation of neutralizing antibodies (if any confirmed positive anti-drug antibodies are detected) prior to DX-2930 administration on Day 0 and on Days 98 ±3 and 182 ±3, as well as prior to Dose 2 for rollover subjects at whatever study visit that second dose occurs. An additional sample will be collected on Day 238 ±3 for subjects who complete the Follow-up Period.

9.6.4 C1-INH, C4 and C1q Assessments:

Samples will be obtained for C1-INH, C4 and C1q assays at screening (or carried forward from the DX-2930-02 or DX-2930-03 studies) for eligibility assessment.

9.7 Analysis of Efficacy Endpoints

9.7.1 Efficacy Endpoints

Efficacy variables will be evaluated by endpoint as outlined below.

The distribution of time from first open-label dose to first HAE attack will be determined for rollover subjects. The estimation will be based on a standard Cox proportional hazards model where several baseline covariates will be tested including baseline attack rate prior to entering DX-2930-03, the treatment arm in DX-2930-03, the time since the last dose given in DX-2930-03, the time since the last HAE attack, and the rate of attacks during DX-2930-03. The distribution of time to first attack will be adjusted for any significant baseline ($p < 0.05$) covariates, and by examining the distribution separately by the treatment arm the patient was in during DX-2930-03. In this survival analysis, one observation (time to first attack) per subject will be generated.

For other efficacy endpoints, mean event rates will be assessed for all subjects (14 days post-second dose to Day 182 for rollover subjects; Day 14 to Day 182 for non-rollover subjects).

In addition, for rollover subjects, the mean change from the documented values in DX-2930-03 at baseline (last measurement prior to randomization into DX-2930-03) and entry (last measurement in DX-2930-03 prior to enrollment into DX-2930-04) will be compared to the values assessed at DX-2930-04 time points from 14 days after the second dose in DX-2930-04 through Day 182 (i.e., 2 weeks after the final scheduled dose on Day 168). Changes will be calculated and presented as descriptive statistics for each DX-2930-03 treatment group (300 mg DX-2930 every 2 weeks, 300 mg DX-2930 every 4 weeks, 150 mg DX-2930 every 4 weeks). For each time period, graphs will be constructed for mean changes in efficacy variables from baseline. Time periods will be defined as relative time from the DX-2930-03 baseline for those who participated.

For non-rollover subjects, efficacy variables will be presented as descriptive statistics only.

Efficacy Endpoints

- Time to first HAE attack for rollover subjects (based upon time from first open label study dose until first HAE attack)
- Mean rate of HAE attacks for all subjects (14 days post-second dose to Day 182 for rollover subjects; Day 14 to Day 182 for non-rollover subjects
- Mean rate of acute therapy usage for all subjects (14 days post-second dose to Day 182 for rollover subjects; Day 14 to Day 182 for non-rollover subjects.
- Mean rate of moderate or severe attacks for all subjects (14 days post-second dose to Day 182 for rollover subjects; Day 14 to Day 182 for non-rollover subjects
- Mean rate of high-morbidity attacks for all subjects (14 days post-second dose to Day 182 for rollover subjects; Day 14 to Day 182 for non-rollover subjects; 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.

9.8 Safety Analysis

Evaluation of safety data will include all patients who received at least one dose of study medication. Clinical interpretation will be based upon review of displays of adverse events and laboratory values. Principal considerations in this evaluation will be time to onset, and investigator-reported relationship of either adverse events or laboratory abnormalities to study medication.

All Subjects:
Safety measures include AEs, concomitant medications, clinical laboratory tests, vital signs (blood pressure, heart rate, respiratory rate, and body temperature), physical examination findings, and ECGs.

Treatment-emergent AEs are defined as AEs with onset at the time of or following the start of treatment with DX-2930, 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. The number and percentage of subjects with TEAEs will be displayed by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries in terms of severity and relationship to DX-2930 will also be provided. SAEs will be summarized separately in a similar fashion. Patient listings of AEs causing discontinuation of DX-2930 treatment, AEs resulting in death, SAEs and AESI will be produced.

AESI will be analyzed according to primary System Organ Classes (SOCs) and Preferred Terms (PTs) determined by the search of relevant Standardized MedDRA Queries (SMQs). Summary tables with SOCs and PTs, from the SMQ searches, will be generated presenting the number and percentage of subjects by AE, severity, seriousness, and relationship to study medication.

Usage of concomitant medications (other than rescue medications) will be summarized descriptively.

Actual values and change from Day 0 in vital signs and clinical laboratory tests will be summarized with descriptive statistics at each assessment obtained. For all laboratory tests, a shift table will be produced summarizing changes from normal to abnormal and vice-versa.

The number and percentage of subjects with normal, abnormal-not clinically significant, and abnormal-clinically significant ECG findings will be displayed. Other safety parameters, such as subject withdrawals will be summarized.

Rollover Subjects: Adverse events that started during subject participation in DX-2930-03 and were ongoing at the time of first open-label dose in DX-2930-04 will not be counted as an AE in DX-2930-04 unless that event has worsened in severity or frequency following the first open-label dose. Adverse events that started during subject participation in DX-2930-03

and resolved following the first open-label dose in DX-2930-04 and then subsequently started again in DX-2930-04 will be counted as a new AE in DX-2930-04.

The incidence of AEs in DX-2930-04 for subjects rolling over from each DX-2930-03 treatment group (300 mg DX-2930 every 2 weeks vs. 300 mg DX-2930 every 4 weeks vs. 150 mg DX-2930 every 4 weeks vs placebo) as well as evaluation of overall AEs in the combined group of all rollover subjects will be assessed. Changes from baseline (last measurement prior to the first dose of DX-2930 received, regardless of if it occurred in DX-2930-03 or DX-2930-04) to the DX-2930-04 time points for physical examination results, vital sign parameters, and clinical laboratory parameters will be summarized by DX-2930-03 treatment group and for the combined group of all rollover subjects.

Non-rollover Subjects: Adverse events will be captured from the time of informed consent through the final study visit. Adverse event tabular summaries will be based on all treatment-emergent AEs.

9.9 Analysis of Quality of Life Assessments

Quality of life data will be obtained using the EQ5D, SF-36, and Angioedema Quality of Life Questionnaire (AE-QoL) at pre-dose on Days 0, 98 ±3, and 182 ±3. An additional assessment will be conducted on Day 238 ±3 for subjects who complete the Follow-up Period. Full details of the planned analyses using these quality of life assessments will be included in the SAP.

10 STUDY ADMINISTRATIVE STRUCTURE

The study administration structure is provided in Table 1.

Table 1. Study Administrative Structure

Sponsor Contact:	[redacted], Clinical Development 55 Network Drive, Burlington, MA 01803 Phone: [redacted] Email: [redacted]
Sponsor Medical Director:	[redacted], MD [redacted], Medical Research 55 Network Drive, Burlington, MA 01803 Phone: [redacted] Email: [redacted]
Medical Monitor (US, Canada):	[redacted], MD Rho, Inc. 6330 Quadrangle Drive, Chapel Hill, NC 27517 Phone: [redacted] Email: [redacted]
Medical Monitor (Jordan, Europe)	[redacted], M.D. Voisin Consulting 3, rue des Longs Prés 92100 Boulogne, France Phone: [redacted] Email: [redacted]
Study Monitoring (US):	Rho, Inc. 6330 Quadrangle Drive, Chapel Hill, NC 27517 Phone: [redacted]
Study Monitoring (Jordan)	Triumpharma 07 Bldg., Al-Yarooty St. P.O. Box 2233, Amman 11941, Jordan Phone: [redacted], [redacted]
Study Monitoring (Canada)	Red Maple Trials Incorporated 1081 Carling Avenue, Suite 707 Ottawa, Ontario, Canada, K1Y4G2 Phone: [redacted]
Study Monitoring (Europe)	Dyax Corp 55 Network Drive, Burlington, MA 01803 Phone: [redacted]

10.1 Institutional Review Board/ Research Ethics Board/Independent Ethics Committee

The protocol and all protocol amendments must be signed and dated by the Investigator and approved in writing by the IRB/REB/IEC in accordance with GCP prior to implementation. In addition, the IRB/REB/IEC must approve the written informed consent form, any consent form updates, subject recruitment materials (e.g., advertisements), and any written information to be provided to subjects prior to implementation. The Investigator must provide an annual report to the IRB/REB/IEC on the progress of the study including number of subjects enrolled, discontinued, and SAEs. It is required that a yearly review of the protocol by the IRB/REB/IEC be documented in a letter from the IRB/REB/IEC. The Investigator must provide notification to the IRB/REB/IEC of the completion, termination or discontinuation of the study.

10.2 Ethical Conduct of the Study

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the Investigator abide by the principles of the International Conference on Harmonisation (ICH) guidelines on GCP, applicable local regulatory requirements, and the Declaration of Helsinki (Version 2008). The clinical study also will be carried out in keeping with national and local legal requirements [in accordance with United States Investigational New Drug (IND) regulations (21 CFR 56)].

10.3 Subject Information and Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained according to the regulatory and legal requirements of the participating country. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. The Investigator or designee will provide the Sponsor with a copy of the IRB/REB/IEC-approved informed consent form prior to the start of the study.

10.4 Subject Confidentiality

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number, initial or birth date (if allowed based on local data protection regulations), not by name. Documents that identify the subject (e.g., the signed informed consent document) must be maintained in confidence by the Investigator.

The Investigator agrees not to use or disclose protected health information other than as permitted or required by the subject authorization or as required by law.

10.5 Study Monitoring

The Sponsor (or designee) will conduct a study initiation visit to verify the qualifications of the Investigator, inspect the facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. The Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to GCP and SOPs for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Investigator.

10.6 Case Report Forms and Study Records

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the clinical sites by means of electronic or manual queries.

The Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each subject receiving randomized study dug.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB/REB/IEC to have direct access to all documents pertaining to the study.

A Trial Master File will be maintained by the Sponsor (or designee). All documents and other materials that pertain to the conduct of the trial quality of the data, and compliance with GCPs will be collected in the Trial Master File.

10.7 Protocol Violations/Deviations

The Investigator will be instructed not to deviate from the protocol, except where necessary to eliminate an immediate hazard to study participants. Should other unexpected circumstances arise that will require deviation from protocol-specific procedures, the Investigator should contact their Sponsor representative to discuss the appropriate course of action.

The Investigator should document all protocol deviations/violations in the subject's eCRF and source documents. In the event of a significant deviation/violation, the Investigator should notify the Sponsor representative. Significant deviations/violations include, but are not limited to those that increase the health risk to the subject, or confound interpretation of primary study assessments. The Investigator will promptly report all changes in research activity and all unanticipated problems involving risks to human subjects or others to his or her IRB/REB/IEC.

10.8 Access to Source Documentation and On-Site Audits

Regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with country regulations. The Investigator should immediately notify the Sponsor representative of any announced or unannounced regulatory agency inspections. An auditing inspection may also be conducted by the Sponsor representative or designee. Any aspect of the trial may be subject to audit by the Sponsor and/or inspection by regulatory authorities or the IRB/REB/IEC. Such audits/inspections may take place at the Sponsor's site(s), the CRO, or at the clinical sites, including laboratories, pharmacies and any other facilities used for the study.

The Investigator will be responsible for the accuracy of the data entered in the eCRF. The Investigator will permit the designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify data represented in the eCRF.

10.9 Data Generation and Analysis

This study will be performed in accordance with regulatory requirements outlined in Food and Drug Administration (FDA) 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 312 and 21 CFR Part 11 as well as the ICH GCP E6 Guidelines. The study monitors will meet with the Investigators and staff shortly before the start of the trial to review the procedures for study conduct and documentation. During the study, the monitors will visit the sites to verify record keeping and adherence to the protocol. For this study, eCRFs will be used. The monitors will conduct 100% source document verification by comparing the eCRFs with the source documents to ensure accuracy and consistency. Edit check programs, other forms of electronic validation, manual listings and a query process will be executed to verify the accuracy of the database. The EDC system will maintain a full audit trail of electronic data changes. Access to all source documentation will be made available for monitoring and audit purposes.

10.10 Retention of Data

All source documents (e.g., informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnosis and pharmacy records, and DX-2930 dispensing/disposition records) that support data in the eCRFs of each study subject must be retained in the files of the responsible Investigator.

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product (IMP). However, these documents should be retained for a longer period if required by the applicable legal requirements.

If the responsible Investigator retires, relocates or for any other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor representative must be notified in writing of the name and address of the new custodian, prior to the transfer.

10.11 Financial Disclosure

Study personnel on the Form FDA 1572 will complete a financial disclosure form (Form FDA 3455) at the beginning of the study and up to one year post completion of the study. New study personnel added to the Form 1572 must also meet these requirements.

10.12 Publication and Disclosure Policy

All information concerning DX-2930, Sponsor operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information, supplied to the Investigator by a Sponsor representative and not previously published, is considered confidential and remains the sole property of the Sponsor. The Investigator must agree to use this information only to accomplish this study, and must not use it for other purposes without the Sponsor's advanced written consent.

The information developed in this study will be used by the Sponsor in connection with the continued development of DX-2930 and thus may be disclosed as required to other clinical Investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

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12 APPENDICES

Appendix 1 Study Activities Schedule

Appendix 2 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases)

Appendix 3 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases

Appendix 4 HAE Attack Assessment and Reporting Procedures (HAARP)

Appendix 5 Summary of Planned Pivotal Study of DX-2930 in HAE Subjects

Appendix 1 Study Activities Schedule

Study Activities Schedule																		
	Screening Visit[1]	Treatment Period ±4 days for each visit															Follow-up Period[2] ±4 days for each visit	
Tests and Assessments		Visit 1 Dose 1 Day 0	Site Check-in[3]	Visit 2 Dose 2[4] Day 14	Visit 3 Dose 3 Day 28	Visit 4 Dose 4 Day 42	Visit 5 Dose 5 Day 56	Visit 6 Dose 6 Day 70	Visit 7 Dose 7 Day 84	Visit 8 Dose 8 Day 98	Visit 9 Dose 9 Day 112	Visit 10 Dose 10 Day 126	Visit 11 Dose 11 Day 140	Visit 12 Dose 12 Day 154	Visit 13 Dose 13 Day168	Visit 14 Day 182	Visit 15 Day 210[5]	Visit 16 Day 238
Informed Consent[6]	X																	
Eligibility Review	X	X																
Long-term prophylactic therapy washout[7]	X																	
DX-2930 Administration		X		X	X	X	X	X	X	X	X	X	X	X	X			
Demographic and Medical History	X																	
C1-INH, C1q and C4 Testing[8]	X																	
Pregnancy Test[9] (females)	X	X								X						X		X
Vital Signs[10]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical Examination[11]	X	X					X			X			X			X		X
Clinical Laboratory Testing[12]	X	X					X			X			X			X		X
12-Lead ECG	X	X								X						X		X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAE Attack Data[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessments[14]		X								X						X		X

Study Activities Schedule																		
	Screening Visit[1]	Treatment Period ±4 days for each visit															Follow-up Period[2] ±4 days for each visit	
Tests and Assessments		Visit 1 Dose 1 Day 0	Site Check -in[3]	Visit 2 Dose 2[4] Day 14	Visit 3 Dose 3 Day 28	Visit 4 Dose 4 Day 42	Visit 5 Dose 5 Day 56	Visit 6 Dose 6 Day 70	Visit 7 Dose 7 Day 84	Visit 8 Dose 8 Day 98	Visit 9 Dose 9 Day 112	Visit 10 Dose 10 Day 126	Visit 11 Dose 11 Day 140	Visit 12 Dose 12 Day 154	Visit 13 Dose 13 Day168	Visit 14 Day 182	Visit 15 Day 210[5]	Visit 16 Day 238
PK Blood Sampling[15]		X								X						X		X
PD Sample Collection[15]		X								X						X		X
Plasma Anti-Drug Antibody Testing[15]		X								X						X		X
Discharge from Study[16]																		X

ECG = Electrocardiogram; PK = Pharmacokinetic; PD = Pharmacodynamic

1. Screening visit is for non-rollover subjects only. Screening visit can occur up to 28 days prior to first open-label dose.
2. The Follow-up Period is not required for subjects who choose to roll over into an ongoing DX-2930 clinical study or access program that permits such a rollover.
3. Site personnel will contact rollover subjects approximately every 7 days following the first dose of open-label DX-2930 to solicit for any HAE attacks not already reported. Site check-in with rollover subjects will continue until the subject receives their second open-label dose.
4. For rollover subjects, the timing of Dose 2 will vary by subject based on when their first HAE attack occurs following Dose 1. Following the first reported HAE attack, subjects will begin receiving regular SC administrations of 300 mg DX-2930 every 2 weeks. A minimum of 10 days between the first and second open-label doses is required. If the second dose is to be administered within the accepted ± 4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit unless that scheduled visit has already occurred. If that scheduled visit has already occurred, or if the second dose is to be administered outside of the accepted ± 4 day window around a scheduled visit, this visit will not replace any scheduled visit and will thus represent an acceptable, extra study visit. Regardless, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical examination, clinical laboratory testing, PK, PD, and anti-drug antibody. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data.
5. The Day 210 Visit is a site check-in for all rollover and non-rollover subjects.
6. Rollover subjects will provide consent no later than the Day 182 DX-2930-03 study visit.
7. Non-rollover 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 treatment period.
8. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment unless already collected as part of protocol DX-2930-02 or DX-2930-03.
9. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 must be urine-based to confirm eligibility prior to first dose. Tests performed at screening, Day 98, Day 182, and Day 238 can be serum or urine-based.
10. There is a ± 15 minute window for all vital signs. Vital signs will be obtained prior to dosing and 1 hour after dosing.
11. Height and weight will be collected at the Screening visit only. Physical examinations will be conducted for all rollover and non-rollover subjects according to the study activities schedule. In addition to the physical examinations specified in the study activities schedule, an additional physical examination will be conducted for these subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs.

[12] Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis. Clinical laboratory testing will be conducted for all rollover and non-rollover subjects according to the study activities schedule. In addition to the testing specified in the study activities schedule, additional testing will be conducted for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs.

[13] Historical attack information will be collected at screening. During the study subjects (or caregivers) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. During study visits, site personnel will solicit for any new HAE attack information that was not given through prior subject contact with the site.

[14] Quality of life data will be obtained using the EQ5D, SF-36, and Angioedema Quality of Life Questionnaire (AE-QoL).

[15] PK, PD and Anti-drug Antibody PD samples will be drawn for all rollover and non-rollover subjects according to the study activities schedule. In addition to the samples specified in the study activities schedule, an additional PK, PD and Anti-drug Antibody sample will be drawn for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs.

[16] 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.

Appendix 2 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases)

Appendix 3 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases

Appendix 4 HAE Attack Assessment and Reporting Procedures (HAARP)

Appendix 5 Summary of Planned Pivotal Study of DX-2930 in HAE Subjects

The proposed pivotal clinical study (DX-2930-03) is entitled "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)." This study will be a multi-center, double-blind, randomized, placebo-controlled parallel-arm study evaluating the efficacy of DX-2930 in preventing acute angioedema attacks in patients with Type I or Type II HAE. The double-blind study is planned to be followed by the study described in the present protocol, an open-label extension (OLE) study (DX-2930-04).

The primary objective of study DX-2930-03 is to evaluate the efficacy of DX-2930 in preventing HAE attacks. The secondary objective is to evaluate the safety of repeated SC administrations of DX-2930. The tertiary objectives are to evaluate the pharmacodynamic effects of chronically administered DX-2930; to assess the immunogenicity of chronically administered DX-2930; to evaluate the pharmacokinetics of chronically administered DX-2930; and to evaluate the effect of DX-2930 upon quality of life assessments.

Subjects aged 12 years and over with a documented diagnosis of Type I or Type II HAE who experience at least 1 attack per 4 weeks will be eligible for the study. Up to 120 subjects are planned for enrollment across approximately 60 sites in the United States, Canada, Italy, Germany, United Kingdom and Jordan.

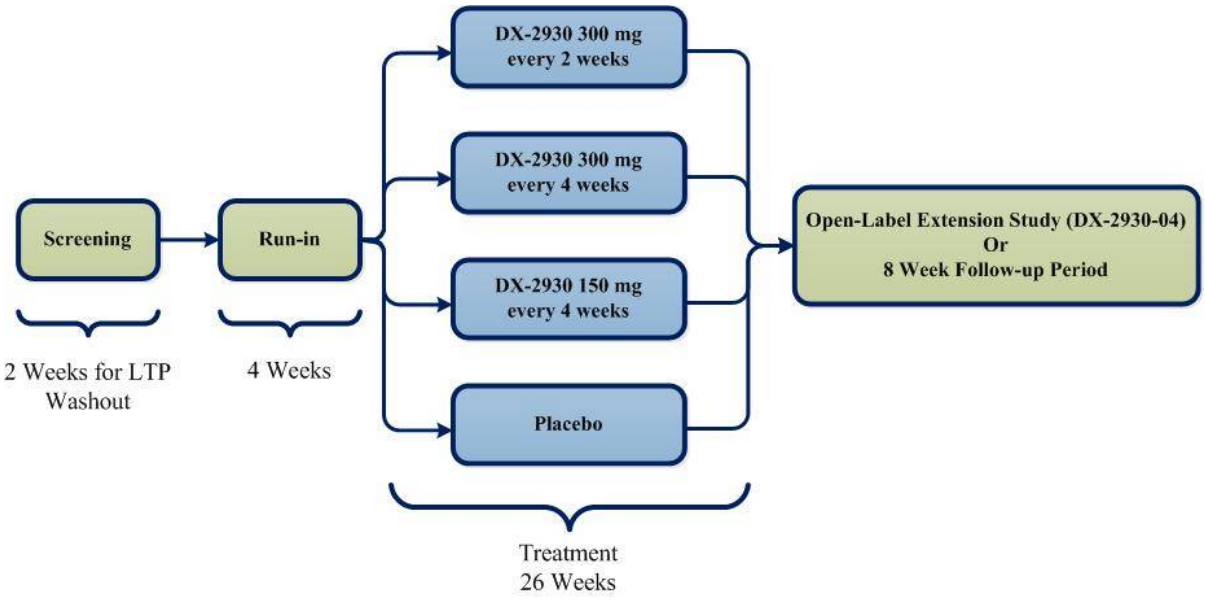
Following informed consent, subjects will undergo screening assessments. Subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. Subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. The run-in period may be extended to 8 weeks if the minimum baseline attack rate is not achieved in the first 4 weeks. HAE subjects will then 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 one of three dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks or 150 mg every 4 weeks. Each subject will undergo a treatment period consisting of 13 doses of blinded study drug, for a period of 26 weeks from the date of first dose on Day 0 through Day 182

Subjects may consent to rollover into the OLE study (present protocol DX-2930-04) upon completion of their participation in the double-blind treatment period.

The primary endpoint will be to compare the mean rate of investigator-confirmed HAE attacks observed in each DX-2930 treatment arm to that in the placebo arm during the efficacy assessment period (Day 14 through Day 182).

Figure 1 shows a schematic of the double-blind, pivotal study.

Figure 1. Overview of the Design of Pivotal Study DX-2930-03



Dose Rationale for Double-Blind, Pivotal Study DX-2930-03

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 while avoiding non-therapeutic or super-therapeutic doses and regimens

Clinical Trial Protocol: DX-2930-04

Study Title:	HELP Study Extension™: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number:	DX-2930-04
Study Phase:	Phase 3
Product Name:	DX-2930
IND Number:	116647
EudraCT Number:	2015-005255-27
Indication:	Prevention of angioedema attacks in patients with HAE
Investigators:	Multicenter
Sponsor:	Dyax Corp., an indirect, wholly-owned subsidiary of Shire plc. 55 Network Drive, Burlington, MA 01803 USA
Sponsor Contact:	[redacted], MD [redacted], Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: [redacted]
Medical Monitor US and Canada:	[redacted], MD [redacted], Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: [redacted]
Medical Monitor Europe and Jordan:	[redacted], MD, MBA Voisin Consulting 3, rue des Longs Prés 92100 Boulogne, France Phone: [redacted]

	Date:
Original Protocol	14 December 2015
Amendment 1.0	27 June 2016

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

Study Title: HELP Study Extension™: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)

Study Number: DX-2930-04

Amendment 1.0 Final Date: 27 June 2016

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The signature of the Sponsor representative indicates that the Sponsor will comply with all Sponsor obligations detailed in applicable regulations and guidelines and will ensure the investigator is informed of all relevant information that becomes available.

Signed: [redacted] Date: [redacted]

[redacted], MD
[redacted], Clinical Development
300 Shire Way, Lexington, MA 02421 USA

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP), and all applicable regulatory requirements and guidelines as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use only the informed consent form approved by Dyax Corp. and my Institutional Review Board (IRB), Research Ethics Board (REB) or Ethics Committee (EC) and will fulfill all responsibilities for submitting pertinent information to the IRB/REB/EC responsible for this study.

I further agree that Dyax Corp. or their designees shall have access to any source documents from which eCRF information may have been generated.

By signing this protocol, I agree to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP to which it conforms.

Signed:_____ Date:_____
Investigator

Address: _____

_____

SYNOPSIS

Sponsor: Dyax Corp., an indirect, wholly-owned subsidiary of Shire plc. 55 Network Drive, Burlington, MA 01803 USA
Name of Finished Product: DX-2930 Drug Product (DP)
Name of Active Ingredient: DX-2930 is a recombinant, Chinese hamster ovary (CHO) cell-expressed, fully human immunoglobulin G subclass 1 (IgG1), kappa light chain, monoclonal antibody.
Names of Inactive Ingredients: Sodium phosphate dibasic dihydrate, citric acid monohydrate, L-histidine, sodium chloride, and Polysorbate 80
Study Title: HELP Study Extension™: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number: DX-2930-04
Study Phase: Phase 3
Study Location: Approximately 60 study sites planned across North America, the European Union and the Middle East
Primary Objective: To evaluate the long-term safety of repeated subcutaneous (SC) administrations of DX-2930
Secondary Objectives: • To evaluate the long-term efficacy of DX-2930 in preventing HAE attacks • To characterize the outer bounds of dosing frequency for DX-2930
Tertiary Objectives: • To assess the immunogenicity of chronically administered DX-2930 • To evaluate the effect of DX-2930 on health-related quality of life (QOL) • To characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profile of SC administration of DX-2930 • To evaluate safety and efficacy in the non-rollover population of switching from long-term prophylactic (LTP) treatment to DX-2930 • To evaluate breakthrough attack characteristics while receiving DX-2930 compared to historical baseline • To evaluate subject experience with self-administration of DX-2930 including ease of SC administration of DX-2930

Study Design:
DX-2930-04 is an open-label, long term safety and efficacy extension study of DX-2930-03, to evaluate the investigational medicinal product (IMP), DX-2930, in preventing acute angioedema attacks in patients with Type I and Type II HAE. There are two types of subjects who will be enrolled into this study:

- Subjects who rollover from the DX-2930-03 study
- Subjects who are non-rollover (i.e., were not participants in DX-2930-03)

Rollover Subjects
Rollover subjects are subjects who complete the double-blind treatment period at Day 182 of the DX-2930-03 study and consent to enter DX-2930-04. Subjects who discontinue from DX-2930-03 after enrollment are not eligible to enroll in DX-2930-04.

Willing subjects must sign informed consent for DX-2930-04 after Day 168 of study DX-2930-03 and no later than the final DX-2930-03 Day 182 treatment period study visit.

Subjects who are eligible to roll over into DX-2930-04 but elect not to, may not enroll in DX-2930-04 at a later time. The first DX-2930-04 visit for rollover subjects (Day 0) will occur on the same day as the DX-2930-03 Day 182 study visit. Rollover subjects will complete all DX-2930-03 final study assessments (Day 182) at which time they will be discharged from that study. No assessments conducted between the DX-2930-03 Day 182 study visit and the first DX-2930-04 visit (Day 0) will be duplicated. Results of the final DX-2930-03 assessments on Day 182 will be used as the pre-dose results for Day 0 Dose 1 of DX-2930-04.

All subjects, caregivers, investigators and study site personnel will remain blinded to the DX-2930-03 treatment assignment until the conclusion of the DX-2930-04 study.

Non-rollover subjects
At least 50 subjects (up to a maximum of 100) who were not participants in the DX-2930-03 study will be permitted to enroll if they meet the eligibility requirements. Subjects who screen fail out of DX-2930-03 for not meeting the minimum attack requirements during the run-in period must wait until enrollment for the double-blind study has ended before they can screen for DX-2930-04. The Sponsor may ease this restriction based on the enrollment rate observed in DX-2930-03. Subjects who are still in the run-in period for DX-2930-03 when enrollment for that study closes, as well as subjects on prior LTP who screen fail out of DX-2930-03 due to an inability to wash-out of their LTP, may screen for DX-2930-04 following discussion with the Sponsor medical monitor.

Screening Period:
There is no screening period for rollover subjects.

Non-rollover subjects must provide informed consent and have screening assessments completed within 4 weeks prior to their first open-label dose. Screened non-rollover subjects (adults and adolescents) who are on LTP with C1-INH therapy for HAE can continue their current LTP until

Day 8 (or Day 15) such that subjects will have received 2 (or 4) doses of C1-INH. For subjects who are on attenuated androgens (e.g., danazol) or anti-fibrinolytics (e.g., tranexamic acid), a similar tapering schedule is recommended. However, the taper can be prolonged by an additional week, if medically indicated, as long as androgen or anti-fibrinolytic therapy is stopped within 3 weeks after receiving the first dose of DX-2930.

Treatment Period:

Rollover Subjects

Following informed consent and pre-dose assessments, rollover subjects will receive a single open-label dose of 300 mg DX-2930 administered subcutaneously (SC) on Day 0. Subjects will not receive any additional DX-2930 doses until their first reported, and investigator-confirmed, HAE attack.

The duration of time between the first open-label dose and first reported HAE attack will vary by rollover subject. All rollover subjects must adhere to the Study Activities Schedule for the entire duration of the study. However, until a rollover subject reports their first HAE attack, only scheduled study visits where the following tests and assessments are performed must be conducted at the investigative site: pregnancy testing, clinical laboratory testing, physical examination, 12-Lead ECG, QoL, PK, PD and anti-drug antibody sample collection. All other scheduled study visits may be conducted via site check-in calls to collect information on adverse events, concomitant therapy, and HAE attack data. See Study Activities Schedule for which visits must be conducted at the study site.

Once a rollover subject reports their first HAE attack they will present to the investigative site for their second open-label dose of DX-2930 as quickly as subject and site schedules allow. If the second dose is to be administered within the accepted ±4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit. If that scheduled visit has already occurred, the day of the visit will be considered an acceptable, extra study visit (i.e., an unscheduled visit). Similarly, if the second dose is administered outside of the accepted ±4 day window around a scheduled visit, the day of the visit will be considered an acceptable extra unscheduled study visit, (i.e., this visit will not replace any scheduled visit).

Regardless of the study day, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical examination, clinical laboratory testing, and blood sampling for PK, PD, and anti-drug antibody assessments. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data.

Regardless of when a rollover subject's first HAE attack occurs, there will be a minimum of 10 days between their first open-label dose and their second open-label dose. Following their second dose, rollover subjects will continue to receive repeated SC administrations of open-label 300 mg DX-2930 every 2 weeks for the remaining duration of the treatment period per the scheduled dosing in the Study Activities Schedule. The treatment period will last 350 days from the date of the first open-label dose. The number of doses administered during this period will vary by subject based on the date of each subject's second dose, but will not exceed 26 doses. The Day

350 study visit is the last visit at which a dose may be administered.

Non-rollover Subjects
Once all screening assessments have been completed and eligibility confirmed, non-rollover subjects will arrive at the study site and, following pre-dose assessments, receive an open-label dose of 300 mg DX-2930 administered SC on Day 0. Non-rollover subjects will continue to receive SC administrations of open-label 300 mg DX-2930 every 2 weeks throughout the duration of the treatment period per the scheduled dosing in the Study Activities Schedule. A total of 26 doses will be administered with the last dose administered at the Day 350 study visit.

All Subjects:
All doses (with the exception of the second dose for rollover subjects) require a minimum of 10 days and maximum of 18 days between administrations, and should fall within the accepted ±4 day window around study visits.

If a subject experiences an acute angioedema attack at any time during the study that in the opinion of the investigator requires medical intervention, standard of care therapy should be provided based on subject's medical history and per locally approved product information. Administration of DX-2930 and study procedures will continue without alteration to the protocol study activities schedule, even if a subject receives treatment for a breakthrough angioedema attack on the day of a scheduled dose of study drug (if self-administering) or scheduled study visit.

Self-Administration
All subjects (adolescent or adult) who are considered suitable candidates (i.e., those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer treatment. Subjects must complete appropriate training by the investigator or designee and understanding of the training must be confirmed by the investigator or designee. Subjects are allowed to initiate self-administration after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may self-administer subsequent doses of DX-2930 at the investigational site (when visits are scheduled study site visits) or the subject's home or other agreed upon location (when the study permits off-site dosing). See Schedule of Activities for details. Adolescent subjects self-administering investigational product will be supervised by a parent/legal guardian/caregiver. Alternatively, a parent/legal guardian/caregiver, after completing appropriate training, will be allowed to administer DX-2930 to an adolescent without study site personnel supervision. Site personnel will call subjects after the planned off-site self-administrations to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.

Throughout the study, study site personnel will document information in source documents (ie, the subject's medical record) and eCRF regarding the subject's experience with self-administration and SC administration of DX-2930.

Follow-up Period
After completion of the 350 day treatment period, all subjects will undergo safety evaluations

during an 8-week follow-up period.

Modifications to Open-Label Dosing
If, at any time, an important dose-related safety signal is identified either from this study or DX-2930-03, the Sponsor may decide to switch the enrolled subjects who have not yet completed the treatment period, and any subsequent subjects, to receive a different open-label DX-2930 dose and/or frequency.

In addition, based on the results of the DX-2930-03 study, the Sponsor may switch to a different dose and/or frequency.

Study Population:
The study is expected to enroll subjects from the DX-2930-03 study, as well as at least 50 (up to a maximum of 100) additional subjects who were not enrolled in DX-2930-03. The total enrollment is expected to be at least 150 but not more than 250 HAE Type I or II subjects. Subjects will be 12 years of age or older who experience at least 1 attack per 12 weeks. HAE diagnosis will be confirmed through documented clinical history and diagnostic testing conducted either during screening or during prior participation in study DX-2930-02 or DX-2930-03. The study will aim to enroll at least 15 subjects who are 12 to 17 years of age, inclusive of the estimated 10 subjects 12 to 17 years old who roll over from the DX-2930-03 study.

Criteria for Inclusion:
Subjects must meet the following criteria to be enrolled in this study:

1. Male and female HAE subjects who are 12 years of age or older at the time of screening.
2. Documented diagnosis of HAE (Type I or II) based on all of the following:
    - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).
    - Diagnostic testing results obtained during screening (or a prior DX-2930 study) that confirm HAE Type I or II: C1 inhibitor (C1-INH) functional level < 40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may be retested if results are incongruent with clinical history or believed by the investigator to be confounded by recent LTP use.
    - At least one of the following: Age at reported onset of first angioedema symptoms ≤ 30 years, a family history consistent with HAE Type I or II, or C1q within normal range.
3. A historical baseline HAE attack rate of at least 1 attack per 12 weeks.
4. Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects age 12 to 17, whose caregiver has provided informed consent, are willing and able to read, understand and sign an assent form.
5. Males and females who are fertile and sexually active must adhere to contraception requirements for the duration of the study as follows:
    - Females of childbearing potential must agree to be abstinent or it is recommended to use highly effective forms of contraception from screening through 30 days after the final

study visit. This includes stable doses (for 3 months prior to study screening) of combined estrogen and progestin-containing hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable), progestin-only hormonal contraception associated with inhibition of ovulation, intra-uterine device (IUD, all types) or intrauterine hormone releasing systems (IUS). Notes: 1) A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. 2) Use of a male condom with or without spermicide or cervical cap, diaphragm or sponge with spermicide or a combination (double barrier methods) are not considered highly effective.

- Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- Males, including males who are surgically sterile (post vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study visit.

Criteria for Exclusion:

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

1. Discontinued from DX-2930-03 after enrollment for any reason.
2. If rolling over from DX-2930-03, presence of important safety concerns that would preclude participation in this study.
3. Concomitant diagnosis of another form of chronic, recurrent angioedema such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.
4. Dosing with an investigational drug (not including DX-2930 or other HAE therapies) or exposure to an investigational device within 4 weeks prior to screening.
5. Exposure to angiotensin-converting enzyme (ACE) inhibitors within 4 weeks prior to study screening or any newly initiated or dose modification of estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) 3 months prior to the screening visit.
6. Unwilling to discontinue use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 3 weeks after starting DX-2930 treatment.
7. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's Syndrome).
8. Pregnancy or breastfeeding.
9. Subject has any condition that, in the opinion of the investigator or Sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., history of substance abuse or dependence, a significant pre-existing illness or other major comorbidity that the investigator considers may confound the interpretation of study results).

Test Product; Dose; and Mode of Administration:

DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated using the following compendial components: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Polysorbate 80. Each open-label vial contains a nominal concentration of 150 mg DX-2930 active ingredient in 1 mL solution.

For each 300 mg dose of DX-2930, each subject will receive a total of 2 mL (2 vials), which will be administered in a single 2 mL SC injection. The injection will be given in the upper arm, thigh or abdomen.

Self-Administration Option: Investigational product can be self-administered without supervision (parental supervision required for adolescent subject) after subjects receive appropriate training by the investigator or designee and their understanding is confirmed. Subjects are allowed to initiate self-administration after receiving the first 2 doses of DX-2930 at the study site and may continue to self-administer all subsequent doses (see Study Activities Schedule).

Duration of Treatment:

All subjects will receive open-label DX-2930 during a 350 day treatment period. The number of doses that rollover subjects receive during this period will vary by subject but will not exceed 26 doses. The last dose of open-label DX-2930 administered to these subjects may be given at the Day 350 study visit. Non-rollover subjects will receive 300 mg DX-2930 every 2 weeks for a total of 26 doses, with the first dose administered on Day 0 and the final dose administered at the Day 350 study visit.

There will be a ±4-day window around each study visit. There will be a minimum of 10 days between any two doses. Excluding the interval between the first and second open-label doses for rollover subjects, there will be a maximum of 18 days between any two doses. Subjects will be monitored at the study site through 1 hour post-dose for scheduled study site visits. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.

Duration of Study for Individual Subjects:

Following informed consent, subjects will either rollover from DX-2930-03 or undergo screening assessments (non-rollover subjects). Screening assessments for non-rollover subjects must occur within 4 weeks prior to the first open-label dose. Eligible subjects will be enrolled and undergo a 350 day treatment period. At the conclusion of the 350 day treatment period, subjects will be followed for an additional 8 weeks.

Prohibited Concomitant Treatments:

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

- Long-term prophylaxis for HAE (e.g., use of C1-INH for LTP, attenuated androgens, or anti-fibrinolytics) once LTP is discontinued (within 3 weeks following the first dose of DX-2930).
- Angiotensin-converting enzyme (ACE) inhibitors.
- Initiating or changing the dose of estrogen-containing medications with systemic absorption

(such as oral contraceptives or hormonal replacement therapy) 3 months prior to study screening.

- Use of androgens (e.g., stanozolol, danazol, oxandrolone, methyltestosterone, and testosterone) for non-HAE related medical conditions or for HAE after discontinuation during the first three weeks.
- Any other investigational drug or device.

The use of short-term prophylactic treatment for HAE will be permitted if medically indicated. Short-term (pre-procedure) prophylaxis is defined as use of C1-INH to avoid angioedema complications from medically indicated procedures.

Management of Acute Attacks:

Acute HAE attacks during the study are to be managed in accord with the investigator's usual care of their patients, including use of acute attack therapies that the investigator deems as medically appropriate. Use of C1-INH will be permitted as an acute attack therapy but not as a long-term prophylactic therapy. Administration of DX-2930 and study procedures will continue without alteration to the protocol-specified study schedule, even if the subject has symptoms of an HAE attack the day of DX-2930 administration and/or receives treatment for an HAE attack. The administration of DX-2930 can also be re-scheduled as long as the minimum and maximum timeframe between doses are met based on patient preference or physician discretion.

Safety Assessments:

Safety assessments will include the following:

- Adverse events (AEs), including serious adverse events (SAEs) and adverse events of special interest (AESI). SAEs and AESI will be reported to the Sponsor within 24 hours of becoming aware of the event.
- Vital signs, including sitting or supine blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR)
- Physical examination
- Clinical laboratory testing (hematology, serum chemistry, coagulation and urinalysis)
- 12-Lead electrocardiogram (ECG)

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

Pharmacokinetic (PK) Assessments:

Blood samples will be collected for the measurement of plasma DX-2930 concentrations.

Pharmacodynamic (PD) Assessments:

Blood samples will be collected to evaluate the pharmacodynamic effects of DX-2930 through biomarker assays.

Immunogenicity Assessments:

Blood samples will be collected to assay for the presence of anti-drug antibodies, including evaluation of neutralizing antibodies (if any confirmed positive anti-drug antibodies are detected).

C1-INH, C1q and C4 Assessments:

Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment, unless already collected as part of protocol DX-2930-02 or DX-2930-03.

Quality of Life Assessments:

Quality of life (QoL) assessments will be conducted using the Angioedema Quality of Life Questionnaire (AE-QoL), EuroQoL 5-Dimensional 5-Level Measure (EQ-5D-5L), Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH), Hospital Anxiety and Depression Scale (HADS), and 12 Item Short Form Survey (SF-12).

DX-2930 Injection Report and Self-Administration and Subcutaneous Injection Survey

An injection report of the subject's experience with self-administration and SC injection will be completed by the subject after all doses of DX-2930.

In addition, assessment survey of subject experience with SC and self-administration injections of DX-2930 will be completed by the subject approximately every 6 months.

Collection of HAE Attack Data:

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

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

At screening, HAE attack history will be collected for non-rollover subjects. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant attack location(s), triggers, average duration, acute attack therapy use and history of LTP (including duration of LTP, medication(s) and dose used for LTP, and frequency of attacks while receiving LTP). If available, information will also be collected on HAE diagnosis (year of confirmation, how many years after onset of symptoms was diagnosis confirmed, or if subject was misdiagnosed).

During the study, subjects (or caregivers) will be instructed to notify and report details to the study site within 72 hours of the onset of an attack. This includes the first attack experienced by rollover subjects following their first open-label dose. In the situation 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 experienced, but its use is not mandatory.

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 (work, school, social interactions) and whether any assistance or medical intervention was required, including hospitalizations, additional laboratory tests or emergency department visits.
- Any medications used to treat the attack (both prescription and over the counter).
- If the attack resolved, date and time the subject was no longer experiencing symptoms.

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

Study site personnel will contact rollover subjects approximately every 7 days following the first dose of open-label DX-2930 to solicit for any HAE attacks not already reported. Site check-ins will continue until the subject has received their second open-label dose.

During each study visit, study site personnel will solicit for any new HAE attack information that was not already provided to the site.

In this study, HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to DX-2930, 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 EDC system within 24 hours of becoming aware of the event. For all serious adverse events that are reported as HAE attacks, the 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 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 to receive additional information. Any subject-reported attack not confirmed by the investigator or physician designee must have an alternate AE diagnosis recorded. All subject-reported and investigator/ physician designee-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 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 or physician designee may still clinically determine that the event did not represent an 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.

Interim Analyses and Data Monitoring

A formal interim analysis will be conducted at least 35 subjects have completed 12 months of consecutive exposure to DX-2930 across the combined DX-2930-03 and DX-2930-04 studies, and only after database lock of the DX-2930-03 study. Subsequent interim analyses may be conducted to support administrative decisions and/or regulatory reporting as required.

An independent Data Safety Monitoring Board (DSMB) has been established to provide ongoing, independent review and assessment of the safety data for the DX-2930-03 study. While an independent DSMB is not currently planned for this study, summary safety data from DX-2930-04 may be reviewed by the DSMB established for the DX-2930-03 study as part of the collection of safety information available on DX-2930.

Individual Stopping Rules:

Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or a DX-2930-related, clinically significant non-serious AE) that, in the assessment of the investigator, warrants discontinuation from further dosing for that subject's well-being. The investigator has the ability to contact and consult with the Medical Monitor on such matters. Subjects will continue to be followed through the completion of all scheduled non-dosing visits, unless they request to be discontinued from the study.

Criteria for Evaluation:

Safety Measures:

- AEs including SAEs and AESI
- Clinical Laboratory testing (hematology, clinical chemistry, coagulation and urinalysis)
- Vitals signs including blood pressure, heart rate, oral body temperature and respiratory rate
- Physical Examination
- 12-lead ECG

Efficacy Endpoints:

- Time to first HAE attack for rollover subjects (based upon time from first open label study dose until first HAE attack)
- Number of investigator confirmed HAE attacks during the treatment period

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

Additional Measures:

- Anti-drug antibody development
- Pharmacokinetics (PK)
- Pharmacodynamic (PD) effects
- Quality of Life Assessments
- DX-2930 Injection Report
- DX-2930 Self-administration and Subcutaneous Injection Survey

Analysis Populations:

- The Safety Population will include all subjects who received any study drug after entering the DX-2930-04 study (i.e., any exposure to open-label DX-2930).

- The Rollover Safety Population is the subset of subjects who participated in the DX-2930-03 study and received any study drug after entering the DX-2930-04 study (i.e., any exposure to open-label DX-2930).

- The Non-rollover Safety Population is the subset of subjects who entered the DX-2930-04 study directly and received any study drug after entering the DX-2930-04 study (i.e., any exposure to open-label DX-2930).

Sample Size Determination:

No formal sample size calculation was performed. The sample size is not based on any statistical considerations. This study is designed to evaluate the safety and efficacy of open-label treatment with DX-2930 in subjects who participated in DX-2930-03 and individuals who were not otherwise able to participate in DX-2930-03.

Statistical Methodology:

Time to the first investigator-confirmed HAE attack will be analyzed using the Rollover Safety Population.

Time to the first investigator-confirmed HAE attack (days) will be calculated from the date and time of the first open-label dose of DX-2930 to the date and time of the first investigator-confirmed HAE attack after the first open-label dose. Subjects who discontinue the study prior to experiencing their first on-study investigator-confirmed HAE attack will be censored at the date and time of study discontinuation. Time to the first investigator-confirmed HAE attack will

be summarized using Kaplan-Meier methods.

Multivariate and univariate Cox proportional hazards regression models will be employed to examine the impact of baseline covariates on the time to the first investigator-confirmed HAE attack, including but not limited to: baseline attack rate prior to entering DX-2930-03, the treatment group in DX-2930-03, the time since the last dose given in DX-2930-03, the time since the last HAE attack, and the rate of attacks during DX-2930-03. Results of this exploratory analysis will be summarized.

Number of Investigator-confirmed HAE Attacks

The number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 350) expressed as a monthly HAE attack rate, will be analyzed using each analysis population.

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

The baseline investigator-confirmed monthly HAE attack rate will be calculated for each subject as the number of investigator-confirmed monthly HAE attacks occurring during the pretreatment period for rollover subjects or historical reporting period for non-rollover subjects divided by the number of days the subject contributed to the pretreatment period for rollover subjects or historical reporting period for non-rollovers multiplied by 28 days.

The baseline, treatment period, and treatment period change from baseline in the investigator-confirmed HAE attack rate will be summarized for each analysis population. The summary will include the total number of investigator-confirmed HAE attacks reported during each period and subject-time in months that each subject contributed to each period. Figures will be created for each analysis population plotting the on-study investigator-confirmed HAE attacks reported during the treatment period relative to Day 0 for each subject.

Similar summary tables will be presented for the following efficacy endpoints for each analysis population:

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

Safety Analysis:

Adverse Events

Treatment-emergent AEs are defined as AEs with onset at the time of or following the first exposure to open-label DX-2930 in this study, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment.

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.

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

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

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

Laboratory Test Results, Vital Signs, and Electrocardiography Results

Baseline is defined as the last non-missing value prior to the first exposure to DX-2930. For rollover subjects previously exposed to DX-2930, baseline is the last non-missing value prior to first exposure to study drug in the DX-2930-03 study.

Actual values and change from baseline in clinical laboratory test results and vital signs will be summarized by study visit.

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. 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 within each category will be summarized by study visit.

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 by study visit.
Other Analyses Plasma concentrations of DX-2930 and plasma kallikrein activity will be summarized by nominal PK and PD sampling times. The number and percentage of subjects with positive antibodies (and whether neutralizing or non-neutralizing) will be summarized by study visit and overall. Quality of life assessments will be summarized by study visit.
Date of Original Protocol: 14 December 2015 **Date of Amendment 1:** 27 June 2016

Study Activities Schedule

Study Activities Schedule																																
Tests and Assessments		**Treatment Period ± 4 days for each visit**																														**Follow-up ±4 Days for each visit**
Non-rollover	**Screen Visit[1]**			Shaded columns: scheduled in-site visits																												
Rollover	-		**Check-in[2]**	Non-shaded columns: potential subject-elected off-site activity and/or self-administration dosing																												
Visit:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28[3]**	**29[4]**
Dose:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	-	-	-
Day:		**0**		**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**	**378**	**392**
Informed Consent[5]	X	(X)[6]																													
Eligibility Review	X	X																													
Long-term prophylactic therapy continued[7]	X	X		X																											
DX-2930 Administration (rollover subjects)		X		(X)[8,9]	(X)[10]	(X)[11]	(X)[10]	(X)[11]	(X)[11]	(X)[10]	(X)[11]	(X)[10]	(X)[11]	(X)[10]	(X)[11]	(X)[10]	(X)[11]	(X)[11]	(X)[10]	(X)[11]	(X)[11]	(X)[10]	(X)[11]	(X)[11]	(X)[10]	(X)[11]	(X)[11]	(X)[10]			
DX-2930 Administration (non-rollover)		X		X	X[10]	X[11]	X[10]	X[11]	X[11]	X[10]	X[11]	X[10]	X[11]	X[10]	X[11]	X[10]	X[11]	X[11]	X[10]	X[11]	X[11]	X[10]	X[11]	X[11]	X[10]	X[11]	X[11]	X[10]			
Demographic and Medical History	X																														
C1-INH, C1q and C4 Testing[12]	X																														
Pregnancy Test[13] (females)	X	X		X	X		X			X		X		X		X			X			X			X			X	X		X
Vital Signs[14]	X	X		X	X		X			X		X		X		X			X			X			X			X	X		X
Physical Exam[15]	X	X		X	X		X			X				X		X						X						X	X		X

Study Activities Schedule																															
Tests and Assessments		**Treatment Period ± 4 days for each visit**																													**Follow-up ±4 Days for each visit**
Non-rollover	**Screen Visit[1]**			Shaded columns: scheduled in-site visits																											
Rollover	-		**Check-in[2]**	Non-shaded columns: potential subject-elected off-site activity and/or self-administration dosing																											
Visit:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28[3]**	**29[4]**
Dose:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	-	-	-
Day:		**0**		**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**	**378**	**392**
Clinical Laboratory Testing[16]	X	X			X		X			X				X		X			X			X			X			X	X		X
12-Lead ECG	X	X								X						X						X						X	X		X
Prior (4 weeks) and Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAE Attack Data[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessments[18]																																
EQ-5D-5L		X			X		X			X		X		X		X			X			X			X			X			X
SF-12		X			X		X			X		X		X		X			X			X			X			X			X
AE-QoL		X			X		X			X		X		X		X			X			X			X			X			X
HADS		X			X		X			X		X		X		X			X			X			X			X			X
WPAI-GH		X			X		X			X		X		X		X			X			X			X			X			X
DX-2930 Injection Report[19]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
DX-2930 Self-administration and SC Injection Survey [20]		X								X						X						X						X			
PK, PD Collection, & Plasma Anti-Drug Antibody Testing[21]		X								X						X						X							X		X

Study Activities Schedule																																
Tests and Assessments		**Treatment Period ± 4 days for each visit**																														**Follow-up ±4 Days for each visit**
Non-rollover	**Screen Visit[1]**			Shaded columns: scheduled in-site visits																												
Rollover	**-**		**Check-in[2]**	Non-shaded columns: potential subject-elected off-site activity and/or self-administration dosing																												
Visit:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28[3]**	**29[4]**
Dose:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**-**	**-**	**-**
Day:		**0**		**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**	**378**	**392**
Discharge from Study																																X

AE-QOL = Angioedema Quality of Life; ECG = Electrocardiogram; EQ-5D-5L = EuroQoL 5-Dimensional 5-Level; HADS = Hospital Anxiety and Depression Scale; PK = Pharmacokinetic; PD = Pharmacodynamic; SF-12 = Short Form-12 (v2); WPAI-GH = Work Productivity and Activity Impairment – General Health

NOTE: Shaded columns represent scheduled in-site visits for all subjects. Non-shaded columns indicate potential subject-elected off-site activity and/or self-administration dosing.

NOTE: "( )"s indicate activities that may occur as applicable (ie, activities for rollover subjects)

1. Screening visit is for non-rollover subjects only. Screening visit can occur up to 28 days prior to first open-label dose.
2. Study site personnel will contact rollover subjects approximately every 7 days following the first dose of open-label DX-2930 to solicit for any HAE attacks not already reported. Site check-in with rollover subjects will continue until the subject receives their second open label dose.
3. Visit 28 is a site check-in call for all rollover and non-rollover subjects.
4. Subjects who terminate from the study early will undergo (if possible) all of the assessments and procedures at Visit 29, their final study visit
5. Rollover subjects must sign informed consent for DX-2930-04 after Day 168 of study DX-2930-03 and no later than the final DX-2930-03 Day 182 treatment period study visit.
6. For rollover subjects Day 182 of the DX-2930-03 study is also Day 0 of the DX-2930-04 study and informed consent may be completed on this visit, if not already provided.
7. Screened non-rollover subjects (adults and adolescents) who are on LTP with C1-INH therapy for HAE can continue their current LTP until Day 8 (or Day 15) such that subjects will have received 2 (or 4) doses of C1-INH. For subjects who are on attenuated androgens (e.g., danazol) or anti-fibrinolytics (e.g., tranexamic acid), a similar tapering schedule is recommended. However, the taper can be prolonged by an additional week as long as androgen or anti-fibrinolytic therapy is stopped within 3 weeks of receiving the first dose of DX-2930.
8. For rollover subjects, the timing of Dose 2 for will vary by subject based on when their first HAE attack occurs following Dose 1. Following the first reported and investigator-confirmed attack, subjects will begin receiving regular SC administrations of 300 mg DX-2930 every 2 weeks.
9. A minimum of 10 days between the first and second open-label doses is required. If the second dose is to be administered within the accepted ±4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit unless that scheduled visit has already occurred. If that scheduled visit has already occurred, or if the second dose is to be administered outside of the accepted ± 4 day window around a scheduled visit, this visit will not replace any scheduled visit and will thus represent an acceptable, extra study visit (i.e., an unscheduled visit). Regardless, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical examination (performed in accordance with standards at the site), clinical laboratory testing, PK, PD, and anti-drug antibody. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data.
10. All subjects (adolescent or adult) who are considered suitable candidates (i.e., those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer DX-2930 after completing appropriate training by the investigator or designee and confirming their understanding. Subjects are allowed to initiate

self-administration after receiving the first 2 doses of DX-2930 at the study site and may elect to self-administer subsequent doses of DX-2930 at the investigational site (during scheduled study site visits; shaded columns).

11. Subjects may self-administer DX-2930 at home or other agreed upon location (during optional off-site self-administration visits; non-shaded columns). Site personnel will call subjects after the planned self-administration to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.
12. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment unless already collected as part of protocol DX-2930-02 or DX-2930-03.
13. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 must be urine-based to confirm eligibility prior to first dose. Tests performed at screening and on indicated visits can be serum or urine-based.
14. There is a recommended ± 15 minute window for all vital signs. Vital signs will be obtained prior to dosing and 1 hour after dosing. Monitoring of vital signs will not be performed for subjects who elect to self-administer away from the investigative site at optional off-site visits (indicated non-shaded columns). Height and weight will be collected at the Screening visit only.
15. Physical examinations will be conducted for all rollover and non-rollover subjects according to the study activities schedule and in accordance with standards at the site. In addition to the physical examinations specified in the study activities schedule, an additional physical examination (performed in accordance with standards at the site) will be conducted for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs.
16. Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis (urinalysis does not need to be done as part of the clinical laboratory testing at Visits 14, 17, 20, and 23). Clinical laboratory testing will be conducted for all rollover and non-rollover subjects according to the study activities schedule. In addition to the testing specified in the study activities schedule, additional testing will be conducted for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs.
17. Historical HAE attack information will be collected at screening. During the study, subjects (or caregivers) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. During study visits, study site personnel will solicit for any new HAE attack information that has not already been reported to the site.
18. Quality of life data will be obtained using the EQ-5D-5L, SF-12, AE-QoL, HADS, and WPAI-GH.
19. Collect subject's injection reports of their experience with DX-2930 self-administration and subcutaneous administration for all doses.
20. Collect subject's injection surveys of their experience with DX-2930 self-administration and subcutaneous injection for indicated visits.
21. PK, PD and Anti-drug Antibody PD samples will be drawn for all rollover and non-rollover subjects according to the study activities schedule. In addition to the samples specified in the study activities schedule, an additional PK, PD and Anti-drug Antibody sample will be drawn for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAE	Acquired angioedema
ACE	Angiotensin converting enzyme
AE	Adverse event
AESI	Adverse Event of Special Interest
AE-QoL	Angioedema Quality of Life Questionnaire
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C1-INH	C1 inhibitor
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
C_{max}	Maximum plasma drug concentration
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRO	Clinical Research Organization
DMID	Division of Microbiology and Infectious Diseases
DP	Drug product
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EQ-5D-5L	EuroQoL 5-Dimensional 5-Level; a standardized instrument for use as a measure of health outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HAE	Hereditary angioedema

HMWK	High molecular weight kininogen
HR	Heart rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G subclass 1
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone releasing systems
IV	Intravenous
K_i	inhibition constant
LTP	Long-term prophylactic/Long-term prophylaxis
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Prothrombin time
PVRM	Pharmacovigilance and Risk Management
QoL	Quality of life
REB	Research ethics board
RBC	Red blood cell (count)
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SC	Subcutaneous
SF-12	Short Form-12; a multi-purpose short form health survey with 12 questions
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SMQ	Standard MedDRA query
SOC	System Organ Class
SOP	Standard operating procedure
TEAE	Treatment-Emergent Adverse Event
US	United States
WBC	White blood cell (count)
WPAI-GH	Work Productivity and Activity Impairment – General Health

1. INTRODUCTION

1.1 DX-2930

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 hereditary angioedema (HAE), a serious and life-threatening disease.

1.2 Hereditary Angioedema

HAE is a long-term, debilitating, and life-threatening disease caused by mutations in the C1-inhibitor (C1-INH) gene, resulting in deficiency or dysfunction of C1-INH protein. HAE manifests clinically as unpredictable, intermittent attacks of subcutaneous or submucosal edema of the face, larynx, gastrointestinal tract, limbs and/or genitalia (Zuraw, 2008). Swelling may last up to five or more days; most patients suffer multiple attacks per year. HAE is an orphan disorder. The exact prevalence of HAE is unknown, but current estimates range from 1 per 10,000 to 1 per 150,000 persons, with many authors agreeing that 1 per 50,000 is likely the closest estimate (Bygum, 2009; Goring et al., 1998; Lei et al., 2011; Nordenfelt et al., 2014; Roche et al., 2005).

Swelling in the larynx can obstruct the airways and cause death from asphyxiation (Bork et al., 2012; Bork et al., 2000). Approximately 50% of all HAE patients will experience a laryngeal attack in their lifetime, and there is no way to predict which patients are at risk of a laryngeal attack (Bork et al., 2003; Bork et al., 2006).

Abdominal attacks are often associated with nausea, vomiting, diarrhea and severe pain; intestinal symptoms resembling abdominal emergencies may lead to unnecessary surgery (Zuraw, 2008).

Approximately 85% of patients have Type I HAE, characterized by very low production of functionally normal C1-INH protein, while the remaining approximately 15% of patients have Type II HAE and produce normal or elevated levels of a functionally impaired C1-INH (Zuraw, 2008). In patients with Types I and II HAE, uncontrolled plasma kallikrein generation results in excess bradykinin release from high-molecular weight kininogen (HMWK) and vascular leak mediated by bradykinin binding to the B2 receptor (B2-R) on the surface of endothelial cells (Zuraw, 2008). Clinical suspicion of Types I and II HAE can be confirmed by available blood tests. In addition to abnormalities in C1-INH level and function, plasma C4 levels are often reduced in blood from most patients.

1.3 Therapeutic Rationale for DX-2930

Plasma kallikrein plays a critical role in the pathogenesis of HAE attacks (Davis, 2006; Kaplan and Joseph, 2010). In normal physiology, C1-INH regulates the activity of plasma kallikrein as well as a variety of other proteases, such as C1r, C1s, factor XIa, and factor XIIa. Plasma kallikrein regulates the release of bradykinin from HMWK. Due to a deficiency of C1-INH in HAE, uncontrolled plasma kallikrein activity occurs and leads to the excessive generation of bradykinin. Bradykinin is a vasodilator which is thought to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain (Craig et al., 2012; Zuraw et al.,

2013). Intervening at the level of bradykinin production with a plasma kallikrein inhibitor therefore represents an attractive and rational therapeutic strategy for HAE. Indeed, the importance of plasma kallikrein as a drug target in HAE has been validated through the observed effectiveness of Kalbitor® (ecallantide), a peptide that specifically targets plasma kallikrein, which was approved by the FDA for the treatment of acute HAE attacks (Kalbitor® Package Insert, 2015).

DX-2930 is a highly potent and specific inhibitor of plasma kallikrein (K_i = 125 pM). X-ray crystallography of DX-2930 combined with plasma kallikrein demonstrates DX-2930 binding to the active site of kallikrein (Kenniston et al., 2014).

1.4 Safety Rationale for DX-2930

Safety data from the Phase 1a clinical study, a first-in-human study with DX-2930 in healthy subjects did not identify any safety concerns. Single doses up to 3 mg/kg of DX-2930 were well-tolerated. There were no dose-limiting toxicities, serious adverse events, or any other safety concerns identified.

Pharmacokinetic (PK) data from the Phase 1a (DX-2930-01) and Phase 1b (DX-2930-02) clinical studies in conjunction with data from the nonclinical toxicity studies support a wide safety margin. The mean C_{max} for human subjects treated at a dose of 300 mg on Days 1 and 15 was approximately 27 µg/ mL. As comparison, a mean C_{max} of 744 µg/ mL was observed following dosing of monkeys with 50 mg/kg DX-2930 subcutaneous (SC) weekly for 6 months resulting in a safety margin of approximately 28-fold. No toxicologically significant findings were observed in these treated animals or in any other nonclinical toxicity study to date for systemically administered DX-2930.

Safety data is also available from the Phase 1b study (DX-2930-02), a multiple-ascending dose study in HAE patients. In this study, two doses of DX-2930 up to 400 mg administered 14 days apart were well-tolerated. There were no dose-limiting toxicities, serious adverse events in any DX-2930 treated subjects, or any other safety concerns identified in this study of HAE patients. Pharmacokinetic data from the 1b study found that the drug exposure following two administrations of DX-2930 (up to a maximum of 400 mg) was substantially less than that attained and evaluated in the nonclinical toxicity studies.

For additional detail regarding the safety rationale for DX-2930, please refer to the DX-2930 Investigator's Brochure.

1.5 DX-2930 Non-Clinical Pharmacology and Toxicology

For more detail regarding the nonclinical findings, please refer to the DX-2930 Investigator's Brochure.

1.6 DX-2930 Clinical Data

The clinical development program to date for DX-2930 consists of 2 studies to evaluate the safety, tolerability, and PK of DX-2930, including one completed Phase 1a single-ascending

dose study in healthy subjects and a Phase 1b multiple-ascending dose study in HAE patients. These studies are summarized in the following sections.

1.6.1 Single-Ascending Dose Study in Healthy Subjects (DX-2930-01)

DX-2930-01 was a Phase 1a randomized, double-blind, placebo-controlled study in healthy subjects to evaluate the safety, tolerability, and PK following a single, SC dose of DX-2930. Participating subjects were randomized to receive placebo or active study drug within one of the following sequential, ascending dose cohorts: 0.1, 0.3, 1.0, or 3.0 mg/kg. For each dosing cohort, 6 subjects were randomized to receive active drug and 2 subjects to receive placebo.

A total of 32 subjects enrolled in the study and were randomized. The treatment groups were well balanced for demographic characteristics. The actual dose of DX-2930 administered to subjects ranged from 6.2 mg (in the 0.1 mg/kg group) to 300 mg (in the 3.0 mg/kg group) across all cohorts.

Based on the safety analysis, a single administration of DX-2930 was well tolerated up to doses of 3.0 mg/kg without evidence of dose-limiting toxicity. There were no deaths, SAEs, or subject discontinuations due to adverse events (AEs) during the study. Furthermore, there was no significant imbalance between placebo and DX-2930 for any particular treatment-emergent adverse event (TEAE). The most commonly reported TEAE was headache, which occurred at a rate of 25% for both DX-2930 and placebo.

The PK profile demonstrated linear, dose-dependent drug exposure with a mean half-life of approximately 17 to 21 days across dose groups. Results from two exploratory biomarker assays provide evidence for an important pharmacodynamic effect of DX-2930 in humans.

For additional detail regarding the single dose, clinical study in healthy subjects, please refer to the DX-2930 Investigator's Brochure.

1.6.2 Multiple-Ascending Dose Study in HAE Patients (DX-2930-02)

DX-2930-02 was a Phase 1b randomized, double-blind, placebo-controlled, multiple ascending-dose study in patients with HAE to evaluate safety, tolerability, and PK of SC DX-2930. Participating subjects were randomized 2:1 to receive either active study drug or placebo within one of the following sequential, ascending dose cohorts: 30, 100, 300, or 400 mg (nominal 6 subjects per cohort). Each subject received 2 doses of study drug separated by 14 days.

A total of 37 subjects were randomized and treated with DX-2930 or placebo. One subject in the 400 mg dose group received a single dose of DX-2930 and, following several unsuccessful attempts to schedule their second dose, was replaced. This subject returned for a single follow-up visit before being lost to follow-up for reasons not related to the study. Routine C1-INH testing revealed that one other subject did not have HAE Type I or II, despite a historical lab test indicating otherwise.

Subject demographics were balanced in terms of age, race, ethnicity and BMI. There were slightly more females in the DX-2930 group than in the placebo group (66.7% versus 53.8%).

The most common AEs reported were HAE attacks, injection site pain, and headache. The rates were not appreciably higher in the DX-2930 subjects compared to placebo. Two subjects were reported to have 3 related severe TEAEs. One of these was a DX-2930 subject (30 mg) with injection site pain lasting 1 minute and one was a DX-2930 subject (400 mg) with worsening headache lasting 1 minute and night sweats.

No safety signals were identified for vital signs, physical examinations, clinical laboratory tests, or electrocardiograms (ECG). Results suggested DX-2930 was well tolerated in this study with no evidence of dose-limiting toxicity at doses up to 400 mg.

A total of 3 out of 92 post-dose samples (3.3%), obtained from 2 out of 23 subjects (8.7%), were confirmed to be anti-drug antibody-positive. No samples were positive for neutralizing activity.

The pharmacokinetic analysis for all subjects in the 30, 100, 300 and 400 mg doses showed drug levels in HAE subjects were dose-dependent and exhibited a prolonged half-life of approximately 2 weeks, typical of a human monoclonal antibody. C_{max} drug levels increased with increasing dose, as expected. These parameters were consistent with values obtained in healthy subjects in study DX-2930-01.

A Western blot assay showed pre-dose baseline levels of mean 2-chain HMWK in unactivated plasma collected from HAE patients was approximately 50%. A statistically significant reduction in 2-chain HMWK levels was observed on study days 8 and 22 in the 300 and 400 mg dose groups compared to pre-dose levels, and approached levels similar to that observed in healthy subjects. This outcome demonstrated the pharmacodynamic activity of DX-2930 and its ability to effectively normalize the instability of HAE plasma in this assay.

Primary efficacy analyses were based on subjects in the 300 mg, 400 mg, and placebo dose groups who reported having at least 2 attacks in the 3 months prior to study entry (0.15 attacks/week). Of those subjects treated with 300 or 400 mg DX-2930, 15 of 16 subjects met these criteria. Of the placebo treated subjects, 11 of 13 subjects met these criteria.

The baseline HAE attack rates (attacks/week) were 0.39 attacks per week in the placebo group, 0.33 attacks per week in the 300 mg group, 0.55 attacks per week in the 400 mg group and 0.49 attacks per week in the 300 and 400 mg combined group. During the pre-specified, primary efficacy interval of 6 weeks (from days 8 to 50; corresponding to a period of notable drug exposure), the HAE attack rate, adjusted for baseline attack rate, was 0 in the 300 mg group and 0.045 attacks per week in the 400 mg group, compared to 0.37 attacks per week in the placebo group. This resulted in a 100% reduction vs placebo for the 300 mg DX-2930 group ($P < 0.0001$) and an 88% reduction vs placebo for 400 mg DX-2930 ($P = 0.005$). During this primary efficacy interval, 100% of subjects in the 300 mg group ($P = 0.026$) and 82% of subjects in the 400 mg group ($P = 0.03$) were attack-free compared with 27% of subjects in the placebo group.

The data from this study demonstrated proof of concept of the ability of DX-2930 to prevent acute attacks of HAE. A statistically significant finding of HAE attack prevention by DX-2930 was observed. DX-2930 was well tolerated in HAE subjects up to 400 mg. Drug exposure appeared to be dose-proportional and consistent with the results obtained in healthy subjects in

study DX-2930-01. Pharmacodynamic effect assays provided evidence that DX-2930 has a direct effect on plasma kallikrein activity in patient plasma.

For additional detail regarding the multiple dose, clinical study in HAE subjects, please refer to the DX-2930 Investigator's Brochure.

1.7 Rationale for Open-Label Extension Study DX-2930-04

The open-label DX-2930 extension study will be preceded by the initiation of a pivotal, multi-center, double-blind, randomized, placebo-controlled parallel-arm study (DX-2930-03) evaluating the efficacy of DX-2930 in preventing acute angioedema attacks in patients with Type I or Type II HAE. Further information on the DX-2930-03 study design can be found in Appendix 5.

Subjects who complete the DX-2930-03 treatment period will be offered the option of rolling into the open-label extension study, DX-2930-04. In addition, a limited number of individuals with HAE Type I or Type II who were not enrolled in DX-2930-03 (up to 100) will be also enrolled.

The rationale for this open-label extension study is to evaluate the long-term safety of repeated subcutaneous treatment with DX-2930 and the long-term efficacy of DX-2930 in preventing HAE attacks. For subjects rolling over from DX-2930-03 who were randomized to one of the active study arms, the total duration of exposure across both studies will cover 18 months. For rollover subjects randomized to placebo in DX-2930-03, and for non-rollover subjects, the total duration of exposure will cover 12 months. Combined, the overall exposure between DX-2930-03 and DX-2930-04 will provide a sizable dataset to evaluate DX-2930 as a life-long, chronic treatment for preventing acute attacks of HAE.

This study seeks to evaluate the outer bounds of DX-2930 dosing frequency (possibly beyond 2 to 4 weeks) by assessing the duration of time between a rollover subject's first open-label dose and their first reported HAE attack. In addition, characteristics of all HAE attacks will be reported and compared to the subject's historical baseline (for non-rollover subjects) or attack history based on attacks reported in the DX-2930-03 study (for rollover subjects).

For non-rollover subjects, the study will evaluate the safety and efficacy of switching from a long-term prevention therapy (eg, C1-INH, anti-fibrinolytics, androgens) to DX-2930 dosing, while evaluating breakthrough attack characteristics compared to historical baseline both prior to and during co-administration with their LTP therapy regimen and while receiving DX-2930 alone.

For all subjects, the study will also assess immunogenicity of chronically administered DX-2930, PK and PD, subject health-related quality of life (QoL), subject experience with self-administration and ease of SC administration with DX-2930.

2. STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the long-term safety of repeated subcutaneous (SC) administrations of DX-2930

2.2 Secondary Objectives

- To evaluate the long-term efficacy of DX-2930 in preventing HAE attacks
- To characterize the outer bounds of dosing frequency for DX-2930

2.3 Tertiary Objectives

- To assess the immunogenicity of chronically administered DX-2930
- To evaluate the effect of DX-2930 on health-related quality of life (QoL)
- To characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profile of SC administration of DX-2930
- To evaluate safety and efficacy in the non-rollover population of switching from long-term prophylactic (LTP) treatment to DX-2930
- To evaluate breakthrough attack characteristics while receiving DX-2930 compared to historical baseline
- To evaluate subject experience with self-administration of DX-2930 including ease of SC administration of DX-2930

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Overview

DX-2930-04 is an open-label, long term safety and efficacy extension study of DX-2930-03, to evaluate the investigational medicinal product (IMP), DX-2930, in preventing acute angioedema attacks in patients with Type I and Type II HAE. There are two types of subjects who will be enrolled into this study:

- Subjects who rollover from the DX-2930-03 study
- Subjects who are non-rollover (i.e., were not participants in DX-2930-03)

Rollover Subjects

Rollover subjects are subjects who complete the double-blind treatment period at Day 182 of the DX-2930-03 study and consent to enter DX-2930-04. Subjects who discontinue from DX-2930-03 after enrollment are not eligible to enroll in DX-2930-04.

Subjects should be asked about their interest in the DX-2930-04 study after enrollment into DX-2930-03 to anticipate enrollment and preparedness for DX-2930-04. Willing subjects must sign informed consent for DX-2930-04 after Day 168 of study DX-2930-03 and no later than the final DX-2930-03 Day 182 treatment period study visit.

The first DX-2930-04 visit for rollover subjects (Day 0) will occur on the same day as the DX-2930-03 Day 182 study visit. Rollover subjects will complete all DX-2930-03 final study assessments (Day 182) at which time they will be discharged from that study. No assessments conducted between the DX-2930-03 Day 182 study visit and the first DX-2930-04 visit (Day 0) will be duplicated. Results of the final DX-2930-03 assessments on Day 182 will be used as the pre-dose results for Day 0 of DX-2930-04.

All subjects, caregivers, investigators and study site personnel will remain blinded to the DX-2930-03 treatment assignment until the conclusion of the DX-2930-04 study.

Non-rollover subjects

At least 50 subjects (up to a maximum of 100) who were not participants in the DX-2930-03 study will be permitted to enroll if they meet the eligibility requirements. Subjects who screen fail out of DX-2930-03 for not meeting the minimum attack requirements during the run-in period must wait until enrollment for the double-blind study has ended before they can screen for DX-2930-04. The Sponsor may ease this restriction based on the enrollment rate observed in DX-2930-03. Subjects who are still in the run-in period for DX-2930-03 when enrollment for that study closes, as well as subjects on prior LTP who screen fail out of DX-2930-03 due to an inability to wash-out of their LTP, may screen for DX-2930-04 following discussion with the Sponsor medical monitor.

Screening Period:

Rollover subjects
There is no screening period for rollover subjects.

Non-rollover subjects
Non-rollover subjects must provide informed consent and have screening assessments completed within 4 weeks prior to their first open-label dose. Screened non-rollover subjects (adults and adolescents) who are on LTP with C1-INH therapy for HAE can continue their current LTP until Day 8 (or Day 15) such that subjects will have received 2 (or 4) doses of C1-INH. For subjects who are on attenuated androgens (e.g., danazol) or anti-fibrinolytics (e.g., tranexamic acid); a similar tapering schedule is recommended. However, the taper can be prolonged by an additional week as long as androgen or anti-fibrinolytic therapy is stopped within 3 weeks of receiving the first dose of DX-2930.

Treatment Period:

Rollover Subjects
Following informed consent and pre-dose assessments, rollover subjects will receive a single open-label dose of DX-2930 administered subcutaneously (SC) on Day 0. Subjects will not receive any additional DX-2930 doses until their first reported and investigator confirmed HAE attack. As such, the total number of doses within the 350 day treatment period will vary by rollover subject.

The duration of time between the first open-label dose and first reported HAE attack will vary by rollover subject. All rollover subjects must adhere to the Study Activities Schedule, for the entire duration of the study. However, until a rollover subject reports their first HAE attack, only scheduled study visits where the following tests and assessments are performed must be conducted at the investigative site: pregnancy testing, clinical laboratory testing, physical examination, 12-Lead ECG, QoL, PK, PD and anti-drug antibody sample collection. All other scheduled study visits may be conducted via site check-in calls to collect information on adverse events, concomitant therapy, and HAE attack data. See Study Activities Schedule for which visits must be conducted at the study site.

Once a rollover subject reports their first HAE attack they will present to the investigative site for their second open-label dose of DX-2930 as quickly as subject and site schedules allow. If the second dose is to be administered within the accepted ± 4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit. If that scheduled visit has already occurred, the day of the visit will be considered an acceptable, extra study visit.

In the event that the second dose is to be administered outside of the accepted ±4 day window around a scheduled visit, the day of the visit will be considered an acceptable extra study visit (i.e., this visit will not replace any scheduled visit).

Regardless of the study day, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical

examination, clinical laboratory testing, and blood sampling for PK, PD, and anti-drug antibody assessments. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data.

Non-rollover Subjects
Once all screening assessments have been completed and eligibility confirmed, non-rollover subjects will arrive at the study site and, following pre-dose assessments, receive an open-label dose of 300 mg DX-2930 administered SC on Day 0. Non-rollover subjects will continue to receive SC administrations of open-label 300 mg DX-2930 every 2 weeks throughout the duration of the treatment period. A total of 26 doses will be administered with the last dose administered at the Day 350 study visit.

All Subjects:
For all subjects, subsequent doses after the second dose require a minimum of 10 days and maximum of 18 days between administrations, and should fall within the accepted ± 4 day window around study visits.

After the second DX-2930 dose is given either within the study window (±4 days) or an acceptable extra study visit, the 3rd dose must be administered at the next pre-defined study visit according to the schedule of assessments.

Regardless of when a subject's first HAE attack occurs, there will be a minimum of 10 days between their first open-label dose and their second open-label dose. Following their second open-label dose, subjects will continue to receive repeated SC administrations of open-label DX-2930 every 2 weeks for the remaining duration of the treatment period. The treatment period will last 350 days from the date of the first open-label dose. The number of doses administered during this period will vary by subject based on the date of each subject's second dose, but will not exceed 26 doses. The Day 350 study visit is the last visit at which a dose may be administered.

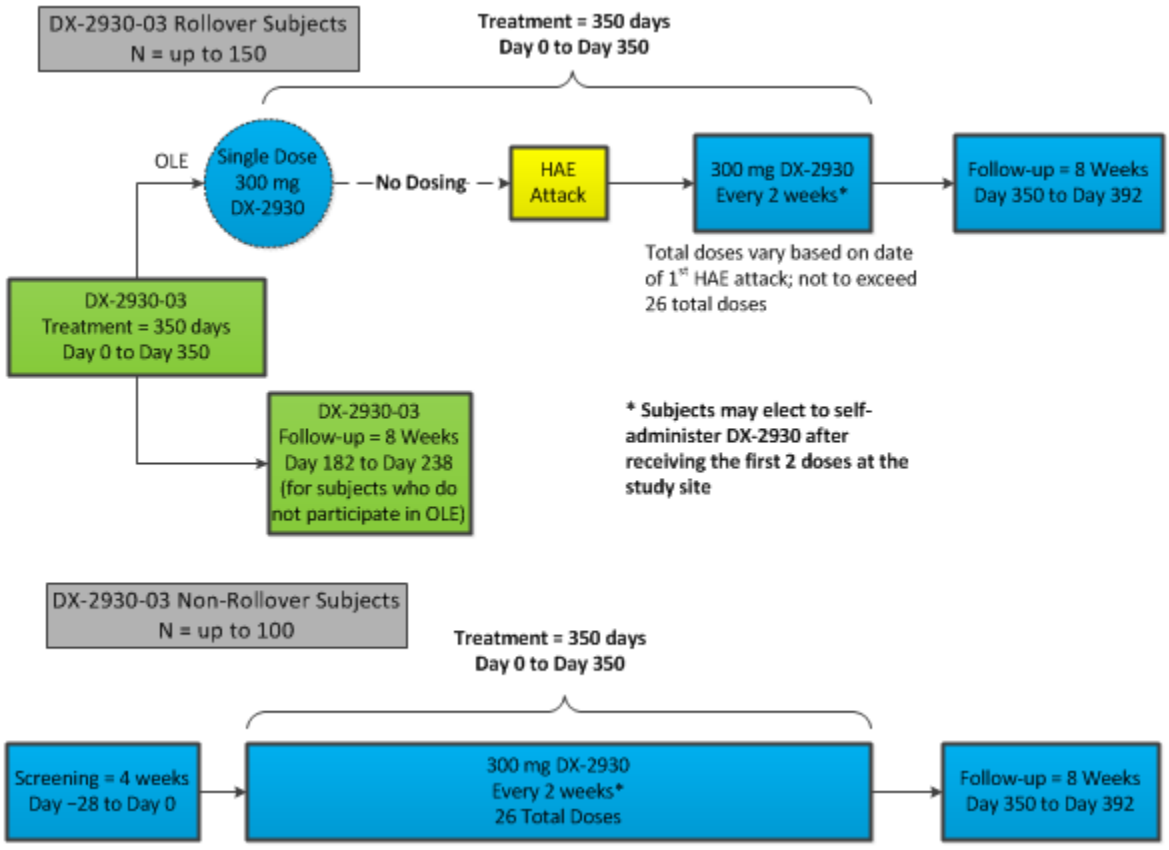
Self-Administration

All subjects (adolescent or adult) who are considered suitable candidates (i.e., those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer treatment. Subjects must complete appropriate training by the investigator or designee and have their understanding of the procedures confirmed by the investigator or designee. Subjects are allowed to initiate self-administration after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may self-administer subsequent doses of DX-2930 at the investigational site (when visits are scheduled study site visits) or the subject's home or other agreed upon location (when the study permits off-site dosing). See Schedule of Activities for details. Adolescent subjects self-administering DX-2930 will be supervised by a parent/legal guardian/caregiver. Alternatively, a parent/legal guardian/caregiver, after completing appropriate training, will be allowed to administer the investigational product to an adolescent without study site personnel supervision. Site personnel will call subjects after the planned self-administration to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.

Follow-up Period

After completion of the 350 day treatment period, all subjects will undergo safety evaluations during an 8-week follow-up period. Figure 1 shows a schematic of the open-label extension study.

Figure 1: Schematic of the Open-Label Extension Study



Modifications to Open-Label Dosing

If at any time an important dose-related safety signal is identified either from this study or DX-2930-03, the Sponsor may decide to switch the enrolled subjects who have not yet completed the treatment period, and any subsequent subjects, to receive a different open-label dose and/or frequency.

In addition, based on the results of the DX-2930-03 study, the Sponsor may switch to a different dose and/or frequency.

3.1.2 Stopping Rules

3.1.2.1 Study Level Stopping Rules

Safety data, including SAEs and AESI, will be monitored regularly throughout the duration of the study. If any potential safety signal is identified as a result of monitoring in this study, or from any safety findings from the DX-2930-03 study, or following DSMB review, the Sponsor may take actions as deemed appropriate, including suspending dosing in the study, while the potential risk is evaluated and a course of action has been determined.

3.1.2.2 Individual Stopping Rules

Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or DX-2930-related, clinically significant non-serious AE) that, in the assessment of the investigator or DSMB recommendation, warrants discontinuation from further dosing for that subject's well-being. The investigator has the ability to contact and consult with the Medical Monitor on such matters. Subjects will continue to be followed through the completion of all scheduled non-dosing visits, unless they request to be discontinued from the study.

3.1.3 Follow-up for Subjects Meeting Stopping Criteria

Subjects that develop either an SAE or other toxicity considered clinically relevant (AE, laboratory, physical examination, vital sign, or ECG finding) will be carefully monitored until resolution, which may include the following:

- Additional clinical laboratory tests and/or other clinical investigations
- Additional visits or extended duration of follow-up
- Obtaining a specialist consultation

3.2 Rationale for Open-Label Extension Dose Selection

The dose selected for the open-label extension (300 mg every 2 weeks) is anticipated to be effective and safe as determined in the pivotal, double-blind DX-2930-03 trial. If at any time an important dose-related safety signal is identified either from this study or DX-2930-03, the Sponsor may decide to switch the enrolled subjects who have not yet completed the treatment period, and any subsequent subjects, to receive a different open-label DX-2930 dose and/or frequency.

Additionally, based on the efficacy results of the DX-2930-03 study, the Sponsor may switch to a different dose and/or frequency.

3.3 Individual Subject Dosing and Follow-Up

All subjects will receive open-label DX-2930 during a 350 day treatment period. The number of doses that rollover subjects receive during this period will vary by subject but will not exceed 26 doses. The last dose of open-label DX-2930 administered to these subjects may be given at the Day 350 study visit. Non-rollover subjects will receive DX-2930 every 2 weeks for a total of 26 doses, with the first dose administered on Day 0 and the final dose administered at the Day 350 study visit.

There will be a ±4 day window around each study visit. There will be a minimum of 10 days between any two doses. Excluding the time interval between the first and second open-label doses for rollover subjects, there will be a maximum of 18 days between any two doses. Subjects will be monitored at the study site through 1 hour post-dose.

All subjects (adolescent or adult) who are considered suitable candidates (i.e., those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer treatment after completing appropriate training by the investigator or designee and confirming their understanding. Subjects are allowed to initiate self-administration after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may continue to self-administer subsequent doses of DX-2930. Subjects who elect to self-administer investigational product will be provided the necessary supplies (see Section 5.7 and Section 6.15.1).

3.4 Study Duration for Individual Subjects

Following informed consent, subjects will either rollover from DX-2930-03 or undergo screening assessments (non-rollover subjects). Screening assessments for non-rollover subjects must occur within 4 weeks prior to the first open-label dose. Eligible subjects will be enrolled and undergo a 350 day treatment period. At the conclusion of the 350 day treatment period, subjects will be followed for an additional 8 weeks.

4. STUDY POPULATION SELECTION

4.1 Study Population

The study is expected to enroll subjects from the DX-2930-03 study, as well as at least 50 (up to a maximum of 100) additional subjects who were not enrolled in DX-2930-03. The total enrollment is expected to be approximately 150, but not more than 250 HAE Type I or II subjects. Subjects will be 12 years of age or older who experience at least 1 attack per 12 weeks. HAE diagnosis will be confirmed through documented clinical history and diagnostic testing conducted either during screening or during participation in study DX-2930-02 or DX-2930-03.

The subject population includes subjects who are 12 to 17 years old. Like adults, children with HAE can suffer from recurrent and debilitating attacks. Symptoms may present very early in childhood, and upper airway angioedema has been reported in HAE patients as young as the age of 3 (Bork et al., 2003). In one case series of 49 pediatric HAE patients, 23 had suffered at least one episode of airway angioedema by the age of 18 (Farkas, 2010). An important unmet medical need exists among children with HAE, especially adolescents, since the disease commonly worsens after puberty (Bennett and Craig, 2015; Zuraw, 2008). The study will aim to enroll at least 15 subjects who are 12 to 17 years of age, inclusive of the estimated 10 subjects 12 to 17 years old who roll over from the DX-2930-03 study.

4.2 Inclusion Criteria

Subjects must meet the following criteria to be enrolled in this study:

1. Male and female HAE subjects who are 12 years of age or older at the time of screening.

2. Documented diagnosis of disease HAE (Type I or II) based on all of the following:

    - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).

    - Diagnostic testing results obtained during screening (or a prior DX-2930 study) that confirm HAE Type I or II: C1 inhibitor (C1-INH) functional level < 40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may be retested if results are incongruent with clinical history or believed by the investigator to be confounded by LPT use.

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

3. A historical baseline HAE attack rate of at least 1 attack per 12 weeks.

4. Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects age 12 to 17, whose caregiver has provided informed consent, are willing and able to read, understand and sign an assent form.

5. Males and females who are fertile and sexually active must adhere to contraception requirements for the duration of the study as follows:

    - Females of childbearing potential must agree to be abstinent or it is recommended to use highly effective forms of contraception from the screening period through 30 days after the final study visit. This includes stable doses (for 3 months prior to study screening) of combined estrogen and progestin-containing hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable), progestin-only hormonal contraception associated with inhibition of ovulation, intra-uterine device (IUD, all types) or intrauterine hormone releasing systems (IUS). Notes: 1) A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. 2) Use of a male condom with or without spermicide or cervical cap, diaphragm or sponge with spermicide or a combination (double barrier methods) are not considered highly effective.

    - Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.

    - Males, including males who are surgically sterile (post vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study visit.

4.3 Exclusion Criteria

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

1. Discontinued from DX-2930-03 after enrollment for any reason.

2. If rolling over from DX-2930-03, presence of important safety concerns that would preclude participation in this study.

3. Concomitant diagnosis of another form of chronic, recurrent angioedema such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.

4. Dosing with an investigational drug (not including DX-2930 or other HAE therapies) or exposure to an investigational device within 4 weeks prior screening.

5. Exposure to angiotensin-converting enzyme (ACE) inhibitors within 4 weeks prior to screening or any newly initiated or dose modification of estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) 3 months prior to the screening visit.

6. Unwilling to discontinue use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 3 weeks after starting DX-2930 treatment.

7. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's Syndrome).

8. Pregnancy or breastfeeding.

9. Subject has any condition that, in the opinion of the investigator or Sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., history of substance abuse or dependence, a significant pre-existing illness or other major comorbidity that the investigator considers may confound the interpretation of study results).

5. STUDY TREATMENT(S)

5.1 Description of Treatment(s)

For detailed information regarding open-label DX-2930 administration, refer to the Pharmacy Manual.

DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated using the following compendial components: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Polysorbate 80. Each open label vial contains a nominal concentration of 150 mg DX-2930 active ingredient in 1 mL solution.

For each 300 mg dose of DX-2930, each subject will receive a total of 2 mL (2 vials), which will be administered in a single 2 mL SC injection. The injection will be given in the upper arm, thigh or abdomen.

Self-Administration
All subjects (adolescent or adult) who are considered suitable candidates (i.e., those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer treatment after completing appropriate training by the investigator or designee and demonstrating the comprehension to self-administer. Subjects are allowed to initiate self-administration after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may continue to self-administer subsequent doses of DX-2930 at the investigational site (when visits are scheduled study site visits) or the subject's home or other agreed upon location (when the study permits off-site dosing). See Schedule of Activities for details. Adolescent subjects self-administering investigational product will be supervised by a parent/legal guardian/caregiver. Alternatively, a parent/legal guardian/caregiver, after completing appropriate training, will be allowed to administer DX-2930 to an adolescent without study site personnel supervision. Site personnel will call subjects after the planned self-administration to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.

Throughout the study, study site personnel will document information in the subject's medical record and eCRF regarding the subject's experience with self-administration and SC administration of DX-2930.

5.2 Dosing and Follow-Up Scheme

Details of subject dosing and follow-up are outlined in Section 3.1.1 and included in the Study Activities Schedule, Appendix 1.

Rollover subjects will receive their first open label SC dose of DX-2930 on Day 0. Subjects will not receive any additional DX-2930 doses until their first reported HAE attack. The second dose of DX-2930 may be administered at an unscheduled visit if it is outside of the accepted ±4 day window around a scheduled visit. Following this attack subjects will receive open label SC doses of DX-2930 every 2 weeks until the end of the treatment period. Subsequent dosing after Dose 2 requires a minimum of 10 days and a maximum of 18 days between administrations.

Regardless of when a rollover subject's first HAE attack occurs, there will be a minimum of 10 days between their first open-label dose and their second open-label dose. Following their second dose, rollover subjects will continue to receive repeated SC administrations of open-label 300 mg DX-2930 every 2 weeks for the remaining duration of the treatment period per the scheduled dosing in the Study Activities Schedule. The treatment period will last 350 days from the date of the first open-label dose. The number of doses administered during this period will vary by subject based on the date of each subject's second dose, but will not exceed 26 doses. The Day 350 study visit is the last visit at which a dose may be administered.

Non-rollover subjects will receive their first open-label dose SC dose of DX-2930 on Day 0 and will continue to receive SC administrations of open-label DX-2930 every 2 weeks throughout the duration of the treatment period. A total of 26 doses will be administered with the last dose administered at the Day 350 study visit.

After completion of the 350 day treatment period, all subjects will undergo safety evaluations during an 8-week follow-up period.

5.3 Method of Identifying Subjects

Subjects meeting all eligibility criteria will be enrolled in the study and sequentially assigned a unique site-based identification number.

5.4 Prior and Concomitant Therapy

For subjects not rolling over from DX-2930-03, reasonable efforts will be made to determine all relevant treatments received by the subject from 4 weeks prior to screening through the final study visit. For subjects rolling over from DX-2930-03, concomitant therapy use will be carried forward from that study and will continue to be collected through the final study visit.

All information on prior and concomitant therapy (including all prescription/non-prescription medications, herbal medications and vitamin supplements) must be recorded on the subject's eCRF and should include the name of the procedure or drug and duration of the treatment (start and stop dates). Concomitant treatments (non-pharmacological treatments) include any surgical or diagnostic procedures.

5.4.1 Allowed Therapies

The following therapies are allowed during the study:

- Therapies for co-existing conditions, including those for acute attacks of HAE, as described in Section 5.4.1.1 are permitted if not excluded in Section 5.4.2. The use of short-term prophylactic treatment for HAE will be permitted if medically indicated. Short-term (pre-procedure) prophylaxis is defined as use of C1-INH to avoid angioedema complications from medically indicated procedures.
- Therapies to treat any AEs the subject experiences during the study are permitted.

5.4.1.1 Management of HAE Attacks

Acute HAE attacks during the study are to be managed in accord with the investigator's usual care of their patients, including use of acute attack therapies that the investigator deems as medically appropriate. Use of C1-INH will be permitted as an acute attack therapy but not as a LTP therapy. Administration of DX-2930 and study procedures will continue without alteration to the protocol-specified study schedule, even if the subject has symptoms of an HAE attack the day of DX-2930 administration and/or receives treatment for an HAE attack. The administration of DX-2930 can also be re-scheduled as long as the minimum and maximum timeframe between doses are met based on patient preference or physician discretion.

5.4.2 Excluded Concomitant Therapies

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

- Long-term prophylaxis for HAE (e.g., use of C1-INH for LTP, attenuated androgens, or anti-fibrinolytics) once LTP is discontinued (within 3 weeks following first dose of DX-2930).
- Angiotensin-converting enzyme (ACE) inhibitors.
- Initiating or changing the dose of estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) 3 months prior to the screening visit.
- Use of androgens (e.g., stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) for non-HAE related medical conditions or for HAE after discontinuation during the first 3 weeks.
- Any other investigational drug or device.

5.5 Restrictions

5.5.1 Medical Interventions

Medical interventions deemed necessary by the investigator for the health and well-being of the subject will not be excluded during this study.

5.5.2 Fluid and Food Intake

There are no restrictions on fluid and food intake. Subjects may continue their usual dietary regimens.

5.5.3 Activity

There are no activity restrictions. Subjects may continue their usual activity regimens.

5.6 Treatment Compliance

All doses of open-label DX-2930 administered at the investigational site will be under the direct supervision of the investigator or qualified study site personnel designated by the investigator.

Subjects are allowed to initiate self-administration after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may continue to self-administer subsequent doses of DX-2930 at the investigational site (when visits are scheduled study site visits) or the subject's home or other agreed upon location (when the study permits off-site dosing). See Schedule of Activities for details. For all subjects, subsequent doses after the second dose require a minimum of 10 days and maximum of 18 days between administrations, and should fall within the accepted ±4 day window around study visits.

For rollover subjects, after the second DX-2930 dose is given either within the study window (±4 days) or an acceptable extra study visit, the 3rd dose must be administered at the next pre-defined study visit according to the schedule of assessments.

5.7 Packaging and Labeling

The open-label DX-2930 will be supplied by the Sponsor and prepackaged in a study kit for investigational studies. Each study kit will contain 1 vial of investigational product. Both the vials and carton (kit) will be appropriately labeled according to local regulations and bear the unique study drug kit number. The investigative site will also be provided with ancillary supplies including syringes, needles, and alcohol wipes. The site has the option of using needles of a different gauge to aid subject comfort with each SC injection. Subjects who elect to self-administer investigational product will be provided the following supplies as applicable:

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

All used and unused vials should be returned to the study kit cartons/boxes and transported to the site for drug accountability. Written instructions on DX-2930 handling and self-administration procedures will be provided to trained subjects prior to initiating self-administration. Refer to the Pharmacy Manual for additional details on DX-2930 and its administration.

5.8 Storage and Accountability

All DX-2930 will be shipped refrigerated to the study site and must be stored at 2ºC to 8ºC/36ºF to 46ºF in the carton and protected from light. Storage must be in a securely locked area, accessible to authorized persons only, until needed for dose preparation. See Section 5.7 and Section 6.15.1 for details.

5.9 Investigational Medicinal Product Retention at Study Site

The investigator (or designee) is responsible for maintaining accurate accountability records of DX-2930 throughout the clinical study. All DX-2930 received at the site must be inventoried and accounted for in an accountability log provided by the Sponsor. All dispensing and accountability records will be available for Sponsor review. Drug accountability will be verified during on-site monitoring visits.

Upon the completion or termination of the study, and upon written authorization from the Sponsor, or its representative, all unused and/or partially used DX-2930 should be returned or destroyed at the investigational site, as specified by Sponsor. It is the investigator's responsibility to ensure that the Sponsor, or its representative, has provided written authorization that procedures for proper disposal of DX-2930 have been established, and that appropriate records of the disposal are documented and maintained. No unused DX-2930 may be disposed until fully accounted for by the Sponsor monitor (or designee).

6. STUDY PROCEDURES

Please refer to the Study Activities Schedule, Appendix 1.

6.1 Informed Consent

The ICF must be executed prior to performing any study related activities and must be approved by the reviewing institutional review board (IRB), research ethics board (REB) or independent ethics committee (IEC). Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the investigator.

Subjects who are not rolling over from the double-blind DX-2930-03 study will provide informed consent at Screening. Subjects who are rolling over from the double-blind DX-2930-03 study will provide consent after Day 168 of study DX-2930-03 and no later than the final DX-2930-03 Day 182 study visit. Upon completion of the final assessments, the subjects will be discharged from the double-blind study and will start participation in the OLE study and receive their first open-label dose.

6.2 Eligibility Review

The investigator or qualified study site personnel will confirm that all Inclusion and Exclusion criteria have been met.

6.3 Demographics and Medical History

Demographics: date of birth (alternately age or year of birth, if full date is not allowed to be collected for legal reasons), sex, race and ethnicity (where locally permitted) and medical history will be obtained at Screening from subjects not rolling over from DX-2930-03 and will be recorded on the source document and eCRF. Medical history will capture the subject's current medical status (current disease processes), past medical status (past disease processes), history of surgery, allergies and concomitant medications. For subjects rolling over from DX-2930-03, these data will be carried forward from that study.

6.4 HAE Attack Information Collection

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

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

At screening, HAE attack history will be collected for non-rollover subjects. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant attack location(s), triggers, average duration, acute attack therapy use and history of LTP (including duration of LTP, medication(s) and dose used for LTP, and frequency of attacks

while receiving LTP). If available, information will also be collected on HAE diagnosis (year of confirmation, how many years after onset of symptoms was diagnosis confirmed, or if subject was misdiagnosed).

During the study, subjects (or caregivers) will be instructed to notify and report details to the study site within 72 hours of the onset of an attack. This includes the first attack experienced by rollover subjects following their first open-label dose. In the situation 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 can be provided to assist in tracking any HAE attacks experienced.

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 (work, school, social interactions) and whether any assistance or medical intervention was required, including hospitalizations, additional laboratory tests, or emergency department visits
- Any medications used to treat the attack (both prescription and over the counter)
- If the attack resolved, date and time the subject was no longer experiencing symptoms

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

For rollover subjects, study site personnel will contact rollover subjects approximately every 7 days following the first dose of open-label until the subject has received their second open label dose. This is to insure accurate reporting for any HAE attacks not already reported by the subject as required within 72 hours. During each study visit, study site personnel will solicit for any new HAE attack information that was not already provided to the site.

In this study, HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to DX-2930, 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 EDC system within 24 hours of becoming aware of the event. For all serious adverse events that are reported as HAE attacks, the 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 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 to receive additional information. Any subject-reported attack not confirmed by the investigator or physician designee must have an alternate AE diagnosis

recorded. All subject-reported and investigator/ physician designee-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 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 or physician designee may still clinically determine that the event did not represent an 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.

6.5 Vital Signs

Vital signs will be assessed by the investigator or his/her qualified designee according to the Study Activities Schedule (Appendix 1) unless the subject has elected to self-administer for that visit. 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. For subjects who rollover from DX-2930-03, vital signs taken during the final study visit in DX-2930-03 will serve as the Day 0 pre-dose vital signs in this study and will not be duplicated.

6.6 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 1). The physical examination will be performed in accordance with standards at the site.

For subjects who rollover from DX-2930-03, the physical exam taken during the final study visit in DX-2930-03 will serve as the Day 0 pre-dose physical exam in this study and will not be duplicated.

6.7 Electrocardiography (ECG)

A standard 12-lead ECG (single recording) will be performed according to the Study Activities Schedule (Appendix 1). 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. For subjects who rollover from DX-2930-03, the ECG taken during the final study visit in DX-2930-03 will serve as the Day 0 pre-dose ECG in this study and will not be duplicated.

6.8 Clinical Laboratory Tests

6.8.1 Laboratory Parameters

Laboratory testing will be performed according to the Study Activities Schedule (Appendix 1).

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

When multiple sample collection types are performed at the same assessment time point, the samples will be drawn in the following order (depending on what sample types are to be collected at that time point): laboratory safety samples (hematology, coagulation, serum chemistry), C1-INH, C4, C1q, PK, anti-drug antibodies, PD. Aliquots from the PK, PD and anti-drug antibody samples may be retained as back-up for additional parameter testing if necessary. Subjects will be in a seated or supine position during blood collection. The total blood draw for each rollover subject will be approximately 269.8 mL. The total blood draw for each non roll-over subject will be approximately 283 mL. For subjects who rollover from DX-2930-03, testing performed during the final study visit in DX-2930-03 will serve as the Day 0 pre-dose laboratory testing in this study and will not be duplicated.

6.8.1.1 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

6.8.1.2 Coagulation

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

6.8.1.3 Chemistry

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

6.8.1.4 Urinalysis

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

Urinalysis does not need to be done as part of the clinical laboratory testing at Visits 14, 17, 20, and 23.

6.8.1.5 Pregnancy Test

Pregnancy tests will be either serum or urine based.

6.8.1.6 C1-INH Functional Assay

Results of a C1-INH functional assay are required for eligibility assessment. Samples will be drawn at the Screening visit unless they were previously drawn in study DX-2930-02 or DX-2930-03. Results of the C1-INH functional assay from DX-2930-02 or DX-2930-03 may be used to confirm diagnosis in this study. Subjects may be retested if results are incongruent with clinical history or believed by the investigator to be confounded by recent LTP use.

6.8.1.7 C4 Assay

Results of a C4 assay may be required for eligibility assessment. The C4 sample will be drawn at the same time as the C1-INH sample is drawn during the Screening visit unless previously drawn in study DX-2930-02 or DX-2930-03. Results of the C4 assay from DX-2930-02 or DX-2930-03 may be used to confirm diagnosis in this study. Subjects may be retested if results are incongruent with clinical history or believed by the investigator to be confounded by recent LTP use.

6.8.1.8 C1q Assay

Results of a C1q assay may be required for eligibility assessment. Any subject who requires C1-INH and C4 assay results for diagnostic confirmation in this study will have C1q assay results obtained as well. The C1q sample will be drawn at the same time as the C1 and C4 sample is drawn during the Screening visit.

6.8.1.9 PK Sample Collection

As outlined in Section 6.9.

6.8.1.10 PD Sample Collection

As outlined in Section 6.10.

6.8.1.11 Plasma Anti-Drug Antibody Testing

As outlined in Section 6.11.

6.8.2 Sample Collection, Storage, and Shipping

Blood samples for laboratory assessments will be collected at the site by a trained phlebotomist designated and/or approved by the study investigator. Details for the collection, processing, storage and shipment of samples for all laboratory determinations will be provided in the Laboratory Manual.

Biological material will be stored and secured in a manner that assures that unauthorized access is prohibited and the samples are not lost, allowed to deteriorate, or accidentally or illegally destroyed.

6.9 Pharmacokinetic Assessments

Blood samples for the measurement of plasma DX-2930 concentration will be obtained as specified in the Study Activities Schedule (Appendix 1).

6.10 Pharmacodynamic Assessments

To evaluate the PD effects of DX-2930 upon plasma kallikrein activity, blood samples will be obtained as specified in the Study Activities Schedule (Appendix 1).

6.11 Plasma Anti-Drug Antibody Testing

Plasma samples for testing for formation of antibodies to DX-2930 will be obtained as specified in the Study Activities Schedule (Appendix 1).

6.12 Prior and Concomitant Therapy

The Sponsor representatives and investigator at the site conducting the trial will review and evaluate prior (4 weeks prior to study screening) and concomitant medication usage on an ongoing basis. For subjects not rolling over from DX-2930-03, 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 on the source document and eCRF following informed consent. For subjects rolling over from DX-2930-03, concomitant therapy use will be carried forward from that study and will continue to be collected through the duration of the study.

6.13 Investigational Medicinal Product Treatment

Instructions for safe handling of DX-2930, preparation of each subcutaneous dose and administration of DX-2930, are provided in the Pharmacy Manual. Preparation and dispensing of DX-2930 will be handled by qualified study site personnel or by subjects who are self-administering after receiving appropriate training by the investigator or designee at the study site. The requirements for maintaining DX-2930 accountability are provided in Section 6.15.1(for subjects self-administering) and Section 5.7 and Section 5.8 of this protocol.

6.14 Quality of Life Assessments

Quality of life (QoL) assessments will be conducted using the Angioedema Quality of Life Questionnaire (AE-QoL), EuroQoL 5-Dimensional 5-Level Measure (EQ-5D-5L), Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH), Hospital Anxiety and Depression Scale (HADS), and 12 Item Short Form Survey (SF-12). See Study Activities Schedule (Appendix 1). For subjects who rollover from DX-2930-03, quality of life assessments obtained during the final study visit in DX-2930-03 will serve as the Day 0 pre-dose quality of life assessments in this study and will not be duplicated.

6.14.1 Angioedema Quality of Life Questionnaire (AE-QoL)

The AE-QoL is a self-administered, symptom-specific tool developed and validated to assess quality of life (QoL) impairment in recurrent angioedema patients (Weller et al. 2012). The AE-QoL consists of 17 questions covering four domains/dimensions (functioning, fatigue/mood, fear/shame, nutrition). Each of the 17 items has a five-point Likert-type response scale ranging from 1 (Never) to 5 (Very Often). The AE-QoL is scored to produce a score for each domain and a total score ranging from 0 to 100, with higher scores indicating stronger impairment. It takes 5 minutes to complete the AE-QoL.

6.14.2 EuroQoL 5-Diminsional 5-Level Measure (EQ-5D-5L)

The EQ-5D-5L is a self-administered standardized measure of health status comprised of a descriptive system and a Visual Analogue Scale (VAS). The descriptive system consists of five health related quality of life dimensions (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is rated on a 5-point response scale (5 levels) indicating severity of problems, where 1 is “no problems” and 5 is “extreme problems”. The EQ-5D VAS is a measure of overall self-rated health status on a 20-cm vertical VAS with endpoints labelled “the best health you can imagine” and “the worst health you can imagine”. The VAS ranges from 0 to 100, with higher scores indicative of better overall health.

6.14.3 Work Productivity and Activity Impairment – General Health (WPAI-GH) Questionnaire

The WPAI-GH is a 6-item instrument assessing work and activity impairment due to health problems during the past 7 days. The instrument elicits four main scores in relation to general health specifically: absenteeism (the percentage of work time missed because of one's health in the past seven days), presenteeism (the percentage of impairment experienced while at work in the past seven days because of one's health), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and activity impairment (the percentage of impairment in daily activities because of one's health in the past seven days) (Reilly et al. 1993).

6.14.4 Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a self-assessment scale to detect states of depression, anxiety and emotional distress amongst patients who were being treated for a variety of clinical problems (Zigmond and Snaith 1983). The scale has a total of 14 items. Seven of the items relate to anxiety and seven relate to depression. The responses are scored on a scale of 0–3 (3 indicates higher symptom frequencies). Scores for each subscale (anxiety and depression) range from 0 to 21 with scores categorized as follows: normal 0–7, mild 8–10, moderate 11–14, and severe 15–21. Scores for the entire scale (emotional distress) range from 0 to 42, with higher scores indicating more distress. This scale reflects how a patient has been feeling during the past week.

6.14.5 12 Item Short Form v2 Health Survey (SF-12v2)

The SF-12v2 Health Survey is a reliable and valid generic measure of functional health and well-being. The SF-12v2 consists of 12 questions, all selected from the SF-36 Health Survey (Ware et al. 1996). The SF-12v2 yields eight health domains (vitality, physical functioning, bodily pain,

general health perceptions, physical role functioning, emotional role functioning, and mental health summary measures. Physical and Mental Health Composite Scores (PCS & MCS) can be computed using the scores of twelve questions and range from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health. The standard form of the instrument asks patients to reply to questions according to how they have felt over the last 4 weeks.

6.15 DX-2930 Injection Report and Self-Administration and Subcutaneous Injection Survey

Assessments of subject experience with self-administration and SC injections of DX-2930 will be conducted.

6.15.1 DX-2930 Injection Report

The investigator or designee will train subjects who elect to self-administer DX-2930 on the following:

- Transportation and recommended storage conditions of investigational product from the study site to the home location.
- Maintenance of accurate records regarding each administration of investigational product including supply identification (ie, lot/kit number), date and time of injection, injection site location, infusion time, and if applicable, any reason the self-administration could not be completed as instructed.
- Retention of all used and unused vials of investigational product for drug accountability purposes.

After receiving appropriate training and demonstrating their understanding of self-administration, subjects are allowed to self-administer DX-2930 after receiving the first 2 doses of DX-2930 at the study site (administered by study personnel). For those subjects who choose to self-administer or have a parent/legal guardian/caregiver administer DX-2930, subjects must complete an assessment of their experience with self-administration and subcutaneous injection for each dose received. Study personnel will document the subject's responses in the subjects' medical record and eCRF.

6.15.2 DX-2930 Self-administration and Subcutaneous Injection Survey

Subjects will complete an assessment on their overall experience with self-administration and experience with receiving SC injections of DX-2930 approximately every 6 months during the study. For subjects who have previously received LTP with C1-INH products via IV administration, they will be asked to indicate the preferred route for medication administration. Study personnel will document the subject's responses in the subjects' medical record and eCRF. In addition, investigators will be asked to indicate their preference (SC, IV, or no preference) on the route to administer medications to prevent angioedema attacks.

6.16 Adverse Event Reporting

Adverse events will be collected from signing of the informed consent through the last study visit.

6.16.1 Definitions

6.16.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical trial subject whether or not it appears to have a causal relationship with the treatment administered.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or participation in a clinical study, whether or not directly related to the medicinal product or study participation.

- AEs may be new events or may be pre-existing conditions that have become aggravated or have worsened in severity or frequency during the course of the study.
- AEs may be clinically significant changes from baseline in physical examination, laboratory tests, or other diagnostic investigation (e.g., laboratory results, x-ray findings).

Laboratory abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. A clinically significant laboratory abnormality that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to DX-2930 interruption or discontinuation, will in itself, be considered an AE. Laboratory or diagnostic testing abnormalities that reflect or are part of a known underlying medical condition are not, in themselves, AEs; rather, the underlying medical condition leading to the abnormalities would be reported as the AE.

Pregnancy is not an AE; however, if a female subject becomes pregnant during the conduct of the study, the investigator must notify the Sponsor according to the procedures provided in Section 6.16.5.2.

6.16.1.2 Serious Adverse Event

A SAE is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening experience; Note: “Life-threatening” refers to a situation in which the subject was at risk of death at the time of the event; it does not refer to an event that might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization; Note: Does not include hospitalization for observation with release within 24 hours. A scheduled hospitalization for a pre-existing condition that has not worsened during participation in the study does not meet this criterion. Pre-planned hospitalizations for an elective medical/surgical procedure or routine check-ups do not meet this criterion.

- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is considered to be an important medical event defined as those that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

6.16.1.3 Overdose

An overdose is defined as a significant variation from the recommended/scheduled dosage for a product. The dosing for this study will be conducted in a controlled clinical setting and an overdose is not anticipated. However, in the event of an accident, for this study, an overdose of DX-2930 is considered a dose that is two-fold higher than the intended dose for the subject.

6.16.1.4 Planned Hospitalization

A hospitalization planned by the subject prior to the first dose of open-label DX-2930 is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the trial, it must be reported as an AE.

6.16.1.5 Treatment-Emergent Adverse Events (TEAE)

An AE is treatment-emergent if the onset time is after first administration of open-label DX-2930 through the final follow-up visit or, in the event that onset time precedes first DX-2930 administration, the AE increases in severity during the open-label treatment period.

For rollover subjects, any adverse event that started during the subject's participation in DX-2930-03 and was ongoing at the time of the first open-label dose in DX-2930-04 will not be counted as an AE in DX-2930-04 unless that event has worsened in severity or frequency following the first open-label dose. Adverse events that started during subject participation in DX-2930-03, resolved following the first open-label dose in DX-2930-04, and then subsequently reappeared in DX-2930-04 will be counted as a new TEAE in DX-2930-04.

6.16.1.6 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) will be captured and monitored during this study. Investigators will report all AESI to the Sponsor, regardless of causality, using the same timelines as described for SAE reporting. The following describe the AESI and the criteria for reporting AESI.

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.

6.16.2 Monitoring

6.16.2.1 Monitoring of Adverse Events

Each subject will be monitored for the occurrence of AEs, including SAEs and AESI, from signing of the ICF through the final follow-up visit.

- Subjects will be questioned and/or examined by the investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.
- Subjects having TEAEs will be monitored until resolution with relevant clinical assessments and laboratory tests, as determined by the investigator.
- AEs, actions taken as a result of AEs, and follow-up results must be recorded in the eCRF as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For any SAEs or AEs that require the subject to be discontinued from dosing, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s). Subjects will continue to be followed through completion of all scheduled visits.

6.16.2.2 Monitoring of Safety Laboratory Assessments

All safety laboratory assessments will be performed at a central laboratory. The clinical laboratory values will be reported to the investigator who will review them for clinical significance and consideration of abnormal values as potential AEs.

6.16.3 Assessment of Adverse Events

6.16.3.1 Assessment of Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

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) (Appendix 2) 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) (Appendix 3). For abnormalities not specifically found in the Toxicity Tables, the following general scale will be used to estimate grade of severity:

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

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

6.16.3.2 Assessment of Causality

A medically qualified investigator must assess the relationship of any AE (including SAEs) to the use of DX-2930, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
- The temporal association between DX-2930 exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of DX-2930.
- The AE resolved or improved with decreasing the dose or stopping use of DX-2930 (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between DX-2930 and the AE will be assessed using one of the following categories:

Not Related: Factors consistent with an assessment of Not Related include:

- Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of DX-2930); or
- Other causative factors more likely explain the event (e.g., a pre-existing condition, other concomitant treatments).

Related: Factors consistent with an assessment of Related include:

- There is a positive temporal relationship (e.g., the event occurred within a reasonable time frame following administration of DX-2930); or
- The AE is more likely explained by administration of DX-2930 than by another cause (i.e., the AE shows a pattern consistent with previous knowledge of DX-2930 or the class of DX-2930).

6.16.3.3 Assessment of Clinical Significance

Clinical significance of individual AEs will be determined by the investigator, with discussion with the Medical Monitor as appropriate.

6.16.4 Clinical Laboratory Adverse Events

Laboratory abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. A clinically significant laboratory abnormality that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to DX-2930 interruption or discontinuation, will be considered an AE.

When laboratory abnormalities are considered to be AEs, the DMID Adult Toxicity Table (Appendix 2) or DMID Pediatric Toxicity Tables (Appendix 3) will be used to assess severity. Where discrepancies in the upper limit of normal (ULN) and lower limit of normal (LLN) of laboratory ranges occur between those included in the DMID tables and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade. Clinical significance of individual laboratory AEs will be determined by the investigator with input from the Medical Monitor as needed.

Following is an exception to defining clinically significant, abnormal laboratory values as AEs:

- APTT prolongation in the absence of any associated bleeding or other evidence of clinical relevance will not be considered a clinically significant laboratory abnormality or AE. In the appropriate physiologic setting, such as IV heparin therapy, aPTT can be used to monitor bleeding risk. However, as noted in the Investigators Brochure, aPTT prolongation due to plasma kallikrein inhibition is an artifactual *in vitro* phenomenon. Although plasma kallikrein drives fibrin formation in the aPTT assay, plasma kallikrein-driven coagulation does not appear to have hemostatic or other physiologically important functions *in vivo*. It is well documented that, in humans, deficiency of factor XII or prekallikrein (and thus plasma kallikrein) is not associated with abnormal bleeding, either spontaneous or during surgical procedures (Renne and Gruber, 2012). Despite the lack of clinical effect, deficiency of either protein is associated with marked prolongation of the aPTT.

6.16.5 Reporting Investigator Safety Observations to the Sponsor

6.16.5.1 Reporting Non-serious Adverse Events

All AEs, regardless of seriousness, severity, or causal relationship to DX-2930, will be recorded on the AE page of the eCRF. In this study all HAE attacks reported by the subject, regardless of whether or not they are confirmed by the investigator, will be captured as AEs.

6.16.5.2 Reporting Pregnancies

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, the investigator must report the pregnancy to the Sponsor's Pharmacovigilance Department using the Pregnancy Reporting Form within 24 hours of becoming aware of the event. The investigator must obtain consent to collect pregnancy information (including the status of the newborn, if applicable).

If some of the information required for completion of the Pregnancy Reporting Form is unavailable at the time of the initial report, follow-up reports will be completed and submitted within 24 hours of becoming aware of the new information. The investigator is required to follow the pregnancy through delivery. The outcome of the pregnancy and the status of the newborn (if applicable) will be reported on the Pregnancy Reporting Form within 24 hours of becoming aware.

6.16.5.3 Safety Observations Requiring Expedited Reporting by the Investigator to the Sponsor

Any occurrence of the following events or outcomes in a subject in the trial must be reported expeditiously by the investigator or qualified designee to the Sponsor's Pharmacovigilance Department:

- SAE
- AESI
- Overdose
- Cancer

The investigator is to report any expedited safety observations from the list above to the Sponsor using the SAE Reporting Form in the EDC system within 24 hours of becoming aware of the event.

Any SAE reported to the Sponsor Pharmacovigilance Department using the SAE Reporting Form in the EDC system is to be recorded in the eCRF, as well as in the subject's source documentation along with any actions taken. If all required information on the form is not available at the time of the initial report, follow-up information will be completed in the EDC system.

The investigator is required to follow SAEs until resolution regardless of whether the subjects are still participating in the study. SAE resolution is defined as:

- Resolved with or without residual effects.

- A return to baseline for a pre-existing condition.
- Laboratory values have returned to baseline or stabilized.
- The investigator does not expect any further improvement or worsening of the event.
- Fatal outcome—if an autopsy is performed; the autopsy report is requested to be provided to the sponsor as soon as it is available.

6.16.5.4 Expedited Reporting by the Sponsor to a Regulatory Health Authority

The Sponsor or designee will report relevant safety information to concerned health authorities in accordance with local laws and regulations.

6.16.5.5 Safety Contact Information

24-Hour Medical Safety Contact for US and Canada
[redacted], MD
[redacted], Clinical Development
300 Shire Way, MA 02421 USA
Phone: [redacted]
Email: [redacted]
Calls or emails received weekends, holidays, or weekdays between 8:00 pm and 8:00 am Eastern (US) time will be responded to the morning of the following business day

24-Hour Medical Safety Contact for Europe and Middle East
[redacted], MD, MBA
[redacted]
Phone: [redacted]

Sponsor Pharmacovigilance Department
Email: [redacted]

6.16.5.6 Safety Notifications by the Sponsor to the Investigator

Investigators will receive prompt notification of any adverse experience related to DX-2930 that is both serious and unexpected, or any finding that suggests a significant risk for subjects. The investigator will promptly inform his / her IRB/REB/IEC of the notification and insert the notification in the Investigator's Regulatory Binder in accordance with local regulations.

6.17 Subject Withdrawal

The investigator may withdraw a subject from DX-2930 treatment for any of the following reasons:

- In the opinion of the investigator, the subject is unable to comply with the requirements of the protocol for satisfactory completion or interpretation of study results (including use of prohibitive medications),

- A serious or intolerable AE occurs,
- A clinically significant change in a laboratory parameter occurs,
- The Sponsor or investigator terminates the study, or
- The subject requests to be discontinued from the study.

Subjects will continue to be followed through completion of all scheduled visits, unless the subject requests to be discontinued from the study.

6.18 Appropriateness of Measurements

This is a Phase 3 open-label extension study that is designed to evaluate the long-term safety and efficacy of DX-2930 in prophylactic therapy for angioedema attacks in subjects with HAE. DX-2930 is a recombinant, fully human IgG1, kappa light chain, monoclonal antibody. The open-label, non-controlled study design is a standard approach for extension studies that follow double-blind pivotal trials. Measures employed in this protocol are standard measures routinely used for the evaluation of the efficacy, safety and tolerability of an investigational product. Measures employed for rollover subjects between the first and second open-label doses are appropriate to characterize the outer bounds of dosing frequency for DX-2930.

7. STUDY ACTIVITIES

Study activities are summarized by study visit in Appendix 1 (Study Activities Schedule).

7.1 Screening Visit (Up to Day −28) For Non-Rollover Subjects

The following procedures and assessments are to be performed during the Screening Visit for subjects not rolling over from the DX-2930-03 study:

- Informed consent (Section 6.1)
- Eligibility review (Section 6.2)
- Demographics and medical history (Section 6.3)
- C1-INH functional assay, C4 and C1q sample collection (Section 6.8)
- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination (Section 6.6); documentation of height and weight
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16); pre-existing signs and symptoms
- Subjects who are on LTP for HAE must complete a minimum 2 week washout period, as confirmed by the investigator, before entering the treatment period

For subjects rolling over from the double-blind DX-2930-03 study, no Screening visit is required as subjects will enter the OLE on the same day that their last DX-2930-03 study visit is completed. Diagnostic test results and demographic and medical history for these subjects will be carried forward from that study.

7.2 Start of Treatment Period: Visit 1, Dose 1 (Day 0)

The following procedures and assessments are to be performed on Day 0 prior to the first dose of DX-2930. For subjects who rollover from DX-2930-03, all final assessments taken during the final study visit in DX-2930-03 will be used as the pre-dose results on Day 0 and will not be duplicated.

- Informed consent (for subjects rolling over from the double-blind DX-2930-03 study; this is Day 182 of that study) (Section 6.1)
- Eligibility review (Section 6.2)
- Urine pregnancy test (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination (Section 6.6)

- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK baseline sample collection (Section 6.9)
- PD baseline sample collection (Section 6.10)
- Baseline anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- First dose of open-label DX-2930 (Section 5.1)

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2
- AE collection (Section 6.16)

7.3 Interval between Dose 1 and Dose 2 for Rollover Subjects

Rollover subjects must adhere to the Study Activities Schedule for the entire duration of the study. Until a rollover subject reports their first HAE attack, study visits may be conducted via site check in calls, except for the following study visits which must be conducted at the investigative site:

- Day 14
- Day 28
- Day 56
- Day 98
- Day 126
- Day 154
- Day 182
- Day 224
- Day 266
- Day 308

- Day 350

The tests and assessments required at these visits are specified in the sections below.

Site check in calls may serve as any of the following study visits until the subject receives their second open-label dose:

- Day 42
- Day 70
- Day 84
- Day 112
- Day 140
- Day 168
- Day 196
- Day 210
- Day 238
- Day 252
- Day 280
- Day 294
- Day 322
- Day 336

Study site personnel will also contact rollover subjects approximately 7 days after each study visit (both site visits and check-in calls) until the subject receives their second open-label dose.

The following assessments are performed during all site calls:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.4 Dose 2 of DX-2930 for Rollover Subjects

The duration of time between Dose 1 and Dose 2 will vary by subject based on when their first HAE attack occurs following Dose 1. As a result, rollover subjects may not receive DX-2930 treatment at every dosing visit as outlined in the Study Activities Schedule.

Once a rollover subject reports their first HAE attack they will present to the investigative site for their second open-label dose of DX-2930 as quickly as subject and site schedules allow. This treatment visit may be counted as a scheduled study visit, or as an acceptable extra study visit. For details on determining whether the second dose is counted as a scheduled or extra study visit, refer to Section 3.1.1. Regardless of when the second dose is administered, the following tests and assessments will be conducted pre-dose on the day it is administered:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

The following tests and assessments will also be performed if the second dose occurs on a scheduled study visit for which they are required:

- Pregnancy test, serum or urine (females) (Section 6.8)
- 12-Lead ECG (Section 6.7)
- Quality of life assessments (Section 6.14)

After the required pre-dose tests and assessments are completed:

- Second dose of open-label DX-2930 (Section 5.1)

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2)
- AE collection (Section 6.16)

7.5 Visit 2 (Day 14 ±4 days); Dose 2 of DX-2930 for Non-Rollover Subjects

On Day 14 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination (Section 6.6)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1)

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.6 Continuation of Treatment Period: Visit 3 (Day 28 ±4 Days)

On Day 28 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 3. At this visit, subjects have the option to self-administer at the investigational site.

After administration of DX-2930, the following post-treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.7 Continuation of Treatment Period: Visit 4 (Day 42 ±4 Days)

On Day 42 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 4. At this visit, subjects have the option to self-administer DX-2930 either at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.8 Continuation of Treatment Period: Visit 5 (Day 56 ±4 Days)

On Day 56 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 5. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose

- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.9 Continuation of Treatment Period: Visits 6 and 7 (Days 70 and 84, All ±4 Days)

On Days 70 and 84 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects these doses represent Dose 6 and Dose 7. At this visit, subjects have the option to self-administer DX-2930 either at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.10 Continuation of Treatment Period: Visit 8 (Day 98 ±4 Days)

On Day 98 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 8. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2)
- AE collection (Section 6.16)

7.11 Continuation of Treatment Period: Visit 9 (Day 112 ±4 Days)

On Day 112 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 9. At this visit, subjects have the option to self-administer DX-2930 either at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.12 Continuation of Treatment Period: Visit 10 (Day 126 ±4 Days)

On Day 126 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 10. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.13 Continuation of Treatment Period: Visit 11 (Day 140 ±4 Days)

On Day 140 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 11. At this visit, subjects have the option to self-administer DX-2930 either at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.14 Continuation of Treatment Period: Visit 12 (Day 154 ±4 Days)

On Day 154 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 12. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.15 Continuation of Treatment Period: Visit 13 (Day 168 ±4 Days)

On Day 168 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 13. At this visit, subjects have the option to self-administer DX-2930 either at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.16 Continuation of Treatment Period: Visit 14 (Day 182 ±4 Days)

On Day 182, the following procedures and assessments will be performed:

- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 14. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2
- AE collection (Section 6.16)

7.17 Continuation of Treatment Period: Visit 15 (Day 196 ±4 Days)

On Day 196 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 15. At this visit, subjects have the option to self-administer DX-2930 either at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.18 Continuation of Treatment Period: Visit 16 (Day 210 ±4 Days)

On Day 210 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 16. At this visit, subjects have the option to self-administer DX-2930 either at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.19 Continuation of Treatment Period: Visit 17 (Day 224 ±4 Days)

On Day 224 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 17. At this visit, subjects have the option to self-administer DX-2930 either at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.20 Continuation of Treatment Period: Visit 18 (Day 238 ±4 Days)

On Day 238 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 18. At this visit, subjects have the option to self-administer DX-2930 either at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.21 Continuation of Treatment Period: Visit 19 (Day 252 ±4 Days)

On Day 252 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 19. At this visit, subjects have the option to self-administer DX-2930 either at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.22 Continuation of Treatment Period: Visit 20 (Day 266 ±4 Days)

On Day 266 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 20. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2)
- AE collection (Section 6.16)

7.23 Continuation of Treatment Period: Visit 21 (Day 280 ±4 Days)

On Day 280 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 21. At this visit, subjects have the option to self-administer DX-2930 either at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.24 Continuation of Treatment Period: Visit 22 (Day 294 ±4 Days)

On Day 294 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 22. At this visit, subjects have the option to self-administer DX-2930 either at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.25 Continuation of Treatment Period: Visit 23 (Day 308 ±4 Days)

On Day 308 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 23. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.26 Continuation of Treatment Period: Visit 24 (Day 322 ±4 Days)

On Day 322 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 24. At this visit, subjects have the option to self-administer DX-2930 either at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.27 Continuation of Treatment Period: Visit 25 (Day 336 ±4 Days)

On Day 336 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 25. At this visit, subjects have the option to self-administer DX-2930 either at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.28 Continuation of Treatment Period: Visit 26 (Day 350 ±4 Days)

On Day 350, the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 26 (final dose). At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2)
- AE collection (Section 6.16)

7.29 Completion of Treatment Period: Visit 27 (Day 364 ±4 Days)

On Day 364 the following procedures and assessments will be performed:

- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.30 Follow-up Period: Visit 28 (Day 378 ±4 Days)

On Day 378 all rollover and non-rollover subjects will receive a site check-in call. During this call study site personnel will collect information regarding the following:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.31 Final Follow-up Visit: Visit 29 (Day 392 ±4 Days)

On Day 392 all rollover and non-rollover subjects will complete a final study visit at the investigative site.

- Pregnancy test, serum or urine (females) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- Quality of life assessments (Section 6.14)
- AE collection (Section 6.16)
- Study Discharge: Subjects will be discharged at this study visit.

7.32 Early Termination

Subjects that terminate early from the study will undergo (if possible) all of the assessments and procedures scheduled for Day 392.

8. QUALITY CONTROL AND ASSURANCE

The Sponsor and the Contract Research Organization (CRO) conducting trial management services, Rho, Inc., will implement a system of quality assurance that includes all elements described in this protocol. Within this system, SOPs from the Sponsor and CRO will be implemented to ensure that the clinical trial is conducted in compliance with regulatory requirements and Good Clinical Practices (GCP). Quality control will be applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The site staff should assist in all aspects of audit/inspection.

9. DATA ANALYSIS / STATISTICAL METHODS

9.1 General Considerations

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

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, standard errors, and 95% confidence intervals for least squares means will be provided. Time-to-event data will be summarized using Kaplan-Meier estimates of the 25th, 50th (median), and 75th percentiles with associated two-sided 95% confidence intervals, as well as percentage of censored observations. Plots of the Kaplan-Meier curves and supporting data listings detailing each subject's contribution to the analysis will be provided.

Formal hypothesis testing will not be performed. Any hypothesis testing will be exploratory in nature and resulting p-values will be considered descriptive.

9.2 Sample Size Determination

No formal sample size calculation was performed. The sample size is not based on any statistical considerations. This study is designed to evaluate the safety and efficacy of open-label treatment with DX-2930 in subjects who participated in DX-2930-03 (rollover subjects) and individuals who were not otherwise able to participate in DX-2930-03 (non-rollover subjects).

9.3 Method of Assigning Study Subjects to Treatment

Subjects meeting all eligibility criteria will be enrolled in the study and sequentially assigned a unique site-based identification number.

9.4 Analysis Populations

9.4.1 Safety Population

The Safety Population will include all subjects who received any study drug after entering the DX-2930-04 study (i.e., any exposure to open-label DX-2930). Unless otherwise specified, summary tabulations conducted with the Safety Population will be presented by the subject's study entry type (rollover or non-rollover) and overall.

9.4.2 Rollover Safety Population

The Rollover Safety Population is the subset of subjects who participated in the DX-2930-03 study and received any study drug after entering the DX-2930-04 study (i.e., any exposure to open-label DX-2930). Unless otherwise specified, summary tabulations conducted with the Rollover Safety Population will be presented by the subject's prior treatment group from the DX-2930-03 study (DX-2930 300 mg every 2 weeks, DX-2930 300 mg every 4 weeks, DX-2930 150 mg every 4 weeks, and Placebo).

9.4.3 Non-rollover Safety Population

The Non-rollover Safety Population is the subset of subjects who entered the DX-2930-04 study directly and received any study drug after entering the DX-2930-04 study (i.e., any exposure to open-label DX-2930). Unless otherwise specified, summary tabulations conducted with the Non-rollover Safety Population will be presented by subject's prior type of LTP therapy prior to study entry (C1-INH, Androgens, Anti-fibrinolytics, and Not on LTP).

9.5 Population Description and Exposure

9.5.1 Subject Disposition

The numbers of subjects treated with study drug, completed the study and discontinued prematurely by reason will be summarized for each analysis population.

9.5.2 Demographics and Other Baseline Characteristics

Baseline and demographic variables will be summarized for each analysis population.

9.5.3 Medical History

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

9.5.4 Treatment Exposure and Compliance

Treatment compliance and the extent of exposure to study drug 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 for each analysis population.

9.5.5 Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD). The number and percentage of subjects with prior or concomitant medications will be summarized by therapeutic class and preferred term for each analysis population. A separate, similar table will be provided for the subset of concomitant medications classified as rescue medications.

9.6 Analysis of Efficacy

9.6.1 Time to the First Investigator-confirmed HAE Attack

Time to the first investigator-confirmed HAE attack will be analyzed using the Rollover Safety Population.

Time to the first investigator-confirmed HAE attack (days) will be calculated from the date and time of the first open-label dose of DX-2930 to the date and time of the first investigator-confirmed HAE attack after the first open-label dose. Subjects who discontinue the study prior to experiencing their first on-study investigator-confirmed HAE attack will be censored at the

date and time of study discontinuation. Time to the first investigator-confirmed HAE attack will be summarized using Kaplan-Meier methods.

Multivariate and univariate Cox proportional hazards regression models will be employed to examine the impact of baseline covariates on the time to the first investigator-confirmed HAE attack, including but not limited to: baseline attack rate prior to entering DX-2930-03, the treatment group in DX-2930-03, the time since the last dose given in DX-2930-03, the time since the last HAE attack, and the rate of attacks during DX-2930-03. Results of this exploratory analysis will be summarized.

9.6.2 Number of Investigator-confirmed HAE Attacks

The number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 350) expressed as a monthly HAE attack rate, will be analyzed using each analysis population.

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

The baseline investigator-confirmed HAE attack rate will be calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the pretreatment period for rollover subjects or historical reporting period for non-rollover subjects divided by the number of days the subject contributed to the pretreatment period for rollover subjects or historical reporting period for non-rollovers multiplied by 28 days.

The baseline, treatment period, and treatment period change from baseline in the investigator-confirmed HAE attack rate will be summarized for each analysis population. The summary will include the total number of investigator-confirmed HAE attacks reported during each period and subject-time in months that each subject contributed to each period. Figures will be created for each analysis population plotting the on-study investigator-confirmed HAE attacks reported during the treatment period relative to Day 0 for each subject.

In addition, the number of investigator-confirmed HAE attacks per month (defined as 28 days) will be summarized descriptively by month (per 28 day interval) for each analysis population. The summary will include the number, change from baseline, and percent change from baseline of investigator-confirmed HAE attacks. Investigator-confirmed HAE attacks will be grouped into 28-day intervals using the start date of the HAE attack. The date of the first exposure to study drug in this study will be used as the start of the first interval and end of the interval will be the date of first exposure to study drug in this study plus 28 days. Each successive interval will start the last day of the prior interval plus 1 day and end 28 days later.

Similar summary tables will be presented for the following efficacy endpoints for each analysis population:

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

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

9.7 Analysis of Safety

9.7.1 Adverse Events

Adverse events will be coded using the MedDRA coding dictionary. Separate summaries will be presented for each analysis population.

Treatment-emergent AEs are defined as AEs with onset at the time of or following the first exposure to open-label DX-2930 in this study, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. For AEs with partial onset times, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, then the AE will be classified as treatment-emergent.

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

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

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

- *Pretreatment Period AEs* will include AEs starting at or after informed consent to those starting before the first exposure to open-label DX-2930 in this study (AEs starting prior to treatment on Day 0). This analysis period is only applicable for the Non-rollover Safety Population in this study.

- *Treatment Period AEs* will include all AEs starting at or after the first exposure to open-label DX-2930 in this study to those starting before or at the subject's last visit date during the treatment period in this study (AEs starting at or after treatment on Day 0 to the Day 350 visit).

- *Follow-up Period AEs* will include all AEs starting at or after the subject's last visit date of the treatment period in this study (AEs starting after the Day 350 visit).

For AEs with partial onset times, non-missing date parts will be used to determine if the AE falls within the period. If a determination cannot be made using the non-missing date parts as to if the AE falls within the period, the AE will be conservatively counted as a treatment-period AE.

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

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized by SOC, and PT for each analysis period. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, and related severe AEs for treatment period and follow-up period AEs.

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

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

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

9.7.2 Laboratory Test Results

Laboratory test results will be summarized using the Safety Population.

Baseline is defined as the last non-missing value prior to the first exposure to DX-2930. For rollover subjects previously exposed to DX-2930, baseline is the last non-missing value prior to first exposure to study drug in the DX-2930-03 study.

Actual values and change from baseline clinical laboratory tests will be summarized by study visit. If more than one laboratory result is reported per study visit per parameter, the last non-missing result will be selected for analysis

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. The number of subjects with a non-missing result, and the number and percentage of subjects with a clinically significant result less than the lower limit of normal, non-clinically significant result less than the lower limit of normal, within the normal range, non-

clinically significant result more than the upper limit of normal, and clinically significant result more than the upper limit of normal will be summarized 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 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.

9.7.3 Vital Signs

Vital signs will be summarized using the Safety Population.

Baseline is defined as the last non-missing value prior to the first exposure to DX-2930. For rollover subjects previously exposed to DX-2930, baseline is the last non-missing value prior to first exposure to study drug in the DX-2930-03 study.

Actual values and changes from baseline in vital signs will be summarized 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 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.

9.7.4 Electrocardiography

Electrocardiography results will be summarized using the Safety Population.

The number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECG results, or ECG no performed, will be summarized by study visit. Subjects with clinically significant ECG results will be listed. This listing will include all results for a subject across study time points to identify any trends.

9.8 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.

9.8.1 Analysis of Pharmacokinetic Data

Plasma concentrations of DX-2930 will be summarized by nominal PK sampling time using the Safety Population.

9.8.2 Analysis of Pharmacodynamic Data

Plasma kallikrein activity will be summarized by nominal PD sampling time using the Safety Population.

9.8.3 Analysis of Immunogenicity Data

The number and percentage of positive antibodies will be summarized by study visit and overall using the Safety Population.

9.8.4 Analysis of Quality of Life Assessments

Quality of life assessments will be summarized using the Safety Population.

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) will be summarized by study visit. In addition, the VAS score for the subject's self-rated health will be summarized by study visit.

The responses to the SF-12 for each item will be tabulated by study visit using the Safety Population. In addition, Physical and Mental Health Composite Scores (PCS & MCS) will be computed using the scores of twelve questions and range from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health.

Responses to the HADS for each item will be tabulated by study visit. In addition, continuous and categorical (0-7: normal, 8-10: mild, 11-14: moderate, 15-21: severe) total scores based on the items related to depression and anxiety, will be summarized by study visit. Each item in the questionnaire is scored from 0-3, with total scores between 0-21 for either depression or anxiety. Scores for the entire scale (emotional distress) will also be presented. Total score for the entire scale range from 0 to 42, with higher scores indicating more distress.

Responses to the WPAI-GH for each item will be summarized by study visit. In addition, four main scores in relation to general health will be summarized by study visit. Scores will be calculated as absenteeism (percentage work time missed due to health), presenteeism (percent impairment while working due to health), work productivity loss (percent overall work impairment due to health), and activity impairment (percent activity impairment due to health). The scores are percentages with higher values indicating greater percentage impairment. Only respondents who report being full-time or part-time employed provide data for absenteeism, presenteeism, and overall work productivity loss. All respondents provide data for activity impairment.

Responses to the AE-QoL for each item will be tabulated by study visit. In addition, the domain scores (functioning, fatigue/mood, fears/shame, nutrition) and total score will be summarized by

study visit. Each item in the questionnaire is scored from 0-4, with domain and total scores calculated using a linear transformation to a 0-100 scale.

9.9 Statistical/Analytic Considerations

9.9.1 Interim Analyses and Data Monitoring

A formal interim analysis will be conducted when at least 35 subjects have completed 12 months of consecutive exposure to DX-2930 across the combined DX-2930-03 and DX-2930-04 studies, and only after database lock of the DX-2930-03 study. Subsequent interim analyses may be conducted to support administrative decisions and/or regulatory reporting as required.

An independent Data Safety Monitoring Board (DSMB) has been established to provide ongoing, independent review and assessment of the safety data for the DX-2930-03 study. While an independent DSMB is not currently planned for this study, summary safety data from DX-2930-04 may be reviewed by the DSMB established for the DX-2930-03 study as part of the collection of safety information available on DX-2930.

9.9.2 Multiple Comparisons/Multiplicity

No adjustment for multiple comparisons will be performed. Any statistical testing will be considered exploratory.

9.9.3 Handling of Missing Data

All available data will be included in the analysis. No imputation of missing data will be performed.

9.9.4 Adjustment for Covariates

The impact of baseline covariates on the time to the first investigator-confirmed HAE attack will be explored to identify and assess the importance of potential prognostic factors.

9.9.5 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.

9.9.6 Subgroup Analyses

Subgroup analyses are planned for the number of investigator-confirmed HAE attacks during the treatment period and adverse events using the Safety Population.

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)
- Baseline HAE Attack Rate (1 to <2, 2 to <3, ≥3 attacks/month)
- HAE Type (Type I, Type II, Unspecified)
- Geographic Region (US, Canada, Jordan, Europe)
- DX-2930 Administration Type (Health Care Provider, Self-administration)

9.9.7 Sensitivity Analyses

The following sensitivity analyses will be performed on the number of investigator-confirmed HAE attacks during the treatment period for each analysis population to evaluate the robustness of the results. Data summaries will parallel those described for the number of investigator-confirmed HAE attacks during the treatment period efficacy endpoint.

1. The analysis will be repeated counting HAE attacks occurring on Day 14 after administration of study drug through Day 350, instead of Day 0 to Day 350. For this analysis, the period of analysis would be a subset of the treatment period, defined as Day 14 to Day 350.

2. The analysis will be repeated counting HAE attacks occurring on Day 7 after administration of study drug through Day 350, instead of Day 0 to Day 350. For this analysis, the period of analysis would be a subset of the treatment period, defined as Day 7 to Day 350.

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

10. STUDY ADMINISTRATIVE STRUCTURE

The study administration structure is provided in Table 1.

Table 1: Study Administrative Structure

Sponsor Contact/Sponsor Medical Director:	[redacted], MD [redacted], Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: [redacted]
Medical Monitor (US, Canada):	[redacted], MD [redacted], Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: [redacted]
Medical Monitor (Jordan, Europe)	[redacted], MD, MBA Voisin Consulting 3, rue des Longs Prés 92100 Boulogne, France Phone: [redacted]
Study Monitoring (US):	Rho, Inc. 6330 Quadrangle Drive, Chapel Hill, NC 27517 Phone: [redacted]
Study Monitoring (Jordan)	Triumpharma 07 Bldg., Al-Yarooty St. P.O. Box 2233, Amman 11941, Jordan Phone: [redacted], [redacted]
Study Monitoring (Canada)	Red Maple Trials Incorporated 1081 Carling Avenue, Suite 707 Ottawa, Ontario, Canada, K1Y4G2 Phone: [redacted]
Study Monitoring (Europe)	Dyax Corp 55 Network Drive, Burlington, MA 01803 Phone: [redacted]

10.1 Institutional Review Board/ Research Ethics Board/Independent Ethics Committee

The protocol and all protocol amendments must be signed and dated by the investigator and approved in writing by the IRB/REB/IEC in accordance with GCP prior to implementation. In addition, the IRB/REB/IEC must approve the written informed consent form, any consent form updates, subject recruitment materials (e.g., advertisements), and any written information to be provided to subjects prior to implementation. The investigator must provide an annual report to the IRB/REB/IEC on the progress of the study including number of subjects enrolled, discontinued, and SAEs. It is required that a yearly review of the protocol by the IRB/REB/IEC

be documented in a letter from the IRB/REB/IEC. The investigator must provide notification to the IRB/REB/IEC of the completion, termination or discontinuation of the study.

10.2 Ethical Conduct of the Study

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the investigator abide by the principles of the International Conference on Harmonisation (ICH) guidelines on GCP, applicable local regulatory requirements, and the Declaration of Helsinki (Version 2008). The clinical study also will be carried out in keeping with national and local legal requirements [in accordance with United States Investigational New Drug (IND) regulations (21 CFR 56)].

10.3 Subject Information and Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained according to the regulatory and legal requirements of the participating country. As part of this procedure, the investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. Subjects who are under the age of 18 (or lower if age of consent is less than 18 in a specific country) and whose legal guardian or caretaker has provided written informed consent will provide their assent to participate. The investigator or designee will provide the Sponsor with a copy of the IRB/REB/IEC-approved informed consent form prior to the start of the study.

10.4 Subject Confidentiality

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number, initial or birth date (if allowed based on local data protection regulations), not by name. Documents that identify the subject (e.g., the signed informed consent document) must be maintained in confidence by the investigator.

The investigator agrees not to use or disclose protected health information other than as permitted or required by the subject authorization or as required by law.

10.5 Study Monitoring

The Sponsor (or designee) will conduct a study initiation visit to verify the qualifications of the investigator, inspect the facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The investigator will make all appropriate safety assessments on an ongoing basis. The Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to GCP and SOPs for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the investigator.

10.6 Case Report Forms and Study Records

The investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the clinical sites by means of electronic or manual queries.

The investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each subject receiving randomized study drug.

The investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB/REB/IEC to have direct access to all documents pertaining to the study.

A Trial Master File will be maintained by the Sponsor (or designee). All documents and other materials that pertain to the conduct of the trial quality of the data, and compliance with GCPs will be collected in the Trial Master File.

10.7 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) has been established to provide ongoing, independent review and assessment of the safety data for the DX-2930-03 study. While an independent DSMB is not currently planned for this study, summary safety data from DX-2930-04 may be reviewed by the DSMB established for the DX-2930-03 study as part of the collection of safety information available on DX-2930.

The DSMB will adhere to a prospectively determined Charter, which will be written by the Sponsor and approved by the DSMB. The Charter will define the responsibilities of the DSMB and Sponsor, the number and timing of the DSMB meetings, the conduct of the meetings, and the data sets to be reviewed by the DSMB. Further details regarding the DSMB can be found in the DSMB charter.

10.8 Protocol Violations/Deviations

The investigator will be instructed not to deviate from the protocol, except where necessary to eliminate an immediate hazard to study participants. Should other unexpected circumstances arise that will require deviation from protocol-specific procedures, the investigator should contact their Sponsor representative to discuss the appropriate course of action.

The investigator should document all protocol deviations/violations in the subject's eCRF and source documents or the Investigator Site File if appropriate. In the event of a significant deviation/violation, the investigator should notify the Sponsor representative. Significant deviations/violations include, but are not limited to those that increase the health risk to the subject, or confound interpretation of primary study assessments. The investigator will promptly report all changes in research activity and all unanticipated problems involving risks to human subjects or others to his or her IRB/REB/IEC.

10.9 Premature Closure of the Study

If the Sponsor, investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated overall or at a specific site after appropriate consultation between the Sponsor and the investigator(s). In addition, a decision on the part of the Sponsor to suspend or discontinue development of the investigational product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to, the following:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure of the investigator to comply with pertinent global regulations
- Submission of knowingly false information from the study site to the Sponsor or other pertinent regulatory authorities
- Insufficient adherence by the investigator to protocol requirements

10.10 Access to Source Documentation and On-Site Audits

Regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with country regulations. The investigator should immediately notify the Sponsor representative of any announced or unannounced regulatory agency inspections. An auditing inspection may also be conducted by the Sponsor representative or designee. Any aspect of the trial may be subject to audit by the Sponsor and/or inspection by regulatory authorities or the IRB/REB/IEC. Such audits/inspections may take place at the Sponsor's site(s), the CRO, or at the clinical sites, including laboratories, pharmacies and any other facilities used for the study.

The investigator will be responsible for the accuracy of the data entered in the eCRF. The investigator will permit the designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify data represented in the eCRF.

10.11 Data Generation and Analysis

This study will be performed in accordance with regulatory requirements outlined in Food and Drug Administration (FDA) 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 312 and 21 CFR Part 11 as well as the ICH GCP E6 Guidelines. The study monitors will meet with the investigators and staff shortly before the start of the trial to review the procedures for study conduct and documentation. During the study, the monitors will visit the sites to verify record keeping and adherence to the protocol. For this study, eCRFs will be used. The monitors will conduct 100% source document verification by comparing the eCRFs with the source documents to ensure accuracy and consistency. Edit check programs, other forms of electronic validation, manual listings and a query process will be executed to verify the accuracy of the database. The EDC system will maintain a full audit trail of electronic data changes. Access to all source documentation will be made available for monitoring and audit purposes.

10.12 Retention of Data

All source documents (e.g., informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnosis and pharmacy records, and DX-2930 dispensing/disposition records) that support data in the eCRFs of each study subject must be retained in the files of the responsible investigator.

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the DX-2930. However, these documents should be retained for a longer period if required by the applicable legal requirements.

If the responsible investigator retires, relocates or for any other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor representative must be notified in writing of the name and address of the new custodian, prior to the transfer.

10.13 Financial Disclosure

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

10.14 Publication and Disclosure Policy

All information concerning DX-2930, Sponsor operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information, supplied to the investigator by a Sponsor representative and not previously published, is considered confidential and remains the sole property of the Sponsor. The investigator must agree to use this information only to accomplish this study, and must not use it for other purposes without the Sponsor's advanced written consent. A description of this clinical study may also be available on the externally facing public websites and registries. A summary of the study results may be potentially disclosed as per local and country specific requirements.

The information developed in this study will be used by the Sponsor in connection with the continued development of DX-2930 and thus may be disclosed as required to other clinical investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the Sponsor with all data obtained in the study.

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12. APPENDICES

Appendix 1 Study Activities Schedule

Appendix 2 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases)

Appendix 3 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases

Appendix 4 HAE Attack Assessment and Reporting Procedures (HAARP)

Appendix 5 Summary of Pivotal Study of DX-2930 in HAE Subjects

Appendix 1 Study Activities Schedule

Study Activities Schedule																																
Tests and Assessments		**Treatment Period ± 4 days for each visit**																													**Follow-up ±4 Days for each visit**	
Non-rollover	**Screen Visit[1]**			Shaded columns: scheduled in-site visits																												
Rollover	-		**Check-in[2]**	Non-shaded columns: potential subject-elected off-site activity and/or self-administration dosing																												
Visit:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28[3]**	**29[4]**
Dose:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	-	-	-
Day:		**0**		**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**	**378**	**392**
Informed Consent[5]	X	(X)[6]																													
Eligibility Review	X	X																													
Long-term prophylactic therapy continued[7]	X	X		X																											
DX-2930 Administration (rollover subjects)		X		(X)[8,9]	(X)[10]	(X)[11]	(X)[10]	(X)[11]	(X)[11]	(X)[10]	(X)[11]	(X)[10]	(X)[11]	(X)[10]	(X)[11]	(X)[10]	(X)[11]	(X)[11]	(X)[10]	(X)[11]	(X)[11]	(X)[10]	(X)[11]	(X)[11]	(X)[10]	(X)[11]	(X)[11]	(X)[10]			
DX-2930 Administration (non-rollover)		X		X	X[10]	X[11]	X[10]	X[11]	X[11]	X[10]	X[11]	X[10]	X[11]	X[10]	X[11]	X[10]	X[11]	X[11]	X[10]	X[11]	X[11]	X[10]	X[11]	X[11]	X[10]	X[11]	X[11]	X[10]			
Demographic and Medical History	X																														
C1-INH, C1q and C4 Testing[12]	X																														
Pregnancy Test[13] (females)	X	X		X	X		X			X		X		X		X			X			X			X			X	X		X
Vital Signs[14]	X	X		X	X		X			X		X		X		X			X			X			X			X	X		X
Physical Exam[15]	X	X		X	X		X			X				X		X						X						X	X		X
Clinical Laboratory Testing[16]	X	X			X		X			X				X		X			X			X			X			X	X		X

Study Activities Schedule																																
Tests and Assessments		**Treatment Period ± 4 days for each visit**																														**Follow-up ±4 Days for each visit**
Non-rollover	**Screen Visit[1]**			Shaded columns: scheduled in-site visits																												
Rollover	-		**Check-in[2]**	Non-shaded columns: potential subject-elected off-site activity and/or self-administration dosing																												
Visit:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28[3]**	**29[4]**
Dose:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	-	-	-
Day:		**0**		**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**	**378**	**392**
12-Lead ECG	X	X								X						X						X						X	X		X
Prior (4 weeks) and Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAE Attack Data[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessments[18]																																
EQ-5D-5L		X			X		X			X		X		X		X			X			X			X			X			X
SF-12		X			X		X			X		X		X		X			X			X			X			X			X
AE-QoL		X			X		X			X		X		X		X			X			X			X			X			X
HADS		X			X		X			X		X		X		X			X			X			X			X			X
WPAI-GH		X			X		X			X		X		X		X			X			X			X			X			X
DX-2930 Injection Report[19]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
DX-2930 Self-administration and SC Injection Survey [20]		X								X						X						X						X				
PK, PD Collection, & Plasma Anti-Drug Antibody Testing[21]		X								X						X						X							X			X
Discharge from Study																																X

AE-QOL = Angioedema Quality of Life; ECG = Electrocardiogram; EQ-5D-5L = EuroQoL 5-Dimensional 5-Level; HADS = Hospital Anxiety and Depression Scale; PK = Pharmacokinetic; PD = Pharmacodynamic; SF-12 = Short Form-12 (v2); WPAI-GH = Work Productivity and Activity Impairment – General Health
NOTE: Shaded columns represent scheduled in-site visits for all subjects. Non-shaded columns indicate potential subject-elected off-site activity and/or self-administration dosing.
NOTE: "( )"s indicate activities that may occur as applicable (ie, activities for rollover subjects)

13. Screening visit is for non-rollover subjects only. Screening visit can occur up to 28 days prior to first open-label dose.
14. Study site personnel will contact rollover subjects approximately every 7 days following the first dose of open-label DX-2930 to solicit for any HAE attacks not already reported. Site check-in with rollover subjects will continue until the subject receives their second open label dose.
15. Visit 28 is a site check-in call for all rollover and non-rollover subjects.
16. Subjects who terminate from the study early will undergo (if possible) all of the assessments and procedures at Visit 29, their final study visit
17. Rollover subjects must sign informed consent for DX-2930-04 after Day 168 of study DX-2930-03 and no later than the final DX-2930-03 Day 182 treatment period study visit.
18. For rollover subjects Day 182 of the DX-2930-03 study is also Day 0 of the DX-2930-04 study and informed consent may be completed on this visit, if not already provided.
19. Screened non-rollover subjects (adults and adolescents) who are on LTP with C1 INH therapy for HAE can continue their current LTP until Day 8 (or Day 15) such that subjects will have received 2 (or 4) doses of C1 INH. For subjects who are on attenuated androgens (e.g., danazol) or anti-fibrinolytics (e.g., tranexamic acid), a similar tapering schedule is recommended. However, the taper can be prolonged by an additional week as long as androgen or anti-fibrinolytic therapy is stopped within 3 weeks of receiving the first dose of DX-2930.
20. For rollover subjects, the timing of Dose 2 for will vary by subject based on when their first HAE attack occurs following Dose 1. Following the first reported and investigator-confirmed attack, subjects will begin receiving regular SC administrations of 300 mg DX-2930 every 2 weeks.
21. A minimum of 10 days between the first and second open-label doses is required. If the second dose is to be administered within the accepted ±4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit unless that scheduled visit has already occurred. If that scheduled visit has already occurred, or if the second dose is to be administered outside of the accepted ± 4 day window around a scheduled visit, this visit will not replace any scheduled visit and will thus represent an acceptable, extra study visit (i.e., an unscheduled visit). Regardless, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical examination (performed in accordance with standards at the site), clinical laboratory testing, PK, PD, and anti-drug antibody. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data.
22. All subjects (adolescent or adult) who are considered suitable candidates (i.e., those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer DX-2930 after completing appropriate training by the investigator or designee and confirming their understanding. Subjects are allowed to initiate self-administration after receiving the first 2 doses of DX-2930 at the study site and may elect to self-administer subsequent doses of DX-2930 at the investigational site (during scheduled study site visits; shaded columns).
23. Subjects may self-administer DX-2930 at home or other agreed upon location (during optional off-site self-administration visits; non-shaded columns). Site personnel will call subjects after the planned self-administration to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.
24. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment unless already collected as part of protocol DX-2930-02 or DX-2930-03.
25. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 must be urine-based to confirm eligibility prior to first dose. Tests performed at screening and on indicated visits can be serum or urine-based.
26. There is a recommended ± 15 minute window for all vital signs. Vital signs will be obtained prior to dosing and 1 hour after dosing. Monitoring of vital signs will not be performed for subjects who elect to self-administer away from the investigative site at optional off-site visits (indicated non-shaded columns). Height and weight will be collected at the Screening visit only.

27. Physical examinations will be conducted for all rollover and non-rollover subjects according to the study activities schedule and in accordance with standards at the site. In addition to the physical examinations specified in the study activities schedule, an additional physical examination (performed in accordance with standards at the site) will be conducted for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs.
28. Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis (urinalysis does not need to be done as part of the clinical laboratory testing at Visits 14, 17, 20, and 23). Clinical laboratory testing will be conducted for all rollover and non-rollover subjects according to the study activities schedule. In addition to the testing specified in the study activities schedule, additional testing will be conducted for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs.
29. Historical HAE attack information will be collected at screening. During the study, subjects (or caregivers) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. During study visits, study site personnel will solicit for any new HAE attack information that has not already been reported to the site.
30. Quality of life data will be obtained using the EQ-5D-5L, SF-12, AE-QoL, HADS, and WPAI-GH.
31. Collect subject's injection reports of their experience with DX-2930 self-administration and subcutaneous administration for all doses.
32. Collect subject's injection surveys of their experience with DX-2930 self-administration and subcutaneous injection for indicated visits.
33. PK, PD and Anti-drug Antibody PD samples will be drawn for all rollover and non-rollover subjects according to the study activities schedule. In addition to the samples specified in the study activities schedule, an additional PK, PD and Anti-drug Antibody sample will be drawn for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs.

Appendix 2 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases)

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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Note: The following toxicity table is a DRAFT and designed to provide general guidance on parameters for monitoring safety in clinical trials. This toxicity table is not comprehensive and should not be applied directly to all trials.

When selecting a toxicity table, the following are some of the items that must be taken into consideration:

- The population being studied
  - Does the clinical trial evaluate healthy subjects, subjects with a particular disease or condition?
- The stage of test article development
  - Is the clinical trial a Phase I, II, III or IV?
- The type of test article
  - Does the clinical trial evaluate a drug, device, vaccine or other biologic agent?
- The prior human and preclinical experience with the test article
  - Are there any specific findings that require adjustment of the toxicity table?

Single site clinical trials evaluating healthy subjects should conform to the laboratory normal values at the single site. Multi-center clinical trials should reconcile among their laboratory normal values when evaluating a healthy volunteer population.

Please confer with the DMID protocol team and DMID's Office of Clinical Research Affairs when selecting or developing a toxicity table for a DMID-sponsored trial.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/mm^3	13,000-15,000/mm^3	15,000-30,000/mm^3	>30,000 or <1,000/mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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CHEMISTRIES (continued)

	Grade 1	Grade 2	Grade 3	Grade 4
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

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ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

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CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

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RESPIRATORY				
	Grade 1	Grade 2	Grade 3	Grade 4
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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MUSCULOSKELATEL				
	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint distruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

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SKIN

	Grade 1	Grade 2	Grade 3	Grade 4
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC

	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25-50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

Appendix 3 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

Note: The following toxicity table is a DRAFT and designed to provide general guidance on parameters for monitoring safety in clinical trials. This toxicity table is not comprehensive and should not be applied directly to all trials.

When selecting a toxicity table, the following are some of the items that must be taken into consideration:

- The population being studied
  - Does the clinical trial evaluate healthy subjects, subjects with a particular disease or condition?
- The stage of test article development
  - Is the clinical trial a Phase I (is it for the fisrt time in human subjects?) , II, III or IV?
- The type of test article
  - Does the clinical trial evaluate a drug, device, vaccine or other biologic agent?
- The prior human and preclinical experience with the test article
  - Are there any specific findings that require adjustment of the toxicity table?
  - Has it been approved for this indication in adult population?

Single site clinical trials evaluating healthy subjects should conform to the laboratory normal values at the single site. Multi-center clinical trials should reconcile among their laboratory normal values when evaluating a healthy volunteer population.

Please confer with the DMID protocol team and DMID's Office of Clinical Research Affairs when selecting or developing a toxicity table for a DMID-sponsored trial.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
GRADE 5	**Death**	

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Selected Values for children less than or equal to 3 months of age – does not apply for preterm infants)

For all parameters not listed on this table, please refer to the DMID Toxicity Table for children > 3 months of age.

HEMATOLOGY				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin				
1-7 days old	13.0-14.0 gm/dL	12.0-12.9 gm/dL	<12 gm/dL	Cardiac Failure secondary to Anemia
8-21 days old	12.0-13.0 gm/dL	10.0-11.9 gm/dL	<10.0 gm/dL	Cardiac Failure secondary to Anemia
22-35 days old	9.5-10.5 gm/dL	8.0-9.4 gm/dL	<8.0 gm/dL	Cardiac Failure secondary to Anemia
36-60 days old	8.5-9.4 gm/dL	7.0-8.4 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
61-90 days old	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
Abs Neutrophil Ct				
1 day old	5000-7000/mm^3	3000-4999/mm^3	1500-2999/mm^3	<1500/mm^3
2-6 days old	1750-2500/mm^3	1250-1749/mm^3	750-1249/mm^3	<750/mm^3
7-60 days old	1200-1800/mm^3	900-1199/mm^3	500-899/mm^3	<500/mm^3
61-90 days old	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3
Bilirubin (Fractionated bilirubin test must be preformed when total bilirubin is elevated)				
<7 days old	.	20-25mg/dL	26-30 mg/dL	>30 mg/dL
7-60 days old	1.1-1.9xN	2.0-2.9Xn	3.0-7.5xN	>7.5xN
61-90 days old	1.1-1.9xN	2.0-2.9xN	3.0-7.5xN	>7.5xN

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(Selected Values for children less than or equal to 3 months of age)

HEMATOLOGY (continued)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Creatinine				
<7 days old	1.0-1.7 mg/dL	1.8-2.4 mg/dL	2.5-3.0 mg/dL	>3.0 mg/dL
7-60 days old	0.5-0.9 mg/dL	1.0-1.4 mg/dL	1.5-2.0 mg/dL	>2.0 mg/dL
61-90 days old	0.6-0.8 mg/dL	0.9-1.1 mg/dL	1.2-1.5 mg/dL	>1.5 mg/dL
Cr Clearance				
<7 days old	35-40 ml/min	30-34 ml/min	25-29 ml/min	<25 ml/min
7-60 days old	45-50 ml/min	40-44 ml/min	35-39 ml/min	<35 ml/min
61-90 days old	60-75 ml/min	50-59 ml/min	35-49 ml/min	<35 ml/min
Hypocalcemia				
<7 days old	6.5–6.9 mEq/L	6.0-6.4 mEq/L	5.5-5.9 mEq/L	<5.5 mEq/L
7-60 days old	7.6-8.0 mEq/L	7.0-7.5 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
61-90 days old	7.8-8.4 mEq/L	7.0-7.7 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
Hypercalcemia				
<7 days old	12.0-12.4 mEq/L	12.5-12.9 mEq/L	13.0-13.5 mEq/L	>13.5 mEq/L
7-60 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L
61-90 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L

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(Greater than 3 months of age)

LOCAL REACTIONS				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Induration	< 10mm	10-25 mm	26-50mm	>50mm
Erythema	< 10mm	10-25 mm	26-50mm	>50mm
Edema	< 10mm	10-25 mm	26-50mm	>50mm
Rash at Injection Site	< 10mm	10-25 mm	26-50mm	>50mm
Pruritus	Slight itching at injection site	Moderate itching at injection extremity	Itching at injection extremity and other sites	Itching over entire body

HEMATOLOGY				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin for children greater than months and less than 2 years of age	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to anemia
Hemoglobin for children greater that 2 years of age	10-10.9 gm/dL	7.0-9.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to anemia
Absolute Neutrophil Count	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3
Platelets	-------	50,000-75,000/mm^3	25,000-49,999/mm^3	<25,000/mm^3
Prothrombin Time (PT)	1.1-1.2 x ULN	1.3 -1.5 x ULN	1.6 -3.0 x ULN	>3.0 x ULN
Partial Thromboplastin Time (PTT)	1.1-1.6 x ULN	1.7-2.3 x ULN	2.4 -3.0 x ULN	>3.0 x ULN

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GASTROINTESTINAL				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Bilirubin (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Bilirubin (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Pancreatic Amylase	1.1-1.4 x ULN	1.5-1.9 x ULN	2.0-3.0 x ULN	>3.0 x ULN
Uric Acid	7.5-9.9mg/dL	10-12.4 mg/dL	12.5-15.0 mg/dL	>15.0 mg/dL
CPK	See Neuromuscular Toxicity			

Appetite	----------	Decreased appetite	Appetite very decreased, no solid food taken	No solid or liquid taken
Abdominal Pain	Mild	Moderate- No Treatment Needed	Moderate- Treatment Needed	Severe- Hospitalized for treatment
Diarrhea	Slight change in consistency and/or frequency of stools	Liquid stools	Liquid stools greater that 4x the amount or number normal for this child	Liquid stools greater than 8x the amount or number normal for this child

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(Greater than 3 months of age)

GASTROINTESTINAL (continued)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Constipation	Slight change in the consistency/frequency of stool	Hard, dry stools with a change in frequency	Abdominal pain	Distention and Vomiting
Nausea	Mild	Moderate-Decreased oral intake	Severe-Little oral intake	Unable to ingest food or fluid for more than 24 hours
Vomiting	1 episode/day	2-3 episodes per day	4-6 episodes per day	Greater than 6 episodes per day or Intractable Vomiting

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(Greater than 3 months of age)

ELECTROLYTES				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
CREATININE				
3 Months -2 Years of age	0.6-0.8 x ULN	0.9-1.1 x ULN	1.2-1.5 x ULN	>1.5 x ULN
2 Years- 12 Years of age	0.7-1.0 x ULN	1.1-1.6 x ULN	1.7-2.0 x ULN	>2.0 x ULN
Greater than 12 Years of age	1.0-1.7 x ULN	1.8-2.4 x ULN	2.5-3.5 x ULN	>3.5 x ULN

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(Greater than 3 months of age)

ELECTROLYTES				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hypernatremia		<145-149 mEq/L	150-155 mEq/L	>155 mEq/L or abnormal sodium AND mental status changes
Hyponatremia		130-135 mEq/L	129-124 mEq/L	<124 mEq/L or abnormal sodium AND mental status changes
Hyperkalemia	5.0-5.9 mEq/L	6.0-6.4 mEq/L	6.5-7.0 mEq/L	>7.0 mEq/L or abnormal potassium AND cardiac arrhythamia
Hypokalemia	3.0-3-5 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L	<2.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypercalcemia	10.5-11.2mg/dL	11.3-11.9 mg/dL	12.0-12.9 mg/dL	>13.0 mg/dL
Hypocalcemia	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.0-6.9 mg/dL	<6.0 mg/dL
Hypomagnesemia	1.2-1.4 mEq/L	0.9-1.1 mEq/L	0.6-0.8 mEq/L	<0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia
Hypoglycemia	55-65 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose AND mental status changes
Hyperglycemia	116-159 mg/dL	160-249 mg/dL	250-400 mg/dL	>400 mg/dL or ketoacidosis
Proteinuria	Tr-1+ or <150 mg/day	2+ or 150-499 mg/day	3+ or 500-1000 mg/day	4+ or Nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25	Microscopic >25		Gross hematuria

	cells/hpf	cells/hpf		

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(Greater than 3 months of age)

CENTRAL NERVOUS SYSTEM (CNS)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Generalized CNS Symptoms			Dizziness	Hypotonic, hyporesponsive episodes; Seizures; Apnea/Bradycardia; Inconsolable crying > 3 hrs;
Headache	Mild	Moderate, Responds to non-narcotic analgesia	Moderate to Severe, Responds to narcotic analgesia	Intractable
Level of Activity		Slightly irritable OR slightly subdued	Very irritable OR Lethargic	Inconsolable OR Obtunded
Visual		Blurriness, diplopia, or horizontal nystagmus of < 1 hour duration, with spontaneous resolution	More than 1 episode of Grade 2 symptoms per week, or an episode of Grade 2 symptoms lasting more than 1 hour with spontaneous resolution by 4 hours or vertical nystagmus	Decrease in visual acuity, visual field deficit, or oculogyric crisis
Myelopathy		None	None	Myelopathic/spinal cord symptoms, such as: pyramidal tract weakness and disinhibition, sensory level, loss of proprioception, bladder/bowel dysfunction

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(Greater than 3 months of age)

PERIPHERAL NERVOUS SYSTEM				
PARAMETER	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Neuropathy/ Lower Motor Neuropathy		Mild transient Paresthesia only	Persistent or progressive paresthesias, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss	Onset of significant weakness, decrease or loss of DTRs, sensory loss in "stocking glove" distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness.
Myopathy or Neuromuscular Junction Impairment	Normal or mild (<2 x ULN) CPK elevation	Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/- mild CPK elevation (<2 x ULN)	Proximal muscle weakness and/or atrophy affecting motor function +/- CPK elevation; or severe myalgias with CPK >2 x ULN;	Onset of myasthenia-like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms

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(Greater than 3 months of age)

OTHER				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Allergy	Pruritus without Rash	Pruritic Rash	Mild Urticaria	Severe Urticaria Anaphylaxis, Angioedema
Drug Fever (Rectal)	.	38.5-40C 101.3 – 104.0F	Greater than 40.0C Greater than 104.0F	Sustained Fever: Equal or greater than 40C (104.0F) for longer than 5 days
Cutaneous	Localized rash	Diffuse maculopapular Rash	Generalized urticaria	Stevens-Johnson Syndrome or Erythema multiforme
Stomatitis	Mild discomfort	Painful, difficulty swallowing, but able to eat and drink	Painful: unable to swallow solids	Painful: unable to swallow liquids; requires IV fluids
Clinical symptoms *not otherwise specified* in this table	No therapy; monitor condition	May require minimal intervention and monitoring	Requires medical care and possible hospitalization	Requires active medical intervention, hospitalization, or hospice care
Laboratory values *not otherwise specified* in this table	Abnormal, but requiring no immediate intervention; follow	Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug	Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug	Life-threatening severity; Requires immediate evaluation, treatment, and usually hospitalization; Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism that study drug

Appendix 4 HAE Attack Assessment and Reporting Procedures (HAARP)

HAE Attack Assessment and Reporting Procedures (HAARP)

Title:	HAE Attack Assessment and Reporting Procedures (HAARP)
Product Name:	DX-2930
Indication:	Prevention of angioedema attacks in patients with HAE
Sponsor:	Dyax Corp. 55 Network Drive Burlington, MA 01803
Original Date:	14 September 2015
Version:	v1.0

TABLE OF CONTENTS

1 PURPOSE

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

2 DEFINITION OF AN ATTACK

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

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

Despite the presence of these symptoms, the investigator may still determine clinically that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an attack (e.g., urticaria), the reported event persists well beyond the typical time course of an attack (e.g., greater than 7 days), 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 their previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.

Attack resolution is defined as the subject no longer having symptoms of the attack.

Prodromal symptoms by themselves are not considered an attack.

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

3 REPORTING AND ASSESSMENT OF ATTACK DATA

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

During the relevant study periods, as defined in the applicable study protocol, subjects (or caregivers, for subjects < 18 years old) will be instructed to contact the site within 72 hours of the start of symptoms of an attack. In the situation that a subject is incapacitated and is

unable to contact the site, a family member or other individual with detailed knowledge of the event can provide the information. If desired by the subject, memory aids may be provided to assist in tracking any HAE attacks subject's experience. Any tools or devices the subject uses to track this information are not intended to serve as source documents for the study.

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

A designated individual at the site (the collector) will contact the subject or caregiver on a regular basis as defined in the study protocol, regardless of whether or not the subject has reported any attacks, in order to solicit for any attacks that may have occurred but were not reported. In addition, during each study visit, site personnel will solicit for any new attack information that was not provided through previous contact with the subject or caregiver.

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

3.1 Subject-Reported Symptoms

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

3.1.1 Attack Information

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

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

Subjects do not have to wait for their symptoms to completely resolve to report an attack. Information about ongoing symptoms can be obtained by the site during the check-in call and/ or at a scheduled study visit. Subjects should not withhold or delay any treatment they would normally receive to treat their attack in order contact the site.

3.1.2 Worsening Symptoms

The site may request the subject call them back if they experience worsening symptoms and/ or new symptoms for a reported attack. Otherwise, the new information will be captured during the next check-in call or scheduled study visit. Subjects may contact the site on their own to provide information about any worsening symptoms.

3.1.3 Subject Training

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

3.1.4 Reporting Multiple Attacks

If a subject experiences symptoms they attribute to more than one unique attack they can report this as multiple attacks to the site. Based on the definition of an attack as stated in Section 2, it will be the determination of the investigator or designee as to whether events reported as being separate are confirmed as separate attacks or not.

3.1.5 Caregiver Report

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

3.1.6 Subject Contact with Sites

Site personnel will establish a recommended method and time window for each subject to contact the site to report any symptoms of an attack. Sites will establish a primary contact person and, if possible, a back-up person, with contact information. Back-up plans, including call backs and/ or use of back-up contacts, should be established in case the subject is unable to reach someone at the site.

3.2 Site Contact with the Subject

Sites will establish a recommended day and time window for check-in calls between study visits. The date and time for check-ins can be modified based on when the last contact with the subject was made, as outlined in the study protocol. When the site is contacted by a subject reporting symptoms of an attack the site should make sure they have the ability to record the information provided in a complete and accurate way. Back-up plans should be

established in case the subject misses a call from the site. A study schedule for each subject's on-site visits will be provided to the subject by the site.

3.2.1 Review of subject report of symptoms

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

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

3.2.2 Documenting a Reported Attack

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

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

Additional probing questions about what the subject experienced to determine:

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

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

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

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

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

3.2.3 Site Training

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

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

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

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

3.3 HAE attacks as Adverse Events

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

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 Dyax using the SAE Reporting Form in the 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.

4 INVESTIGATOR ATTACK ASSESSMENT

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

The assessor must review the information and determine whether the event is an actual attack or not. If needed, the assessor can contact the subject and/or caregiver to clarify information or ask for any additional detail. The determination will be documented along with the date and time the determination was made. Any event deemed not an attack must be accompanied by an explanation and alternative diagnosis by the assessor.

When reviewing subject information, the assessor will follow the definitions of an attack as outlined in these procedures and, taking all available information about the event into consideration, will determine if it is a confirmed attack. The assessment of the attack is the Investigator or designee's own, and not the opinion of the subject, the subject's caregiver or any other site personnel. Assessors may consult with one another about a particular subject's attack but only one assessor makes the documented determination. It is possible for both the Principal Investigator and physician designee to assess different attacks for the same subject.

Appendix 5 Summary of Pivotal Study of DX-2930 in HAE Subjects

The proposed pivotal clinical study (DX-2930-03) is entitled "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)." This study will be a multi-center, double-blind, randomized, placebo-controlled parallel-arm study evaluating the efficacy of DX-2930 in preventing acute angioedema attacks in patients with Type I or Type II HAE. The double-blind study is planned to be followed by the study described in the present protocol, an open-label extension (OLE) study (DX-2930-04).

The primary objective of study DX-2930-03 is to evaluate the efficacy of DX-2930 in preventing HAE attacks. The secondary objective is to evaluate the safety of repeated SC administrations of DX-2930. The tertiary objectives are to evaluate the pharmacodynamic effects of chronically administered DX-2930; to assess the immunogenicity of chronically administered DX-2930; to evaluate the pharmacokinetics of chronically administered DX-2930; and to evaluate the effect of DX-2930 upon quality of life assessments.

Subjects aged 12 years and over with a documented diagnosis of Type I or Type II HAE who experience at least 1 attack per 4 weeks will be eligible for the study. Up to 120 subjects are planned for enrollment across approximately 60 sites in the United States, Canada, Italy, Germany, United Kingdom and Jordan.

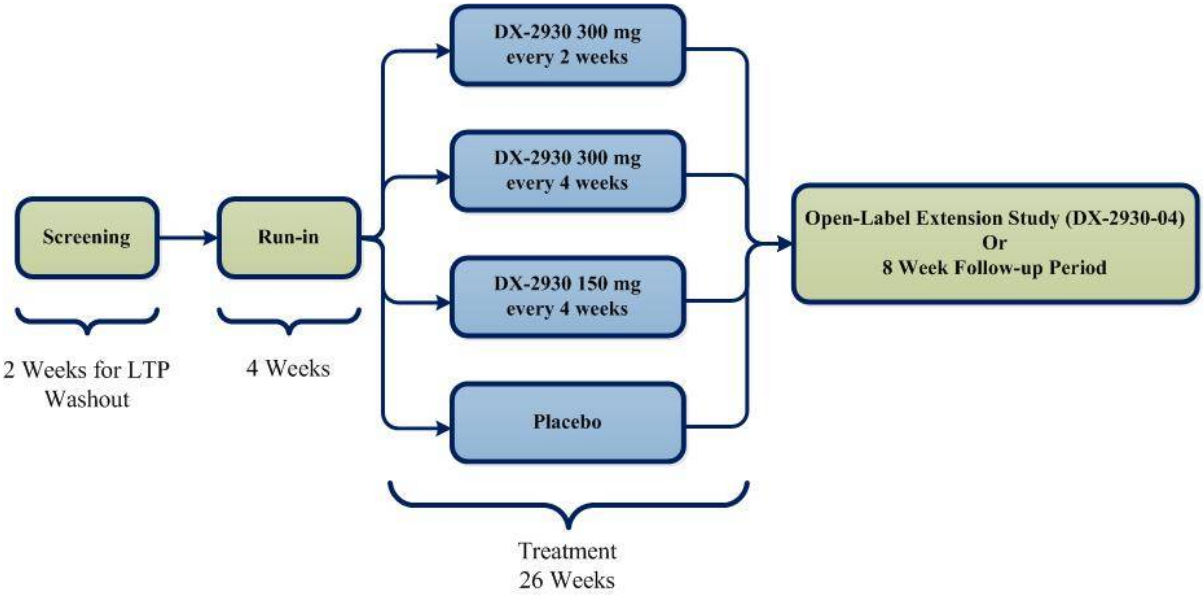
Following informed consent, subjects will undergo screening assessments. Subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. Subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. The run-in period may be extended to 8 weeks if the minimum baseline attack rate is not achieved in the first 4 weeks. HAE subjects will then 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 one of three dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks or 150 mg every 4 weeks. Each subject will undergo a treatment period consisting of 13 doses of blinded study drug, for a period of 26 weeks from the date of first dose on Day 0 through Day 182

Subjects may consent to rollover into the OLE study (present protocol DX-2930-04) upon completion of their participation in the double-blind treatment period.

The primary endpoint will be to compare the mean rate of investigator-confirmed HAE attacks observed in each DX-2930 treatment arm to that in the placebo arm during the efficacy assessment period (Day 14 through Day 182).

Figure 2 shows a schematic of the double-blind, pivotal study.

Figure 2: Overview of the Design of Pivotal Study DX-2930-03



Dose Rationale for Double-Blind, Pivotal Study DX-2930-03

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 while avoiding non-therapeutic or super-therapeutic doses and regimens

Clinical Trial Protocol: DX-2930-04

Study Title:	HELP Study Extension™: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number:	DX-2930-04
Study Phase:	Phase 3
Product Name:	DX-2930
IND Number:	116647
EudraCT Number:	2015-005255-27
Indication:	Prevention of angioedema attacks in patients with HAE
Investigators:	Multicenter
Sponsor:	Dyax Corp., an indirect, wholly-owned subsidiary of Shire plc. 55 Network Drive, Burlington, MA 01803 USA
Sponsor Contact:	[redacted], MD [redacted], Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: [redacted]
Global Medical Monitor:	[redacted], MD [redacted] 300 Shire Way, Lexington, MA 02421 USA Phone: [redacted]

	Date:
Original Protocol	14 December 2015
Amendment 1.0	27 June 2016
Amendment 2.0	20 January 2017

PROTOCOL SIGNATURE PAGE

Study Title:	HELP Study Extension™: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number:	DX-2930-04
Amendment 2.0 Final Date:	20 January 2017

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The signature of the Sponsor representative indicates that the Sponsor will comply with all Sponsor obligations detailed in applicable regulations and guidelines and will ensure the investigator is informed of all relevant information that becomes available.

Signed: [redacted] Date: [redacted]

[redacted], MD
[redacted], Clinical Development
300 Shire Way, Lexington, MA 02421 USA

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP), and all applicable regulatory requirements and guidelines as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use only the informed consent form approved by Dyax Corp. and my Institutional Review Board (IRB), Research Ethics Board (REB) or Ethics Committee (EC) and will fulfill all responsibilities for submitting pertinent information to the IRB/REB/EC responsible for this study.

I further agree that Dyax Corp. or their designees shall have access to any source documents from which eCRF information may have been generated.

By signing this protocol, I agree to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP to which it conforms.

Signed:_____ Date:_____
Investigator
Address: _____

_____

AMENDMENT SUMMARY AND RATIONALE

Amendment 2 to Protocol DX-2930-04 includes the following revisions:

- Updated administrative structure and contact information
- Clarification that female rollover subjects of childbearing potential may continue to use the effective birth control method used during Study DX-2930-03
- Editorial changes throughout the protocol to remove inconsistencies in the protocol text and ensure all agreed changes from Amendment 1 and administrative letters are accurately presented across all sections.

Noteworthy changes to the protocol related to the topics above are captured in the table below. Additional minor revisions in grammar, spelling, punctuation, and format have been made for clarity and are not reflected in the summary of changes.

Summary of Changes from Previous Version

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **20 Jan 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated administrative information to reflect current contact information, including contact information for the 24-Hour Global Medical Monitor and Back-Up Global Medical Monitor and Sponsor Contact.		Title Page, Section 6.16.5.5, Section 10
Included clarifying note that female rollover subjects (those who previously participated in Study DX-2930-03) of childbearing potential may continue to use the effective birth control method used during Study DX-2930-03.		Synopsis, Section 4.2
Introduced the international nonproprietary name "lanadelumab."		Synopsis, Section 5.1
Clarified that sites will call subjects within approximately 3 days of planned off-site self-administrations.		Synopsis, Section 4.1, Section 5.1, Section 5.6
Clarified that adolescent subjects should complete the WPAI-GH questionnaire and use the term "school" instead of "work" when filling out this questionnaire. These data will be analyzed separately.		Section 6.14.3
Refined language on interim analyses options to allow for interim analyses to be performed as appropriate for regulatory reporting and/or internal administrative decisions.		Synopsis, Section 9.9.1
The following editorial changes were made to remove inconsistencies in the text and to ensure all agreed changes from Amendment 1 and administrative letters are accurately presented across all sections		
Removed the duplicate Study Activities Schedule from Appendix 1 and changed in-text references/linking to the Study Activities Schedule from Appendix 1, to ensure a single location for the Study Activities Schedule.		Entire protocol, Appendix 1
Corrected the numbers in Figure 1 to correctly present the length of treatment period.		Figure 1
Corrected text regarding the treatment period duration: the treatment period is 364 days, with the last dose of study drug administered on Day 350.		Synopsis, entire protocol

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **20 Jan 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Added text from Section 3.1.1. to the synopsis for clarity; specifically, that the 3rd dose must be administered at the next pre-defined study visit according to the Study Activities Schedule.		Synopsis
Clarified that subjects in Study DX-2930-03 can be consented for enrollment in Study DX-2930-04 on or after Day 168 of Study DX-2930-03.		Synopsis, Table 1 (footnote "5"), Section 3.1.1, Section 6.1,Section 7.2
Revised text in Section 3.1.1 to match correct text in Synopsis, including text regarding standard of care treatment for subjects who experience an acute attack of HAE during the study.		Synopsis, Section 3.1.1
Updated wording regarding the enrollment number for non-rollover subjects from "up to a maximum of 100" to "approximately 100" in total.		Synopsis, Section 3.1.1, Section 4.1
Corrected text regarding the follow-up period: the follow-up period is 4 weeks from the last visit of the protocol-defined treatment period. Removed inconsistent text that erroneously mentioned an 8-week follow up period.		Synopsis, Section 3.1.1, Section 3.4, and Section 5.2
Removed text indicating that the Sponsor would provide ancillary supplies to sites since the sites are responsible for sourcing them.		Section 5.7
Clarified text to align with Study Activities Schedule; specifically, subject surveys on their experience with SC and self-administration injections of DX-2930 are to be completed by the subject during the study.		Synopsis, Section 6.15.2
Clarified text to align with Study Activities Schedule; specifically, that vital signs will be monitored both prior to dosing and at 1 hour post-dosing when dosing occurs at the investigational site, with a ±15 minutes window for all vital signs. Vital signs are not monitored when subjects elect to self-administer study drug away from the site.		Section 6.5, Section 7 itemization per visit
Clarified text to align with Study Activities Schedule; specifically, that weight is collected during each physical exam.		Table 1, Section 6.6, Section 7
Clarified text to align with Study Activities Schedule; specifically, that height is only collected at the Screening visit.		Table 1, Section 6.6, Section 7.1
Clarified text to align with Study Activities Schedule; specifically, that pregnancy tests performed on Day 0 must be urine-based to confirm eligibility prior to dosing while subsequent pregnancy tests can be urine or serum-based.		Section 6.8.1.5
Removed outdated contact information from safety reporting text.		Section 6.16.5.5
Removed remnant text regarding the requirement to complete a 2-week wash-out period before entering the treatment period for non-rollover subjects on LTP for HAE. Washout period does not exist for non-rollover subjects.		Section 7.1
Removed remnant text regarding the requirement for urinalysis for Visits 14, 17, 20, and 23. Urinalysis is not required at these visits.		Section 7.16, Section 7.19, Section 7.22, and Section 7.25
Removed text indicating a subject could self-administer study drug at their home or other agreed upon location and that no monitoring of vital signs will be performed for Visit 17 since this is a mandated investigational site visit.		Section 7.19

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **20 Jan 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Removed safety analysis category called “pretreatment group” since a pretreatment period does not exist in this study.		Section 9.7.1

See Appendix 1 for protocol history, including amendments.

SYNOPSIS

Sponsor: Dyax Corp., an indirect, wholly-owned subsidiary of Shire plc. 55 Network Drive, Burlington, MA 01803 USA
Name of Finished Product: DX-2930 Drug Product (DP)
Name of Active Ingredient: DX-2930 (lanadelumab) is a recombinant, Chinese hamster ovary (CHO) cell-expressed, fully human immunoglobulin G subclass 1 (IgG1), kappa light chain, monoclonal antibody.
Names of Inactive Ingredients: Sodium phosphate dibasic dihydrate, citric acid monohydrate, L-histidine, sodium chloride, and Polysorbate 80
Study Title: HELP Study Extension™: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number: DX-2930-04
Study Phase: Phase 3
Study Location: Approximately 60 study sites planned across North America, the European Union, and the Middle East
Primary Objective: To evaluate the long-term safety of repeated subcutaneous (SC) administrations of DX-2930
Secondary Objectives: • To evaluate the long-term efficacy of DX-2930 in preventing HAE attacks • To characterize the outer bounds of dosing frequency for DX-2930
Tertiary Objectives: • To assess the immunogenicity of chronically administered DX-2930 • To evaluate the effect of DX-2930 on health-related quality of life (QoL) • To characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of SC administration of DX-2930 • To evaluate safety and efficacy in the non-rollover population of switching from long-term prophylactic (LTP) treatment to DX-2930 • To evaluate breakthrough attack characteristics while receiving DX-2930 compared to historical baseline • To evaluate subject experience with self-administration of DX-2930 including ease of SC administration of DX-2930

Study Design:

Study DX-2930-04 is an open-label, long term safety and efficacy extension study of Study DX-2930-03, to evaluate the investigational medicinal product (IMP), DX-2930, in preventing acute angioedema attacks in patients with Type I and Type II HAE. There are two types of subjects who will be enrolled into this study:

- Subjects who rollover from Study DX-2930-03
- Subjects who are non-rollover (ie, were not participants in Study DX-2930-03)

Rollover Subjects

Rollover subjects are subjects who complete the double-blind treatment period at Day 182 of Study DX-2930-03 and consent to enter Study DX-2930-04. Subjects who discontinue from Study DX-2930-03 after enrollment are not eligible to enroll in Study DX-2930-04.

Subjects should be asked about their interest in Study DX-2930-04 study after enrollment into Study DX-2930-03 to anticipate enrollment and preparedness for Study DX-2930-04. Willing subjects must sign informed consent for Study DX-2930-04 on or after Day 168 of Study DX-2930-03.

Subjects who are eligible to roll over into Study DX-2930-04 but elect not to, may not enroll in Study DX-2930-04 at a later time. The first Study DX-2930-04 visit for rollover subjects (Day 0) will occur on the same day as the Study DX-2930-03 Day 182 study visit. Rollover subjects will complete all Study DX-2930-03 final study assessments (Day 182) at which time they will be discharged from that study. No assessments conducted between the Study DX-2930-03 Day 182 study visit and the first Study DX-2930-04 visit (Day 0) will be duplicated. Results of the final Study DX-2930-03 assessments on Day 182 will be used as the pre-dose results for Day 0 of Study DX-2930-04.

All subjects, caregivers, investigators and study site personnel will remain blinded to the Study DX-2930-03 treatment assignment until the conclusion of Study DX-2930-04.

Non-rollover subjects

At least 50 subjects (to approximately 100) who were not participants in Study DX-2930-03 will be permitted to enroll if they meet the eligibility requirements. Subjects who screen fail out of Study DX-2930-03 for not meeting the minimum attack requirements during the run-in period must wait until enrollment for the double-blind study has ended before they can screen for Study DX-2930-04. The Sponsor may ease this restriction based on the enrollment rate observed in Study DX-2930-03. Subjects who are still in the run-in period for Study DX-2930-03 when enrollment for that study closes, as well as subjects on prior LTP who screen fail out of Study DX-2930-03 due to an inability to wash-out of their LTP, may screen for Study DX-2930-04 following discussion with the Sponsor medical monitor.

Screening Period:

Rollover Subjects

There is no screening period for rollover subjects.

Non-rollover Subjects

Non-rollover subjects must provide informed consent and have screening assessments completed within 4 weeks prior to their first open-label dose. Screened non-rollover subjects (adults and adolescents) who are on LTP with C1-INH therapy for HAE can continue their current LTP until Day 8 (or Day 15) such that subjects will have received 2 (or 4) doses of C1-INH. For subjects who are on attenuated androgens (eg, danazol) or anti-fibrinolytics (eg, tranexamic acid), a similar tapering schedule is recommended. However, the taper can be prolonged by an additional week, if medically indicated, as long as androgen or anti-fibrinolytic therapy is stopped within 3 weeks after receiving the first dose of DX-2930.

Treatment Period:

Rollover Subjects

Following informed consent and pre-dose assessments, rollover subjects will receive a single open-label dose of 300 mg DX-2930 administered subcutaneously (SC) on Day 0. Subjects will not receive any additional DX-2930 doses until their first reported, and investigator-confirmed, HAE attack. As such, the total number of doses within the treatment period will vary by rollover subject.

The duration of time between the first open-label dose and first reported HAE attack will vary by rollover subject. All rollover subjects must adhere to the Study Activities Schedule for the entire duration of the study. However, until a rollover subject reports their first HAE attack, only scheduled study visits where the following tests and assessments are performed must be conducted at the investigative site: pregnancy testing, clinical laboratory testing, physical examination, 12-Lead ECG, QoL, PK, PD and anti-drug antibody sample collection. All other scheduled study visits may be conducted via site check-in calls to collect information on adverse events, concomitant therapy, and HAE attack data. See Study Activities Schedule for which visits must be conducted at the study site.

Once a rollover subject reports their first HAE attack they will present to the investigative site for their second open-label dose of DX-2930 as quickly as subject and site schedules allow. If the second dose is to be administered within the accepted ±4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit. If that scheduled visit has already occurred, the day of the visit will be considered an acceptable, extra study visit (ie, an unscheduled visit). Similarly, if the second dose is administered outside of the accepted ±4 day window around a scheduled visit, the day of the visit will be considered an acceptable extra unscheduled study visit, (ie, this visit will not replace any scheduled visit).

Regardless of the study day, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical examination, clinical laboratory testing, blood sampling for PK, PD, and anti-drug antibody. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data.

Regardless of when a rollover subject's first HAE attack occurs, there will be a minimum of 10 days between their first open-label dose and their second open-label dose. Following their second open-label dose, rollover subjects will continue to receive repeated SC administrations of open-label 300 mg DX-2930 every 2 weeks for the remaining duration of the treatment period per the scheduled dosing in the Study Activities Schedule. The treatment period will last 364 days from the date of the first open-label dose. The number of doses administered during this period will vary by subject based on the date of each subject's second dose, but will not exceed 26 doses. The Day 350 study visit is the last visit at which a dose may be administered.

Non-rollover Subjects
Once all screening assessments have been completed and eligibility confirmed, non-rollover subjects will arrive at the study site and, following pre-dose assessments, receive an open-label dose of 300 mg DX-2930 administered SC on Day 0. Non-rollover subjects will continue to receive SC administrations of open-label 300 mg DX-2930 every 2 weeks throughout the duration of the treatment period per the scheduled dosing in the Study Activities Schedule. A total of 26 doses will be administered with the last dose administered at the Day 350 study visit.

All Subjects:
All doses (with the exception of the second dose for rollover subjects) require a minimum of 10 days and maximum of 18 days between administrations, and should fall within the accepted ±4 day window around study visits.

After the second DX-2930 dose is given either within the study window (±4 days) or an acceptable extra study visit, the 3rd dose must be administered at the next pre-defined study visit according to the schedule of assessments.

If a subject experiences an acute angioedema attack at any time during the study that in the opinion of the investigator requires medical intervention, standard of care therapy should be provided based on subject's medical history and per locally approved product information. Administration of DX-2930 and study procedures will continue without alteration to the protocol study activities schedule, even if a subject receives treatment for a breakthrough angioedema attack on the day of a scheduled dose of study drug (if self-administering) or scheduled study visit.

Self Administration
All subjects (adolescent or adult) who are considered suitable candidates (ie, those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer treatment. Subjects must complete appropriate training by the investigator or designee and understanding of the training must be confirmed by the investigator or designee. Subjects are allowed to initiate self-administration at the subject's home or other agreed upon location after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may self-administer subsequent doses of DX-2930 at the investigational site (when visits are scheduled study site visits) or the subject's home or other agreed upon location (when the study permits off-site dosing). See Schedule of Activities for details. Adolescent subjects self-administering investigational product will be supervised by a parent/legal guardian/caregiver. Alternatively, a

parent/legal guardian/caregiver, after completing appropriate training, will be allowed to administer DX-2930 to an adolescent without study site personnel supervision. Site personnel will call subjects within approximately 3 days of the planned off-site self-administrations to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.

Throughout the study, study site personnel will document information in source documents (ie, the subject's medical record) and eCRF regarding the subject's experience with self-administration and SC administration of DX-2930.

Follow-up Period
After completion of the treatment period, all subjects will undergo safety evaluations during a 4-week follow-up period.

Modifications to Open-Label Dosing
If, at any time, an important dose-related safety signal is identified either from this study or Study DX-2930-03, the Sponsor may decide to switch the enrolled subjects who have not yet completed the treatment period, and any subsequent subjects, to receive a different open-label DX-2930 dose and/or frequency.

In addition, based on the results of Study DX-2930-03, the Sponsor may switch to a different dose and/or frequency.

Study Population:
The study is expected to enroll subjects from Study DX-2930-03, as well as at least 50 (to approximately 100) additional subjects who were not enrolled in Study DX-2930-03. The total enrollment is expected to be at least 150 but not more than 250 HAE Type I or II subjects. Subjects will be 12 years of age or older who experience at least 1 attack per 12 weeks. HAE diagnosis will be confirmed through documented clinical history and diagnostic testing conducted either during screening or during prior participation in Study DX-2930-02 or Study DX-2930-03. The study will aim to enroll at least 15 subjects who are 12 to 17 years of age, inclusive of the estimated 10 subjects 12 to 17 years old who are expected to roll over from Study DX-2930-03.

Criteria for Inclusion:
Subjects must meet the following criteria to be enrolled in this study:

1. Male and female HAE subjects who are 12 years of age or older at the time of screening.
2. Documented diagnosis of HAE (Type I or II) based on all of the following:
    - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).
    - Diagnostic testing results obtained during screening (or a prior DX-2930 study) that confirm HAE Type I or II: C1 inhibitor (C1-INH) functional level < 40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may be retested if results are incongruent with clinical history or believed by the investigator to be confounded by recent LTP use.

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

3. A historical baseline HAE attack rate of at least 1 attack per 12 weeks.
4. Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects age 12 to 17, whose caregiver has provided informed consent, are willing and able to read, understand and sign an assent form.
5. Males and females who are fertile and sexually active must adhere to contraception requirements for the duration of the study as follows:
   - Females* of childbearing potential must agree to be abstinent or it is recommended to use highly effective forms of contraception from screening through 30 days after the final study visit. This includes stable doses (for 3 months prior to study screening) of combined estrogen and progestin-containing hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable), progestin-only hormonal contraception associated with inhibition of ovulation, intra-uterine device (IUD, all types) or intrauterine hormone releasing systems (IUS). Notes: 1) A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. 2) Use of a male condom with or without spermicide or cervical cap, diaphragm or sponge with spermicide or a combination (double barrier methods) are not considered highly effective.
   - Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
   - Males, including males who are surgically sterile (post vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study visit.

     *NOTE: Female rollover subjects (those who previously participated in Study DX-2930-03) of childbearing potential may continue to use the effective birth control method used during Study DX2930-03.

Criteria for Exclusion:

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

1. Discontinued from Study DX-2930-03 after enrollment for any reason.
2. If rolling over from Study DX-2930-03, presence of important safety concerns that would preclude participation in this study.
3. Concomitant diagnosis of another form of chronic, recurrent angioedema such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.
4. Dosing with an investigational drug (not including DX-2930 or other HAE therapies) or exposure to an investigational device within 4 weeks prior to screening.
5. Exposure to angiotensin-converting enzyme (ACE) inhibitors within 4 weeks prior to study screening or any newly initiated or dose modification of estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) 3

months prior to the screening visit.

6. Unwilling to discontinue use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 3 weeks after starting DX-2930 treatment.
7. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's Syndrome).
8. Pregnancy or breastfeeding.
9. Subject has any condition that, in the opinion of the investigator or Sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (eg, history of substance abuse or dependence, a significant pre-existing illness or other major comorbidity that the investigator considers may confound the interpretation of study results).

Test Product; Dose; and Mode of Administration:

DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated using the following compendial components: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Polysorbate 80. Each open-label vial contains a nominal concentration of 150 mg DX-2930 active ingredient in 1 mL solution.

For each 300 mg dose of DX-2930, each subject will receive a total of 2 mL (2 vials), which will be administered in a single 2 mL SC injection. The injection will be given in the upper arm, thigh or abdomen.

Self-Administration Option: Investigational product can be self-administered without supervision (parental supervision required for adolescent subjects) after subjects receive appropriate training by the investigator or designee and their understanding is confirmed. Subjects are allowed to initiate offsite self-administration after receiving the first 2 doses of DX-2930 at the study site and may continue to self-administer all subsequent doses (see Study Activities Schedule).

Duration of Treatment:

All subjects will receive open-label DX-2930 during a 364 day treatment period. The number of doses that rollover subjects receive during this period will vary by subject but will not exceed 26 doses. The last dose of open-label DX-2930 administered to these subjects may be given at the Day 350 study visit. Non-rollover subjects will receive 300 mg DX-2930 every 2 weeks for a total of 26 doses, with the first dose administered on Day 0 and the final dose administered at the Day 350 study visit.

There will be a ±4-day window around each study visit. There will be a minimum of 10 days between any two doses. Excluding the interval between the first and second open-label doses for rollover subjects, there will be a maximum of 18 days between any two doses. Subjects will be monitored at the study site through 1 hour post-dose for scheduled study site visits. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.

Duration of Study for Individual Subjects:

Following informed consent, subjects will either rollover from DX-2930-03 or undergo screening assessments (non-rollover subjects). Screening assessments for non-rollover subjects must occur within 4 weeks prior to the first open-label dose. Eligible subjects will be enrolled and undergo a 364 day treatment period. At the conclusion of the treatment period, subjects will be followed for an additional 4 weeks.

Prohibited Concomitant Treatments:

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

- Long-term prophylaxis for HAE (eg, use of C1-INH for LTP, attenuated androgens, or anti-fibrinolytics) once LTP is discontinued (within 3 weeks following the first dose of DX-2930).
- Angiotensin-converting enzyme (ACE) inhibitors.
- Initiating or changing the dose of estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) 3 months prior to study screening.
- Use of androgens (eg, stanozolol, danazol, oxandrolone, methyltestosterone, and testosterone) for non-HAE related medical conditions or for HAE after discontinuation during the first three weeks.
- Any other investigational drug or device.

The use of short-term prophylactic treatment for HAE will be permitted if medically indicated. Short-term (pre-procedure) prophylaxis is defined as use of C1-INH to avoid angioedema complications from medically indicated procedures.

Management of Acute Attacks:

Acute HAE attacks during the study are to be managed in accord with the investigator's usual care of their patients, including use of acute attack therapies that the investigator deems as medically appropriate. Use of C1-INH will be permitted as an acute attack therapy but not as a long-term prophylactic therapy. Administration of DX-2930 and study procedures will continue without alteration to the protocol-specified study schedule, even if the subject has symptoms of an HAE attack the day of DX-2930 administration and/or receives treatment for an HAE attack. The administration of DX-2930 can also be re-scheduled as long as the minimum and maximum timeframe between doses are met based on subject preference or physician discretion.

Safety Assessments:

Safety assessments will include the following:

- Adverse events (AEs), including serious adverse events (SAEs) and adverse events of special interest (AESI). SAEs and AESI will be reported to the Sponsor within 24 hours of becoming aware of the event.
- Vital signs, including sitting or supine blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR)
- Physical examination
- Clinical laboratory testing (hematology, serum chemistry, coagulation, and urinalysis)

- 12-Lead electrocardiogram (ECG)

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

Pharmacokinetic (PK) Assessments:
Blood samples will be collected for the measurement of plasma DX-2930 concentrations.

Pharmacodynamic (PD) Assessments:
Blood samples will be collected to evaluate the pharmacodynamic effects of DX-2930 through biomarker assays.

Immunogenicity Assessments:
Blood samples will be collected to assay for the presence of anti-drug antibodies, including evaluation of neutralizing antibodies (if any confirmed positive anti-drug antibodies are detected).

C1-INH, C1q and C4 Assessments:
Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment, unless already collected as part of protocol DX-2930-02 or DX-2930-03.

Quality of Life Assessments:
Quality of life (QoL) assessments will be conducted using the Angioedema Quality of Life Questionnaire (AE-QoL), EuroQoL 5-Dimensional 5-Level Measure (EQ-5D-5L), Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH), Hospital Anxiety and Depression Scale (HADS), and 12 Item Short Form Survey (SF-12).

DX-2930 Injection Report and Self-Administration and Subcutaneous Injection Survey
An injection report of the subject's experience with self-administration and SC injection will be completed by the subject after all doses of DX-2930.

In addition, assessment survey of subject experience with SC and self-administration injections of DX-2930 will be completed by the subject as indicated in the Study Activities Schedule.

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

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

At screening, HAE attack history will be collected for non-rollover subjects. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant attack location(s), triggers, average duration, acute attack therapy use and history of LTP (including duration of LTP, medication(s) and dose used for LTP, and frequency of attacks while receiving LTP). If available, information will also be collected on HAE diagnosis (year of confirmation, how many years after onset of symptoms was diagnosis confirmed, or if subject

was misdiagnosed).

During the study, subjects (or caregivers) will be instructed to notify and report details to the study site within 72 hours of the onset of an attack. This includes the first attack experienced by rollover subjects following their first open-label dose. In the situation 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 experienced, but their use is not mandatory.

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 (work, school, social interactions) and whether any assistance or medical intervention was required, including hospitalizations, additional laboratory tests or emergency department visits.
- Any medications used to treat the attack (both prescription and over the counter).
- If the attack resolved, date and time the subject was no longer experiencing symptoms.

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

Study site personnel will contact rollover subjects approximately every 7 days following the first dose of open-label DX-2930 to solicit for any HAE attacks not already reported. Site check-ins will continue until the subject has received their second open-label dose.

During each study visit, study site personnel will solicit for any new HAE attack information that was not already provided to the site.

In this study, HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to DX-2930, 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 EDC system within 24 hours of becoming aware of the event. For all serious adverse events that are reported as HAE attacks, the 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 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 to receive additional information. Any subject-reported attack not confirmed by the investigator or physician designee must have an alternate AE diagnosis

recorded. All subject-reported and investigator/ physician designee-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 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 or physician designee may still clinically determine that the event did not represent an attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (eg, urticaria), the reported event persists well beyond the typical time course of an HAE attack, or there is a likely alternate etiology for the event (eg, the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

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

Interim Analyses and Data Monitoring

Interim analyses may be conducted to support administrative decisions and/or regulatory reporting when a reasonable number of subjects have completed 12 months of consecutive exposure to DX-2930 across the combined DX-2930-03 and DX-2930-04 studies, and only after database lock of Study DX-2930-03.

An independent Data Safety Monitoring Board (DSMB) has been established to provide ongoing, independent review and assessment of the safety data for Study DX-2930-03. While an independent DSMB is not currently planned for this study, summary safety data from Study DX-2930-04 may be reviewed by the Study DX-2930-03 DSMB as part of the collection of safety information available on DX-2930.

Individual Stopping Rules:

Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or a DX-2930-related, clinically significant non-serious AE) that, in the assessment of the investigator, warrants discontinuation from further dosing for that subject's well-being. The investigator has the ability to contact and consult with the Medical Monitor on such matters. Subjects will continue to be followed through the completion of all scheduled non-dosing visits, unless they request to be discontinued from the study.

Criteria for Evaluation:

Safety Measures:

- AEs including SAEs and AESI
- Clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis)
- Vitals signs including blood pressure, heart rate, oral body temperature, and respiratory rate
- Physical Examination
- 12-lead ECG

Efficacy Endpoints:

- Time to first HAE attack for rollover subjects (based upon time from first open label study dose until first HAE attack)
- Number of investigator-confirmed HAE attacks during the treatment period
- Number of investigator confirmed HAE attacks requiring acute treatment during the treatment period
- Number of moderate or severe HAE attacks during the treatment period
- Number of high-morbidity 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.

Additional Measures:

- Anti-drug antibody development
- Pharmacokinetics (PK) effects
- Pharmacodynamic (PD) effects
- Quality of Life Assessments
- DX-2930 Injection Report
- DX-2930 Self-administration and Subcutaneous Injection Survey

Analysis Populations:

- The Safety Population will include all subjects who received any study drug after entering the Study DX-2930-04 (ie, any exposure to open-label DX-2930).

- The Rollover Safety Population is the subset of subjects who participated in Study DX-2930-03 and received any study drug after entering Study DX-2930-04 (ie, any exposure to open-label DX-2930).

- The Non-rollover Safety Population is the subset of subjects who entered Study DX-2930-04 directly and received any study drug after entering Study DX-2930-04 (ie, any exposure to open-label DX-2930).

Sample Size Determination:
No formal sample size calculation was performed. The sample size is not based on any statistical considerations. This study is designed to evaluate the safety and efficacy of open-label treatment with DX-2930 in subjects who participated in Study DX-2930-03 and individuals who were not otherwise able to participate in Study DX-2930-03.

Statistical Methodology:
Time to the first investigator-confirmed HAE attack will be analyzed using the Rollover Safety Population.

Time to the first investigator-confirmed HAE attack (days) will be calculated from the date and time of the first open-label dose of DX-2930 to the date and time of the first investigator-confirmed HAE attack after the first open-label dose. Subjects who discontinue the study prior to experiencing their first on-study investigator-confirmed HAE attack will be censored at the date and time of study discontinuation. Time to the first investigator-confirmed HAE attack will be summarized using Kaplan-Meier methods.

Multivariate and univariate Cox proportional hazards regression models will be employed to examine the impact of baseline covariates on the time to the first investigator-confirmed HAE attack, including but not limited to: baseline attack rate prior to entering Study DX-2930-03, the treatment group in Study DX-2930-03, the time since the last dose given in Study DX-2930-03, the time since the last HAE attack, and the rate of attacks during Study DX-2930-03. Results of this exploratory analysis will be summarized.

<u>Number of Investigator-confirmed HAE Attacks</u>

The number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 364) expressed as a monthly HAE attack rate, will be analyzed using each analysis population.

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

The baseline investigator-confirmed monthly HAE attack rate will be calculated for each subject as the number of investigator-confirmed monthly HAE attacks occurring during the pretreatment period for rollover subjects or historical reporting period for non-rollover subjects divided by the number of days the subject contributed to the pretreatment period for rollover subjects or historical reporting period for non-rollovers multiplied by 28 days.

The baseline, treatment period, and treatment period change from baseline in the investigator-confirmed HAE attack rate will be summarized for each analysis population. The summary will include the total number of investigator-confirmed HAE attacks reported during each period and subject-time in months that each subject contributed to each period. Figures will be created for

each analysis population plotting the on-study investigator-confirmed HAE attacks reported during the treatment period relative to Day 0 for each subject.

Similar summary tables will be presented for the following efficacy endpoints for each analysis population:

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

Safety Analysis:

Adverse Events

Treatment-emergent AEs are defined as AEs with onset at the time of or following the first exposure to open-label DX-2930 in this study, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment.

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.

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

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

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

Laboratory Test Results, Vital Signs, and Electrocardiography Results

Baseline is defined as the last non-missing value prior to the first exposure to DX-2930. For rollover subjects previously exposed to DX-2930, baseline is the last non-missing value prior to first exposure to study drug in Study DX-2930-03.

Actual values and change from baseline in clinical laboratory test results and vital signs will be summarized by study visit.

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. 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 within each category will be summarized by study visit.

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 by study visit.

Other Analyses

Plasma concentrations of DX-2930 and plasma kallikrein activity will be summarized by nominal PK and PD sampling times.

The number and percentage of subjects with positive antibodies (and whether neutralizing or non-neutralizing) will be summarized by study visit and overall.

Quality of life assessments will be summarized by study visit.

Date of Original Protocol: 14 December 2015
Date of Amendment 1: 27 June 2016
Date of Amendment 2: 20 January 2017

Table 1 Study Activities Schedule

Study Activities Schedule																																
Tests and Assessments		**Treatment Period ± 4 days for each visit**																														**Follow-up ±4 Days for each visit**
Non-rollover	**Screen Visit[1]**			Shaded columns: scheduled in-site visits																												
Rollover	**-**		**Check-in[2]**	Non-shaded columns: potential subject-elected off-site activity and/or self-administration dosing																												
Visit:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28[3]**	**29[4]**
Dose:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**-**	**-**	**-**
Day:		**0**		**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**	**378**	**392**
Informed Consent[5]	X	(X)[6]																												
Eligibility Review	X	X																												
Long-term prophylactic therapy continued[7]	X	X		X																										
DX-2930 Administration (rollover subjects)		X		(X)[8,9]	(X)[10]	(X)[11]	(X)[10]	(X)[11]	(X)[11]	(X)[10]	(X)[11]	(X)[10]	(X)[11]	(X)[10]	(X)[11]	(X)[10]	(X)[11]	(X)[11]	(X)[10]	(X)[11]	(X)[11]	(X)[10]	(X)[11]	(X)[11]	(X)[10]	(X)[11]	(X)[11]	(X)[10]			
DX-2930 Administration (non-rollover)		X		X	X[10]	X[11]	X[10]	X[11]	X[11]	X[10]	X[11]	X[10]	X[11]	X[10]	X[11]	X[10]	X[11]	X[11]	X[10]	X[11]	X[11]	X[10]	X[11]	X[11]	X[10]	X[11]	X[11]	X[10]			
Demographic and Medical History	X																													
C1-INH, C1q and C4 Testing[12]	X																													
Pregnancy Test[13] (females)	X	X		X	X		X			X		X		X		X			X			X			X			X	X		X
Vital Signs[14]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical Exam[15]	X	X		X	X		X			X				X		X						X						X	X		X

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Rollover	-		**Check-in[2]**	Non-shaded columns: potential subject-elected off-site activity and/or self-administration dosing																											
Visit:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28[3]**	**29[4]**
Dose:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	-	-	-
Day:		**0**		**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**	**378**	**392**
Clinical Laboratory Testing[16]	X	X			X		X			X				X		X			X			X			X			X	X		X
12-Lead ECG	X	X								X						X						X						X	X		X
Prior (4 weeks) and Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAE Attack Data[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessments[18]																																
EQ-5D-5L		X			X		X			X		X		X		X			X			X			X			X			X
SF-12		X			X		X			X		X		X		X			X			X			X			X			X
AE-QoL		X			X		X			X		X		X		X			X			X			X			X			X
HADS		X			X		X			X		X		X		X			X			X			X			X			X
WPAI-GH		X			X		X			X		X		X		X			X			X			X			X			X
DX-2930 Injection Report[19]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

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Visit:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28[3]**	**29[4]**
Dose:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**-**	**-**	**-**
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DX-2930 Self-administration and SC Injection Survey [20]		X								X						X						X								
PK, PD Collection, & Plasma Anti-Drug Antibody Testing[21]		X								X						X						X						X		X
Discharge from Study																															X

AE-QOL = Angioedema Quality of Life; ECG = Electrocardiogram; EQ-5D-5L = EuroQoL 5-Dimensional 5-Level; HADS = Hospital Anxiety and Depression Scale; PK = Pharmacokinetic; PD = Pharmacodynamic; SF-12 = Short Form-12; WPAI-GH = Work Productivity and Activity Impairment – General Health

NOTE: Shaded columns represent scheduled in-site visits for all subjects. Non-shaded columns indicate potential subject-elected off-site activity and/or self-administration dosing.

NOTE: "( )"s indicate activities that may occur as applicable (ie, activities for rollover subjects)

1. Screening visit is for non-rollover subjects only. Screening visit can occur up to 28 days prior to first open-label dose.
2. Study site personnel will contact rollover subjects approximately every 7 days following the first dose of open-label DX-2930 to solicit for any HAE attacks not already reported. Site check-in with rollover subjects will continue until the subject receives their second open label dose.
3. Visit 28 is a site check-in call for all rollover and non-rollover subjects.
4. Subjects who terminate from the study early will undergo (if possible) all of the assessments and procedures at Visit 29, the final study visit.
5. Rollover subjects must sign informed consent for Study DX-2930-04 on or after Day 168 of Study DX-2930-03.
6. For rollover subjects Day 182 of Study DX-2930-03 is also Day 0 of Study DX-2930-04 and informed consent may be completed on this visit, if not already provided.
7. Screened non-rollover subjects (adults and adolescents) who are on LTP with C1-INH therapy for HAE can continue their current LTP until Day 8 (or Day 15) such that subjects will have received 2 (or 4) doses of C1-INH. For subjects who are on attenuated androgens (eg, danazol) or anti-fibrinolytics (eg,

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Dose:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**-**	**-**	**-**
Day:		**0**		**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**	**378**	**392**

tranexamic acid), a similar tapering schedule is recommended. However, the taper can be prolonged by an additional week as long as androgen or anti-fibrinolytic therapy is stopped within 3 weeks of receiving the first dose of DX-2930.

8. For rollover subjects, the timing of Dose 2 for will vary by subject based on when their first HAE attack occurs following Dose 1. Following the first reported and investigator-confirmed attack, subjects will begin receiving regular SC administrations of 300 mg DX-2930 every 2 weeks.
9. A minimum of 10 days between the first and second open-label doses is required. If the second dose is to be administered within the accepted ±4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit unless that scheduled visit has already occurred. If that scheduled visit has already occurred, or if the second dose is to be administered outside of the accepted ± 4 day window around a scheduled visit, this visit will not replace any scheduled visit and will thus represent an acceptable, extra study visit (ie, an unscheduled visit). Regardless, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical examination (performed in accordance with standards at the site), clinical laboratory testing, PK, PD, and anti-drug antibody. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data.
10. All subjects (adolescent or adult) who are considered suitable candidates (ie, those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer DX-2930 after completing appropriate training by the investigator or designee and confirming their understanding. Subjects are allowed to initiate home self-administration after receiving the first 2 doses of DX-2930 at the study site and may elect to self-administer subsequent doses of DX-2930 at the investigational site (during scheduled study site visits; shaded columns).
11. Subjects may self-administer DX-2930 at home or other agreed upon location (during optional off-site self-administration visits; non-shaded columns). Site personnel will call subjects within approximately 3 days of the planned self-administration to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.
12. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment unless already collected as part of Study DX-2930-02 or Study DX-2930-03.
13. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 must be urine-based to confirm eligibility prior to first dose. Tests performed at screening and on indicated visits can be serum or urine-based.
14. There is a recommended ± 15 minute window for all vital signs. Vital signs will be obtained prior to dosing and 1 hour after dosing. Monitoring of vital signs will not be performed for subjects who elect to self-administer away from the investigative site at optional off-site visits (indicated non-shaded

Table 1 Study Activities Schedule

Study Activities Schedule																															
Tests and Assessments		**Treatment Period ± 4 days for each visit**																													**Follow-up ±4 Days for each visit**
Non-rollover	**Screen Visit[1]**			Shaded columns: scheduled in-site visits																											
Rollover	**-**		**Check-in[2]**	Non-shaded columns: potential subject-elected off-site activity and/or self-administration dosing																											
Visit:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28[3]**	**29[4]**
Dose:		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**-**	**-**	**-**
Day:		**0**		**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**	**378**	**392**

columns).

15. Physical examinations, including weight, will be conducted for all rollover and non-rollover subjects according to the study activities schedule and in accordance with standards at the site. In addition to the physical examinations specified in the study activities schedule, an additional physical examination (performed in accordance with standards at the site) will be conducted for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs. Height will be collected at the Screening visit only.
16. Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis (urinalysis does not need to be done as part of the clinical laboratory testing at Visits 14, 17, 20, and 23). Clinical laboratory testing will be conducted for all rollover and non-rollover subjects according to the study activities schedule. In addition to the testing specified in the study activities schedule, additional testing will be conducted for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs.
17. Historical HAE attack information will be collected at screening. During the study, subjects (or caregivers) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. During study visits, study site personnel will solicit for any new HAE attack information that has not already been reported to the site.
18. Quality of life data will be obtained using the EQ-5D-5L, SF-12, AE-QoL, HADS, and WPAI-GH.
19. Collect subject's injection reports of their experience with DX-2930 self-administration and subcutaneous administration for all doses.
20. Collect subject's injection surveys of their experience with DX-2930 self-administration and subcutaneous injection for indicated visits.
21. PK, PD, and anti-drug antibody samples will be drawn for all rollover and non-rollover subjects according to the study activities schedule. In addition to the samples specified in the study activities schedule, an additional PK, PD and anti-drug antibody sample will be drawn for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAE	Acquired angioedema
ACE	Angiotensin converting enzyme
AE	Adverse event
AESI	Adverse Event of Special Interest
AE-QoL	Angioedema Quality of Life Questionnaire
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C1-INH	C1 inhibitor
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
C_{max}	Maximum plasma drug concentration
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRO	Clinical Research Organization
DMID	Division of Microbiology and Infectious Diseases
DP	Drug product
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EQ-5D-5L	EuroQoL 5-Dimensional 5-Level; a standardized instrument for use as a measure of health outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HAE	Hereditary angioedema

HMWK	High molecular weight kininogen
HR	Heart rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G subclass 1
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone releasing systems
IV	Intravenous
K_i	inhibition constant
LTP	Long-term prophylactic/Long-term prophylaxis
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Prothrombin time
PVRM	Pharmacovigilance and Risk Management
QoL	Quality of life
REB	Research ethics board
RBC	Red blood cell (count)
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SC	Subcutaneous
SF-12	Short Form-12; a multi-purpose short form health survey with 12 questions
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SMQ	Standard MedDRA query
SOC	System Organ Class
SOP	Standard operating procedure
TEAE	Treatment-Emergent Adverse Event
US	United States
WBC	White blood cell (count)
WPAI-GH	Work Productivity and Activity Impairment – General Health

1. INTRODUCTION

1.1 DX-2930

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 hereditary angioedema (HAE), a serious and life-threatening disease.

1.2 Hereditary Angioedema

HAE is a long-term, debilitating, and life-threatening disease caused by mutations in the C1-inhibitor (C1-INH) gene, resulting in deficiency or dysfunction of C1-INH protein. HAE manifests clinically as unpredictable, intermittent attacks of subcutaneous or submucosal edema of the face, larynx, gastrointestinal tract, limbs and/or genitalia (Zuraw, 2008). Swelling may last up to five or more days; most patients suffer multiple attacks per year. HAE is an orphan disorder. The exact prevalence of HAE is unknown, but current estimates range from 1 per 10,000 to 1 per 150,000 persons, with many authors agreeing that 1 per 50,000 is likely the closest estimate (Bygum, 2009; Goring et al., 1998; Lei et al., 2011; Nordenfelt et al., 2014; Roche et al., 2005).

Swelling in the larynx can obstruct the airways and cause death from asphyxiation (Bork et al., 2000; Bork et al., 2012). Approximately 50% of all patients with HAE will experience a laryngeal attack in their lifetime, and there is no way to predict which patients are at risk of a laryngeal attack (Bork et al., 2003; Bork et al., 2006).

Abdominal attacks are often associated with nausea, vomiting, diarrhea, and severe pain; intestinal symptoms resembling abdominal emergencies may lead to unnecessary surgery (Zuraw, 2008).

Approximately 85% of patients with HAE have Type I HAE, characterized by very low production of functionally normal C1-INH protein, while the remaining approximately 15% of patients with HAE have Type II HAE and produce normal or elevated levels of a functionally impaired C1-INH (Zuraw, 2008). In patients with Types I and II HAE, uncontrolled plasma kallikrein generation results in excess bradykinin release from high-molecular weight kininogen (HMWK) and vascular leak mediated by bradykinin binding to the B2 receptor (B2-R) on the surface of endothelial cells (Zuraw, 2008). Clinical suspicion of Types I and II HAE can be confirmed by available blood tests. In addition to abnormalities in C1-INH level and function, plasma C4 levels are often reduced in blood from most patients with HAE.

1.3 Therapeutic Rationale for DX-2930

Plasma kallikrein plays a critical role in the pathogenesis of HAE attacks (Davis, 2006; Kaplan and Joseph, 2010). In normal physiology, C1-INH regulates the activity of plasma kallikrein as well as a variety of other proteases, such as C1r, C1s, factor XIa, and factor XIIa. Plasma kallikrein regulates the release of bradykinin from HMWK. Due to a deficiency of C1-INH in HAE, uncontrolled plasma kallikrein activity occurs and leads to the excessive generation of bradykinin. Bradykinin is a vasodilator which is thought to be responsible for the characteristic

HAE symptoms of localized swelling, inflammation, and pain (Craig et al., 2012; Zuraw et al., 2013). Intervening at the level of bradykinin production with a plasma kallikrein inhibitor therefore represents an attractive and rational therapeutic strategy for HAE. Indeed, the importance of plasma kallikrein as a drug target in HAE has been validated through the observed effectiveness of Kalbitor® (ecallantide), a peptide that specifically targets plasma kallikrein, which was approved by the FDA for the treatment of acute HAE attacks (Kalbitor®, 2015).

DX-2930 is a highly potent and specific inhibitor of plasma kallikrein (K_i = 125 pM). X-ray crystallography of DX-2930 combined with plasma kallikrein demonstrates DX-2930 binding to the active site of kallikrein (Kenniston et al., 2014).

1.4 Safety Rationale for DX-2930

Safety data from the Phase 1a clinical study, a first-in-human study with DX-2930 in healthy subjects, did not identify any safety concerns. Single doses up to 3 mg/kg of DX-2930 were well-tolerated. There were no dose-limiting toxicities, serious adverse events, or any other safety concerns identified.

Pharmacokinetic (PK) data from the Phase 1a (DX-2930-01) and Phase 1b (DX-2930-02) clinical studies in conjunction with data from the nonclinical toxicity studies support a wide safety margin. The mean C_{max} for human subjects treated at a dose of 300 mg on Days 1 and 15 was approximately 27 µg/mL. As comparison, a mean C_{max} of 744 µg/ mL was observed following dosing of monkeys with 50 mg/kg DX-2930 subcutaneous (SC) weekly for 6 months resulting in a safety margin of approximately 28-fold. No toxicologically significant findings were observed in these treated animals or in any other nonclinical toxicity study to date for systemically administered DX-2930.

Safety data is also available from the Phase 1b study (DX-2930-02), a multiple-ascending dose study in patients with HAE. In this study, two doses of DX-2930 up to 400 mg administered 14 days apart were well-tolerated. There were no dose-limiting toxicities, serious adverse events in any DX-2930 treated subjects, or any other safety concerns identified in this study of patients with HAE. Pharmacokinetic data from the 1b study found that the drug exposure following two administrations of DX-2930 (up to a maximum of 400 mg) was substantially less than that attained and evaluated in the nonclinical toxicity studies.

For additional detail regarding the safety rationale for DX-2930, please refer to the DX-2930 Investigator's Brochure.

1.5 DX-2930 Non-Clinical Pharmacology and Toxicology

For more detail regarding the nonclinical findings, please refer to the DX-2930 Investigator's Brochure.

1.6 DX-2930 Clinical Data

The clinical development program to date for DX-2930 consists of 2 studies to evaluate the safety, tolerability, and PK of DX-2930, including one completed Phase 1a single-ascending

dose study in healthy subjects and a Phase 1b multiple-ascending dose study in patients with HAE. These studies are summarized in the following sections.

1.6.1 Single-Ascending Dose Study in Healthy Subjects (DX-2930-01)

DX-2930-01 was a Phase 1a randomized, double-blind, placebo-controlled study in healthy subjects to evaluate the safety, tolerability, and PK following a single, SC dose of DX-2930. Participating subjects were randomized to receive placebo or active study drug within one of the following sequential, ascending dose cohorts: 0.1, 0.3, 1.0, or 3.0 mg/kg. For each dosing cohort, 6 subjects were randomized to receive active drug and 2 subjects to receive placebo.

A total of 32 subjects enrolled in the study and were randomized. The treatment groups were well balanced for demographic characteristics. The actual dose of DX-2930 administered to subjects ranged from 6.2 mg (in the 0.1 mg/kg group) to 300 mg (in the 3.0 mg/kg group) across all cohorts.

Based on the safety analysis, a single administration of DX-2930 was well tolerated up to doses of 3.0 mg/kg without evidence of dose-limiting toxicity. There were no deaths, SAEs, or subject discontinuations due to adverse events (AEs) during the study. Furthermore, there was no significant imbalance between placebo and DX-2930 for any particular treatment-emergent adverse event (TEAE). The most commonly reported TEAE was headache, which occurred at a rate of 25% for both DX-2930 and placebo.

The PK profile demonstrated linear, dose-dependent drug exposure with a mean half-life of approximately 17 to 21 days across dose groups. Results from two exploratory biomarker assays provide evidence for an important pharmacodynamic effect of DX-2930 in humans.

For additional detail regarding the single dose, clinical study in healthy subjects, please refer to the DX-2930 Investigator's Brochure.

1.6.2 Multiple-Ascending Dose Study in HAE Patients (DX-2930-02)

DX-2930-02 was a Phase 1b randomized, double-blind, placebo-controlled, multiple ascending-dose study in patients with HAE to evaluate safety, tolerability, and PK of SC DX-2930. Participating subjects were randomized 2:1 to receive either active study drug or placebo within one of the following sequential, ascending dose cohorts: 30, 100, 300, or 400 mg (nominal 6 subjects per cohort). Each subject received 2 doses of study drug separated by 14 days.

A total of 37 subjects were randomized and treated with DX-2930 or placebo. One subject in the 400 mg dose group received a single dose of DX-2930 and, following several unsuccessful attempts to schedule their second dose, was replaced. This subject returned for a single follow-up visit before being lost to follow-up for reasons not related to the study. Routine C1-INH testing revealed that one other subject did not have HAE Type I or II, despite a historical lab test indicating otherwise.

Subject demographics were balanced in terms of age, race, ethnicity and BMI. There were slightly more females in the DX-2930 group than in the placebo group (66.7% versus 53.8%).

The most common AEs reported were HAE attacks, injection site pain, and headache. The rates were not appreciably higher in the DX-2930 subjects compared to placebo. Two subjects were reported to have 3 related severe TEAEs. One of these was a DX-2930 subject (30 mg) with injection site pain lasting 1 minute and one was a DX-2930 subject (400 mg) with worsening headache lasting 1 minute and night sweats.

No safety signals were identified for vital signs, physical examinations, clinical laboratory tests, or electrocardiograms (ECG). Results suggested DX-2930 was well tolerated in this study with no evidence of dose-limiting toxicity at doses up to 400 mg.

A total of 3 out of 92 post-dose samples (3.3%), obtained from 2 out of 23 subjects (8.7%), were confirmed to be anti-drug antibody-positive. No samples were positive for neutralizing activity.

The pharmacokinetic analysis for all subjects in the 30, 100, 300, and 400 mg doses showed drug levels in HAE subjects were dose-dependent and exhibited a prolonged half-life of approximately 2 weeks, typical of a human monoclonal antibody. C_{max} drug levels increased with increasing dose, as expected. These parameters were consistent with values obtained in healthy subjects in Study DX-2930-01.

A Western blot assay showed pre-dose baseline levels of mean 2-chain HMWK in unactivated plasma collected from patients with HAE was approximately 50%. A statistically significant reduction in 2-chain HMWK levels was observed on study days 8 and 22 in the 300 and 400 mg dose groups compared to pre-dose levels, and approached levels similar to that observed in healthy subjects. This outcome demonstrated the pharmacodynamic activity of DX-2930 and its ability to effectively normalize the instability of HAE plasma in this assay.

Primary efficacy analyses were based on subjects in the 300 mg, 400 mg, and placebo dose groups who reported having at least 2 attacks in the 3 months prior to study entry (0.15 attacks/week). Of those subjects treated with 300 or 400 mg DX-2930, 15 of 16 subjects met these criteria. Of the placebo treated subjects, 11 of 13 subjects met these criteria.

The baseline HAE attack rates (attacks/week) were 0.39 attacks per week in the placebo group, 0.33 attacks per week in the 300 mg group, 0.55 attacks per week in the 400 mg group and 0.49 attacks per week in the 300 and 400 mg combined group. During the pre-specified, primary efficacy interval of 6 weeks (from days 8 to 50; corresponding to a period of notable drug exposure), the HAE attack rate, adjusted for baseline attack rate, was 0 in the 300 mg group and 0.045 attacks per week in the 400 mg group, compared to 0.37 attacks per week in the placebo group. This resulted in a 100% reduction vs placebo for the 300 mg DX-2930 group ($P < 0.0001$) and an 88% reduction vs placebo for 400 mg DX-2930 ($P = 0.005$). During this primary efficacy interval, 100% of subjects in the 300 mg group ($P = 0.026$) and 82% of subjects in the 400 mg group ($P = 0.03$) were attack-free compared with 27% of subjects in the placebo group.

The data from this study demonstrated proof of concept of the ability of DX-2930 to prevent acute attacks of HAE. A statistically significant finding of HAE attack prevention by DX-2930 was observed. DX-2930 was well tolerated in HAE subjects up to 400 mg. Drug exposure appeared to be dose-proportional and consistent with the results obtained in healthy subjects in

Study DX-2930-01. Pharmacodynamic effect assays provided evidence that DX-2930 has a direct effect on plasma kallikrein activity in patient plasma.

For additional detail regarding Study DX-2930-02, please refer to the DX-2930 Investigator's Brochure.

1.7 Rationale for Open-Label Extension Study DX-2930-04

The open-label DX-2930 extension study will be preceded by the initiation of a pivotal, multi-center, double-blind, randomized, placebo-controlled parallel-arm study (Study DX-2930-03) evaluating the efficacy of DX-2930 in preventing acute angioedema attacks in patients with Type I or Type II HAE. Further information on Study DX-2930-03 design can be found in Appendix 5.

Subjects who complete the Study DX-2930-03 treatment period will be offered the option of rolling into the open-label extension study, Study DX-2930-04. In addition, a limited number of individuals with HAE Type I or Type II who were not enrolled in Study DX-2930-03 (up to approximately100) will be also enrolled.

The rationale for this open-label extension study is to evaluate the long-term safety of repeated subcutaneous treatment with DX-2930 and the long-term efficacy of DX-2930 in preventing HAE attacks. For subjects rolling over from DX-2930-03 who were randomized to one of the active study arms, the total duration of exposure across both studies will cover 18 months. For rollover subjects randomized to placebo in DX-2930-03, and for non-rollover subjects, the total duration of exposure will cover 12 months. Combined, the overall exposure between Study DX-2930-03 and Study DX-2930-04 will provide a sizable dataset to evaluate DX-2930 as a life-long, chronic treatment for preventing acute attacks of HAE.

This study seeks to evaluate the outer bounds of DX-2930 dosing frequency (possibly beyond 2 to 4 weeks) by assessing the duration of time between a rollover subject's first open-label dose and their first reported HAE attack. In addition, characteristics of all HAE attacks will be reported and compared to the subject's historical baseline (for non-rollover subjects) or attack history based on attacks reported in Study DX-2930-03 (for rollover subjects).

For non-rollover subjects, the study will evaluate the safety and efficacy of switching from a long-term prevention therapy (eg, C1-INH, anti-fibrinolytics, androgens) to DX-2930 dosing, while evaluating breakthrough attack characteristics compared to historical baseline both prior to and during co-administration with their LTP therapy regimen and while receiving DX-2930 alone.

For all subjects, the study will also assess immunogenicity of chronically administered DX-2930, PK and PD, subject health-related quality of life (QoL), subject experience with self-administration, and ease of SC administration with DX-2930.

2. STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the long-term safety of repeated subcutaneous (SC) administrations of DX-2930

2.2 Secondary Objectives

- To evaluate the long-term efficacy of DX-2930 in preventing HAE attacks
- To characterize the outer bounds of dosing frequency for DX-2930

2.3 Tertiary Objectives

- To assess the immunogenicity of chronically administered DX-2930
- To evaluate the effect of DX-2930 on health-related quality of life (QoL)
- To characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profile of SC administration of DX-2930
- To evaluate safety and efficacy in the non-rollover population of switching from long-term prophylactic (LTP) treatment to DX-2930
- To evaluate breakthrough attack characteristics while receiving DX-2930 compared to historical baseline
- To evaluate subject experience with self-administration of DX-2930 including ease of SC administration of DX-2930

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Overview

Study DX-2930-04 is an open-label, long term safety and efficacy extension study of DX-2930-03, to evaluate the investigational medicinal product (IMP), DX-2930, in preventing acute angioedema attacks in patients with Type I and Type II HAE. There are two types of subjects who will be enrolled into this study:

- Subjects who rollover from Study DX-2930-03
- Subjects who are non-rollover (ie, were not participants in Study DX-2930-03)

Rollover Subjects

Rollover subjects are subjects who complete the double-blind treatment period at Day 182 of Study DX-2930-03 and consent to enter Study DX-2930-04. Subjects who discontinue from Study DX-2930-03 after enrollment are not eligible to enroll in Study DX-2930-04.

Subjects should be asked about their interest in Study DX-2930-04 after enrollment into Study DX-2930-03 to anticipate enrollment and preparedness for Study DX-2930-04. Willing subjects must sign informed consent for Study DX-2930-04 on or after Day 168 of Study DX-2930-03.

Subjects who are eligible to roll over into Study DX-2930-04 but elect not to, may not enroll in Study DX-2930-04 at a later time. The first Study DX-2930-04 visit for rollover subjects (Day 0) will occur on the same day as Study DX-2930-03 Day 182 study visit. Rollover subjects will complete all Study DX-2930-03 final study assessments (Day 182) at which time they will be discharged from that study. No assessments conducted between Study DX-2930-03 Day 182 study visit and the first Study DX-2930-04 visit (Day 0) will be duplicated. Results of the final DX-2930-03 assessments on Day 182 will be used as the pre-dose results for Day 0 of Study DX-2930-04.

All subjects, caregivers, investigators and study site personnel will remain blinded to the DX-2930-03 treatment assignment until the conclusion of Study DX-2930-04.

Non-rollover subjects

At least 50 subjects (to approximately 100) who were not participants in Study DX-2930-03 will be permitted to enroll if they meet the eligibility requirements. Subjects who screen fail out of Study DX-2930-03 for not meeting the minimum attack requirements during the run-in period must wait until enrollment for the double-blind study has ended before they can screen for Study DX-2930-04. The Sponsor may ease this restriction based on the enrollment rate observed in Study DX-2930-03. Subjects who are still in the run-in period for Study DX-2930-03 when enrollment for that study closes, as well as subjects on prior LTP who screen fail out of Study DX-2930-03 due to an inability to wash-out of their LTP, may screen for Study DX-2930-04 following discussion with the Sponsor medical monitor.

Screening Period:

Rollover subjects

There is no screening period for rollover subjects.

Non-rollover subjects

Non-rollover subjects must provide informed consent and have screening assessments completed within 4 weeks prior to their first open-label dose. Screened non-rollover subjects (adults and adolescents) who are on LTP with C1-INH therapy for HAE can continue their current LTP until Day 8 (or Day 15) such that subjects will have received 2 (or 4) doses of C1-INH. For subjects who are on attenuated androgens (eg, danazol) or anti-fibrinolytics (eg, tranexamic acid); a similar tapering schedule is recommended. However, the taper can be prolonged by an additional week, if medically indicated, as long as androgen or anti-fibrinolytic therapy is stopped within 3 weeks of receiving the first dose of DX-2930.

Treatment Period:

Rollover Subjects

Following informed consent and pre-dose assessments, rollover subjects will receive a single open-label dose of DX-2930 administered subcutaneously (SC) on Day 0. Subjects will not receive any additional DX-2930 doses until their first reported and investigator confirmed HAE attack. As such, the total number of doses within the treatment period will vary by rollover subject.

The duration of time between the first open-label dose and first reported HAE attack will vary by rollover subject. All rollover subjects must adhere to the Study Activities Schedule, for the entire duration of the study. However, until a rollover subject reports their first HAE attack, only scheduled study visits where the following tests and assessments are performed must be conducted at the investigative site: pregnancy testing, clinical laboratory testing, physical examination, 12-Lead ECG, QoL, PK, PD and anti-drug antibody sample collection. All other scheduled study visits may be conducted via site check-in calls to collect information on adverse events, concomitant therapy, and HAE attack data. See Study Activities Schedule for which visits must be conducted at the study site.

Once a rollover subject reports their first HAE attack they will present to the investigative site for their second open-label dose of DX-2930 as quickly as subject and site schedules allow. If the second dose is to be administered within the accepted ± 4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit. If that scheduled visit has already occurred, the day of the visit will be considered an acceptable, extra study visit.

In the event that the second dose is to be administered outside of the accepted ±4 day window around a scheduled visit, the day of the visit will be considered an acceptable extra study visit (ie, this visit will not replace any scheduled visit).

Regardless of the study day, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical examination, clinical laboratory testing, and blood sampling for PK, PD, and anti-drug antibody. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data.

Regardless of when a rollover subject's first HAE attack occurs, there will be a minimum of 10 days between their first open-label dose and their second open-label dose. Following their second open-label dose, rollover subjects will continue to receive repeated SC administrations of open-label DX-2930 every 2 weeks for the remaining duration of the treatment period per the scheduled dosing in the Study Activities Schedule. The treatment period will last 364 days from the date of the first open-label dose. The number of doses administered during this period will vary by subject based on the date of each subject's second dose, but will not exceed 26 doses. The Day 350 study visit is the last visit at which a dose may be administered.

Non-rollover Subjects
Once all screening assessments have been completed and eligibility confirmed, non-rollover subjects will arrive at the study site and, following pre-dose assessments, receive an open-label dose of 300 mg DX-2930 administered SC on Day 0. Non-rollover subjects will continue to receive SC administrations of open-label 300 mg DX-2930 every 2 weeks throughout the duration of the treatment period per the scheduled dosing in the Study Activities Schedule. A total of 26 doses will be administered with the last dose administered at the Day 350 study visit.

All Subjects:
All doses (with the exception of the second dose for rollover subjects) require a minimum of 10 days and maximum of 18 days between administrations, and should fall within the accepted ± 4 day window around study visits.

After the second DX-2930 dose is given either within the study window (±4 days) or an acceptable extra study visit, the 3rd dose must be administered at the next pre-defined study visit according to the schedule of assessments.

If a subject experiences an acute angioedema attack at any time during the study that in the opinion of the investigator requires medical intervention, standard of care therapy should be provided based on subject's medical history and per locally approved product information. Administration of DX-2930 and study procedures will continue without alteration to the protocol study activities schedule, even if a subject receives treatment for a breakthrough angioedema attack on the day of a scheduled dose of study drug (if self-administering) or scheduled study visit.

Self-Administration

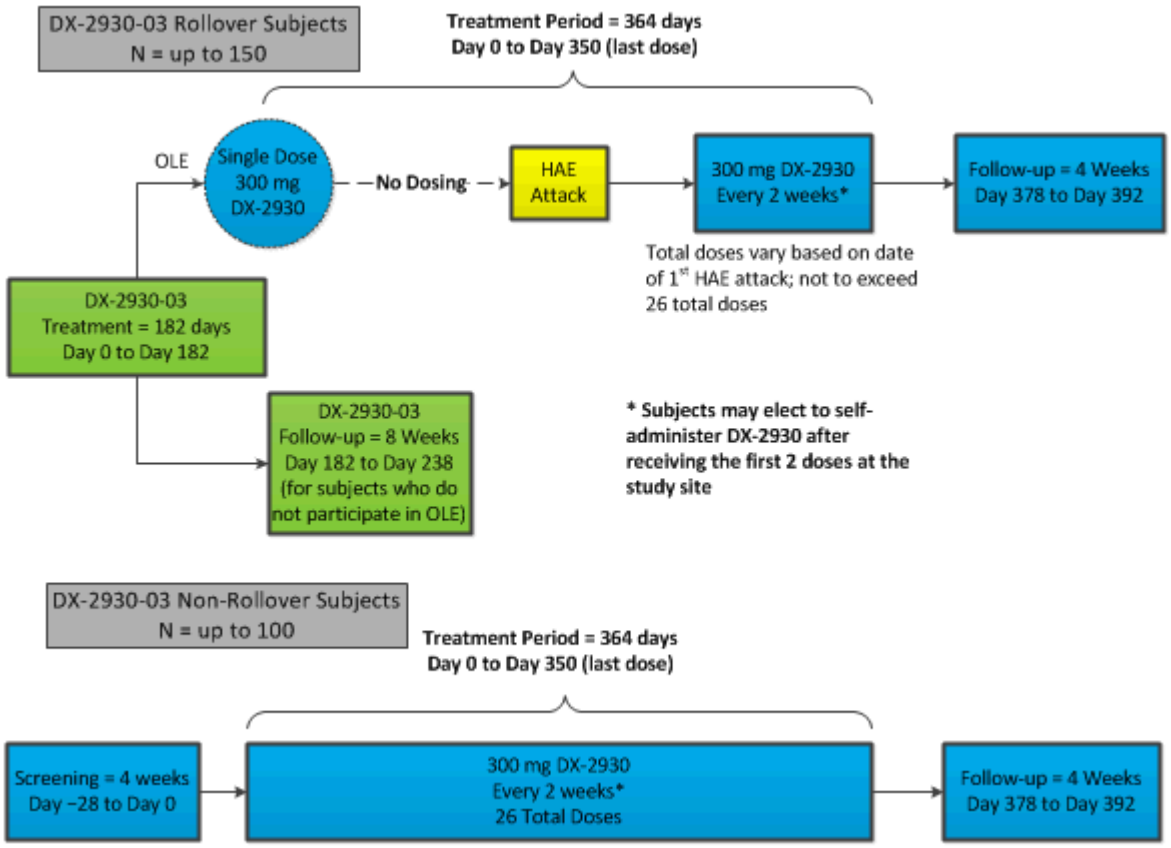
All subjects (adolescent or adult) who are considered suitable candidates (ie, those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer treatment. Subjects must complete appropriate training by the investigator or designee and have their understanding of the procedures confirmed by the investigator or designee. Subjects are allowed to initiate self-administration at the subject's home or other agreed upon

location after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may self-administer subsequent doses of DX-2930 at the investigational site (when visits are scheduled study site visits) or the subject's home or other agreed upon location (when the study permits off-site dosing). See the Schedule of Activities for details. Adolescent subjects self-administering DX-2930 will be supervised by a parent/legal guardian/caregiver. Alternatively, a parent/legal guardian/caregiver, after completing appropriate training, will be allowed to administer the investigational product to an adolescent without study site personnel supervision. Site personnel will call subjects within approximately 3 days of the planned off-site self-administrations to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented. Throughout the study, study site personnel will document information in source documents (ie, the subject's medical record) and eCRF regarding the subject's experience with self-administration and SC administration of DX-2930.

Follow-up Period

After completion of the treatment period, all subjects will undergo safety evaluations during a 4-week follow-up period. Figure 1 shows a schematic of the open-label extension study.

Figure 1 Schematic of the Open-Label Extension Study



Modifications to Open-Label Dosing

If, at any time, an important dose-related safety signal is identified either from this study or Study DX-2930-03, the Sponsor may decide to switch the enrolled subjects who have not yet completed the treatment period, and any subsequent subjects, to receive a different open-label dose and/or frequency.

In addition, based on the results of Study DX-2930-03, the Sponsor may switch to a different dose and/or frequency.

3.1.2 Stopping Rules

3.1.2.1 Study Level Stopping Rules

Safety data, including SAEs and AESI, will be monitored regularly throughout the duration of the study. If any potential safety signal is identified as a result of monitoring in this study, or from any safety findings from Study DX-2930-03, or following DSMB review, the Sponsor may take actions as deemed appropriate, including suspending dosing in the study, while the potential risk is evaluated and a course of action has been determined.

3.1.2.2 Individual Stopping Rules

Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or DX-2930-related, clinically significant non-serious AE) that, in the assessment of the investigator or DSMB recommendation, warrants discontinuation from further dosing for that subject's well-being. The investigator has the ability to contact and consult with the Medical Monitor on such matters. Subjects will continue to be followed through the completion of all scheduled non-dosing visits, unless they request to be discontinued from the study.

3.1.3 Follow-up for Subjects Meeting Stopping Criteria

Subjects that develop either an SAE or other toxicity considered clinically relevant (AE, laboratory, physical examination, vital sign, or ECG finding) will be carefully monitored until resolution, which may include the following:

- Additional clinical laboratory tests and/or other clinical investigations
- Additional visits or extended duration of follow-up
- Obtaining a specialist consultation

3.2 Rationale for Open-Label Extension Dose Selection

The dose selected for the open-label extension (300 mg every 2 weeks) is anticipated to be effective and safe as determined in the pivotal, double-blind DX-2930-03 study. If at any time an important dose-related safety signal is identified either from this study or Study DX-2930-03, the Sponsor may decide to switch the enrolled subjects who have not yet completed the treatment period, and any subsequent subjects, to receive a different open-label DX-2930 dose and/or frequency.

Additionally, based on the efficacy results of Study DX-2930-03, the Sponsor may switch to a different dose and/or frequency.

3.3 Individual Subject Dosing and Follow-Up

All subjects will receive open-label DX-2930 during a 364 day treatment period. The number of doses that rollover subjects receive during this period will vary by subject but will not exceed 26 doses. The last dose of open-label DX-2930 administered to these subjects may be given at the Day 350 study visit. Non-rollover subjects will receive DX-2930 every 2 weeks for a total of 26 doses, with the first dose administered on Day 0 and the final dose administered at the Day 350 study visit.

There will be a ±4 day window around each study visit. There will be a minimum of 10 days between any two doses. Excluding the time interval between the first and second open-label doses for rollover subjects, there will be a maximum of 18 days between any two doses. Subjects will be monitored at the study site through 1 hour post-dose.

All subjects (adolescent or adult) who are considered suitable candidates (ie, those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer treatment after completing appropriate training by the investigator or designee and confirming their understanding. Subjects are allowed to initiate self-administration at the subject's home or other agreed upon location after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may continue to self-administer subsequent doses of DX-2930. Subjects who elect to self-administer investigational product will be provided the necessary supplies (see Section 5.7 and Section 6.15.1).

3.4 Study Duration for Individual Subjects

Following informed consent, subjects will either rollover from Study DX-2930-03 or undergo screening assessments (non-rollover subjects). Screening assessments for non-rollover subjects must occur within 4 weeks prior to the first open-label dose. Eligible subjects will be enrolled and undergo a 364 day treatment period. At the conclusion of the treatment period, subjects will be followed for an additional 4 weeks.

4. STUDY POPULATION SELECTION

4.1 Study Population

The study is expected to enroll subjects from Study DX-2930-03, as well as at least 50 (to approximately100) additional subjects who were not enrolled in Study DX-2930-03. The total enrollment is expected to be at least 150, but not more than 250 HAE Type I or II subjects. Subjects will be 12 years of age or older who experience at least 1 attack per 12 weeks. HAE diagnosis will be confirmed through documented clinical history and diagnostic testing conducted either during screening or during participation in Study DX-2930-02 or Study DX-2930-03.

The subject population includes subjects who are 12 to 17 years old. Like adults, children with HAE can suffer from recurrent and debilitating attacks. Symptoms may present very early in childhood, and upper airway angioedema has been reported in patients with HAE as young as the age of 3 (Bork et al., 2003). In one case series of 49 pediatric patients with HAE, 23 had suffered at least one episode of airway angioedema by the age of 18 (Farkas, 2010). An important unmet medical need exists among children with HAE, especially adolescents, since the disease commonly worsens after puberty (Bennett and Craig, 2015; Zuraw, 2008). The study will aim to enroll at least 15 subjects who are 12 to 17 years of age, inclusive of the estimated 10 subjects 12 to 17 years old who are expected to roll over from Study DX-2930-03.

4.2 Inclusion Criteria

Subjects must meet the following criteria to be enrolled in this study:

1. Male and female HAE subjects who are 12 years of age or older at the time of screening.

2. Documented diagnosis of disease HAE (Type I or II) based on all of the following:

    - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).

    - Diagnostic testing results obtained during screening (or a prior DX-2930 study) that confirm HAE Type I or II: C1 inhibitor (C1-INH) functional level < 40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may be retested if results are incongruent with clinical history or believed by the investigator to be confounded by LTP use.

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

3. A historical baseline HAE attack rate of at least 1 attack per 12 weeks.

4. Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects age 12 to 17, whose caregiver has provided informed consent, are willing and able to read, understand and sign an assent form.

5. Males and females who are fertile and sexually active must adhere to contraception requirements for the duration of the study as follows:

   - Females* of childbearing potential must agree to be abstinent or it is recommended to use highly effective forms of contraception from the screening period through 30 days after the final study visit. This includes stable doses (for 3 months prior to study screening) of combined estrogen and progestin-containing hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable), progestin-only hormonal contraception associated with inhibition of ovulation, intra-uterine device (IUD, all types) or intrauterine hormone releasing systems (IUS). Notes: 1) A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. 2) Use of a male condom with or without spermicide or cervical cap, diaphragm or sponge with spermicide or a combination (double barrier methods) are not considered highly effective.

   - Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.

   - Males, including males who are surgically sterile (post vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study visit.

     *NOTE: Female rollover subjects (those who previously participated in Study DX-2930-03) of childbearing potential may continue to use the birth control method used during Study DX-2930-03.

4.3 Exclusion Criteria

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

1. Discontinued from Study DX-2930-03 after enrollment for any reason.

2. If rolling over from Study DX-2930-03, presence of important safety concerns that would preclude participation in this study.

3. Concomitant diagnosis of another form of chronic, recurrent angioedema such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.

4. Dosing with an investigational drug (not including DX-2930 or other HAE therapies) or exposure to an investigational device within 4 weeks prior screening.

5. Exposure to angiotensin-converting enzyme (ACE) inhibitors within 4 weeks prior to screening or any newly initiated or dose modification of estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) 3 months prior to the screening visit.

6. Unwilling to discontinue use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 3 weeks after starting DX-2930 treatment.

7. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's Syndrome).

8. Pregnancy or breastfeeding.

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

5. STUDY TREATMENT(S)

5.1 Description of Treatment(s)

For detailed information regarding open-label DX-2930 (lanadelumab) administration, refer to the Pharmacy Manual.

DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated using the following compendial components: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Polysorbate 80. Each open-label vial contains a nominal concentration of 150 mg DX-2930 active ingredient in 1 mL solution.

For each 300 mg dose of DX-2930, each subject will receive a total of 2 mL (2 vials), which will be administered in a single 2 mL SC injection. The injection will be given in the upper arm, thigh or abdomen.

Self-Administration
All subjects (adolescent or adult) who are considered suitable candidates (ie, those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer treatment after completing appropriate training by the investigator or designee and demonstrating the comprehension to self-administer. Subjects are allowed to initiate self-administration at the subject's home or other agreed upon location after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may continue to self-administer subsequent doses of DX-2930 at the investigational site (when visits are scheduled study site visits) or the subject's home or other agreed upon location (when the study permits off-site dosing). See Schedule of Activities for details. Adolescent subjects self-administering investigational product will be supervised by a parent/legal guardian/caregiver. Alternatively, a parent/legal guardian/caregiver, after completing appropriate training, will be allowed to administer DX-2930 to an adolescent without study site personnel supervision. Site personnel will call subjects within approximately 3 days of the planned off-site self-administrations to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.

Throughout the study, study site personnel will document information in the subject's medical record and eCRF regarding the subject's experience with self-administration and SC administration of DX-2930.

5.2 Dosing and Follow-Up Scheme

Details of subject dosing and follow-up are outlined in Section 3.1.1 and included in the Study Activities Schedule, Table 1.

Rollover subjects will receive their first open label SC dose of DX-2930 on Day 0. Subjects will not receive any additional DX-2930 doses until their first reported HAE attack. The second dose of DX-2930 may be administered at an unscheduled visit if it is outside of the accepted ±4 day window around a scheduled visit. Following this attack subjects will receive open label SC doses

of DX-2930 every 2 weeks until the end of the treatment period. Subsequent dosing after Dose 2 requires a minimum of 10 days and a maximum of 18 days between administrations.

Regardless of when a rollover subject's first HAE attack occurs, there will be a minimum of 10 days between their first open-label dose and their second open-label dose. Following their second dose, rollover subjects will continue to receive repeated SC administrations of open-label 300 mg DX-2930 every 2 weeks for the remaining duration of the treatment period per the scheduled dosing in the Study Activities Schedule. The treatment period will last 364 days from the date of the first open-label dose. The number of doses administered during this period will vary by subject based on the date of each subject's second dose, but will not exceed 26 doses. The Day 350 study visit is the last visit at which a dose may be administered.

Non-rollover subjects will receive their first open-label dose SC dose of DX-2930 on Day 0 and will continue to receive SC administrations of open-label DX-2930 every 2 weeks throughout the duration of the treatment period. A total of 26 doses will be administered with the last dose administered at the Day 350 study visit.

After completion of the treatment period, all subjects will undergo safety evaluations during a 4-week follow-up period.

5.3 Method of Identifying Subjects

Subjects meeting all eligibility criteria will be enrolled in the study and sequentially assigned a unique site-based identification number.

5.4 Prior and Concomitant Therapy

For subjects not rolling over from Study DX-2930-03, reasonable efforts will be made to determine all relevant treatments received by the subject from 4 weeks prior to screening through the final study visit. For subjects rolling over from Study DX-2930-03, concomitant therapy use will be carried forward from that study and will continue to be collected through the final study visit.

All information on prior and concomitant therapy (including all prescription/non-prescription medications, herbal medications and vitamin supplements) must be recorded on the subject's eCRF and should include the name of the procedure or drug and duration of the treatment (start and stop dates). Concomitant treatments (non-pharmacological treatments) include any surgical or diagnostic procedures.

5.4.1 Allowed Therapies

The following therapies are allowed during the study:

- Therapies for co-existing conditions, including those for acute attacks of HAE, as described in Section 5.4.1.1 are permitted if not excluded in Section 5.4.2. The use of short-term prophylactic treatment for HAE will be permitted if medically indicated. Short-term (pre-

procedure) prophylaxis is defined as use of C1-INH to avoid angioedema complications from medically indicated procedures.

- Therapies to treat any AEs the subject experiences during the study are permitted.

5.4.1.1 Management of HAE Attacks

Acute HAE attacks during the study are to be managed in accord with the investigator's usual care of their patients, including use of acute attack therapies that the investigator deems as medically appropriate. Use of C1-INH will be permitted as an acute attack therapy but not as a LTP therapy. Administration of DX-2930 and study procedures will continue without alteration to the protocol-specified study schedule, even if the subject has symptoms of an HAE attack the day of DX-2930 administration and/or receives treatment for an HAE attack. The administration of DX-2930 can also be re-scheduled as long as the minimum and maximum timeframe between doses are met based on patient preference or physician discretion.

5.4.2 Excluded Concomitant Therapies

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

- Long-term prophylaxis for HAE (eg, use of C1-INH for LTP, attenuated androgens, or anti-fibrinolytics) once LTP is discontinued (within 3 weeks following first dose of DX-2930).
- Angiotensin-converting enzyme (ACE) inhibitors.
- Initiating or changing the dose of estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) 3 months prior to the screening visit.
- Use of androgens (eg, stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) for non-HAE related medical conditions or for HAE after discontinuation during the first 3 weeks.
- Any other investigational drug or device.

5.5 Restrictions

5.5.1 Medical Interventions

Medical interventions deemed necessary by the investigator for the health and well-being of the subject will not be excluded during this study.

5.5.2 Fluid and Food Intake

There are no restrictions on fluid and food intake. Subjects may continue their usual dietary regimens.

5.5.3 Activity

There are no activity restrictions. Subjects may continue their usual activity regimens.

5.6 Treatment Compliance

All doses of open-label DX-2930 administered at the investigational site will be under the direct supervision of the investigator or qualified study site personnel designated by the investigator.

Subjects are allowed to initiate self-administration at the subject's home or other agreed upon location after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may continue to self-administer subsequent doses of DX-2930 at the investigational site (when visits are scheduled study site visits) or the subject's home or other agreed upon location (when the study permits offsite dosing). Site personnel will call subjects within approximately 3 days of the planned off-site self-administrations to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented. See Schedule of Activities for details. For all subjects, subsequent doses after the second dose require a minimum of 10 days and maximum of 18 days between administrations, and should fall within the accepted ±4 day window around study visits.

For rollover subjects, after the second DX-2930 dose is given either within the study window (±4 days) or an acceptable extra study visit, the 3rd dose must be administered at the next pre-defined study visit according to the schedule of assessments.

5.7 Packaging and Labeling

The open-label DX-2930 will be supplied by the Sponsor and prepackaged in a study kit for investigational studies. Each study kit will contain 1 vial of investigational product. Both the vials and carton (kit) will be appropriately labeled according to local regulations and bear the unique study drug kit number. The investigative site will provide ancillary supplies including syringes, needles, and alcohol wipes to subjects. The site has the option of using needles of a different gauge to aid subject comfort with each SC injection. Subjects who elect to self-administer investigational product will be provided the following supplies as applicable:

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

All used and unused vials should be returned to the study kit cartons/boxes and transported to the site for drug accountability. Written instructions on DX-2930 handling and self-administration procedures will be provided to trained subjects prior to initiating self-administration. Refer to the Pharmacy Manual for additional details on DX-2930 and its administration.

5.8 Storage and Accountability

All DX-2930 will be shipped refrigerated to the study site and must be stored at 2ºC to 8ºC/36ºF to 46ºF in the carton and protected from light. Storage must be in a securely locked area, accessible to authorized persons only, until needed for dose preparation. See Section 5.7 and Section 6.15.1 for details.

5.9 Investigational Medicinal Product Retention at Study Site

The investigator (or designee) is responsible for maintaining accurate accountability records of DX-2930 throughout the clinical study. All DX-2930 received at the site must be inventoried and accounted for in an accountability log provided by the Sponsor. All dispensing and accountability records will be available for Sponsor review. Drug accountability will be verified during on-site monitoring visits.

Upon the completion or termination of the study, and upon written authorization from the Sponsor, or its representative, all unused and/or partially used DX-2930 should be returned or destroyed at the investigational site, as specified by Sponsor. It is the investigator's responsibility to ensure that the Sponsor, or its representative, has provided written authorization that procedures for proper disposal of DX-2930 have been established, and that appropriate records of the disposal are documented and maintained. No unused DX-2930 may be disposed until fully accounted for by the Sponsor monitor (or designee).

6. STUDY PROCEDURES

Please refer to Table 1: Study Activities Schedule.

6.1 Informed Consent

The ICF must be executed prior to performing any study related activities and must be approved by the reviewing institutional review board (IRB), research ethics board (REB), or independent ethics committee (IEC). Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the investigator.

Subjects who are not rolling over from the double-blind DX-2930-03 study will provide informed consent at Screening. Subjects who are rolling over from the double-blind DX-2930-03 study will provide consent on or after Day 168 of Study DX-2930-03. Upon completion of the final assessments, the subjects will be discharged from the double-blind study and will start participation in the OLE study and receive their first open-label dose.

6.2 Eligibility Review

The investigator or qualified study site personnel will confirm that all Inclusion and Exclusion criteria have been met.

6.3 Demographics and Medical History

Demographics: date of birth (alternately age or year of birth, if full date is not allowed to be collected for legal reasons), sex, race, and ethnicity (where locally permitted) and medical history will be obtained at Screening from subjects not rolling over from Study DX-2930-03 and will be recorded on the source document and eCRF. Medical history will capture the subject's current medical status (current disease processes), past medical status (past disease processes), history of surgery, allergies and concomitant medications. For subjects rolling over from Study DX-2930-03, these data will be carried forward from that study.

6.4 HAE Attack Information Collection

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

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

At screening, HAE attack history will be collected for non-rollover subjects. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant attack location(s), triggers, average duration, acute attack therapy use and history of LTP (including duration of LTP, medication(s) and dose used for LTP, and frequency of attacks

while receiving LTP). If available, information will also be collected on HAE diagnosis (year of confirmation, how many years after onset of symptoms was diagnosis confirmed, or if subject was misdiagnosed).

During the study, subjects (or caregivers) will be instructed to notify and report details to the study site within 72 hours of the onset of an attack. This includes the first attack experienced by rollover subjects following their first open-label dose. In the situation 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 experienced, but their use is not mandatory.

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 (work, school, social interactions) and whether any assistance or medical intervention was required, including hospitalizations, additional laboratory tests, or emergency department visits
- Any medications used to treat the attack (both prescription and over the counter)
- If the attack resolved, date and time the subject was no longer experiencing symptoms

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

Study site personnel will contact rollover subjects approximately every 7 days following the first dose of open-label until the subject has received their second open label dose. This is to insure accurate reporting for any HAE attacks not already reported by the subject as required within 72 hours. During each study visit, study site personnel will solicit for any new HAE attack information that was not already provided to the site.

In this study, HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to DX-2930, 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 EDC system within 24 hours of becoming aware of the event. For all serious adverse events that are reported as HAE attacks, the 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 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 to receive additional information. Any subject-reported attack not confirmed by the investigator or physician designee must have an alternate AE diagnosis

recorded. All subject-reported and investigator/ physician designee-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 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 or physician designee may still clinically determine that the event did not represent an attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (eg, urticaria), the reported event persists well beyond the typical time course of an HAE attack, or there is a likely alternate etiology for the event (eg, the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

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

6.5 Vital Signs

Vital signs prior to dosing and at 1 hour post-dosing (±15 min) will be assessed by the investigator or his/her qualified designee according to the Study Activities Schedule (Table 1) unless the subject has elected to self-administer off-site for that visit. 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. For subjects who rollover from Study DX-2930-03, vital signs taken during the final study visit in Study DX-2930-03 will serve as the Day 0 pre-dose vital signs in this study and will not be duplicated.

6.6 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 (Table 1). The physical examination will be performed in accordance with standards at the site.

For subjects who rollover from Study DX-2930-03, the physical exam taken during the final study visit in Study DX-2930-03 will serve as the Day 0 pre-dose physical exam in this study and will not be duplicated. Weight should be collected at every exam.

6.7 Electrocardiography (ECG)

A standard 12-lead ECG (single recording) will be performed according to the Study Activities Schedule (Table 1). 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. For subjects who rollover from Study DX-2930-03, the ECG taken during the final study visit in Study DX-2930-03 will serve as the Day 0 pre-dose ECG in this study and will not be duplicated.

6.8 Clinical Laboratory Tests

6.8.1 Laboratory Parameters

Laboratory testing will be performed according to the Study Activities Schedule (Table 1).

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

When multiple sample collection types are performed at the same assessment time point, the samples will be drawn in the following order (depending on what sample types are to be collected at that time point): laboratory safety samples (hematology, coagulation, serum chemistry), C1-INH, C4, C1q, PK, anti-drug antibodies, PD. Aliquots from the PK, PD and anti-drug antibody samples may be retained as back-up for additional parameter testing if necessary. Subjects will be in a seated or supine position during blood collection. The total blood draw for each rollover subject will be approximately 269.8 mL. The total blood draw for each non roll-over subject will be approximately 283 mL. For subjects who rollover from Study DX-2930-03, testing performed during the final study visit in Study DX-2930-03 will serve as the Day 0 pre-dose laboratory testing in this study and will not be duplicated.

6.8.1.1 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

6.8.1.2 Coagulation

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

6.8.1.3 Chemistry

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

6.8.1.4 Urinalysis

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

Urinalysis does not need to be done as part of the clinical laboratory testing at Visits 14, 17, 20, and 23.

6.8.1.5 Pregnancy Test

Pregnancy tests will be either serum or urine based according to the Study Activities Schedule (Table 1).

6.8.1.6 C1-INH Functional Assay

Results of a C1-INH functional assay are required for eligibility assessment. Samples will be drawn at the Screening visit unless they were previously drawn in Study DX-2930-02 or Study DX-2930-03. Results of the C1-INH functional assay from DX-2930-02 or Study DX-2930-03 may be used to confirm diagnosis in this study. Subjects may be retested if results are incongruent with clinical history or believed by the investigator to be confounded by recent LTP use.

6.8.1.7 C4 Assay

Results of a C4 assay may be required for eligibility assessment. The C4 sample will be drawn at the same time as the C1-INH sample is drawn during the Screening visit unless previously drawn in Study DX-2930-02 or Study DX-2930-03. Results of the C4 assay from DX-2930-02 or Study DX-2930-03 may be used to confirm diagnosis in this study. Subjects may be retested if results are incongruent with clinical history or believed by the investigator to be confounded by recent LTP use.

6.8.1.8 C1q Assay

Results of a C1q assay may be required for eligibility assessment. Any subject who requires C1-INH and C4 assay results for diagnostic confirmation in this study will have C1q assay results obtained as well. The C1q sample will be drawn at the same time as the C1 and C4 sample is drawn during the Screening visit.

6.8.1.9 PK Sample Collection

As outlined in Section 6.9.

6.8.1.10 PD Sample Collection

As outlined in Section 6.10.

6.8.1.11 Plasma Anti-Drug Antibody Testing

As outlined in Section 6.11.

6.8.2 Sample Collection, Storage, and Shipping

Blood samples for laboratory assessments will be collected at the site by a trained site staff designated and/or approved by the study investigator. Details for the collection, processing, storage and shipment of samples for all laboratory determinations will be provided in the Laboratory Manual.

Biological material will be stored and secured in a manner that assures that unauthorized access is prohibited and the samples are not lost, allowed to deteriorate, or accidentally or illegally destroyed.

6.9 Pharmacokinetic Assessments

Blood samples for the measurement of plasma DX-2930 concentration will be obtained as specified in the Study Activities Schedule (Table 1).

6.10 Pharmacodynamic Assessments

To evaluate the PD effects of DX-2930 upon plasma kallikrein activity, blood samples will be obtained as specified in the Study Activities Schedule (Table 1).

6.11 Plasma Anti-Drug Antibody Testing

Plasma samples for testing for formation of antibodies to DX-2930 will be obtained as specified in the Study Activities Schedule (Table 1).

6.12 Prior and Concomitant Therapy

The Sponsor representatives and investigator at the site conducting the trial will review and evaluate prior (4 weeks prior to study screening) and concomitant medication usage on an ongoing basis. For subjects not rolling over from Study DX-2930-03, all prescription, over-the-counter medications, herbals, and supplements that are being taken or have been taken by subjects from 4 weeks prior to screening through the duration of the study will be regarded as concomitant medications and must be documented on the source document and eCRF following informed consent. For subjects rolling over from Study DX-2930-03, concomitant therapy use will be carried forward from that study and will continue to be collected through the duration of the study.

6.13 Investigational Medicinal Product Treatment

Instructions for safe handling of DX-2930, preparation of each subcutaneous dose and administration of DX-2930, are provided in the Pharmacy Manual. Preparation and dispensing of DX-2930 will be handled by qualified study site personnel or by subjects who are self-administering after receiving appropriate training by the investigator or designee at the study site. The requirements for maintaining DX-2930 accountability are provided in Section 6.15.1 (for subjects self-administering) and Section 5.7 and Section 5.8 of this protocol.

6.14 Quality of Life Assessments

Quality of life (QoL) assessments will be conducted using the Angioedema Quality of Life Questionnaire (AE-QoL), EuroQoL 5-Dimensional 5-Level Measure (EQ-5D-5L), Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH), Hospital Anxiety and Depression Scale (HADS), and 12 Item Short Form Survey (SF-12). See Study Activities Schedule (Table 1). For subjects who rollover from Study DX-2930-03, quality of life

assessments obtained during the final study visit in Study DX-2930-03 will serve as the Day 0 pre-dose quality of life assessments in this study and will not be duplicated.

6.14.1 Angioedema Quality of Life Questionnaire (AE-QoL)

The AE-QoL is a self-administered, symptom-specific tool developed and validated to assess quality of life (QoL) impairment in patients with recurrent angioedema (Weller et al., 2012). The AE-QoL consists of 17 questions covering four domains/dimensions (functioning, fatigue/mood, fear/shame, nutrition). Each of the 17 items has a five-point Likert-type response scale ranging from 1 (Never) to 5 (Very Often). The AE-QoL is scored to produce a score for each domain and a total score ranging from 0 to 100, with higher scores indicating stronger impairment. It takes 5 minutes to complete the AE-QoL.

6.14.2 EuroQoL 5-Dimensional 5-Level Measure (EQ-5D-5L)

The EQ-5D-5L is a self-administered standardized measure of health status comprised of a descriptive system and a Visual Analogue Scale (VAS). The descriptive system consists of five health related quality of life dimensions (ie, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is rated on a 5-point response scale (5 levels) indicating severity of problems, where 1 is “no problems” and 5 is “extreme problems”. The EQ-5D VAS is a measure of overall self-rated health status on a 20-cm vertical VAS with endpoints labelled “the best health you can imagine” and “the worst health you can imagine”. The VAS ranges from 0 to 100, with higher scores indicative of better overall health.

6.14.3 Work Productivity and Activity Impairment – General Health (WPAI-GH) Questionnaire

The WPAI-GH is a 6-item instrument assessing work and activity impairment due to health problems during the past 7 days. The instrument elicits four main scores in relation to general health specifically: absenteeism (the percentage of work time missed because of one's health in the past seven days), presenteeism (the percentage of impairment experienced while at work in the past seven days because of one's health), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and activity impairment (the percentage of impairment in daily activities because of one's health in the past seven days) (Reilly et al., 1993). Adolescent subjects should complete the WPAI questionnaire and use the term “school” instead of “work” when filling out this questionnaire. These data will be analyzed separately.

6.14.4 Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a self-assessment scale to detect states of depression, anxiety, and emotional distress amongst patients who were being treated for a variety of clinical problems (Zigmond and Snaith, 1983). The scale has a total of 14 items. Seven of the items relate to anxiety and seven relate to depression. The responses are scored on a scale of 0–3 (3 indicates higher symptom frequencies). Scores for each subscale (anxiety and depression) range from 0 to 21 with scores categorized as follows: normal 0–7, mild 8–10, moderate 11–14, and severe 15–21. Scores for the entire scale (emotional distress) range from 0 to 42, with higher scores indicating more distress. This scale reflects how a subject has been feeling during the past week.

6.14.5 12 Item Short Form v2 Health Survey (SF-12v2)

The SF-12v2 Health Survey is a reliable and valid generic measure of functional health and well-being. The SF-12v2 consists of 12 questions, all selected from the SF-36 Health Survey (Ware et al., 1996). The SF-12v2 yields eight health domains (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, and mental health summary measures. Physical and Mental Health Composite Scores (PCS & MCS) can be computed using the scores of twelve questions and range from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health. The standard form of the instrument asks subjects to reply to questions according to how they have felt over the last 4 weeks.

6.15 DX-2930 Injection Report and Self-Administration and Subcutaneous Injection Survey

Assessments of subject experience with self-administration and SC injections of DX-2930 will be conducted.

6.15.1 DX-2930 Injection Report

The investigator or designee will train subjects who elect to self-administer DX-2930 on the following:

- Transportation and recommended storage conditions of investigational product from the study site to the offsite location.
- Maintenance of accurate records regarding each administration of investigational product including supply identification (ie, lot/kit number), date and time of injection, injection site location, infusion time, and if applicable, any reason the self-administration could not be completed as instructed.
- Retention of all used and unused vials of investigational product for drug accountability purposes.

After receiving appropriate training and demonstrating their understanding of self-administration, subjects are allowed to self-administer DX-2930 after receiving the first 2 doses of DX-2930 at the study site (administered by study personnel). For those subjects who choose to self-administer or have a parent/legal guardian/caregiver administer DX-2930, subjects must complete an assessment of their experience with self-administration and subcutaneous injection for each dose received. Study personnel will document the subject's responses in the subjects' medical record and eCRF.

6.15.2 DX-2930 Self-administration and Subcutaneous Injection Survey

Subjects will complete an assessment on their overall experience with self-administration and experience with receiving SC injections of DX-2930 according to the Study Activities Schedule during the study. For subjects who have previously received LTP with C1-INH products via IV administration, they will be asked to indicate the preferred route for medication administration. Study personnel will document the subject's responses in the subjects' medical record and eCRF.

In addition, investigators will be asked to indicate their preference (SC, IV, or no preference) on the route to administer medications to prevent angioedema attacks.

6.16 Adverse Event Reporting

Adverse events will be collected from signing of the informed consent through the last study visit.

6.16.1 Definitions

6.16.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical trial subject whether or not it appears to have a causal relationship with the treatment administered.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or participation in a clinical study, whether or not directly related to the medicinal product or study participation.

- AEs may be new events or may be pre-existing conditions that have become aggravated or have worsened in severity or frequency during the course of the study.
- AEs may be clinically significant changes from baseline in physical examination, laboratory tests, or other diagnostic investigation (eg, laboratory results, x-ray findings).

Laboratory abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. A clinically significant laboratory abnormality that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to DX-2930 interruption or discontinuation, will in itself, be considered an AE. Laboratory or diagnostic testing abnormalities that reflect or are part of a known underlying medical condition are not, in themselves, AEs; rather, the underlying medical condition leading to the abnormalities would be reported as the AE.

Pregnancy is not an AE; however, if a female subject becomes pregnant during the conduct of the study, the investigator must notify the Sponsor according to the procedures provided in Section 6.16.5.2.

6.16.1.2 Serious Adverse Event

A SAE is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening experience; Note: “Life-threatening” refers to a situation in which the subject was at risk of death at the time of the event; it does not refer to an event that might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization; Note: Does not include hospitalization for observation with release within 24 hours. A scheduled

hospitalization for a pre-existing condition that has not worsened during participation in the study does not meet this criterion. Pre-planned hospitalizations for an elective medical/surgical procedure or routine check-ups do not meet this criterion.

- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is considered to be an important medical event defined as those that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

6.16.1.3 Overdose

An overdose is defined as a significant variation from the recommended/scheduled dosage for a product. The dosing for this study will be conducted in a controlled clinical setting and an overdose is not anticipated. However, in the event of an accident, for this study, an overdose of DX-2930 is considered a dose that is two-fold higher than the intended dose for the subject.

6.16.1.4 Planned Hospitalization

A hospitalization planned by the subject prior to the first dose of open-label DX-2930 is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the trial, it must be reported as an AE.

6.16.1.5 Treatment-Emergent Adverse Events (TEAE)

An AE is treatment-emergent if the onset time is after first administration of open-label DX-2930 through the final follow-up visit or, in the event that onset time precedes first DX-2930 administration, the AE increases in severity during the open-label treatment period.

For rollover subjects, any adverse event that started during the subject's participation in Study DX-2930-03 and was ongoing at the time of the first open-label dose in Study DX-2930-04 will not be counted as an AE in Study DX-2930-04 unless that event has worsened in severity or frequency following the first open-label dose. Adverse events that started during subject participation in Study DX-2930-03, resolved following the first open-label dose in Study DX-2930-04, and then subsequently reappeared in Study DX-2930-04 will be counted as a new TEAE in Study DX-2930-04.

6.16.1.6 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) will be captured and monitored during this study. Investigators will report all AESI to the Sponsor, regardless of causality, using the same timelines as described for SAE reporting. The following describe the AESI and the criteria for reporting AESI.

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.

6.16.2 Monitoring

6.16.2.1 Monitoring of Adverse Events

Each subject will be monitored for the occurrence of AEs, including SAEs and AESI, from signing of the ICF through the final follow-up visit.

- Subjects will be questioned and/or examined by the investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.
- Subjects having TEAEs will be monitored until resolution with relevant clinical assessments and laboratory tests, as determined by the investigator.
- AEs, actions taken as a result of AEs, and follow-up results must be recorded in the eCRF as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For any SAEs or AEs that require the subject to be discontinued from dosing, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s). Subjects will continue to be followed through completion of all scheduled visits.

6.16.2.2 Monitoring of Safety Laboratory Assessments

All safety laboratory assessments will be performed at a central laboratory. The clinical laboratory values will be reported to the investigator who will review them for clinical significance and consideration of abnormal values as potential AEs.

6.16.3 Assessment of Adverse Events

6.16.3.1 Assessment of Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

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) (Appendix 1, Appendix 2) 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) (Appendix 3). For abnormalities not specifically found in the Toxicity Tables, the following general scale will be used to estimate grade of severity:

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

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

All HAE attacks will be captured as AEs and assessed with DMID & HAE Attack Assessment and Reporting Procedures (HAARP) criteria.

6.16.3.2 Assessment of Causality

A medically qualified investigator must assess the relationship of any AE (including SAEs) to the use of DX-2930, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
- The temporal association between DX-2930 exposure and onset of the AE.

- Whether the manifestations of the AE are consistent with known actions or toxicity of DX-2930.
- The AE resolved or improved with decreasing the dose or stopping use of DX-2930 (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between DX-2930 and the AE will be assessed using one of the following categories:

Not Related: Factors consistent with an assessment of Not Related include:

- Temporal relationship is lacking (eg, the event did not occur within a reasonable time frame following administration of DX-2930); or
- Other causative factors more likely explain the event (eg, a pre-existing condition, other concomitant treatments).

Related: Factors consistent with an assessment of Related include:

- There is a positive temporal relationship (eg, the event occurred within a reasonable time frame following administration of DX-2930); or
- The AE is more likely explained by administration of DX-2930 than by another cause (ie, the AE shows a pattern consistent with previous knowledge of DX-2930 or the class of DX-2930).

6.16.3.3 Assessment of Clinical Significance

Clinical significance of individual AEs will be determined by the investigator, with discussion with the Medical Monitor as appropriate.

6.16.4 Clinical Laboratory Adverse Events

Laboratory abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. A clinically significant laboratory abnormality that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to DX-2930 interruption or discontinuation, will be considered an AE.

When laboratory abnormalities are considered to be AEs, the DMID Adult Toxicity Table (Appendix 2) or DMID Pediatric Toxicity Tables (Appendix 3) will be used to assess severity. Where discrepancies in the upper limit of normal (ULN) and lower limit of normal (LLN) of laboratory ranges occur between those included in the DMID tables and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade. Clinical significance of individual laboratory AEs will be determined by the investigator with input from the Medical Monitor as needed.

Following is an exception to defining clinically significant, abnormal laboratory values as AEs:

- APTT prolongation in the absence of any associated bleeding or other evidence of clinical relevance will not be considered a clinically significant laboratory abnormality or AE. In the appropriate physiologic setting, such as IV heparin therapy, aPTT can be used to monitor bleeding risk. However, as noted in the Investigators Brochure, aPTT prolongation due to plasma kallikrein inhibition is an artifactual *in vitro* phenomenon. Although plasma kallikrein drives fibrin formation in the aPTT assay, plasma kallikrein-driven coagulation does not appear to have hemostatic or other physiologically important functions *in vivo*. It is well documented that, in humans, deficiency of factor XII or prekallikrein (and thus plasma kallikrein) is not associated with abnormal bleeding, either spontaneous or during surgical procedures (Renne and Gruber, 2012). Despite the lack of clinical effect, deficiency of either protein is associated with marked prolongation of the aPTT.

6.16.5 Reporting Investigator Safety Observations to the Sponsor

6.16.5.1 Reporting Non-serious Adverse Events

All AEs, regardless of seriousness, severity, or causal relationship to DX-2930, will be recorded on the AE page of the eCRF. In this study all HAE attacks reported by the subject, regardless of whether or not they are confirmed by the investigator, will be captured as AEs.

6.16.5.2 Reporting Pregnancies

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, the investigator must report the pregnancy to the Sponsor's Pharmacovigilance Department using the Pregnancy Reporting Form within 24 hours of becoming aware of the event. The investigator must obtain consent to collect pregnancy information (including the status of the newborn, if applicable).

If some of the information required for completion of the Pregnancy Reporting Form is unavailable at the time of the initial report, follow-up reports will be completed and submitted within 24 hours of becoming aware of the new information. The investigator is required to follow the pregnancy through delivery. The outcome of the pregnancy and the status of the newborn (if applicable) will be reported on the Pregnancy Reporting Form within 24 hours of becoming aware.

6.16.5.3 Safety Observations Requiring Expedited Reporting by the Investigator to the Sponsor

Any occurrence of the following events or outcomes in a subject in the trial must be reported expeditiously by the investigator or qualified designee to the Sponsor's Pharmacovigilance Department:

- SAE
- AESI
- Overdose
- Cancer

The investigator is to report any expedited safety observations from the list above to the Sponsor using the SAE Reporting Form in the EDC system within 24 hours of becoming aware of the event.

Any SAE reported to the Sponsor Pharmacovigilance Department using the SAE Reporting Form in the EDC system is to be recorded in the eCRF, as well as in the subject's source documentation along with any actions taken. If all required information on the form is not available at the time of the initial report, follow-up information will be completed in the EDC system.

The investigator is required to follow SAEs until resolution regardless of whether the subjects are still participating in the study. SAE resolution is defined as:

- Resolved with or without residual effects.
- A return to baseline for a pre-existing condition.
- Laboratory values have returned to baseline or stabilized.
- The investigator does not expect any further improvement or worsening of the event.
- Fatal outcome—if an autopsy is performed; the autopsy report is requested to be provided to the Sponsor as soon as it is available.

6.16.5.4 Expedited Reporting by the Sponsor to a Regulatory Health Authority

The Sponsor or designee will report relevant safety information to concerned health authorities in accordance with local laws and regulations.

6.16.5.5 Safety Contact Information

24-Hour Global Safety Contact: Pharmacovigilance Department
Email: [redacted]
Telephone (US) [redacted]

6.16.5.6 Safety Notifications by the Sponsor to the Investigator

Investigators will receive prompt notification of any adverse experience related to DX-2930 that is both serious and unexpected, or any finding that suggests a significant risk for subjects. The investigator will promptly inform his / her IRB/REB/IEC of the notification and insert the notification in the Investigator's Regulatory Binder in accordance with local regulations.

6.17 Subject Withdrawal

The investigator may withdraw a subject from DX-2930 treatment for any of the following reasons:

- In the opinion of the investigator, the subject is unable to comply with the requirements of the protocol for satisfactory completion or interpretation of study results (including use of prohibitive medications),
- A serious or intolerable AE occurs,

- A clinically significant change in a laboratory parameter occurs,
- The Sponsor or investigator terminates the study, or
- The subject requests to be discontinued from the study.

Subjects will continue to be followed through completion of all scheduled visits, unless the subject requests to be discontinued from the study.

6.18 Appropriateness of Measurements

This is a Phase 3 open-label extension study that is designed to evaluate the long-term safety and efficacy of DX-2930 in prophylactic therapy for angioedema attacks in subjects with HAE. DX-2930 is a recombinant, fully human IgG1, kappa light chain, monoclonal antibody. The open-label, non-controlled study design is a standard approach for extension studies that follow double-blind pivotal trials. Measures employed in this protocol are standard measures routinely used for the evaluation of the efficacy, safety and tolerability of an investigational product. Measures employed for rollover subjects between the first and second open-label doses are appropriate to characterize the outer bounds of dosing frequency for DX-2930.

7. STUDY ACTIVITIES

Study activities are summarized by study visit in Study Activities Schedule (Table 1).

7.1 Screening Visit (Up to Day −28) For Non-Rollover Subjects

The following procedures and assessments are to be performed during the Screening Visit for subjects not rolling over from Study DX-2930-03:

- Informed consent (Section 6.1)
- Eligibility review (Section 6.2)
- Demographics and medical history (Section 6.3)
- C1-INH functional assay, C4 and C1q sample collection (Section 6.8)
- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including height and weight (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16); pre-existing signs and symptoms

For subjects rolling over from the double-blind DX-2930-03 study, no Screening visit is required as subjects will enter the OLE on the same day that their last Study DX-2930-03 study visit is completed. Diagnostic test results and demographic and medical history for these subjects will be carried forward from that study.

7.2 Start of Treatment Period: Visit 1, Dose 1 (Day 0)

The following procedures and assessments are to be performed on Day 0 prior to the first dose of DX-2930. For subjects who rollover from Study DX-2930-03, all final assessments taken during the final study visit in Study DX-2930-03 will be used as the pre-dose results on Day 0 and will not be duplicated.

- Informed consent (for subjects rolling over from the double-blind DX-2930-03 study; this can be on or after Day 168 of that study) (Section 6.1)
- Eligibility review (Section 6.2)
- Urine pregnancy test (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- 12-Lead ECG (Section 6.7)

- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK baseline sample collection (Section 6.9)
- PD baseline sample collection (Section 6.10)
- Baseline anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- First dose of open-label DX-2930 (Section 5.1)

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2)
- AE collection (Section 6.16)

7.3 Interval between Dose 1 and Dose 2 for Rollover Subjects

Rollover subjects must adhere to the Study Activities Schedule for the entire duration of the study. Until a rollover subject reports their first HAE attack, study visits may be conducted via site check in calls, except for the following study visits which must be conducted at the investigative site:

- Day 14
- Day 28
- Day 56
- Day 98
- Day 126
- Day 154
- Day 182
- Day 224
- Day 266
- Day 308
- Day 350

The tests and assessments required at these visits are specified in the sections below.

Site check in calls may serve as any of the following study visits until the subject receives their second open-label dose:

- Day 42
- Day 70
- Day 84
- Day 112
- Day 140
- Day 168
- Day 196
- Day 210
- Day 238
- Day 252
- Day 280
- Day 294
- Day 322
- Day 336

Study site personnel will also contact rollover subjects approximately 7 days after each study visit (both site visits and check-in calls) until the subject receives their second open-label dose.

The following assessments are performed during all site calls:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.4 Dose 2 of DX-2930 for Rollover Subjects

The duration of time between Dose 1 and Dose 2 will vary by subject based on when their first HAE attack occurs following Dose 1. As a result, rollover subjects may not receive DX-2930 treatment at every dosing visit as outlined in the Study Activities Schedule.

Once a rollover subject reports their first HAE attack they will present to the investigative site for their second open-label dose of DX-2930 as quickly as subject and site schedules allow. This treatment visit may be counted as a scheduled study visit, or as an acceptable extra study visit. For details on determining whether the second dose is counted as a scheduled or extra study visit, refer to Section 3.1.1. Regardless of when the second dose is administered, the following tests and assessments will be conducted pre-dose on the day it is administered:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

The following tests and assessments will also be performed if the second dose occurs on a scheduled study visit for which they are required:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- 12-Lead ECG (Section 6.7)
- Quality of life assessments (Section 6.14)

After the required pre-dose tests and assessments are completed:

- Second dose of open-label DX-2930 (Section 5.1)

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.5 Visit 2 (Day 14 ±4 days); Dose 2 of DX-2930 for Non-Rollover Subjects

On Day 14 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1)

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.6 Continuation of Treatment Period: Visit 3 (Day 28 ±4 Days)

On Day 28 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 3. At this visit, subjects have the option to self-administer at the investigational site.

After administration of DX-2930, the following post-treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.7 Continuation of Treatment Period: Visit 4 (Day 42 ±4 Days)

On Day 42 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 4. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.8 Continuation of Treatment Period: Visit 5 (Day 56 ±4 Days)

On Day 56 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 5. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.9 Continuation of Treatment Period: Visits 6 and 7 (Days 70 and 84, All ±4 Days)

On Days 70 and 84 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects these doses represent Dose 6 and Dose 7. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.10 Continuation of Treatment Period: Visit 8 (Day 98 ±4 Days)

On Day 98 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)

- Physical examination, including weight (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 8. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2)
- AE collection (Section 6.16)

7.11 Continuation of Treatment Period: Visit 9 (Day 112 ±4 Days)

On Day 112 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 9. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.12 Continuation of Treatment Period: Visit 10 (Day 126 ±4 Days)

On Day 126 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 10. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.13 Continuation of Treatment Period: Visit 11 (Day 140 ±4 Days)

On Day 140 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)

- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 11. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.14 Continuation of Treatment Period: Visit 12 (Day 154 ±4 Days)

On Day 154 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 12. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)

- AE collection (Section 6.16)

7.15 Continuation of Treatment Period: Visit 13 (Day 168 ±4 Days)

On Day 168 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 13. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.16 Continuation of Treatment Period: Visit 14 (Day 182 ±4 Days)

On Day 182, the following procedures and assessments will be performed:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, and serum chemistry (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)

- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 14. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2
- AE collection (Section 6.16)

7.17 Continuation of Treatment Period: Visit 15 (Day 196 ±4 Days)

On Day 196 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 15. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.18 Continuation of Treatment Period: Visit 16 (Day 210 ±4 Days)

On Day 210 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 16. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.19 Continuation of Treatment Period: Visit 17 (Day 224 ±4 Days)

On Day 224 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Laboratory testing including hematology, coagulation, and serum chemistry (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 17. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.20 Continuation of Treatment Period: Visit 18 (Day 238 ±4 Days)

On Day 238 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 18. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.21 Continuation of Treatment Period: Visit 19 (Day 252 ±4 Days)

On Day 252 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 19. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.22 Continuation of Treatment Period: Visit 20 (Day 266 ±4 Days)

On Day 266 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, and serum chemistry (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 20. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.

- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2)
- AE collection (Section 6.16)

7.23 Continuation of Treatment Period: Visit 21 (Day 280 ±4 Days)

On Day 280 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 21. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.24 Continuation of Treatment Period: Visit 22 (Day 294 ±4 Days)

On Day 294 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 22. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.25 Continuation of Treatment Period: Visit 23 (Day 308 ±4 Days)

On Day 308 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Laboratory testing including hematology, coagulation, and serum chemistry (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 23. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.26 Continuation of Treatment Period: Visit 24 (Day 322 ±4 Days)

On Day 322 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 24. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.27 Continuation of Treatment Period: Visit 25 (Day 336 ±4 Days)

On Day 336 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 25. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)

- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.28 Continuation of Treatment Period: Visit 26 (Day 350 ±4 Days)

On Day 350, the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 26 (final dose). At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2)
- AE collection (Section 6.16)

7.29 Completion of Treatment Period: Visit 27 (Day 364 ±4 Days)

On Day 364 the following procedures and assessments will be performed; note that DX-2930 will not be administered during this visit:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)

- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.30 Follow-up Period: Visit 28 (Day 378 ±4 Days)

On Day 378 all rollover and non-rollover subjects will receive a site check-in call. During this call study site personnel will collect information regarding the following:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.31 Final Follow-up Visit: Visit 29 (Day 392 ±4 Days)

On Day 392 all rollover and non-rollover subjects will complete a final study visit at the investigative site.

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- Quality of life assessments (Section 6.14)
- AE collection (Section 6.16)
- Study Discharge: Subjects will be discharged at this study visit.

7.32 Early Termination

Subjects that terminate early from the study will undergo (if possible) all of the assessments and procedures scheduled for Day 392.

8. QUALITY CONTROL AND ASSURANCE

The Sponsor and the Contract Research Organization (CRO) conducting trial management services, Rho, Inc., will implement a system of quality assurance that includes all elements described in this protocol. Within this system, SOPs from the Sponsor and CRO will be implemented to ensure that the clinical trial is conducted in compliance with regulatory requirements and Good Clinical Practices (GCP). Quality control will be applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The site staff should assist in all aspects of audit/inspection.

9. DATA ANALYSIS / STATISTICAL METHODS

9.1 General Considerations

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

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, standard errors, and 95% confidence intervals for least squares means will be provided. Time-to-event data will be summarized using Kaplan-Meier estimates of the 25th, 50th (median), and 75th percentiles with associated two-sided 95% confidence intervals, as well as percentage of censored observations. Plots of the Kaplan-Meier curves and supporting data listings detailing each subject's contribution to the analysis will be provided.

Formal hypothesis testing will not be performed. Any hypothesis testing will be exploratory in nature and resulting p-values will be considered descriptive.

9.2 Sample Size Determination

No formal sample size calculation was performed. The sample size is not based on any statistical considerations. This study is designed to evaluate the safety and efficacy of open-label treatment with DX-2930 in subjects who participated in Study DX-2930-03 (rollover subjects) and individuals who were not otherwise able to participate in Study DX-2930-03 (non-rollover subjects).

9.3 Method of Assigning Study Subjects to Treatment

Subjects meeting all eligibility criteria will be enrolled in the study and sequentially assigned a unique site-based identification number.

9.4 Analysis Populations

9.4.1 Safety Population

The Safety Population will include all subjects who received any study drug after entering Study DX-2930-04(ie, any exposure to open-label DX-2930). Unless otherwise specified, summary tabulations conducted with the Safety Population will be presented by the subject's study entry type (rollover or non-rollover) and overall.

9.4.2 Rollover Safety Population

The Rollover Safety Population is the subset of subjects who participated in Study DX-2930-03 and received any study drug after entering Study DX-2930-04(ie, any exposure to open-label DX-2930). Unless otherwise specified, summary tabulations conducted with the Rollover Safety Population will be presented by the subject's prior treatment group from Study DX-2930-03

(DX-2930 300 mg every 2 weeks, DX-2930 300 mg every 4 weeks, DX-2930 150 mg every 4 weeks, and Placebo).

9.4.3 Non-rollover Safety Population

The Non-rollover Safety Population is the subset of subjects who directly entered Study DX-2930-04 and received any study drug after entering Study DX-2930-04 (ie, any exposure to open-label DX-2930). Unless otherwise specified, summary tabulations conducted with the Non-rollover Safety Population will be presented by subject's prior type of LTP therapy prior to study entry (C1-INH, androgens, anti-fibrinolytics, and not on LTP).

9.5 Population Description and Exposure

9.5.1 Subject Disposition

The numbers of subjects treated with study drug, completed the study and discontinued prematurely by reason will be summarized for each analysis population.

9.5.2 Demographics and Other Baseline Characteristics

Baseline and demographic variables will be summarized for each analysis population.

9.5.3 Medical History

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

9.5.4 Treatment Exposure and Compliance

Treatment compliance and the extent of exposure to study drug 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 for each analysis population.

9.5.5 Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD). The number and percentage of subjects with prior or concomitant medications will be summarized by therapeutic class and preferred term for each analysis population. A separate, similar table will be provided for the subset of concomitant medications classified as rescue medications.

9.6 Analysis of Efficacy

9.6.1 Time to the First Investigator-confirmed HAE Attack

Time to the first investigator-confirmed HAE attack will be analyzed using the Rollover Safety Population.

Time to the first investigator-confirmed HAE attack (days) will be calculated from the date and time of the first open-label dose of DX-2930 to the date and time of the first investigator-confirmed HAE attack after the first open-label dose. Subjects who discontinue the study prior to experiencing their first on-study investigator-confirmed HAE attack will be censored at the date and time of study discontinuation. Time to the first investigator-confirmed HAE attack will be summarized using Kaplan-Meier methods.

Multivariate and univariate Cox proportional hazards regression models will be employed to examine the impact of baseline covariates on the time to the first investigator-confirmed HAE attack, including but not limited to: baseline attack rate prior to entering Study DX-2930-03, the treatment group in Study DX-2930-03, the time since the last dose given in Study DX-2930-03, the time since the last HAE attack, and the rate of attacks during Study DX-2930-03 . Results of this exploratory analysis will be summarized.

9.6.2 Number of Investigator-confirmed HAE Attacks

The number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 364) expressed as a monthly HAE attack rate, will be analyzed using each analysis population.

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

The baseline investigator-confirmed HAE attack rate will be calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the pretreatment period for rollover subjects or historical reporting period for non-rollover subjects divided by the number of days the subject contributed to the pretreatment period for rollover subjects or historical reporting period for non-rollovers multiplied by 28 days.

The baseline, treatment period, and treatment period change from baseline in the investigator-confirmed HAE attack rate will be summarized for each analysis population. The summary will include the total number of investigator-confirmed HAE attacks reported during each period and subject-time in months that each subject contributed to each period. Figures will be created for each analysis population plotting the on-study investigator-confirmed HAE attacks reported during the treatment period relative to Day 0 for each subject.

In addition, the number of investigator-confirmed HAE attacks per month (defined as 28 days) will be summarized descriptively by month (per 28 day interval) for each analysis population. The summary will include the number, change from baseline, and percent change from baseline of investigator-confirmed HAE attacks. Investigator-confirmed HAE attacks will be grouped into 28-day intervals using the start date of the HAE attack. The date of the first exposure to study drug in this study will be used as the start of the first interval and end of the interval will be the date of first exposure to study drug in this study plus 28 days. Each successive interval will start the last day of the prior interval plus 1 day and end 28 days later.

Similar summary tables will be presented for the following efficacy endpoints for each analysis population:

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

9.7 Analysis of Safety

9.7.1 Adverse Events

Adverse events will be coded using the MedDRA coding dictionary. Separate summaries will be presented for each analysis population.

Treatment-emergent AEs are defined as AEs with onset at the time of or following the first exposure to open-label DX-2930 in this study, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. For AEs with partial onset times, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, then the AE will be classified as treatment-emergent.

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

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

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

- *Treatment Period AEs* will include all AEs starting at or after the first exposure to open-label DX-2930 in this study to those starting before or at the subject's last visit date during the treatment period in this study (AEs starting at or after treatment on Day 0 to the Day 364 visit).

Follow-up Period AEs will include all AEs starting at or after the subject's last visit date of the treatment period in this study (AEs starting after the Day 364 visit).

For AEs with partial onset times, non-missing date parts will be used to determine if the AE falls within the period. If a determination cannot be made using the non-missing date parts as to if the AE falls within the period, the AE will be conservatively counted as a treatment-period AE.

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

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized by SOC, and PT for each analysis period. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, and related severe AEs for treatment period and follow-up period AEs.

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

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

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

9.7.2 Laboratory Test Results

Laboratory test results will be summarized using the Safety Population.

Baseline is defined as the last non-missing value prior to the first exposure to DX-2930. For rollover subjects previously exposed to DX-2930, baseline is the last non-missing value prior to first exposure to study drug in Study DX-2930-03.

Actual values and change from baseline clinical laboratory tests will be summarized by study visit. If more than one laboratory result is reported per study visit per parameter, the last non-missing result will be selected for analysis.

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. The number of subjects with a non-missing result, and the number and percentage of subjects with a clinically significant result less than the lower limit of normal, non-clinically significant result less than the lower limit of normal, within the normal range, non-

clinically significant result more than the upper limit of normal, and clinically significant result more than the upper limit of normal will be summarized 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 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.

9.7.3 Vital Signs

Vital signs will be summarized using the Safety Population.

Baseline is defined as the last non-missing value prior to the first exposure to DX-2930. For rollover subjects previously exposed to DX-2930, baseline is the last non-missing value prior to first exposure to study drug in Study DX-2930-03.

Actual values and changes from baseline in vital signs will be summarized 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 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.

9.7.4 Electrocardiography

Electrocardiography results will be summarized using the Safety Population.

The number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECG results, or ECG no performed, will be summarized by study visit. Subjects with clinically significant ECG results will be listed. This listing will include all results for a subject across study time points to identify any trends.

9.8 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.

9.8.1 Analysis of Pharmacokinetic Data

Plasma concentrations of DX-2930 will be summarized by nominal PK sampling time using the Safety Population.

9.8.2 Analysis of Pharmacodynamic Data

Plasma kallikrein activity will be summarized by nominal PD sampling time using the Safety Population.

9.8.3 Analysis of Immunogenicity Data

The number and percentage of positive antibodies will be summarized by study visit and overall using the Safety Population.

9.8.4 Analysis of Quality of Life Assessments

Quality of life assessments will be summarized using the Safety Population.

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) will be summarized by study visit. In addition, the VAS score for the subject's self-rated health will be summarized by study visit.

The responses to the SF-12 for each item will be tabulated by study visit using the Safety Population. In addition, Physical and Mental Health Composite Scores (PCS & MCS) will be computed using the scores of twelve questions and range from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health.

Responses to the HADS for each item will be tabulated by study visit. In addition, continuous and categorical (0-7: normal, 8-10: mild, 11-14: moderate, 15-21: severe) total scores based on the items related to depression and anxiety, will be summarized by study visit. Each item in the questionnaire is scored from 0-3, with total scores between 0-21 for either depression or anxiety. Scores for the entire scale (emotional distress) will also be presented. Total score for the entire scale range from 0 to 42, with higher scores indicating more distress.

Responses to the WPAI-GH for each item will be summarized by study visit. In addition, four main scores in relation to general health will be summarized by study visit. Scores will be calculated as absenteeism (percentage work time missed due to health), presenteeism (percent impairment while working due to health), work productivity loss (percent overall work impairment due to health), and activity impairment (percent activity impairment due to health). The scores are percentages with higher values indicating greater percentage impairment. Only respondents who report being full-time or part-time employed provide data for absenteeism, presenteeism, and overall work productivity loss. All respondents provide data for activity impairment.

Responses to the AE-QoL for each item will be tabulated by study visit. In addition, the domain scores (functioning, fatigue/mood, fears/shame, nutrition) and total score will be summarized by study visit. Each item in the questionnaire is scored from 0-4, with domain and total scores calculated using a linear transformation to a 0-100 scale.

9.9 Statistical/Analytic Considerations

9.9.1 Interim Analyses and Data Monitoring

Interim analyses may be conducted to support administrative decisions and/or regulatory reporting when a reasonable number of subjects have completed 12 months of consecutive exposure to DX-2930 across the combined DX-2930-03 and DX-2930-04 studies, and only after database lock of Study DX-2930-03.

An independent Data Safety Monitoring Board (DSMB) has been established to provide ongoing, independent review and assessment of the safety data for Study DX-2930-03. While an independent DSMB is not currently planned for this study, summary safety data from Study DX-2930-04 may be reviewed by the DSMB established for Study DX-2930-03 as part of the collection of safety information available on DX-2930.

9.9.2 Multiple Comparisons/Multiplicity

No adjustment for multiple comparisons will be performed. Any statistical testing will be considered exploratory.

9.9.3 Handling of Missing Data

All available data will be included in the analysis. No imputation of missing data will be performed.

9.9.4 Adjustment for Covariates

The impact of baseline covariates on the time to the first investigator-confirmed HAE attack will be explored to identify and assess the importance of potential prognostic factors.

9.9.5 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.

9.9.6 Subgroup Analyses

Subgroup analyses are planned for the number of investigator-confirmed HAE attacks during the treatment period and adverse events using the Safety Population. 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)
- Baseline HAE Attack Rate (1 to <2, 2 to <3, ≥3 attacks/month)
- HAE Type (Type I, Type II, Unspecified)
- Geographic Region (US, Canada, Jordan, Europe)
- DX-2930 Administration Type (Health Care Provider, Self-administration)

9.9.7 Sensitivity Analyses

The following sensitivity analyses will be performed on the number of investigator-confirmed HAE attacks during the treatment period for each analysis population to evaluate the robustness of the results. Data summaries will parallel those described for the number of investigator-confirmed HAE attacks during the treatment period efficacy endpoint.

1. The analysis will be repeated counting HAE attacks occurring on Day 14 after administration of study drug through Day 364, instead of Day 0 to Day 364. For this analysis, the period of analysis would be a subset of the treatment period, defined as Day 14 to Day 364.

2. The analysis will be repeated counting HAE attacks occurring on Day 7 after administration of study drug through Day 364, instead of Day 0 to Day 364. For this analysis, the period of analysis would be a subset of the treatment period, defined as Day 7 to Day 364.

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

10. STUDY ADMINISTRATIVE STRUCTURE

The study administration structure is provided in Table 2.

Table 2 Study Administrative Structure

Sponsor Contact:	[redacted], MD [redacted], Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: [redacted]
Global Medical Monitor:	[redacted], MD 300 Shire Way, Lexington, MA 02421 USA Phone: [redacted]
Study Monitoring (US):	Rho, Inc. 6330 Quadrangle Drive, Chapel Hill, NC 27517 Phone: [redacted]
Study Monitoring (Jordan)	Triumpharma 07 Bldg., Al-Yarooty St. P.O. Box 2233, Amman 11941, Jordan Phone: [redacted], [redacted]
Study Monitoring (Canada)	Red Maple Trials Incorporated 1081 Carling Avenue, Suite 707 Ottawa, Ontario, Canada, K1Y4G2 Phone: [redacted]
Study Monitoring (Europe)	Dyax Corp. 55 Network Drive, Burlington, MA 01803 Phone: [redacted]

10.1 Institutional Review Board/ Research Ethics Board/Independent Ethics Committee

The protocol and all protocol amendments must be signed and dated by the investigator and approved in writing by the IRB/REB/IEC in accordance with GCP prior to implementation. In addition, the IRB/REB/IEC must approve the written informed consent form, any consent form updates, subject recruitment materials (eg, advertisements), and any written information to be provided to subjects prior to implementation. The investigator must provide an annual report to the IRB/REB/IEC on the progress of the study including number of subjects enrolled, discontinued, and SAEs. It is required that a yearly review of the protocol by the IRB/REB/IEC be documented in a letter from the IRB/REB/IEC. The investigator must provide notification to the IRB/REB/IEC of the completion, termination or discontinuation of the study.

10.2 Ethical Conduct of the Study

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the investigator abide by the principles of the International Conference on Harmonisation (ICH) guidelines on GCP, applicable local regulatory requirements, and the Declaration of Helsinki (Version 2008). The clinical study also will be carried out in keeping with national and local legal requirements [in accordance with United States Investigational New Drug (IND) regulations (21 CFR 56)].

10.3 Subject Information and Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained according to the regulatory and legal requirements of the participating country. As part of this procedure, the investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. Subjects who are under the age of 18 (or lower if age of consent is less than 18 in a specific country) and whose legal guardian or caretaker has provided written informed consent will provide their assent to participate. The investigator or designee will provide the Sponsor with a copy of the IRB/REB/IEC-approved informed consent form prior to the start of the study.

10.4 Subject Confidentiality

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number, initial or birth date (if allowed based on local data protection regulations), not by name. Documents that identify the subject (eg, the signed informed consent document) must be maintained in confidence by the investigator.

The investigator agrees not to use or disclose protected health information other than as permitted or required by the subject authorization or as required by law.

10.5 Study Monitoring

The Sponsor (or designee) will conduct a study initiation visit to verify the qualifications of the investigator, inspect the facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The investigator will make all appropriate safety assessments on an ongoing basis. The Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to GCP and SOPs for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the investigator.

10.6 Case Report Forms and Study Records

The investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the clinical sites by means of electronic or manual queries.

The investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each subject receiving randomized study drug.

The investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB/REB/IEC to have direct access to all documents pertaining to the study.

A Trial Master File will be maintained by the Sponsor (or designee). All documents and other materials that pertain to the conduct of the trial quality of the data, and compliance with GCPs will be collected in the Trial Master File.

10.7 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) has been established to provide ongoing, independent review and assessment of the safety data for Study DX-2930-03. While an independent DSMB is not currently planned for this study, summary safety data from Study DX-2930-04 may be reviewed by the DSMB established for Study DX-2930-03 as part of the collection of safety information available on DX-2930.

The DSMB will adhere to a prospectively determined Charter, which will be written by the Sponsor and approved by the DSMB. The Charter will define the responsibilities of the DSMB and Sponsor, the number and timing of the DSMB meetings, the conduct of the meetings, and the data sets to be reviewed by the DSMB. Further details regarding the DSMB can be found in the DSMB charter.

10.8 Protocol Violations/Deviations

The investigator will be instructed not to deviate from the protocol, except where necessary to eliminate an immediate hazard to study participants. Should other unexpected circumstances arise that will require deviation from protocol-specific procedures, the investigator should contact their Sponsor representative to discuss the appropriate course of action.

The investigator should document all protocol deviations/violations in the subject's eCRF and source documents or the Investigator Site File if appropriate. In the event of a significant deviation/violation, the investigator should notify the Sponsor representative. Significant deviations/violations include, but are not limited to those that increase the health risk to the subject, or confound interpretation of primary study assessments. The investigator will promptly report all changes in research activity and all unanticipated problems involving risks to human subjects or others to his or her IRB/REB/IEC.

10.9 Premature Closure of the Study

If the Sponsor, investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable subject risk, the study may be terminated overall or at a specific site after appropriate consultation between the Sponsor and the investigator(s). In addition, a decision on the part of the Sponsor to suspend or discontinue development of the investigational product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to, the following:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- Failure of the investigator to comply with pertinent global regulations
- Submission of knowingly false information from the study site to the Sponsor or other pertinent regulatory authorities
- Insufficient adherence by the investigator to protocol requirements

10.10 Access to Source Documentation and On-Site Audits

Regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with country regulations. The investigator should immediately notify the Sponsor representative of any announced or unannounced regulatory agency inspections. An auditing inspection may also be conducted by the Sponsor representative or designee. Any aspect of the trial may be subject to audit by the Sponsor and/or inspection by regulatory authorities or the IRB/REB/IEC. Such audits/inspections may take place at the Sponsor's site(s), the CRO, or at the clinical sites, including laboratories, pharmacies and any other facilities used for the study.

The investigator will be responsible for the accuracy of the data entered in the eCRF. The investigator will permit the designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify data represented in the eCRF.

10.11 Data Generation and Analysis

This study will be performed in accordance with regulatory requirements outlined in Food and Drug Administration (FDA) 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 312 and 21 CFR Part 11 as well as the ICH GCP E6 Guidelines. The study monitors will meet with the investigators and staff shortly before the start of the trial to review the procedures for study conduct and documentation. During the study, the monitors will visit the sites to verify record keeping and adherence to the protocol. For this study, eCRFs will be used. The monitors will conduct 100% source document verification by comparing the eCRFs with the source documents to ensure accuracy and consistency. Edit check programs, other forms of electronic validation, manual listings and a query process will be executed to verify the accuracy of the database. The EDC system will maintain a full audit trail of electronic data changes. Access to all source documentation will be made available for monitoring and audit purposes.

10.12 Retention of Data

All source documents (eg, informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnosis and pharmacy records, and DX-2930 dispensing/disposition records) that support data in the eCRFs of each study subject must be retained in the files of the responsible investigator.

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the DX-2930. However, these documents should be retained for a longer period if required by the applicable legal requirements.

If the responsible investigator retires, relocates or for any other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor representative must be notified in writing of the name and address of the new custodian, prior to the transfer.

10.13 Financial Disclosure

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

10.14 Publication and Disclosure Policy

All information concerning DX-2930, Sponsor operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information, supplied to the investigator by a Sponsor representative and not previously published, is considered confidential and remains the sole property of the Sponsor. The investigator must agree to use this information only to accomplish this study, and must not use it for other purposes without the Sponsor's advanced written consent. A description of this clinical study may also be available on the externally facing public websites and registries. A summary of the study results may be potentially disclosed as per local and country specific requirements.

The information developed in this study will be used by the Sponsor in connection with the continued development of DX-2930 and thus may be disclosed as required to other clinical investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the Sponsor with all data obtained in the study.

11. REFERENCE LIST

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12. APPENDICES

Appendix 1	Protocol History
Appendix 2	National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Tables (Modified) (US National Institutes of Health; National Institute of Allergy and Infection Diseases)
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APPENDIX 1 Protocol History

Amendment Summary and Rationale

Amendment 1 to Protocol DX-2930-04 expanded upon the scope of the original protocol. Key revisions included extension of the study from 6 months to approximately 1 year, a corresponding increase in the number of study drug doses a subject may receive, allowance for subjects to elect self-administration both at and away from the site after completion and understanding of training, addition of 3 tertiary objectives, and revision of statistical methodology to accommodate changes in efficacy and other endpoints to allow for a more robust analysis.

Noteworthy changes to the protocol are captured in the table below. Additional minor revisions in grammar, spelling, punctuation, and format have been made for clarity and are not reflected in the summary of changes.

Document	Date	Global/Country/Site Specific
Original Protocol	14 December 2015	Global
Amendment 1.0	27 June 2016	Global
Amendment 2.0	20 Jan 2017	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date 27 June 2016**	**Global/Country/Site Specific Global**
Description of Change		**Section(s) Affected by Change**
Administrative updates related to changes in parties responsible for the study (eg, Sponsor, Sponsor Contact/Medical Director, and Medical Monitor) were made to reflect current information.		Title page, Protocol Signature Page, Section 10 Study Administrative Structure
Study location was updated to reflect study sites planned across regions rather than individual countries.		Synopsis Study Location
The tertiary objective to evaluate the effect of DX-2930 on health-related quality of life (QoL) was rephrased for clarity.		Synopsis Tertiary Objectives and Section 2.3 Tertiary Objectives
The tertiary objective to characterize the Pharmacokinetic (PK) and Pharmacodynamic (PD) profile of DX-2930 was clarified to indicate administration would be subcutaneous.		Synopsis Tertiary Objectives and Section 2.3 Tertiary Objectives
Three additional tertiary objectives were added to obtain more comprehensive information: • To evaluate safety and efficacy in the non-rollover population of switching from long-term prophylactic (LTP) treatment to DX-2930 • To evaluate breakthrough attack characteristics while receiving DX-2930 compared to historical baseline • To evaluate subject experience with self-administration of DX-2930 including ease of SC administration of DX-2930		Synopsis Tertiary Objectives and Section 2.3 Tertiary Objectives

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **27 June 2016**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
The number of non-rollover subjects allowed in DX-2930-04 was increased to at least 50 subjects with up to a maximum of 100 subjects.		Synopsis Study Design, Section 3.1.1 Overview
The number of non-rollover subjects was increased from at least 50 subjects up to a maximum of 100 subjects. Enrollment of subjects 12 to 17 years age was revised to be at least 15 including the estimated 10 rollover subjects from Study DX-2930-03. Therefore, the total enrollment for the study was updated to be at least 150, but not more than 250.		Synopsis Study Population and Section 4.1 Study Population
Revised to allow non-rollover subjects to continue long-term prophylactic HAE therapy with C1-INH, androgens or anti-fibrinolytics, for 2 weeks; initiation of tapering and discontinuation of LTP must occur within 3 weeks of receiving the first dose of DX-2930.		Synopsis Study Design, Section 3.1.1 Overview
Clarified that rollover subjects who experience their first attack outside the window of accepted scheduled visits are allowed to have an extra (unscheduled) study visit.		Synopsis Treatment Period, Section 3.1.1 Overview
The study has been extended in duration from 6 months to approximately one year and subsequently the number of doses of study drug a subject may receive has been increased.		Synopsis Duration of Treatment and Duration of Study for Individual Subjects, Study Activities Schedule
The study was expanded to allow subjects to self-administer doses of DX-2930 without supervision after receiving the first 2 doses of DX-2930 at the study site. Subjects must be considered suitable candidates; receive training; confirm understanding; and record specific information regarding subcutaneous administration and experience with self-administration. Subjects who elect to self-administer investigational product will be provided with supplies and be instructed on investigational product transport, storage, treatment compliance, and retention of all used and unused product vials for drug accountability purposes. Written instructions on DX-2930 handling and self-administration procedures will be provided to trained subjects prior to initiating self-administration. Vital signs will not be monitored for doses self-administered away from the investigational site.		Synopsis Self-Administration, Section 3.1.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **27 June 2016**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Since no data on embryo-fetal development toxicity are available for DX-2930, the clinical trial facilitation group's (CTFG) provided recommendations related to contraception and pregnancy testing. The inclusion criterion for contraception requirements was modified to emphasize the use of highly effective contraceptive measures and details for allowances (including stable estrogen doses) during treatment and until the end of relevant systemic exposure for women of childbearing potential. It was also clarified that the use of a male condom with or without spermicide or cervical cap, diaphragm, or sponge with spermicide or a combination (double-barrier methods) is not considered highly effective. Additional pregnancy tests (urine or serum) were also added for monitoring of pregnancy during treatment.		Synopsis Criteria for Inclusion, Section 4.2
Management of acute attacks was clarified to indicate that administration of the investigational product and study procedures will continue without alteration to the protocol-specified study schedule, even if the subject has HAE symptoms or receives treatment for an HAE attack.		Synopsis, Management of Acute Attacks, Section 5.4.1.1
Additional information was added to the study collection of data for HAE attacks to obtain more comprehensive information.		Section 6.4
Efficacy endpoints were revised from mean rates to number of attacks.		Synopsis Statistical Methodology, Section 9.6.2
Where appropriate, "Dyax" was replaced with the generic term of "the Sponsor."		Entire protocol Sections 1-10
A section on management of HAE attacks was added to Study Treatment(s).		Synopsis Management of Acute Attacks, Section 5.4.1.1
The study has been extended to incorporate an additional 6 months of treatment with DX-2930. Therefore the Study Activities Schedule has been revised to accommodate study assessments at dosing Visits 14-26. Follow-up visits (following end of treatment) are now occurring at Days 264, 378, and 392 (Visits 27, 28, and 29).		Study Activities Table, Section 7
The exclusion criterion prohibiting dosing with an investigational drug or exposure to an investigational device with 4 weeks prior to screening was clarified to not include DX-2930 or other HAE therapies.		Synopsis Exclusion Criteria, Section 4.3
The analysis population was clarified and is based on subjects who receive any exposure to DX-2930 in this study.		Synopsis Analysis Populations, Section 9.4
Data analysis and statistical methodology was revised to accommodate changes in efficacy or other study endpoints and to allow for more robust analyses.		Synopsis Statistical Methodology , Section 9.6
An interim analysis was added and will be conducted when at least 35 subjects complete 12 months of DX-2930 exposure.		Synopsis Interim Analysis and Data Monitoring, Section 9.9.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **27 June 2016**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
The efficacy evaluation period was updated to begin at Day 0 instead of Day 14 to be consistent with the intent-to-treat analysis principle.		Synopsis Statistical Methodology, Section 9.6.2
Quality of life assessments were revised and expanded to include EQ-5D-5L, SF-12, HADS, WPAI-GH and AE-QoL.		Synopsis Quality of Life Assessments, Section 6.14
An injection report and self-administration and SC injection survey were added to the study activities schedule and study procedures.		Synopsis DX-2930 Injection Report and Self-Administration and Subcutaneous Injection Survey, Section 6.15
Details on collection of prior medications were added to indicate documentation should extend to 4 weeks prior to study screening for non-rollover subjects.		Section 5.4
Information on packaging and labeling was expanded to detail the supplies for self-administration.		Section 5.7
Clarifying language was added to subject information and consent to indicate that subjects under 18 years will provide their assent to participate in the study if their legal guardian or caretaker has provided written informed consent.		Section 10.3 Subject Information and Consent
A new section was added for a Data Safety Monitoring Board (DSMB) who will provide an independent review of safety		Section 10.7 Data Safety Monitoring Board
To ensure subject safety, information on premature closure of the study was added to indicate some examples of conditions under which the study may be terminated overall or at a specific site after consultation between the Sponsor and investigators.		Section 10.9 Premature Closures of the Study
Financial disclosure language was updated to be consistent with 21 CFR 54 2(b) (1998).		Section 10.13 Financial Disclosure
Study Results/Publication Policy was updated to include language regarding posting of appropriate study information on applicable websites by the Sponsor. Additional detail on publication and disclosure of study information was added to indicate potential for public information.		Section 10.14 Publication and Disclosure Policy

APPENDIX 2 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases)

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
NOVEMBER 2007
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Note: The following toxicity table is a DRAFT and designed to provide general guidance on parameters for monitoring safety in clinical trials. This toxicity table is not comprehensive and should not be applied directly to all trials.

When selecting a toxicity table, the following are some of the items that must be taken into consideration:

- The population being studied
  - Does the clinical trial evaluate healthy subjects, subjects with a particular disease or condition?
- The stage of test article development
  - Is the clinical trial a Phase I, II, III or IV?
- The type of test article
  - Does the clinical trial evaluate a drug, device, vaccine or other biologic agent?
- The prior human and preclinical experience with the test article
  - Are there any specific findings that require adjustment of the toxicity table?

Single site clinical trials evaluating healthy subjects should conform to the laboratory normal values at the single site. Multi-center clinical trials should reconcile among their laboratory normal values when evaluating a healthy volunteer population.

Please confer with the DMID protocol team and DMID's Office of Clinical Research Affairs when selecting or developing a toxicity table for a DMID-sponsored trial.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/mm^3	13,000-15,000/mm^3	15,000-30,000/mm^3	>30,000 or <1,000/mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
NOVEMBER 2007
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CHEMISTRIES (continued)

	Grade 1	Grade 2	Grade 3	Grade 4
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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RESPIRATORY				
	Grade 1	Grade 2	Grade 3	Grade 4
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
NOVEMBER 2007
DRAFT

NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELATEL				
	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint distruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE
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DRAFT

SKIN

	Grade 1	Grade 2	Grade 3	Grade 4
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC

	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25-50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

Appendix 3 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

Note: The following toxicity table is a DRAFT and designed to provide general guidance on parameters for monitoring safety in clinical trials. This toxicity table is not comprehensive and should not be applied directly to all trials.

When selecting a toxicity table, the following are some of the items that must be taken into consideration:

- The population being studied
  - Does the clinical trial evaluate healthy subjects, subjects with a particular disease or condition?
- The stage of test article development
  - Is the clinical trial a Phase I (is it for the fisrt time in human subjects?) , II, III or IV?
- The type of test article
  - Does the clinical trial evaluate a drug, device, vaccine or other biologic agent?
- The prior human and preclinical experience with the test article
  - Are there any specific findings that require adjustment of the toxicity table?
  - Has it been approved for this indication in adult population?

Single site clinical trials evaluating healthy subjects should conform to the laboratory normal values at the single site. Multi-center clinical trials should reconcile among their laboratory normal values when evaluating a healthy volunteer population.

Please confer with the DMID protocol team and DMID's Office of Clinical Research Affairs when selecting or developing a toxicity table for a DMID-sponsored trial.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
GRADE 5	**Death**	

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Selected Values for children less than or equal to 3 months of age – does not apply for preterm infants)

For all parameters not listed on this table, please refer to the DMID Toxicity Table for children > 3 months of age.

HEMATOLOGY				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin				
1-7 days old	13.0-14.0 gm/dL	12.0-12.9 gm/dL	<12 gm/dL	Cardiac Failure secondary to Anemia
8-21 days old	12.0-13.0 gm/dL	10.0-11.9 gm/dL	<10.0 gm/dL	Cardiac Failure secondary to Anemia
22-35 days old	9.5-10.5 gm/dL	8.0-9.4 gm/dL	<8.0 gm/dL	Cardiac Failure secondary to Anemia
36-60 days old	8.5-9.4 gm/dL	7.0-8.4 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
61-90 days old	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
Abs Neutrophil Ct				
1 day old	5000-7000/mm^3	3000-4999/mm^3	1500-2999/mm^3	<1500/mm^3
2-6 days old	1750-2500/mm^3	1250-1749/mm^3	750-1249/mm^3	<750/mm^3
7-60 days old	1200-1800/mm^3	900-1199/mm^3	500-899/mm^3	<500/mm^3
61-90 days old	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3
Bilirubin (Fractionated bilirubin test must be preformed when total bilirubin is elevated)				
<7 days old	.	20-25mg/dL	26-30 mg/dL	>30 mg/dL
7-60 days old	1.1-1.9xN	2.0-2.9Xn	3.0-7.5xN	>7.5xN
61-90 days old	1.1-1.9xN	2.0-2.9xN	3.0-7.5xN	>7.5xN

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Selected Values for children less than or equal to 3 months of age)

HEMATOLOGY (continued)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Creatinine				
<7 days old	1.0-1.7 mg/dL	1.8-2.4 mg/dL	2.5-3.0 mg/dL	>3.0 mg/dL
7-60 days old	0.5-0.9 mg/dL	1.0-1.4 mg/dL	1.5-2.0 mg/dL	>2.0 mg/dL
61-90 days old	0.6-0.8 mg/dL	0.9-1.1 mg/dL	1.2-1.5 mg/dL	>1.5 mg/dL
Cr Clearance				
<7 days old	35-40 ml/min	30-34 ml/min	25-29 ml/min	<25 ml/min
7-60 days old	45-50 ml/min	40-44 ml/min	35-39 ml/min	<35 ml/min
61-90 days old	60-75 ml/min	50-59 ml/min	35-49 ml/min	<35 ml/min
Hypocalcemia				
<7 days old	6.5–6.9 mEq/L	6.0-6.4 mEq/L	5.5-5.9 mEq/L	<5.5 mEq/L
7-60 days old	7.6-8.0 mEq/L	7.0-7.5 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
61-90 days old	7.8-8.4 mEq/L	7.0-7.7 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
Hypercalcemia				
<7 days old	12.0-12.4 mEq/L	12.5-12.9 mEq/L	13.0-13.5 mEq/L	>13.5 mEq/L
7-60 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L
61-90 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

LOCAL REACTIONS				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Induration	< 10mm	10-25 mm	26-50mm	>50mm
Erythema	< 10mm	10-25 mm	26-50mm	>50mm
Edema	< 10mm	10-25 mm	26-50mm	>50mm
Rash at Injection Site	< 10mm	10-25 mm	26-50mm	>50mm
Pruritus	Slight itching at injection site	Moderate itching at injection extremity	Itching at injection extremity and other sites	Itching over entire body

HEMATOLOGY				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin for children greater than months and less than 2 years of age	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to anemia
Hemoglobin for children greater that 2 years of age	10-10.9 gm/dL	7.0-9.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to anemia
Absolute Neutrophil Count	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3
Platelets	-------	50,000-75,000/mm^3	25,000-49,999/mm^3	<25,000/mm^3
Prothrombin Time (PT)	1.1-1.2 x ULN	1.3 -1.5 x ULN	1.6 -3.0 x ULN	>3.0 x ULN
Partial Thromboplastin Time (PTT)	1.1-1.6 x ULN	1.7-2.3 x ULN	2.4 -3.0 x ULN	>3.0 x ULN

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

GASTROINTESTINAL				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Bilirubin (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Bilirubin (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Pancreatic Amylase	1.1-1.4 x ULN	1.5-1.9 x ULN	2.0-3.0 x ULN	>3.0 x ULN
Uric Acid	7.5-9.9mg/dL	10-12.4 mg/dL	12.5-15.0 mg/dL	>15.0 mg/dL
CPK	See Neuromuscular Toxicity			
Appetite	----------	Decreased appetite	Appetite very decreased, no solid food taken	No solid or liquid taken
Abdominal Pain	Mild	Moderate- No Treatment Needed	Moderate- Treatment Needed	Severe- Hospitalized for treatment
Diarrhea	Slight change in consistency and/or frequency of stools	Liquid stools	Liquid stools greater that 4x the amount or number normal for this child	Liquid stools greater than 8x the amount or number normal for this child

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

GASTROINTESTINAL (continued)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Constipation	Slight change in the consistency/frequency of stool	Hard, dry stools with a change in frequency	Abdominal pain	Distention and Vomiting
Nausea	Mild	Moderate-Decreased oral intake	Severe-Little oral intake	Unable to ingest food or fluid for more than 24 hours
Vomiting	1 episode/day	2-3 episodes per day	4-6 episodes per day	Greater than 6 episodes per day or Intractable Vomiting

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

ELECTROLYTES				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
CREATININE				
3 Months -2 Years of age	0.6-0.8 x ULN	0.9-1.1 x ULN	1.2-1.5 x ULN	>1.5 x ULN
2 Years- 12 Years of age	0.7-1.0 x ULN	1.1-1.6 x ULN	1.7-2.0 x ULN	>2.0 x ULN
Greater than 12 Years of age	1.0-1.7 x ULN	1.8-2.4 x ULN	2.5-3.5 x ULN	>3.5 x ULN

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

ELECTROLYTES				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hypernatremia		<145-149 mEq/L	150-155 mEq/L	>155 mEq/L or abnormal sodium AND mental status changes
Hyponatremia		130-135 mEq/L	129-124 mEq/L	<124 mEq/L or abnormal sodium AND mental status changes
Hyperkalemia	5.0-5.9 mEq/L	6.0-6.4 mEq/L	6.5-7.0 mEq/L	>7.0 mEq/L or abnormal potassium AND cardiac arrhythamia
Hypokalemia	3.0-3-5 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L	<2.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypercalcemia	10.5-11.2mg/dL	11.3-11.9 mg/dL	12.0-12.9 mg/dL	>13.0 mg/dL
Hypocalcemia	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.0-6.9 mg/dL	<6.0 mg/dL
Hypomagnesemia	1.2-1.4 mEq/L	0.9-1.1 mEq/L	0.6-0.8 mEq/L	<0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia
Hypoglycemia	55-65 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose AND mental status changes
Hyperglycemia	116-159 mg/dL	160-249 mg/dL	250-400 mg/dL	>400 mg/dL or ketoacidosis
Proteinuria	Tr-1+ or <150 mg/day	2+ or 150-499 mg/day	3+ or 500-1000 mg/day	4+ or Nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25	Microscopic >25		Gross hematuria

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

	cells/hpf	cells/hpf		

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(Greater than 3 months of age)

CENTRAL NERVOUS SYSTEM (CNS)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Generalized CNS Symptoms			Dizziness	Hypotonic, hyporesponsive episodes; Seizures; Apnea/Bradycardia; Inconsolable crying > 3 hrs;
Headache	Mild	Moderate, Responds to non-narcotic analgesia	Moderate to Severe, Responds to narcotic analgesia	Intractable
Level of Activity		Slightly irritable OR slightly subdued	Very irritable OR Lethargic	Inconsolable OR Obtunded
Visual		Blurriness, diplopia, or horizontal nystagmus of < 1 hour duration, with spontaneous resolution	More than 1 episode of Grade 2 symptoms per week, or an episode of Grade 2 symptoms lasting more than 1 hour with spontaneous resolution by 4 hours or vertical nystagmus	Decrease in visual acuity, visual field deficit, or oculogyric crisis
Myelopathy		None	None	Myelopathic/spinal cord symptoms, such as: pyramidal tract weakness and disinhibition, sensory level, loss of proprioception, bladder/bowel dysfunction

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

PERIPHERAL NERVOUS SYSTEM				
PARAMETER	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Neuropathy/ Lower Motor Neuropathy		Mild transient Paresthesia only	Persistent or progressive paresthesias, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss	Onset of significant weakness, decrease or loss of DTRs, sensory loss in "stocking glove" distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness.
Myopathy or Neuromuscular Junction Impairment	Normal or mild (<2 x ULN) CPK elevation	Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/- mild CPK elevation (<2 x ULN)	Proximal muscle weakness and/or atrophy affecting motor function +/- CPK elevation; or severe myalgias with CPK >2 x ULN;	Onset of myasthenia-like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(Greater than 3 months of age)

OTHER				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Allergy	Pruritus without Rash	Pruritic Rash	Mild Urticaria	Severe Urticaria Anaphylaxis, Angioedema
Drug Fever (Rectal)	.	38.5-40C 101.3 – 104.0F	Greater than 40.0C Greater than 104.0F	Sustained Fever: Equal or greater than 40C (104.0F) for longer than 5 days
Cutaneous	Localized rash	Diffuse maculopapular Rash	Generalized urticaria	Stevens-Johnson Syndrome or Erythema multiforme
Stomatitis	Mild discomfort	Painful, difficulty swallowing, but able to eat and drink	Painful: unable to swallow solids	Painful: unable to swallow liquids; requires IV fluids
Clinical symptoms *not otherwise specified* in this table	No therapy; monitor condition	May require minimal intervention and monitoring	Requires medical care and possible hospitalization	Requires active medical intervention, hospitalization, or hospice care
Laboratory values *not otherwise specified* in this table	Abnormal, but requiring no immediate intervention; follow	Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug	Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug	Life-threatening severity; Requires immediate evaluation, treatment, and usually hospitalization; Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism that study drug

Appendix 4 HAE Attack Assessment and Reporting Procedures (HAARP)

HAE Attack Assessment and Reporting Procedures (HAARP)

Title:	HAE Attack Assessment and Reporting Procedures (HAARP)
Product Name:	DX-2930
Indication:	Prevention of angioedema attacks in patients with HAE
Sponsor:	Dyax Corp. 55 Network Drive Burlington, MA 01803
Original Date:	14 September 2015
Version:	v1.0

TABLE OF CONTENTS

1 PURPOSE

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

2 DEFINITION OF AN ATTACK

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

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

Despite the presence of these symptoms, the investigator may still determine clinically that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an attack (e.g., urticaria), the reported event persists well beyond the typical time course of an attack (e.g., greater than 7 days), 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 their previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.

Attack resolution is defined as the subject no longer having symptoms of the attack.

Prodromal symptoms by themselves are not considered an attack.

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

3 REPORTING AND ASSESSMENT OF ATTACK DATA

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

During the relevant study periods, as defined in the applicable study protocol, subjects (or caregivers, for subjects < 18 years old) will be instructed to contact the site within 72 hours of the start of symptoms of an attack. In the situation that a subject is incapacitated and is

unable to contact the site, a family member or other individual with detailed knowledge of the event can provide the information. If desired by the subject, memory aids may be provided to assist in tracking any HAE attacks subject's experience. Any tools or devices the subject uses to track this information are not intended to serve as source documents for the study.

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

A designated individual at the site (the collector) will contact the subject or caregiver on a regular basis as defined in the study protocol, regardless of whether or not the subject has reported any attacks, in order to solicit for any attacks that may have occurred but were not reported. In addition, during each study visit, site personnel will solicit for any new attack information that was not provided through previous contact with the subject or caregiver.

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

3.1 Subject-Reported Symptoms

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

3.1.1 Attack Information

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

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

Subjects do not have to wait for their symptoms to completely resolve to report an attack. Information about ongoing symptoms can be obtained by the site during the check-in call and/ or at a scheduled study visit. Subjects should not withhold or delay any treatment they would normally receive to treat their attack in order contact the site.

3.1.2 Worsening Symptoms

The site may request the subject call them back if they experience worsening symptoms and/ or new symptoms for a reported attack. Otherwise, the new information will be captured during the next check-in call or scheduled study visit. Subjects may contact the site on their own to provide information about any worsening symptoms.

3.1.3 Subject Training

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

3.1.4 Reporting Multiple Attacks

If a subject experiences symptoms they attribute to more than one unique attack they can report this as multiple attacks to the site. Based on the definition of an attack as stated in Section 2, it will be the determination of the investigator or designee as to whether events reported as being separate are confirmed as separate attacks or not.

3.1.5 Caregiver Report

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

3.1.6 Subject Contact with Sites

Site personnel will establish a recommended method and time window for each subject to contact the site to report any symptoms of an attack. Sites will establish a primary contact person and, if possible, a back-up person, with contact information. Back-up plans, including call backs and/ or use of back-up contacts, should be established in case the subject is unable to reach someone at the site.

3.2 Site Contact with the Subject

Sites will establish a recommended day and time window for check-in calls between study visits. The date and time for check-ins can be modified based on when the last contact with the subject was made, as outlined in the study protocol. When the site is contacted by a subject reporting symptoms of an attack the site should make sure they have the ability to record the information provided in a complete and accurate way. Back-up plans should be

established in case the subject misses a call from the site. A study schedule for each subject's on-site visits will be provided to the subject by the site.

3.2.1 Review of subject report of symptoms

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

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

3.2.2 Documenting a Reported Attack

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

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

Additional probing questions about what the subject experienced to determine:

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

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

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

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

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

3.2.3 Site Training

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

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

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

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

3.3 HAE attacks as Adverse Events

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

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 Dyax using the SAE Reporting Form in the 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.

4 INVESTIGATOR ATTACK ASSESSMENT

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

The assessor must review the information and determine whether the event is an actual attack or not. If needed, the assessor can contact the subject and/or caregiver to clarify information or ask for any additional detail. The determination will be documented along with the date and time the determination was made. Any event deemed not an attack must be accompanied by an explanation and alternative diagnosis by the assessor.

When reviewing subject information, the assessor will follow the definitions of an attack as outlined in these procedures and, taking all available information about the event into consideration, will determine if it is a confirmed attack. The assessment of the attack is the Investigator or designee's own, and not the opinion of the subject, the subject's caregiver or any other site personnel. Assessors may consult with one another about a particular subject's attack but only one assessor makes the documented determination. It is possible for both the Principal Investigator and physician designee to assess different attacks for the same subject.

APPENDIX 5 Summary of Pivotal Study DX-2930-03 in Subjects with HAE

The proposed pivotal clinical study (Study DX-2930-03) is entitled "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)." This study will be a multi-center, double-blind, randomized, placebo-controlled parallel-arm study evaluating the efficacy of DX-2930 in preventing acute angioedema attacks in patients with Type I or Type II HAE. The double-blind study is planned to be followed by the study described in the present protocol, an open-label extension (OLE) study (DX-2930-04).

The primary objective of Study DX-2930-03 is to evaluate the efficacy of DX-2930 in preventing HAE attacks. The secondary objective is to evaluate the safety of repeated SC administrations of DX-2930. The tertiary objectives are to evaluate the pharmacodynamic effects of chronically administered DX-2930; to assess the immunogenicity of chronically administered DX-2930; to evaluate the pharmacokinetics of chronically administered DX-2930; and to evaluate the effect of DX-2930 upon quality of life assessments.

Subjects aged 12 years and over with a documented diagnosis of Type I or Type II HAE who experience at least 1 attack per 4 weeks will be eligible for the study. Up to 120 subjects are planned for enrollment across approximately 60 sites in the United States, Canada, Italy, Germany, United Kingdom and Jordan.

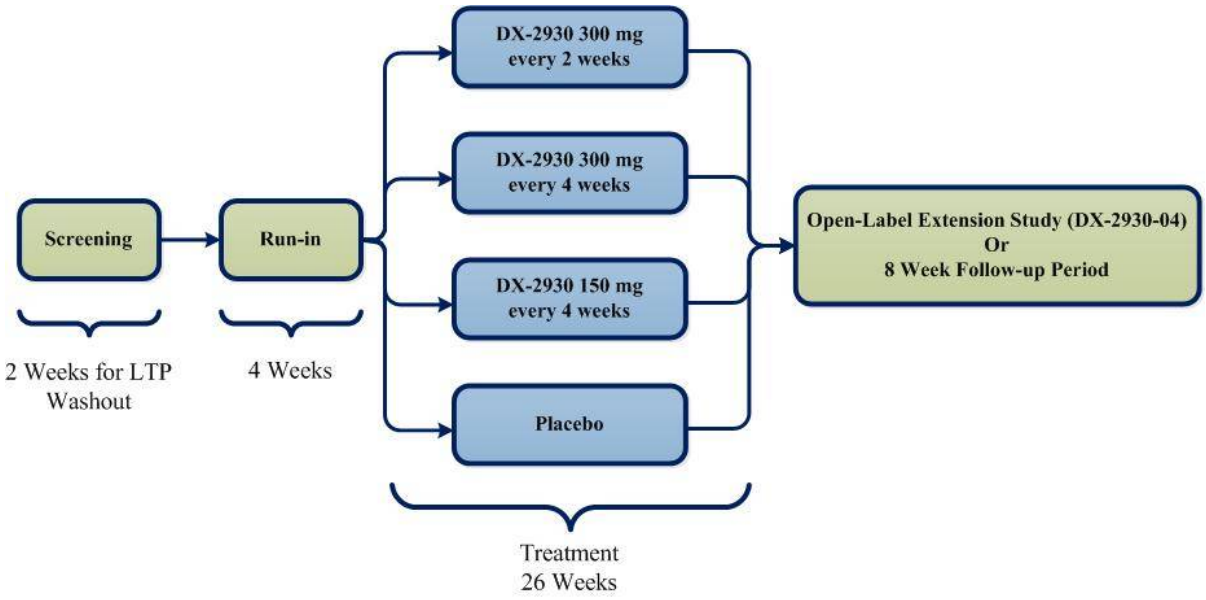
Following informed consent, subjects will undergo screening assessments. Subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. Subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. The run-in period may be extended to 8 weeks if the minimum baseline attack rate is not achieved in the first 4 weeks. HAE subjects will then 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 one of three dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks or 150 mg every 4 weeks. Each subject will undergo a treatment period consisting of 13 doses of blinded study drug, for a period of 26 weeks from the date of first dose on Day 0 through Day 182

Subjects may consent to rollover into the OLE study (present protocol DX-2930-04) upon completion of their participation in the double-blind treatment period.

The primary endpoint will be to compare the number of investigator-confirmed HAE attacks observed in each DX-2930 treatment arm to that in the placebo arm during the efficacy assessment period (Day 0 through Day 182).

Figure 2 shows a schematic of the double-blind, pivotal study.

Figure 2 Overview of the Design of Pivotal Study DX-2930-03



Dose Rationale for Double-Blind, Pivotal Study DX-2930-03

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 while avoiding non-therapeutic or super-therapeutic doses and regimens.

Clinical Trial Protocol: DX-2930-04

Study Title:	HELP Study Extension™: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number:	DX-2930-04
Study Phase:	Phase 3
Product Name:	DX-2930 (SHP643)
IND Number:	116647
EudraCT Number:	2015-005255-27
Indication:	Prevention of angioedema attacks in patients with HAE
Investigators:	Multicenter
Sponsor:	Dyax Corp. (an indirect, wholly owned subsidiary of Shire plc.) 300 Shire Way, Lexington, MA 02421
Sponsor Contact:	[redacted], MD [redacted], Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: [redacted]
Global Medical Monitor:	[redacted], MD 300 Shire Way, Lexington, MA 02421 USA Phone: [redacted]

	Date:
Original Protocol	14 December 2015
Amendment 1.0	27 June 2016
Amendment 2.0	20 January 2017
Amendment 3.0	29 June 2017

PROTOCOL SIGNATURE PAGE

Study Title:	HELP Study Extension™: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number:	DX-2930-04
Amendment 3.0 Final Date:	29 June 2017

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The signature of the Sponsor representative indicates that the Sponsor will comply with all Sponsor obligations detailed in applicable regulations and guidelines and will ensure the investigator is informed of all relevant information that becomes available.

Signed: [redacted] Date: [redacted]

[redacted] MD [redacted]
[redacted], Clinical Development
300 Shire Way, Lexington, MA 02421 USA

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP), and all applicable regulatory requirements and guidelines as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use only the informed consent form approved by Dyax Corp. and my Institutional Review Board (IRB), Research Ethics Board (REB) or Ethics Committee (EC) and will fulfill all responsibilities for submitting pertinent information to the IRB/REB/EC responsible for this study.

I further agree that Dyax Corp. or their designees shall have access to any source documents from which eCRF information may have been generated.

By signing this protocol, I agree to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP to which it conforms.

Signed:_____ Date:_____
Investigator

Address: _____

_____

AMENDMENT SUMMARY AND RATIONALE

The purpose of this amendment is to add new objectives and related measurements, add quality of life (QoL) endpoints, and extend the study from 12 months to 30 months to continue to obtain data important for the assessment of DX-2930 (ie, safety and efficacy data).

Noteworthy changes to the protocol are captured in the table below. Additional minor revisions in grammar, spelling, punctuation, and format have been made for clarity and are not reflected in the summary of changes.

Summary of Changes from Previous Version

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **29 June 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
A new tertiary objective and related measurement have been added to evaluate exploratory biomarker(s) of angioedema disease-state bioactivity in blood. Additional biomarker assessments have been added to the study to evaluate the effect of DX-2930 on disease activity. • Objective: To evaluate exploratory biomarker(s) of angioedema disease-state bioactivity in blood Measurement: Exploratory biomarker(s) of angioedema disease state bioactivity in plasma and serum A new tertiary efficacy objective and related measurement have been added to better understand the clinical response to rescue medications while on DX-2930 therapy. • Objective: To assess the clinical response of rescue medications for the treatment of acute angioedema attacks while on DX-2930 therapy (applicable for subjects ≥18 years of age) Measurement: Subject response to rescue medications A new tertiary objective has been added to assess subjects' satisfaction with DX-2930. • Objective: To assess treatment satisfaction Measurement: Treatment satisfaction will be measured using Treatment Satisfaction Questionnaire for Medication (TSQM-9). The TSQM-9 is a 9-item validated instrument. A new tertiary objective has been added to assess subjects' and investigators' overall perception of treatment response. • Objective: To assess global impression of treatment response Measurement: Global Impression of Treatment Response will be measured by a 1-item question to assess overall perception of treatment response. A new tertiary objective has been added to assess control of angioedema among study subjects. • Objective: To assess control of angioedema		Synopsis, Section 2, Section 6, Section 9.8, Table 1, Table 2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **29 June 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Measurement: The control of angioedema will be measured using the Angioedema control test (AECT).		
A new tertiary objective and related measurement have been added to evaluate subject experience and ease of use of the prefilled syringe, if utilized. • Objective: To evaluate subject experience and ease of use of the prefilled syringe, if available Measurement: Subject experience with the prefilled syringe		Synopsis, Section 2, Section 3.3, Section 5.1, Section 5.7, Section 6, Section 9.8, Table 1, Table 2
A brief exit interview has been added to obtain information about subjects' overall experience with DX-2930 studies and any changes in signs and symptoms during the between-attack period and related changes to subject health.		Section 6, Table 1, Table 2
The treatment period has been extended from 12 to 30 months to accommodate the additional changes to the study described above.		Entire protocol, Table 1, Table 2, Section 7
Table 2 has been added to present the schedule of assessments to be performed from Day 365 through Day 952. To reduce site burden, the frequency of required on-site visits in the second year has been reduced relative to the first year. Key refinements represented in Table 2 include: • The frequency of on-site visits has been decreased so that subjects are only required to come to the clinic once every 2 months (instead of once a month or once every third visit, as appropriate for each subject) The requirement that each attack be confirmed by the investigator within 72 hours for non-serious AE attacks has been expanded to 7 calendar days. (Note: This refers only to confirmation of attacks, *not* reporting of SAEs or AEs.) ECGs will be assessed through Day 364, at the end of the study, and when clinically required.		Table 2
For purposes of internal consistency, Table 1 also reflects the updated requirement that each attack be confirmed by the investigator within 7 calendar days for non-serious AE attacks.		Table 1
A clarification note has been added to Inclusion Criteria 2 to ensure proper documentation occurs for subjects previously treated with C1-INH: "It is understood that C1-INH therapy may alter the lab results of C1-INH and investigator's discretion in collaboration with Medical Monitor is advised for proper documentation of eligibility."		Synopsis, Table 1, Section 4.2, Section 6.8.1.6
Potential modifications to open-label dosing have been expanded to include the following: "In addition, an individual subject's dose may be modified based on a benefit-risk assessment and recommendation from the treating physician. Consultation with and approval by the Sponsor's Medical Monitor is required."		Synopsis, Section 3.1.1
The following subgroup analysis has been added to the statistical section for		Section 9.9.6

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **29 June 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
consistency with statistical analysis used in Study DX-2930-03: "• History of laryngeal HAE attacks (history of laryngeal attack, no history of laryngeal attack)"		
Updated the address to: 300 Shire Way, Lexington, MA 02421 USA Added clarification that Dyax Corp. is now an indirect, wholly owned subsidiary of Shire plc.		Title page, Synopsis, Section 10, Table 3, Appendix 4
The first and second sentences of Section 3.2 were updated for clarity and consistency with the protocol.		Appendix 4 (Section 3.2)

See Appendix 1 for protocol history, including amendments.

SYNOPSIS

Sponsor:
Dyax Corp., an indirect, wholly owned subsidiary of Shire plc.
300 Shire Way, Lexington, MA 02421 USA

Name of Finished Product:
DX-2930 Drug Product (DP)

Name of Active Ingredient:
DX-2930 (lanadelumab) is a recombinant, Chinese hamster ovary (CHO) cell-expressed, fully human immunoglobulin G subclass 1 (IgG1), kappa light chain, monoclonal antibody.

Names of Inactive Ingredients:
Sodium phosphate dibasic dihydrate, citric acid monohydrate, L-histidine, sodium chloride, and Polysorbate 80

Study Title:
HELP Study Extension™: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)

Study Number:
DX-2930-04

Study Phase: Phase 3

Study Location:
Approximately 60 study sites planned across North America, the European Union, and the Middle East

Primary Objective:
To evaluate the long-term safety of repeated subcutaneous (SC) administrations of DX-2930

Secondary Objectives:

- To evaluate the long-term efficacy of DX-2930 in preventing HAE attacks
- To characterize the outer bounds of dosing frequency for DX-2930

Tertiary Objectives:

- To assess the immunogenicity of chronically administered DX-2930
- To evaluate the effect of DX-2930 on health-related quality of life (QoL)
- To characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of SC administration of DX-2930
- To evaluate safety and efficacy in the non-rollover population of switching from long-term prophylactic (LTP) treatment to DX-2930
- To evaluate breakthrough attack characteristics while receiving DX-2930 compared to historical baseline
- To evaluate subject experience with self-administration of DX-2930 including ease of SC administration of DX-2930
- To evaluate exploratory biomarker(s) of angioedema disease-state bioactivity in plasma and

serum

- To evaluate subject experience and ease of use of the prefilled syringe, if available
- To assess the clinical response of rescue medications for the treatment of acute angioedema attacks while on DX-2930 therapy (applicable for subjects ≥18 years of age)
- To assess treatment satisfaction
- To assess global impression of treatment response
- To assess control of angioedema

Study Design:

Study DX-2930-04 is an open-label, long-term safety and efficacy extension study of Study DX-2930-03, to evaluate the investigational medicinal product (IMP), DX-2930, in preventing acute angioedema attacks in patients with Type I and Type II HAE. There are two types of subjects who will be enrolled into this study:

- Subjects who rollover from Study DX-2930-03
- Subjects who are non-rollover (ie, were not participants in Study DX-2930-03)

Rollover Subjects

Rollover subjects are subjects who complete the double-blind treatment period at Day 182 of Study DX-2930-03 and consent to enter Study DX-2930-04. Subjects who discontinue from Study DX-2930-03 after enrollment are not eligible to enroll in Study DX-2930-04.

Subjects should be asked about their interest in Study DX-2930-04 study after enrollment into Study DX-2930-03 to anticipate enrollment and preparedness for Study DX-2930-04. Willing subjects must sign informed consent for Study DX-2930-04 on or after Day 168 of Study DX-2930-03.

Subjects who are eligible to roll over into Study DX-2930-04 but elect not to, may not enroll in Study DX-2930-04 at a later time. The first Study DX-2930-04 visit for rollover subjects (Day 0) will occur on the same day as the Study DX-2930-03 Day 182 study visit. Rollover subjects will complete all Study DX-2930-03 final study assessments (Day 182) at which time they will be discharged from that study. No assessments conducted between the Study DX-2930-03 Day 182 study visit and the first Study DX-2930-04 visit (Day 0) will be duplicated. Results of the final Study DX-2930-03 assessments on Day 182 will be used as the pre-dose results for Day 0 of Study DX-2930-04.

All subjects, caregivers, investigators and study site personnel will remain blinded to the Study DX-2930-03 treatment assignment until the conclusion of Study DX-2930-04.

Non-rollover subjects

At least 50 subjects (to approximately 100) who were not participants in Study DX-2930-03 will be permitted to enroll if they meet the eligibility requirements. Subjects who screen fail out of Study DX-2930-03 for not meeting the minimum attack requirements during the run-in period must wait until enrollment for the double-blind study has ended before they can screen for Study DX-2930-04. The Sponsor may ease this restriction based on the enrollment rate observed in

Study DX-2930-03. Subjects who are still in the run-in period for Study DX-2930-03 when enrollment for that study closes, as well as subjects on prior LTP who screen fail out of Study DX-2930-03 due to an inability to wash-out of their LTP, may screen for Study DX-2930-04 following discussion with the Sponsor medical monitor.

Screening Period:

Rollover Subjects

There is no screening period for rollover subjects.

Non-rollover Subjects

Non-rollover subjects must provide informed consent and have screening assessments completed within 4 weeks prior to their first open-label dose. Screened non-rollover subjects (adults and adolescents) who are on LTP with C1-INH therapy for HAE can continue their current LTP until Day 8 (or Day 15) such that subjects will have received 2 (or 4) doses of C1-INH. (It is understood that C1-INH therapy may alter the lab results of C1-INH assessments; therefore, the investigator's discretion in collaboration with Medical Monitor is advised for proper documentation of eligibility). For subjects who are on attenuated androgens (eg, danazol) or anti-fibrinolytics (eg, tranexamic acid), a similar tapering schedule is recommended. However, the taper can be prolonged by an additional week, if medically indicated, as long as androgen or anti-fibrinolytic therapy is stopped within 3 weeks after receiving the first dose of DX-2930.

Treatment Period:

Rollover Subjects

Following informed consent and pre-dose assessments, rollover subjects will receive a single open-label dose of 300 mg DX-2930 administered subcutaneously (SC) on Day 0. Subjects will not receive any additional DX-2930 doses until their first reported, and investigator-confirmed HAE attack. As such, the total number of doses within the treatment period will vary by rollover subject.

The duration of time between the first open-label dose and first reported HAE attack will vary by rollover subject. All rollover subjects must adhere to the Study Activities Schedules (Table 1 and Table 2) for the entire duration of the study. However, until a rollover subject reports their first HAE attack, only scheduled study visits where the following tests and assessments are performed must be conducted at the investigative site: pregnancy testing, clinical laboratory testing, physical examination, 12-Lead ECG, QoL, PK, PD, and anti-drug antibody sample collection. All other scheduled study visits may be conducted via site check-in calls to collect information on adverse events, concomitant therapy, and HAE attack data. See Study Activities Schedules (Table 1 and Table 2) for which visits must be conducted at the study site.

Once a rollover subject reports their first HAE attack they will present to the investigative site for their second open-label dose of DX-2930 as quickly as subject and site schedules allow. If the second dose is to be administered within the accepted ±4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit. If that scheduled visit has already occurred, the day of the visit will be considered an acceptable, extra study visit (ie, an unscheduled visit). Similarly, if the second dose is administered outside of the accepted ±4 day window around a scheduled visit, the day of the visit will be considered an acceptable extra

unscheduled study visit, (ie, this visit will not replace any scheduled visit).

Regardless of the study day, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical examination, clinical laboratory testing, blood sampling for PK, PD, and anti-drug antibody. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data.

Regardless of when a rollover subject's first HAE attack occurs, there will be a minimum of 10 days between their first open-label dose and their second open-label dose. Following their second open-label dose, rollover subjects will continue to receive repeated SC administrations of open-label 300 mg DX-2930 every 2 weeks for the remaining duration of the treatment period per the scheduled dosing in the Study Activities Schedules. The treatment period will last up to 924 days from the date of the first open-label dose. The number of doses administered during this period will vary by subject based on the date of each subject's second dose, but will not exceed 66 doses. The Day 910 study visit is the last visit at which a dose may be administered.

Non-rollover Subjects
Once all screening assessments have been completed and eligibility confirmed, non-rollover subjects will arrive at the study site and, following pre-dose assessments, receive an open-label dose of 300 mg DX-2930 administered SC on Day 0. Non-rollover subjects will continue to receive SC administrations of open-label 300 mg DX-2930 every 2 weeks throughout the duration of the treatment period per the scheduled dosing in the Study Activities Schedules.

All Subjects:
All doses (with the exception of the second dose for rollover subjects) require a minimum of 10 days and maximum of 18 days between administrations and should fall within the accepted ±4 day window around study visits.

After the second DX-2930 dose is given either within the study window (±4 days) or an acceptable extra study visit, the 3rd dose must be administered at the next pre-defined study visit according to the schedule of assessments.

If a subject experiences an acute angioedema attack at any time during the study that in the opinion of the investigator requires medical intervention, standard of care therapy should be provided based on subject's medical history and per locally approved product information. Administration of DX-2930 and study procedures will continue without alteration to the protocol study activities schedules, even if a subject receives treatment for a breakthrough angioedema attack on the day of a scheduled dose of study drug (if self-administering) or scheduled study visit.

Self Administration
All subjects (adolescent or adult) who are considered suitable candidates (ie, those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer treatment. Subjects must complete appropriate training by the investigator or designee and understanding of the training must be confirmed by the investigator or designee. Subjects are

allowed to initiate self-administration at the subject's home, or other agreed upon location after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may self-administer subsequent doses of DX-2930 at the investigational site (when visits are scheduled study site visits) or the subject's home or other agreed upon location (when the study permits off-site dosing). See Schedule of Activities for details. Adolescent subjects self-administering investigational product will be supervised by a parent/legal guardian/caregiver. Alternatively, a parent/legal guardian/caregiver, after completing appropriate training, will be allowed to administer DX-2930 to an adolescent without study site personnel supervision. Site personnel will call subjects within approximately 3 days after the planned off-site self-administrations to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.

Throughout the study, study site personnel will document information in source documents (ie, the subject's medical record) and eCRF regarding the subject's experience with self-administration and SC administration of DX-2930.

Subjects may be offered the opportunity to utilize a prefilled syringe (if available) for self-administration of DX-2930.

Follow-up Period
After completion of the treatment period, all subjects will undergo safety evaluations during a 4-week follow-up period.

Modifications to Open-Label Dosing
If, at any time, a dose-related safety signal is identified either from this study or Study DX-2930-03, the Sponsor may decide to modify the open-label DX-2930 dose and/or frequency. In addition, an individual subject's dose may be modified based on a benefit-risk assessment and recommendation from the treating physician. Consultation with and approval by the Sponsor's Medical Monitor is required.

In addition, based on the results of Study DX-2930-03, the Sponsor may switch to a different dose and/or frequency.

Study Population:
The study is expected to enroll subjects from Study DX-2930-03, as well as at least 50 (to approximately 100) additional subjects who were not enrolled in Study DX-2930-03. The total enrollment is expected to be at least 150 but not more than 250 HAE Type I or II subjects. Subjects will be 12 years of age or older who experience at least 1 attack per 12 weeks. HAE diagnosis will be confirmed through documented clinical history and diagnostic testing conducted either during screening or during prior participation in Study DX-2930-02 or Study DX-2930-03. The study will aim to enroll at least 15 subjects who are 12 to 17 years of age, inclusive of the estimated 10 subjects 12 to 17 years old who are expected to roll over from Study DX-2930-03.

Criteria for Inclusion:
Subjects must meet the following criteria to be enrolled in this study:

1. Male and female HAE subjects who are 12 years of age or older at the time of screening.

2. Documented diagnosis of HAE (Type I or II) based on all of the following:
    - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).
    - Diagnostic testing results obtained during screening (or a prior DX-2930 study) that confirm HAE Type I or II: C1 inhibitor (C1-INH) functional level < 40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may be retested if results are incongruent with clinical history or believed by the investigator to be confounded by recent LTP use. (It is understood that C1-INH therapy may alter the lab results of C1-INH assessments; therefore, the investigator's discretion in collaboration with Medical Monitor is advised for proper documentation of eligibility).
    - At least one of the following: Age at reported onset of first angioedema symptoms ≤ 30 years, a family history consistent with HAE Type I or II, or C1q within normal range.
3. A historical baseline HAE attack rate of at least 1 attack per 12 weeks.
4. Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects age 12 to 17, whose caregiver has provided informed consent, are willing and able to read, understand and sign an assent form.
5. Males and females who are fertile and sexually active must adhere to contraception requirements for the duration of the study as follows:
    - Females* of childbearing potential must agree to be abstinent, or it is recommended to use highly effective forms of contraception from screening through 30 days after the final study visit. This includes stable doses (for 3 months prior to study screening) of combined estrogen and progestin-containing hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable), progestin-only hormonal contraception associated with inhibition of ovulation, intra-uterine device (IUD, all types) or intrauterine hormone releasing systems (IUS). Notes: 1) A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. 2) Use of a male condom with or without spermicide or cervical cap, diaphragm or sponge with spermicide or a combination (double barrier methods) are not considered highly effective.
    - Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
    - Males, including males who are surgically sterile (post vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study visit.

      *NOTE: Female rollover subjects (those who previously participated in Study DX-2930-03) of childbearing potential may continue to use the effective birth control method used during Study DX-2930-03.

Criteria for Exclusion:

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

1. Discontinued from Study DX-2930-03 after enrollment for any reason.
2. If rolling over from Study DX-2930-03, presence of important safety concerns that would preclude participation in this study.
3. Concomitant diagnosis of another form of chronic, recurrent angioedema such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.
4. Dosing with an investigational drug (not including DX-2930 or other HAE therapies) or exposure to an investigational device within 4 weeks prior to screening.
5. Exposure to angiotensin-converting enzyme (ACE) inhibitors within 4 weeks prior to study screening or any newly initiated or dose modification of estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) 3 months prior to the screening visit.
6. Unwilling to discontinue use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 3 weeks after starting DX-2930 treatment.
7. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's Syndrome).
8. Pregnancy or breastfeeding.
9. Subject has any condition that, in the opinion of the investigator or Sponsor, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (eg, history of substance abuse or dependence, a significant pre-existing illness or other major comorbidity that the investigator considers may confound the interpretation of study results).

Test Product; Dose; and Mode of Administration:

DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated using the following compendial components: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Polysorbate 80. Each open-label vial contains a nominal concentration of 150 mg DX-2930 active ingredient in 1 mL solution OR 300 mg DX-2930 active ingredient in 2 mL solution.

For each 300 mg dose of DX-2930, each subject will receive a total of 2 mL, which will be administered in a single 2-mL SC injection.

The injection will be given in the upper arm, thigh or abdomen.

Self-Administration Option: Investigational product can be self-administered without supervision (parental supervision required for adolescent subjects) after subjects receive appropriate training by the investigator or designee and their understanding is confirmed. Subjects are allowed to initiate offsite self-administration after receiving the first 2 doses of DX-2930 at the study site and may continue to self-administer all subsequent doses (see Study Activities Schedules).

Duration of Treatment:

All subjects will receive open-label DX-2930 during a treatment period of up to 924 days.

The last dose of open-label DX-2930 administered to rollover subjects may be given at the Day 910 study visit. Non-rollover subjects will receive 300 mg DX-2930 every 2 weeks for up to 66 doses, with the first dose administered on Day 0 and the final dose administered at the Day 910 study visit.

There will be a ± 4-day window around each study visit. There will be a minimum of 10 days between any two doses. Excluding the interval between the first and second open-label doses for rollover subjects, there will be a maximum of 18 days between any two doses. Subjects will be monitored at the study site through 1 hour post-dose for scheduled study site visits. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.

Duration of Study for Individual Subjects:

Following informed consent, subjects will either rollover from DX-2930-03 or undergo screening assessments (non-rollover subjects). Screening assessments for non-rollover subjects must occur within 4 weeks prior to the first open-label dose. Eligible subjects will be enrolled and undergo a treatment period of up to 924 days. At the conclusion of the treatment period, subjects will be followed for an additional 4 weeks.

Prohibited Concomitant Treatments:

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

- Long-term prophylaxis for HAE (eg, use of C1-INH for LTP, attenuated androgens, or anti-fibrinolytics) once LTP is discontinued (within 3 weeks following the first dose of DX-2930).
- Angiotensin-converting enzyme (ACE) inhibitors.

- Initiating or changing the dose of estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) 3 months prior to study screening.
- Use of androgens (eg, stanozolol, danazol, oxandrolone, methyltestosterone, and testosterone) for non-HAE related medical conditions or for HAE after discontinuation during the first three weeks.
- Any other investigational drug or device.

The use of short-term prophylactic treatment for HAE will be permitted if medically indicated. Short-term (pre-procedure) prophylaxis is defined as the use of C1-INH to avoid angioedema complications from medically indicated procedures.

Management of Acute Attacks:

Acute HAE attacks during the study are to be managed in accord with the investigator's usual care of their patients, including the use of acute attack therapies that the investigator deems as medically appropriate. Use of C1-INH will be permitted as an acute attack therapy but not as a long-term prophylactic therapy. Administration of DX-2930 and study procedures will continue without alteration to the protocol-specified study schedule, even if the subject has symptoms of an HAE attack the day of DX-2930 administration and/or receives treatment for an HAE attack. The administration of DX-2930 can also be re-scheduled as long as the minimum and maximum timeframe between doses are met based on subject preference or physician discretion.

Safety Assessments:

Safety assessments will include the following:

- Adverse events (AEs), including serious adverse events (SAEs) and adverse events of special interest (AESI). SAEs and AESI will be reported to the Sponsor within 24 hours of becoming aware of the event.
- Vital signs, including sitting or supine blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR)
- Physical examination
- Clinical laboratory testing (hematology, serum chemistry, coagulation, and urinalysis)
- 12-Lead electrocardiogram (ECG)

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

Pharmacokinetic (PK) Assessments:

Blood samples will be collected for the measurement of plasma DX-2930 concentrations.

Pharmacodynamic (PD) Assessments:

Blood samples will be collected to evaluate the pharmacodynamic effects of DX-2930 through biomarker assays.

Immunogenicity Assessments:

Blood samples will be collected to assay for the presence of anti-drug antibodies, including evaluation of neutralizing antibodies (if any confirmed positive anti-drug antibodies are detected).

C1-INH, C4, and C1q and Exploratory Biomarker Assessments:
Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment, unless already collected as part of protocol DX-2930-02 or DX-2930-03. C1-INH, C1q, C4 and exploratory biomarkers will be measured throughout the study and at the end of the study to evaluate the effect of DX-2930 on these biomarkers of disease activity.

Quality of Life Assessments:
Quality of life (QoL) assessments will be conducted using the Angioedema Quality of Life Questionnaire (AE-QoL), EuroQoL 5-Dimensional 5-Level Measure (EQ-5D-5L), Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH), Hospital Anxiety and Depression Scale (HADS), and 12 Item Short Form Survey (SF-12), the Angioedema Control Test (AECT), the Global Impression of Treatment Response, and Treatment Satisfaction Questionnaire for Medication (TSQM-9). Additionally, subjects will complete a brief exit interview to obtain data on the subjects' experience in the DX-2930 studies.

DX-2930 Injection Report and Self-Administration and Subcutaneous Injection Survey
An injection report of the subject's experience with self-administration and SC injection will be completed by the subject after all doses of DX-2930.

In addition, an assessment survey of the subject experience with SC and self-administration injections of DX-2930, and the prefilled syringe (if utilized), will be completed by the subject as indicated in the Study Activities Schedules.

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

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

At screening, HAE attack history will be collected for non-rollover subjects. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant attack location(s), triggers, average duration, acute attack therapy use and history of LTP (including duration of LTP, medication(s) and dose used for LTP, and frequency of attacks while receiving LTP). If available, information will also be collected on HAE diagnosis (year of confirmation, how many years after onset of symptoms was diagnosis confirmed, or if subject was misdiagnosed).

During the study, subjects (or caregivers) will be instructed to notify and report details to the study site within 72 hours of the onset of an attack. This includes the first attack experienced by rollover subjects following their first open-label dose. In the situation 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 experienced, but their use is

not mandatory.

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 (work, school, social interactions) and whether any assistance or medical intervention was required, including hospitalizations, additional laboratory tests or emergency department visits.
- Any medications used to treat the attack (both prescription and over the counter).
- If the attack resolved, date and time the subject was no longer experiencing symptoms.

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

Study site personnel will contact rollover subjects approximately every 7 days following the first dose of open-label DX-2930 to solicit for any HAE attacks not already reported. Site check-ins will continue until the subject has received their second open-label dose.

During each study visit, study site personnel will solicit for any new attack information that was not already provided to the site.

In this study, HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to DX-2930, 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 EDC system within 24 hours of becoming aware of the event.

In addition to reporting AEs and SAEs as described above, the investigator or physician designee is also required to evaluate each attack within 7 calendar days and evaluate if it represents a confirmed HAE attack in accordance with HAARP. If necessary for the evaluation, the investigator or designee may contact the subject to receive additional information. Any subject-reported attack not confirmed by the investigator or physician designee must have an alternate AE diagnosis recorded. All subject-reported and investigator/ physician designee-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 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 or physician designee may still clinically determine that the event did not represent an attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (eg, urticaria), the reported event persists well beyond the typical time course of an HAE attack, or there is a likely alternate etiology for the event (eg, the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

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

Interim Analyses and Data Monitoring

Interim analyses may be conducted when a reasonable number of subjects have completed at least 12 months of consecutive exposure to DX-2930 across the combined DX-2930-03 and DX-2930-04 studies, and only after database lock of Study DX-2930-03. Interim analyses may be performed to support administrative decisions and/or regulatory reporting.

An independent Data Safety Monitoring Board (DSMB) has been established to provide ongoing, independent review and assessment of the safety data for Study DX-2930-03. While an independent DSMB is not currently planned for this study, summary safety data from Study DX-2930-04 may be reviewed by the Study DX-2930-03 DSMB as part of the collection of safety information available on DX-2930.

Individual Stopping Rules:

Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or a DX-2930-related, clinically significant non-serious AE) that, in the assessment of the investigator, warrants discontinuation from further dosing for that subject's well-being. The investigator has the ability to contact and consult with the Medical Monitor on such matters. Subjects will continue to be followed through the completion of all scheduled non-dosing visits, unless they request to be discontinued from the study.

Criteria for Evaluation:

<u>Safety Measures:</u>

- AEs including SAEs and AESI
- Clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis)
- Vitals signs including blood pressure, heart rate, oral body temperature, and respiratory rate
- Physical Examination
- 12-lead ECG

Efficacy Endpoints:

- Time to first HAE attack for rollover subjects (based upon time from first open label study dose until first HAE attack)
- Number of investigator-confirmed HAE attacks during the treatment period
- Number of investigator confirmed HAE attacks requiring acute treatment during the treatment period
- Number of moderate or severe HAE attacks during the treatment period
- Number of high-morbidity 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.

Additional Measures:

- Anti-drug antibody development
- Pharmacokinetics (PK) effects
- Pharmacodynamic (PD) effects
- Quality of Life Assessments
- DX-2930 Injection Report
- DX-2930 Self-administration and Subcutaneous Injection Survey
- Exploratory biomarker(s) of angioedema disease-state bioactivity in plasma and serum
- Subject response to prefilled syringe, if available
- Subject response to rescue medication
- Subject treatment satisfaction
- Subject and Investigator Global Impression of Treatment Response survey
- Subject assessment of angioedema control

Analysis Populations:

- The Safety Population will include all subjects who received any study drug after entering the Study DX-2930-04 (ie, any exposure to open-label DX-2930).

- The Rollover Safety Population is the subset of subjects who participated in Study DX-2930-03 and received any study drug after entering Study DX-2930-04 (ie, any exposure to open-label DX-2930).

- The Non-rollover Safety Population is the subset of subjects who entered Study DX-2930-04 directly and received any study drug after entering Study DX-2930-04 (ie, any exposure to open-label DX-2930).

Sample Size Determination:

No formal sample size calculation was performed. The sample size is not based on any statistical considerations. This study is designed to evaluate the safety and efficacy of open-label treatment with DX-2930 in subjects who participated in Study DX-2930-03 and individuals who were not otherwise able to participate in Study DX-2930-03.

Statistical Methodology:

Time to the first investigator-confirmed HAE attack will be analyzed using the Rollover Safety Population.

Time to the first investigator-confirmed HAE attack (days) will be calculated from the date and time of the first open-label dose of DX-2930 to the date and time of the first investigator-confirmed HAE attack after the first open-label dose. Subjects who discontinue the study prior to experiencing their first on-study investigator-confirmed HAE attack will be censored at the date and time of study discontinuation. Time to the first investigator-confirmed HAE attack will be summarized using Kaplan-Meier methods.

Multivariate and univariate Cox proportional hazards regression models will be employed to examine the impact of baseline covariates on the time to the first investigator-confirmed HAE attack, including but not limited to: baseline attack rate prior to entering Study DX-2930-03, the treatment group in Study DX-2930-03, the time since the last dose given in Study DX-2930-03, the time since the last HAE attack, and the rate of attacks during Study DX-2930-03. Results of this exploratory analysis will be summarized.

<u>Number of Investigator-confirmed HAE Attacks</u>

The number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 924) expressed as a monthly HAE attack rate, will be analyzed using each analysis population.

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

The baseline investigator-confirmed monthly HAE attack rate will be calculated for each subject as the number of investigator-confirmed monthly HAE attacks occurring during the pretreatment period for rollover subjects or historical reporting period for non-rollover subjects divided by the number of days the subject contributed to the pretreatment period for rollover subjects or historical reporting period for non-rollovers multiplied by 28 days.

The baseline, treatment period, and treatment period change from baseline in the investigator-confirmed HAE attack rate will be summarized for each analysis population. The summary will include the total number of investigator-confirmed HAE attacks reported during each period and subject-time in months that each subject contributed to each period. Figures will be created for each analysis population plotting the on-study investigator-confirmed HAE attacks reported

during the treatment period relative to Day 0 for each subject.

Similar summary tables will be presented for the following efficacy endpoints for each analysis population:

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

Safety Analysis:

Adverse Events

Treatment-emergent AEs are defined as AEs with onset at the time of or following the first exposure to open-label DX-2930 in this study, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment.

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.

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

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

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

Laboratory Test Results, Vital Signs, and Electrocardiography Results

Baseline is defined as the last non-missing value prior to the first exposure to DX-2930. For rollover subjects previously exposed to DX-2930, baseline is the last non-missing value prior to first exposure to study drug in Study DX-2930-03.

Actual values and change from baseline in clinical laboratory test results and vital signs will be summarized by study visit.

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. 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 within each category will be summarized by study visit.

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 by study visit.

Other Analyses

Plasma concentrations of DX-2930 and plasma kallikrein activity will be summarized by nominal PK and PD sampling times.

The number and percentage of subjects with positive antibodies (and whether neutralizing or non-neutralizing) and exploratory biomarkers will be summarized by study visit and overall.

Quality of life assessments will be summarized by study visit.

Date of Original Protocol: 14 December 2015
Date of Amendment 1: 27 June 2016
Date of Amendment 2: 20 January 2017
Date of Amendment 3: 29 June 2017

Table 1 Study Activities Schedule –Day -28 through Day 365

Activities Occurring at		**Treatment Period, Visit Window ± 4 days** ■ = scheduled in-site visits for all subjects. □ = potential subject-elected off-site activity and/or self-administration dosing.																												
Non Rollover Visit	Scr[a]	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**See Protocol Section below for details**
Rollover Visit	-	Chk[b]																												
Dose Number	-	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	
Study Day (± 4 days)	-28	**0**		**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**	
Informed Consent[c]	•	•																												6.1
Eligibility Review[d]	•	•																												6.2
Long-term prophylactic therapy cont'd[d]	•	•		•																										3.1.1
DX-2930-04 Administration[e, f] (rollover subjects)[g]		•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	5.1
(non-rollover subjects)[d]		•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	5.1
Demographic and Medical History[h]	•																													6.3
Pregnancy Test[i] (females)	•	•[i]		•	•		•			•		•		•		•			•			•			•				•	6.8
Vital Signs[j]	•	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	6.5
Physical Exam[k]	•	•		•	•		•			•				•		•						•							•	6.6
Clinical Laboratory Testing[l]	•	•			•		•			•				•		•			•			•			•				•	6.8
12-Lead ECG[m]	•	•								•						•						•							•	6.7
Prior (4 wks) & Concomitant Therapy	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	6.12
Adverse Events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	6.16
HAE Attack Data[n]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	6.4
Quality of Life AE-QoL, EQ-5D-5L, WPAI-GH, HADS, SF-12		•			•		•			•		•		•		•			•			•			•				•	6.14.1-6.14.5
AECT, TSQM-9, Global Impression of Treatment Response																														•	6.14.6-6.14.8
DX-2930 Injection Report		•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	6.15.1
DX-2930 Self-administration & SC Injection Survey		•								•						•						•							•	6.15.2
PK, PD, ADA,[o] & Biomarker[p] Sample collection	•	•								•						•						•							•	6.8-11

Table 1 Study Activities Schedule –Day -28 through Day 365

Abbreviations: ADA = anti-drug antibody; AECT = Angioedema Control Test; AE-QOL = Angioedema Quality of Life; Chk = check-in; Cont'd = continued; ECG = Electrocardiogram; EQ-5D-5L = EuroQoL 5-Dimensional 5-Level; HADS = Hospital Anxiety and Depression Scale; PK = Pharmacokinetic; PD = Pharmacodynamic; Scr=screening visit; Scr=screening; SF-12 = Short Form-12; Treatment Satisfaction Questionnaire for Medication= TSQM-9; WPAI-GH = Work Productivity and Activity Impairment – General Health

a Screening visit is for non-rollover subjects only. Screening visit can occur up to 28 days prior to first open-label dose.

b Study site personnel will contact rollover subjects approximately every 7 days following the first dose of open-label DX-2930 to solicit for any HAE attacks not already reported. Site check-in with rollover subjects will continue until the subject receives their second open label dose.

c Rollover subjects must sign informed consent for Study DX-2930-04 on or after Day 168 of Study DX-2930-03. Day 182 of Study DX-2930-03 is also Day 0 of Study DX-2930-04, and informed consent may be completed on this visit, if not already provided.

d Screened non-rollover subjects (adults and adolescents) who are on LTP with C1-INH therapy for HAE can continue their current LTP until Day 8 (or Day 15) such that subjects will have received 2 (or 4) doses of C1-INH. For subjects who are on attenuated androgens (eg, danazol) or anti-fibrinolytics (eg, tranexamic acid), a similar tapering schedule is recommended. However, the taper can be prolonged by an additional week as long as androgen or anti-fibrinolytic therapy is stopped within 3 weeks of receiving the first dose of DX-2930. Since C1-INH therapy may alter the lab results of C1-INH assessments, the investigator's discretion in collaboration with Medical Monitor is advised for proper documentation of eligibility.

e Doses are administered every 14 ± 4 days. All subjects (adolescent or adult) who are considered suitable candidates (ie, those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer DX-2930 after (1) completing appropriate training by the investigator or designee, (2) confirming their understanding, and (3) receiving the first 2 doses of DX-2930 at the study site. Subjects are then allowed to initiate home self-administration and may elect to self-administer subsequent doses of DX-2930 at the investigational site. Subjects who receive a new product format (ie, a single vial or a PFS) will receive additional training in how to self-administer with that format.

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

g Rollover subjects will not receive Dose 2 until they have experienced the first reported, investigator-confirmed attack. In addition, a minimum of 10 days is required between Dose 1 and Dose 2. If the second dose is to be administered within the accepted ±4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit unless that scheduled visit has already occurred. If that scheduled visit has already occurred, or if the second dose is to be administered outside of the accepted ± 4 day window around a scheduled visit, this visit will not replace any scheduled visit and will thus represent an acceptable, extra study visit (ie, an unscheduled visit). Regardless, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical examination (performed in accordance with standards at the site), clinical laboratory testing, PK, PD, biomarkers and anti-drug antibody. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data. Following Dose 2, subjects will begin regular administrations every 2 weeks.

h For rollover subjects, demography data from DX-2930-03 will be re-entered for DX-2930-04. However, medical history reported in the DX2930-03 study will *not* be re-entered into the CRF for DX-2930-04; only *new* medical history data will be entered.

i The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 must be urine-based to confirm eligibility prior to first dose. Tests performed at screening and on indicated visits could be serum or urine-based.

Table 1 Study Activities Schedule –Day -28 through Day 365

j	There is a recommended ± 15 minute window for all vital signs. Vital signs will be obtained prior to dosing and 1 hour after dosing. Monitoring of vital signs will not be performed for subjects who elect to self-administer away from the investigative site at optional off-site visits (indicated non-shaded columns).
k	Physical examinations, including weight, will be conducted for all rollover and non-rollover subjects according to the study activities schedule and in accordance with standards at the site. In addition to the physical examinations specified in the study activities schedule, an additional physical examination (performed in accordance with standards at the site) will be conducted for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs. Height will be collected at the Screening visit only.
l	Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis (urinalysis does *not* need to be done as part of the clinical laboratory testing at Visits 14, 17, 20, and 23). Clinical laboratory testing will be conducted for all rollover and non-rollover subjects according to the study activities schedule. In addition to the testing specified in the study activities schedule, additional testing will be conducted for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs.
m	In addition to the timepoints shown, ECG is to be performed when clinically indicated.
n	Historical HAE attack information will be collected at screening for non-rollover subjects. During the study, subjects (or caregivers) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. During study visits, study site personnel will solicit for any new HAE attack information that has not already been reported to the site. Study site personnel will utilize the HAARP guidelines in order to confirm the HAE attack within 7 days.
o	PK, PD, biomarker, and anti-drug antibody samples will be drawn for all rollover and non-rollover subjects at the visits shown. An additional sample will be drawn for rollover subjects prior to dosing on the day of their second open-label dose, at whatever study visit that occurs.
p	Samples for C1-INH, C4, and C1q assays will be collected at screening for eligibility. In addition, C1-INH, C4, C1q, and other biomarkers will be collected at Visit 14, and Visit 27, as applicable. Samples need not be obtained at screening for eligibility assessment if they were already collected as part of Study DX-2930-02 or Study DX-2930-03.

Table 2 Study Activities Schedule for Day 366 through Day 952

Activities Occurring at	**Treatment Period, Visit Window ± 4 days for each visit** ■ = scheduled in-site visits for all subjects. □ = potential subject-elected off-site activity and/or self-administration dosing.																					**Follow Up Period**		**See Protocol Section below for details**
Visit	28	29	30	31 32 33	34	35 36 37	38	39 40 41	42	43 44 45	46	47 48 49	50	51 52 53	54	55 56 57	58	59 60 61	62	63 64 65	66	67	68[a]	69 EOS ET[b]	
Study Day (± 4 days)	378	392	406	420 434 448	462	476 490 504	518	532 546 560	574	588 602 616	630	644 658 672	686	700 714 728	742	756 770 784	798	812 826 840	854	868 882 896	910	924	938	952	
DX-2930 Administration[c,d]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•				5.1
Physical Exam[e]			•		•		•		•		•		•		•		•		•		•	•		•	6.6
Pregnancy Test[f] (females)			•		•		•		•		•		•		•		•		•		•	•		•	6.8
Vital Signs[g]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		•	6.5
Concomitant Therapy	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	6.12
Adverse Events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	6.16
HAE Attack Data[h]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	6.4
Clinical Laboratory Testing[i]			•		•		•		•		•		•		•		•		•		•	•		•	6.8
PK, PD Collection, ADA Testing & Biomarkers[j]					•				•				•				•				•	•		•	6.8-11
12-Lead ECG																								•	6.7
Quality of Life AE-QoL, EQ-5D-5L, WPAI-GH, HADS, SF-12			•		•		•		•		•		•		•		•		•		•			•	6.14
AECT			•		•		•		•		•		•		•		•		•		•			•	6.14.6
TSQM-9									•															•	6.14.7
Global Impression of Treatment Response																								•	6.14.8
Exit Interview																								•	6.14.9
Site Check In Call[k]	•	•		•		•		•		•		•		•		•		•		•			•		
DX-2930 Injection Report[l]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•				6.15.1
DX-2930 Self-admin & SC			•		•		•		•		•		•		•		•		•		•				6.15.2

Table 2 Study Activities Schedule for Day 366 through Day 952

Injection Survey[l], PFS Survey																								
Discharge from Study																						•	7.3.5	

Abbreviations: AECT=Angioedema Control Test; EOS = End of Study; ET = Early Termination; PFS = prefilled syringe; Self-admin = Self-administration; Treatment Satisfaction Questionnaire for Medication = TSQM-9

NOTE: Although the first visit shown on this Schedule is at Day 378, this schedule covers the entire period following the end of the previous schedule. Certain assessments should be collected continuously throughout the study (for example, AEs) are collected continuously throughout the study.

a Visit 68 is a site check-in call for all rollover and non-rollover subjects.

b Subjects who terminate from the study early will undergo (if possible) all of the assessments and procedures at Visit 69, the final study visit.

c Doses are administered every 14 ± 4 days.

d All subjects (adolescent or adult) who are considered suitable candidates (i.e., those with a physical and mental capability of learning and willing to be trained) may self-administer DX-2930 at all visits following the training described in Table 1. Subjects who receive a new product format (ie, a single vial or a PFS) will receive additional training in how to self-administer with that format. Subjects may administer at home or other agreed upon location (during off-site self-administration visits; non-shaded columns). Subjects can opt to be seen in clinic for this visit.

e Physical examinations, including weight, will be conducted for all rollover and non-rollover subjects according to the study activities schedule and in accordance with standards at the site.

f The pregnancy test will only be conducted in females of childbearing potential. Tests performed at screening and indicated visits could be serum or urine-based.

g There is a recommended ± 15-minute window for all vital signs. Vital signs will be obtained prior to dosing and 1 hour after dosing. Monitoring of vital signs will not be performed for subjects who elect to self-administer away from the investigative site at optional off-site visits (indicated non-shaded columns).

h During the study, subjects (or caregivers) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. During study visits, study site personnel will solicit for any new HAE attack information that has not already been reported to the site. Study site personnel will utilize the HAARP guidelines in order to confirm the HAE attack within 7 days.

i Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis (urinalysis is performed as part of the clinical laboratory testing at Visits 42, 54, 66, 69).

j Biomarker samples for C1-INH, C4, and C1q assays will be collected at Visits 34, 42, 50, 58, 66, 67, and 69.

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

l Collect subject's injection reports of their experience with DX-2930 self-administration, subcutaneous administration, and prefilled syringe (if relevant) for all doses.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAE	Acquired angioedema
ACE	Angiotensin converting enzyme
AE	Adverse event
AECT	Angioedema Control Test
AESI	Adverse Event of Special Interest
AE-QoL	Angioedema Quality of Life Questionnaire
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C1-INH	C1 inhibitor
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
C_{max}	Maximum plasma drug concentration
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRO	Clinical Research Organization
DMID	Division of Microbiology and Infectious Diseases
DP	Drug product
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EQ-5D-5L	EuroQoL 5-Dimensional 5-Level; a standardized instrument for use as a measure of health outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAARP	HAE Attack Assessment and Reporting Procedures

HADS	Hospital Anxiety and Depression Scale
HAE	Hereditary angioedema
cHMWK	High molecular weight 2-chain kininogen
HR	Heart rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G subclass 1
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone releasing systems
IV	Intravenous
K_i	inhibition constant
LTP	Long-term prophylactic/Long-term prophylaxis
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Prothrombin time
PVRM	Pharmacovigilance and Risk Management
QoL	Quality of life
REB	Research ethics board
RBC	Red blood cell (count)
RR	Respiratory rate

SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SF-12	Short Form-12; a multi-purpose short form health survey with 12 questions
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SMQ	Standard MedDRA query
SOC	System Organ Class
SOP	Standard operating procedure
TEAE	Treatment-Emergent Adverse Event
TSQM-9	Treatment Satisfaction Questionnaire for Medication version 9
US	United States
WBC	White blood cell (count)
WPAI-GH	Work Productivity and Activity Impairment – General Health

1. INTRODUCTION

1.1 DX-2930

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 hereditary angioedema (HAE), a serious and life-threatening disease.

1.2 Hereditary Angioedema

HAE is a long-term, debilitating, and life-threatening disease caused by mutations in the C1-inhibitor (C1-INH) gene, resulting in deficiency or dysfunction of C1-INH protein. HAE manifests clinically as unpredictable, intermittent attacks of subcutaneous or submucosal edema of the face, larynx, gastrointestinal tract, limbs and/or genitalia (Zuraw 2008). Swelling may last up to five or more days; most patients suffer multiple attacks per year. HAE is an orphan disorder. The exact prevalence of HAE is unknown, but current estimates range from 1 per 10,000 to 1 per 150,000 persons, with many authors agreeing that 1 per 50,000 is likely the closest estimate (Bygum 2009; Goring et al. 1998; Lei et al. 2011; Nordenfelt et al. 2014; Roche et al. 2005).

Swelling in the larynx can obstruct the airways and cause death from asphyxiation (Bork et al. 2000; Bork et al. 2012). Approximately 50% of all patients with HAE will experience a laryngeal attack in their lifetime, and there is no way to predict which patients are at risk of a laryngeal attack (Bork et al. 2003; Bork et al. 2006).

Abdominal attacks are often associated with nausea, vomiting, diarrhea, and severe pain; intestinal symptoms resembling abdominal emergencies may lead to unnecessary surgery (Zuraw 2008).

Approximately 85% of patients with HAE have Type I HAE, characterized by very low production of functionally normal C1-INH protein, while the remaining approximately 15% of patients with HAE have Type II HAE and produce normal or elevated levels of a functionally impaired C1-INH (Zuraw 2008). In patients with Types I and II HAE, uncontrolled plasma kallikrein generation results in excess bradykinin release from high-molecular weight 2-chain kininogen (HMWK) and vascular leak mediated by bradykinin binding to the B2 receptor (B2-R) on the surface of endothelial cells (Zuraw 2008). Clinical suspicion of Types I and II HAE can be confirmed by available blood tests. In addition to abnormalities in C1-INH level and function, plasma C4 levels are often reduced in blood from most patients with HAE.

1.3 Therapeutic Rationale for DX-2930

Plasma kallikrein plays a critical role in the pathogenesis of HAE attacks (Davis 2006; Kaplan and Joseph 2010). In normal physiology, C1-INH regulates the activity of plasma kallikrein as well as a variety of other proteases, such as C1r, C1s, factor XIa, and factor XIIa. Plasma kallikrein regulates the release of bradykinin from HMWK. Due to a deficiency of C1-INH in HAE, uncontrolled plasma kallikrein activity occurs and leads to the excessive generation of bradykinin. Bradykinin is a vasodilator which is thought to be responsible for the characteristic

HAE symptoms of localized swelling, inflammation, and pain (Craig et al. 2012; Zuraw et al. 2013). Intervening at the level of bradykinin production with a plasma kallikrein inhibitor therefore represents an attractive and rational therapeutic strategy for HAE. Indeed, the importance of plasma kallikrein as a drug target in HAE has been validated through the observed effectiveness of Kalbitor® (ecallantide), a peptide that specifically targets plasma kallikrein, which was approved by the FDA for the treatment of acute HAE attacks (Kalbitor® 2015).

DX-2930 is a highly potent and specific inhibitor of plasma kallikrein (K_i = 125 pM). X-ray crystallography of DX-2930 combined with plasma kallikrein demonstrates DX-2930 binding to the active site of kallikrein (Kenniston et al. 2014).

1.4 Safety Rationale for DX-2930

Safety data from the Phase 1a clinical study, a first-in-human study with DX-2930 in healthy subjects, did not identify any safety concerns. Single doses up to 3 mg/kg of DX-2930 were well-tolerated. There were no dose-limiting toxicities, serious adverse events, or any other safety concerns identified.

Pharmacokinetic (PK) data from the Phase 1a (DX-2930-01) and Phase 1b (DX-2930-02) clinical studies in conjunction with data from the nonclinical toxicity studies support a wide safety margin. The mean C_{max} for human subjects treated at a dose of 300 mg on Days 1 and 15 was approximately 27 µg/mL. As comparison, a mean C_{max} of 744 µg/ mL was observed following dosing of monkeys with 50 mg/kg DX-2930 subcutaneous (SC) weekly for 6 months resulting in a safety margin of approximately 28-fold. No toxicologically significant findings were observed in these treated animals or in any other nonclinical toxicity study to date for systemically administered DX-2930.

Safety data is also available from the Phase 1b study (DX-2930-02), a multiple-ascending dose study in patients with HAE. In this study, two doses of DX-2930 up to 400 mg administered 14 days apart were well-tolerated. There were no dose-limiting toxicities, serious adverse events in any DX-2930 treated subjects, or any other safety concerns identified in this study of patients with HAE. Pharmacokinetic data from the 1b study found that the drug exposure following two administrations of DX-2930 (up to a maximum of 400 mg) was substantially less than that attained and evaluated in the nonclinical toxicity studies.

For additional detail regarding the safety rationale for DX-2930, please refer to the DX-2930 Investigator's Brochure.

1.5 DX-2930 Non-Clinical Pharmacology and Toxicology

For more detail regarding the nonclinical findings, please refer to the DX-2930 Investigator's Brochure.

1.6 DX-2930 Clinical Data

The clinical development program to date for DX-2930 consists of 2 studies to evaluate the safety, tolerability, and PK of DX-2930, including one completed Phase 1a single-ascending

dose study in healthy subjects and a Phase 1b multiple-ascending dose study in patients with HAE. These studies are summarized in the following sections.

1.6.1 Single-Ascending Dose Study in Healthy Subjects (DX-2930-01)

DX-2930-01 was a Phase 1a randomized, double-blind, placebo-controlled study in healthy subjects to evaluate the safety, tolerability, and PK following a single, SC dose of DX-2930. Participating subjects were randomized to receive placebo or active study drug within one of the following sequential, ascending dose cohorts: 0.1, 0.3, 1.0, or 3.0 mg/kg. For each dosing cohort, 6 subjects were randomized to receive active drug and 2 subjects to receive placebo.

A total of 32 subjects enrolled in the study and were randomized. The treatment groups were well balanced for demographic characteristics. The actual dose of DX-2930 administered to subjects ranged from 6.2 mg (in the 0.1 mg/kg group) to 300 mg (in the 3.0 mg/kg group) across all cohorts.

Based on the safety analysis, a single administration of DX-2930 was well tolerated up to doses of 3.0 mg/kg without evidence of dose-limiting toxicity. There were no deaths, SAEs, or subject discontinuations due to adverse events (AEs) during the study. Furthermore, there was no significant imbalance between placebo and DX-2930 for any particular treatment-emergent adverse event (TEAE). The most commonly reported TEAE was headache, which occurred at a rate of 25% for both DX-2930 and placebo.

The PK profile demonstrated linear, dose-dependent drug exposure with a mean half-life of approximately 17 to 21 days across dose groups. Results from two exploratory biomarker assays provide evidence for an important pharmacodynamic effect of DX-2930 in humans.

For additional detail regarding the single dose, clinical study in healthy subjects, please refer to the DX-2930 Investigator's Brochure.

1.6.2 Multiple-Ascending Dose Study in HAE Patients (DX-2930-02)

DX-2930-02 was a Phase 1b randomized, double-blind, placebo-controlled, multiple ascending-dose study in patients with HAE to evaluate safety, tolerability, and PK of SC DX-2930. Participating subjects were randomized 2:1 to receive either active study drug or placebo within one of the following sequential, ascending dose cohorts: 30, 100, 300, or 400 mg (nominal 6 subjects per cohort). Each subject received 2 doses of study drug separated by 14 days.

A total of 37 subjects were randomized and treated with DX-2930 or placebo. One subject in the 400 mg dose group received a single dose of DX-2930 and, following several unsuccessful attempts to schedule their second dose, was replaced. This subject returned for a single follow-up visit before being lost to follow-up for reasons not related to the study. Routine C1-INH testing revealed that one other subject did not have HAE Type I or II, despite a historical lab test indicating otherwise.

Subject demographics were balanced in terms of age, race, ethnicity and BMI. There were slightly more females in the DX-2930 group than in the placebo group (66.7% versus 53.8%).

The most common AEs reported were HAE attacks, injection site pain, and headache. The rates were not appreciably higher in the DX-2930 subjects compared to placebo. Two subjects were reported to have 3 related severe TEAEs. One of these was a DX-2930 subject (30 mg) with injection site pain lasting 1 minute and one was a DX-2930 subject (400 mg) with worsening headache lasting 1 minute and night sweats.

No safety signals were identified for vital signs, physical examinations, clinical laboratory tests, or electrocardiograms (ECG). Results suggested DX-2930 was well tolerated in this study with no evidence of dose-limiting toxicity at doses up to 400 mg.

A total of 3 out of 92 post-dose samples (3.3%), obtained from 2 out of 23 subjects (8.7%), were confirmed to be anti-drug antibody-positive. No samples were positive for neutralizing activity.

The pharmacokinetic analysis for all subjects in the 30, 100, 300, and 400 mg doses showed drug levels in HAE subjects were dose-dependent and exhibited a prolonged half-life of approximately 2 weeks, typical of a human monoclonal antibody. C_{max} drug levels increased with increasing dose, as expected. These parameters were consistent with values obtained in healthy subjects in Study DX-2930-01.

A Western blot assay showed pre-dose baseline levels of mean 2-chain HMWK in unactivated plasma collected from patients with HAE was approximately 50%. A statistically significant reduction in 2-chain HMWK levels was observed on study days 8 and 22 in the 300 and 400 mg dose groups compared to pre-dose levels, and approached levels similar to that observed in healthy subjects. This outcome demonstrated the pharmacodynamic activity of DX-2930 and its ability to effectively normalize the instability of HAE plasma in this assay.

Primary efficacy analyses were based on subjects in the 300 mg, 400 mg, and placebo dose groups who reported having at least 2 attacks in the 3 months prior to study entry (0.15 attacks/week). Of those subjects treated with 300 or 400 mg DX-2930, 15 of 16 subjects met these criteria. Of the placebo treated subjects, 11 of 13 subjects met these criteria.

The baseline HAE attack rates (attacks/week) were 0.39 attacks per week in the placebo group, 0.33 attacks per week in the 300 mg group, 0.55 attacks per week in the 400 mg group and 0.49 attacks per week in the 300 and 400 mg combined group. During the pre-specified, primary efficacy interval of 6 weeks (from days 8 to 50; corresponding to a period of notable drug exposure), the HAE attack rate, adjusted for baseline attack rate, was 0 in the 300 mg group and 0.045 attacks per week in the 400 mg group, compared to 0.37 attacks per week in the placebo group. This resulted in a 100% reduction vs placebo for the 300 mg DX-2930 group ($P < 0.0001$) and an 88% reduction vs placebo for 400 mg DX-2930 ($P = 0.005$). During this primary efficacy interval, 100% of subjects in the 300 mg group ($P = 0.026$) and 82% of subjects in the 400 mg group ($P = 0.03$) were attack-free compared with 27% of subjects in the placebo group.

The data from this study demonstrated proof of concept of the ability of DX-2930 to prevent acute attacks of HAE. A statistically significant finding of HAE attack prevention by DX-2930 was observed. DX-2930 was well tolerated in HAE subjects up to 400 mg. Drug exposure appeared to be dose-proportional and consistent with the results obtained in healthy subjects in

Study DX-2930-01. Pharmacodynamic effect assays provided evidence that DX-2930 has a direct effect on plasma kallikrein activity in patient plasma.

For additional detail regarding Study DX-2930-02, please refer to the DX-2930 Investigator's Brochure.

1.7 Rationale for Open-Label Extension Study DX-2930-04

The open-label DX-2930 extension study will be preceded by the initiation of a pivotal, multi-center, double-blind, randomized, placebo-controlled parallel-arm study (Study DX-2930-03) evaluating the efficacy of DX-2930 in preventing acute angioedema attacks in patients with Type I or Type II HAE. Further information on Study DX-2930-03 design can be found in Appendix 5.

Subjects who complete the Study DX-2930-03 treatment period will be offered the option of rolling into the open-label extension study, Study DX-2930-04. In addition, a limited number of individuals with HAE Type I or Type II who were not enrolled in Study DX-2930-03 (up to approximately100) will be also enrolled.

The rationale for this open-label extension study is to evaluate the long-term safety of repeated subcutaneous treatment with DX-2930 and the long-term efficacy of DX-2930 in preventing HAE attacks. For subjects rolling over from DX-2930-03 who were randomized to one of the active study arms, the total duration of exposure across both studies will cover 36 months. For rollover subjects randomized to placebo in DX-2930-03, and for non-rollover subjects, the total duration of exposure will cover 30 months. Combined, the overall exposure between Study DX-2930-03 and Study DX-2930-04 will provide a sizable dataset to evaluate DX-2930 as a life-long, chronic treatment for preventing acute attacks of HAE.

This study seeks to evaluate the outer bounds of DX-2930 dosing frequency (possibly beyond 2 to 4 weeks) by assessing the duration of time between a rollover subject's first open-label dose and their first reported HAE attack. In addition, characteristics of all HAE attacks will be reported and compared to the subject's historical baseline (for non-rollover subjects) or attack history based on attacks reported in Study DX-2930-03 (for rollover subjects).

For non-rollover subjects, the study will evaluate the safety and efficacy of switching from a long-term prevention therapy (eg, C1-INH, anti-fibrinolytics, androgens) to DX-2930 dosing, while evaluating breakthrough attack characteristics compared to historical baseline both prior to and during co-administration with their LTP therapy regimen and while receiving DX-2930 alone.

For all subjects, the study will also assess immunogenicity of chronically administered DX-2930, PK and PD, biomarkers of angioedema disease state bioactivity, subject response to the pre-filled syringe (if available), subject response to rescue medications, subject health-related quality of life (QoL), subject experience with self-administration, ease of SC administration with DX-2930 subject treatment satisfaction, subjects' and investigators' global impression of treatment response, subject assessment of angioedema control, and an exit interview of subjects.

2. STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the long-term safety of repeated subcutaneous (SC) administrations of DX-2930

2.2 Secondary Objectives

- To evaluate the long-term efficacy of DX-2930 in preventing HAE attacks
- To characterize the outer bounds of dosing frequency for DX-2930

2.3 Tertiary Objectives

- To assess the immunogenicity of chronically administered DX-2930
- To evaluate the effect of DX-2930 on health-related quality of life (QoL)
- To characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profile of SC administration of DX-2930
- To evaluate safety and efficacy in the non-rollover population of switching from long-term prophylactic (LTP) treatment to DX-2930
- To evaluate breakthrough attack characteristics while receiving DX-2930 compared to historical baseline
- To evaluate subject experience with self-administration of DX-2930 including ease of SC administration of DX-2930
- To evaluate exploratory biomarker(s) of angioedema disease-state bioactivity in plasma and serum
- To evaluate subject experience and ease of use of the prefilled syringe, if available
- To assess the clinical response of rescue medications for the treatment of acute angioedema attacks while on DX-2930 therapy (applicable for subjects ≥18 years of age)
- To assess treatment satisfaction
- To assess global impression of treatment response
- To assess control of angioedema

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Overview

Study DX-2930-04 is an open-label, long-term safety and efficacy extension study of DX-2930-03, to evaluate the investigational medicinal product (IMP), DX-2930, in preventing acute angioedema attacks in patients with Type I and Type II HAE. There are two types of subjects who will be enrolled into this study:

- Subjects who rollover from Study DX-2930-03
- Subjects who are non-rollover (ie, were not participants in Study DX-2930-03)

Rollover Subjects

Rollover subjects are subjects who complete the double-blind treatment period at Day 182 of Study DX-2930-03 and consent to enter Study DX-2930-04. Subjects who discontinue from Study DX-2930-03 after enrollment are not eligible to enroll in Study DX-2930-04.

Subjects should be asked about their interest in Study DX-2930-04 after enrollment into Study DX-2930-03 to anticipate enrollment and preparedness for Study DX-2930-04. Willing subjects must sign informed consent for Study DX-2930-04 on or after Day 168 of Study DX-2930-03.

Subjects who are eligible to roll over into Study DX-2930-04 but elect not to, may not enroll in Study DX-2930-04 at a later time. The first Study DX-2930-04 visit for rollover subjects (Day 0) will occur on the same day as Study DX-2930-03 Day 182 study visit. Rollover subjects will complete all Study DX-2930-03 final study assessments (Day 182) at which time they will be discharged from that study. No assessments conducted between Study DX-2930-03 Day 182 study visit and the first Study DX-2930-04 visit (Day 0) will be duplicated. Results of the final DX-2930-03 assessments on Day 182 will be used as the pre-dose results for Day 0 of Study DX-2930-04.

All subjects, caregivers, investigators and study site personnel will remain blinded to the DX-2930-03 treatment assignment until the conclusion of Study DX-2930-04.

Non-rollover subjects

At least 50 subjects (to approximately 100) who were not participants in Study DX-2930-03 will be permitted to enroll if they meet the eligibility requirements. Subjects who screen fail out of Study DX-2930-03 for not meeting the minimum attack requirements during the run-in period must wait until enrollment for the double-blind study has ended before they can screen for Study DX-2930-04. The Sponsor may ease this restriction based on the enrollment rate observed in Study DX-2930-03. Subjects who are still in the run-in period for Study DX-2930-03 when enrollment for that study closes, as well as subjects on prior LTP who screen fail out of Study DX-2930-03 due to an inability to wash-out of their LTP, may screen for Study DX-2930-04 following discussion with the Sponsor medical monitor.

Screening Period:

Rollover subjects

There is no screening period for rollover subjects.

Non-rollover subjects

Non-rollover subjects must provide informed consent and have screening assessments completed within 4 weeks prior to their first open-label dose. Screened non-rollover subjects (adults and adolescents) who are on LTP with C1-INH therapy for HAE can continue their current LTP until Day 8 (or Day 15) such that subjects will have received 2 (or 4) doses of C1-INH. For subjects who are on attenuated androgens (eg, danazol) or anti-fibrinolytics (eg, tranexamic acid); a similar tapering schedule is recommended. However, the taper can be prolonged by an additional week, if medically indicated, as long as androgen or anti-fibrinolytic therapy is stopped within 3 weeks of receiving the first dose of DX-2930.

Treatment Period:

Rollover Subjects

Following informed consent and pre-dose assessments, rollover subjects will receive a single open-label dose of DX-2930 administered subcutaneously (SC) on Day 0. Subjects will not receive any additional DX-2930 doses until their first reported and investigator confirmed HAE attack. As such, the total number of doses within the treatment period will vary by rollover subject.

The duration of time between the first open-label dose and first reported HAE attack will vary by rollover subject. All rollover subjects must adhere to the Study Activities Schedules (Table 1 and Table 2), for the entire duration of the study. However, until a rollover subject reports their first HAE attack, only scheduled study visits where the following tests and assessments are performed must be conducted at the investigative site: pregnancy testing, clinical laboratory testing, physical examination, 12-Lead ECG, QoL, PK, PD and anti-drug antibody sample collection. All other scheduled study visits may be conducted via site check-in calls to collect information on adverse events, concomitant therapy, and HAE attack data. See Study Activities Schedules (Table 1 and Table 2) for which visits must be conducted at the study site.

Once a rollover subject reports their first HAE attack they will present to the investigative site for their second open-label dose of DX-2930 as quickly as subject and site schedules allow. If the second dose is to be administered within the accepted ± 4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit. If that scheduled visit has already occurred, the day of the visit will be considered an acceptable, extra study visit.

In the event that the second dose is to be administered outside of the accepted ±4 day window around a scheduled visit, the day of the visit will be considered an acceptable extra study visit (ie, this visit will not replace any scheduled visit).

Regardless of the study day, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical examination, clinical laboratory testing, and blood sampling for PK, PD, and anti-drug antibody. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data.

Regardless of when a rollover subject's first HAE attack occurs, there will be a minimum of 10 days between their first open-label dose and their second open-label dose. Following their second open-label dose, rollover subjects will continue to receive repeated SC administrations of open-label DX-2930 every 2 weeks for the remaining duration of the treatment period per the scheduled dosing in the Study Activities Schedules (Table 1 and Table 2). The treatment period will last up to 924 days from the date of the first open-label dose. The number of doses administered during this period will vary by subject based on the date of each subject's second dose, but will not exceed 66 doses. The Day 910 study visit is the last visit at which a dose may be administered.

Non-rollover Subjects
Once all screening assessments have been completed and eligibility confirmed, non-rollover subjects will arrive at the study site and, following pre-dose assessments, receive an open-label dose of 300 mg DX-2930 administered SC on Day 0. Non-rollover subjects will continue to receive SC administrations of open-label 300 mg DX-2930 every 2 weeks throughout the duration of the treatment period per the scheduled dosing in the Study Activities Schedules. Up to 66 doses will be administered with the last dose administered at the Day 910 study visit.

All Subjects:
All doses (with the exception of the second dose for rollover subjects) require a minimum of 10 days and maximum of 18 days between administrations, and should fall within the accepted ± 4 day window around study visits.

After the second DX-2930 dose is given either within the study window (±4 days) or an acceptable extra study visit, the 3rd dose must be administered at the next pre-defined study visit according to the schedule of assessments.

If a subject experiences an acute angioedema attack at any time during the study that in the opinion of the investigator requires medical intervention, standard of care therapy should be provided based on subject's medical history and per locally approved product information. Administration of DX-2930 and study procedures will continue without alteration to the protocol Study Activities Schedules (Table 1 and Table 2), even if a subject receives treatment for a breakthrough angioedema attack on the day of a scheduled dose of study drug (if self-administering) or scheduled study visit.

Self-Administration

All subjects (adolescent or adult) who are considered suitable candidates (ie, those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer treatment. Subjects must complete appropriate training by the investigator or designee and have their understanding of the procedures confirmed by the investigator or designee.

Subjects are allowed to initiate self-administration at the subject's home or other agreed upon location after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may self-administer subsequent doses of DX-2930 at the investigational site (when visits are scheduled study site visits) or the subject's home or other agreed upon location (when the study permits off-site dosing).

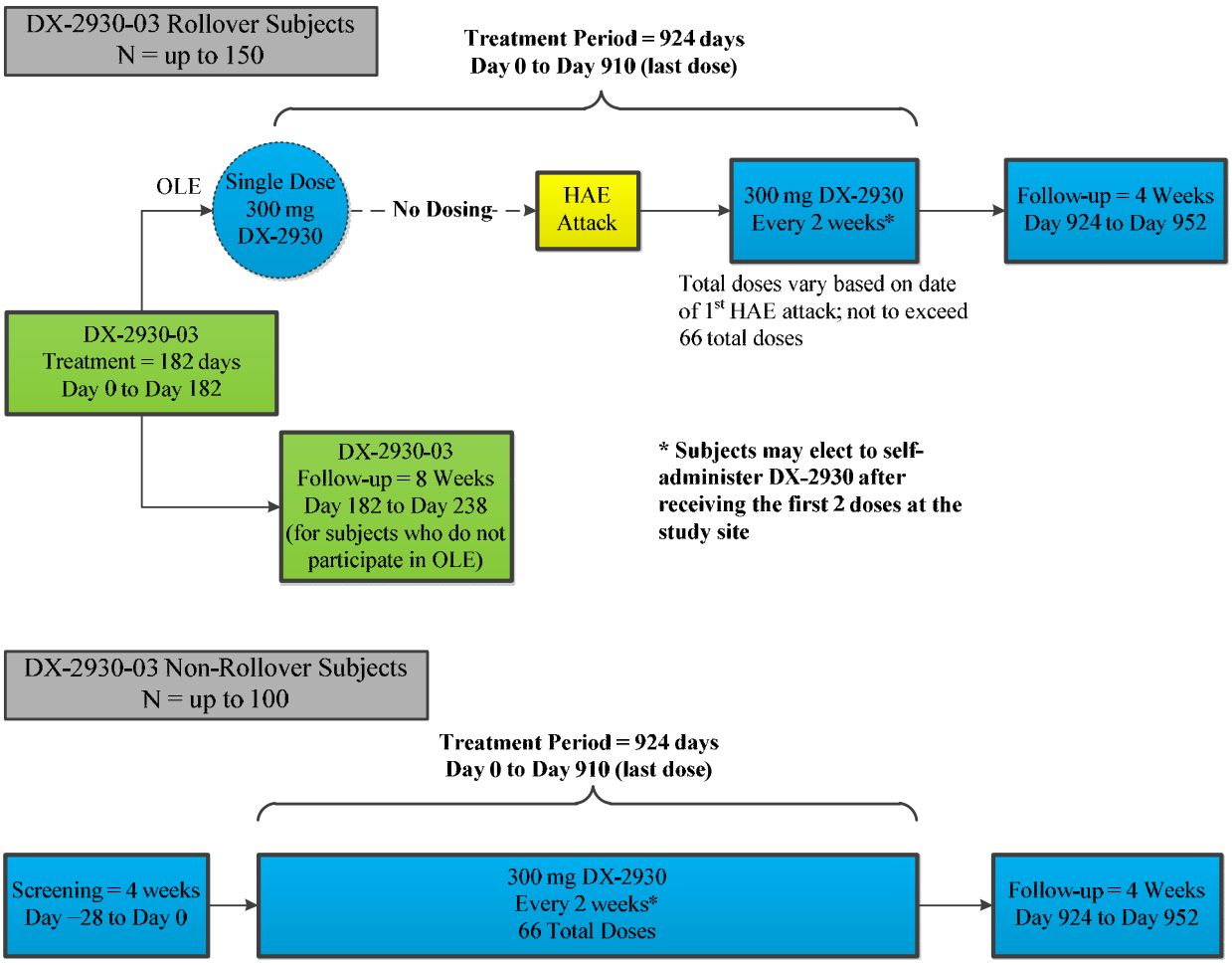
Adolescent subjects self-administering DX-2930 will be supervised by a parent/legal guardian/caregiver. Alternatively, a parent/legal guardian/caregiver, after completing appropriate training, will be allowed to administer the investigational product to an adolescent without study site personnel supervision.

Site personnel will call subjects within approximately 3 days after the planned off-site self-administrations to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented. Throughout the study, study site personnel will document information in source documents (ie, the subject's medical record) and eCRF regarding the subject's experience with self-administration and SC administration of DX-2930.

Follow-up Period

After completion of the treatment period, all subjects will undergo safety evaluations during a 4-week follow-up period. Figure 1 shows a schematic of the open-label extension study.

Figure 1 Schematic of the Open-Label Extension Study



Modifications to Open-Label Dosing

If, at any time, a dose-related safety signal is identified either from this study or Study DX-2930-03, the Sponsor may decide to modify the open-label DX-2930 dose and/or frequency. In addition, an individual subject's dose may be modified based on a benefit-risk assessment and recommendation from the treating physician. Consultation with and approval by the Sponsor's medical monitor is required.

In addition, based on the results of Study DX-2930-03, the Sponsor may switch to a different dose and/or frequency.

3.1.2 Stopping Rules

3.1.2.1 Study Level Stopping Rules

Safety data, including SAEs and AESI, will be monitored regularly throughout the duration of the study. If any potential safety signal is identified as a result of monitoring in this study, or

from any safety findings from Study DX-2930-03, or following DSMB review, the Sponsor may take actions as deemed appropriate, including suspending dosing in the study, while the potential risk is evaluated and a course of action has been determined.

3.1.2.2 Individual Stopping Rules

Dosing for any individual subject will be discontinued if the subject experiences a DX-2930-related SAE (or DX-2930-related, clinically significant non-serious AE) that, in the assessment of the investigator or DSMB recommendation, warrants discontinuation from further dosing for that subject's well-being. The investigator has the ability to contact and consult with the Medical Monitor on such matters. Subjects will continue to be followed through the completion of all scheduled non-dosing visits, unless they request to be discontinued from the study.

3.1.3 Follow-up for Subjects Meeting Stopping Criteria

Subjects that develop either an SAE or other toxicity considered clinically relevant (AE, laboratory, physical examination, vital sign, or ECG finding) will be carefully monitored until resolution, which may include the following:

- Additional clinical laboratory tests and/or other clinical investigations
- Additional visits or extended duration of follow-up
- Obtaining a specialist consultation

3.2 Rationale for Open-Label Extension Dose Selection

The dose selected for the open-label extension (300 mg every 2 weeks) is anticipated to be effective and safe as determined in the pivotal, double-blind DX-2930-03 study. If at any time an important dose-related safety signal is identified either from this study or Study DX-2930-03, the Sponsor may decide to switch the enrolled subjects who have not yet completed the treatment period, and any subsequent subjects, to receive a different open-label DX-2930 dose and/or frequency.

Additionally, based on the efficacy results of Study DX-2930-03, the Sponsor may switch to a different dose and/or frequency.

3.3 Individual Subject Dosing and Follow-Up

All subjects will receive open-label DX-2930 during a treatment period of up to 924 days. The number of doses that rollover subjects receive during this period will vary by subject but will not exceed 66 doses. The last dose of open-label DX-2930 administered to these subjects may be given at the Day 910 study visit. Non-rollover subjects will receive DX-2930 every 2 weeks for up to 66 doses, with the first dose administered on Day 0 and the final dose administered at the Day 910 study visit.

There will be a ±4 day window around each study visit. There will be a minimum of 10 days between any two doses. Excluding the time interval between the first and second open-label

doses for rollover subjects, there will be a maximum of 18 days between any two doses. Subjects will be monitored at the study site through 1 hour post-dose.

All subjects (adolescent or adult) who are considered suitable candidates (ie, those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer treatment after completing appropriate training by the investigator or designee and confirming their understanding. Subjects are allowed to initiate self-administration at the subject's home or other agreed upon location after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may continue to self-administer subsequent doses of DX-2930. Subjects who elect to self-administer investigational product will be provided the necessary supplies (see Section 5.7 and Section 6.15.1). Subjects who receive a new product format (ie, a single vial or a PFS) will receive additional training in how to self-administer with that format.

3.4 Study Duration for Individual Subjects

Following informed consent, subjects will either rollover from Study DX-2930-03 or undergo screening assessments (non-rollover subjects). Screening assessments for non-rollover subjects must occur within 4 weeks prior to the first open-label dose. Eligible subjects will be enrolled and undergo a treatment period of up to 924 days. At the conclusion of the treatment period, subjects will be followed for an additional 4 weeks.

4. STUDY POPULATION SELECTION

4.1 Study Population

The study is expected to enroll subjects from Study DX-2930-03, as well as at least 50 (to approximately100) additional subjects who were not enrolled in Study DX-2930-03. The total enrollment is expected to be at least 150, but not more than 250 HAE Type I or II subjects. Subjects will be 12 years of age or older who experience at least 1 attack per 12 weeks. HAE diagnosis will be confirmed through documented clinical history and diagnostic testing conducted either during screening or during participation in Study DX-2930-02 or Study DX-2930-03.

The subject population includes subjects who are 12 to 17 years old. Like adults, children with HAE can suffer from recurrent and debilitating attacks. Symptoms may present very early in childhood, and upper airway angioedema has been reported in patients with HAE as young as the age of 3 (Bork et al. 2003). In one case series of 49 pediatric patients with HAE, 23 had suffered at least one episode of airway angioedema by the age of 18 (Farkas 2010). An important unmet medical need exists among children with HAE, especially adolescents, since the disease commonly worsens after puberty (Bennett and Craig 2015; Zuraw 2008). The study will aim to enroll at least 15 subjects who are 12 to 17 years of age, inclusive of the estimated 10 subjects 12 to 17 years old who are expected to roll over from Study DX-2930-03.

4.2 Inclusion Criteria

Subjects must meet the following criteria to be enrolled in this study:

1. Male and female HAE subjects who are 12 years of age or older at the time of screening.

2. Documented diagnosis of disease HAE (Type I or II) based on all of the following:

    - Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).

    - Diagnostic testing results obtained during screening (or a prior DX-2930 study) that confirm HAE Type I or II: C1 inhibitor (C1-INH) functional level < 40% of the normal level. Subjects with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may be retested if results are incongruent with clinical history or believed by the investigator to be confounded by LTP use. (It is understood that C1-INH therapy may alter the lab results of C1-INH assessments; therefore, the investigator's discretion in collaboration with Medical Monitor is advised for proper documentation of eligibility).
    - At least one of the following: Age at reported onset of first angioedema symptoms ≤ 30 years, a family history consistent with HAE Type I or II, or C1q within normal range.

3. A historical baseline HAE attack rate of at least 1 attack per 12 weeks.

4. Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects age 12 to 17, whose caregiver has provided informed consent, are willing and able to read, understand and sign an assent form.

5. Males and females who are fertile and sexually active must adhere to contraception requirements for the duration of the study as follows:

   - Females* of childbearing potential must agree to be abstinent or it is recommended to use highly effective forms of contraception from the screening period through 30 days after the final study visit. This includes stable doses (for 3 months prior to study screening) of combined estrogen and progestin-containing hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable), progestin-only hormonal contraception associated with inhibition of ovulation, intra-uterine device (IUD, all types) or intrauterine hormone releasing systems (IUS). Notes: 1) A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. 2) Use of a male condom with or without spermicide or cervical cap, diaphragm or sponge with spermicide or a combination (double barrier methods) are not considered highly effective.

   - Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.

   - Males, including males who are surgically sterile (post vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study visit.

     *NOTE: Female rollover subjects (those who previously participated in Study DX-2930-03) of childbearing potential may continue to use the birth control method used during Study DX-2930-03.

4.3 Exclusion Criteria

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

1. Discontinued from Study DX-2930-03 after enrollment for any reason.

2. If rolling over from Study DX-2930-03, presence of important safety concerns that would preclude participation in this study.

3. Concomitant diagnosis of another form of chronic, recurrent angioedema such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.

4. Dosing with an investigational drug (not including DX-2930 or other HAE therapies) or exposure to an investigational device within 4 weeks prior screening.

5. Exposure to angiotensin-converting enzyme (ACE) inhibitors within 4 weeks prior to screening or any newly initiated or dose modification of estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) 3 months prior to the screening visit.

6. Unwilling to discontinue use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 3 weeks after starting DX-2930 treatment.

7. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's Syndrome).

8. Pregnancy or breastfeeding.

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

5. STUDY TREATMENT(S)

5.1 Description of Treatment(s)

For detailed information regarding open-label DX-2930 (lanadelumab) administration, refer to the Pharmacy Manual.

DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated using the following compendial components: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Polysorbate 80. Each open-label vial contains a nominal concentration of *either* 150 mg DX-2930 active ingredient in 1 mL solution *or* 300 mg in 2 mL solution.

For each 300 mg dose of DX-2930, each subject will receive a total of 2 mL, which will be administered in a single 2 mL SC injection. The subject may receive the dose as *either* 2 vials containing 150 mg in 1 mL each, *or* 1 vial containing 300 mg in 2 mL. If available, subjects may receive a PFS instead of vial(s). The injection will be given in the upper arm, thigh or abdomen.

Self-Administration

All subjects (adolescent or adult) who are considered suitable candidates (ie, those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer treatment after completing appropriate training by the investigator or designee and demonstrating the comprehension to self-administer. Subjects are allowed to initiate self-administration at the subject's home or other agreed upon location after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may continue to self-administer subsequent doses of DX-2930 at the investigational site (when visits are scheduled study site visits) or the subject's home or other agreed upon location (when the study permits off-site dosing). See Study Activities Schedule (Table 1) for details. Subjects who receive a new product format (ie, a single vial or a PFS) will receive additional training in how to self-administer with that format. Adolescent subjects self-administering investigational product will be supervised by a parent/legal guardian/caregiver. Alternatively, a parent/legal guardian/caregiver, after completing appropriate training, will be allowed to administer DX-2930 to an adolescent without study site personnel supervision. Site personnel will call subjects within approximately 3 days after the planned off-site self-administrations to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.

Throughout the study, study site personnel will document information in the subject's medical record and eCRF regarding the subject's experience with self-administration and SC administration of DX-2930 and experience with the PFS, if applicable.

5.2 Dosing and Follow-Up Scheme

Details of subject dosing and follow-up are outlined in Section 3.1.1 and included in the Study Activities Schedules (Table 1 and Table 2).

Rollover subjects will receive their first open label SC dose of DX-2930 on Day 0. Subjects will not receive any additional DX-2930 doses until their first reported HAE attack. The second dose

of DX-2930 may be administered at an unscheduled visit if it is outside of the accepted ±4 day window around a scheduled visit. Following this attack subjects will receive open label SC doses of DX-2930 every 2 weeks until the end of the treatment period. Subsequent dosing after Dose 2 requires a minimum of 10 days and a maximum of 18 days between administrations.

Regardless of when a rollover subject's first HAE attack occurs, there will be a minimum of 10 days between their first open-label dose and their second open-label dose. Following their second dose, rollover subjects will continue to receive repeated SC administrations of open-label 300 mg DX-2930 every 2 weeks for the remaining duration of the treatment period per the scheduled dosing in the Study Activities Schedules. The treatment period will last up to 924 days from the date of the first open-label dose. The number of doses administered during this period will vary by subject based on the date of each subject's second dose, but will not exceed 66 doses. The Day 910 study visit is the last visit at which a dose may be administered.

Non-rollover subjects will receive their first open-label dose SC dose of DX-2930 on Day 0 and will continue to receive SC administrations of open-label DX-2930 every 2 weeks throughout the duration of the treatment period. Up to 66 doses will be administered with the last dose administered at the Day 910 study visit.

After completion of the treatment period, all subjects will undergo safety evaluations during a 4-week follow-up period.

5.3 Method of Identifying Subjects

Subjects meeting all eligibility criteria will be enrolled in the study and sequentially assigned a unique site-based identification number.

5.4 Prior and Concomitant Therapy

For subjects not rolling over from Study DX-2930-03, reasonable efforts will be made to determine all relevant treatments received by the subject from 4 weeks prior to screening through the final study visit. For subjects rolling over from Study DX-2930-03, concomitant therapy use will be carried forward from that study and will continue to be collected through the final study visit.

All information on prior and concomitant therapy (including all prescription/non-prescription medications, herbal medications and vitamin supplements) must be recorded on the subject's eCRF and should include the name of the procedure or drug and duration of the treatment (start and stop dates). Concomitant treatments (non-pharmacological treatments) include any surgical or diagnostic procedures.

5.4.1 Allowed Therapies

The following therapies are allowed during the study:

- Therapies for co-existing conditions, including those for acute attacks of HAE, as described in Section 5.4.1.1 are permitted if not excluded in Section 5.4.2. The use of short-term

prophylactic treatment for HAE will be permitted if medically indicated. Short-term (pre-procedure) prophylaxis is defined as use of C1-INH to avoid angioedema complications from medically indicated procedures.

- Therapies to treat any AEs the subject experiences during the study are permitted.

5.4.1.1 Management of HAE Attacks

Acute HAE attacks during the study are to be managed in accord with the investigator's usual care of their patients, including use of acute attack therapies that the investigator deems as medically appropriate. Use of C1-INH will be permitted as an acute attack therapy but not as a LTP therapy. Administration of DX-2930 and study procedures will continue without alteration to the protocol-specified study schedule, even if the subject has symptoms of an HAE attack the day of DX-2930 administration and/or receives treatment for an HAE attack. The administration of DX-2930 can also be re-scheduled as long as the minimum and maximum timeframe between doses are met based on patient preference or physician discretion.

5.4.2 Excluded Concomitant Therapies

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

- Long-term prophylaxis for HAE (eg, use of C1-INH for LTP, attenuated androgens, or anti-fibrinolytics) once LTP is discontinued (within 3 weeks following first dose of DX-2930).
- Angiotensin-converting enzyme (ACE) inhibitors.
- Initiating or changing the dose of estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) 3 months prior to the screening visit.
- Use of androgens (eg, stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) for non-HAE related medical conditions or for HAE after discontinuation during the first 3 weeks.
- Any other investigational drug or device.

5.5 Restrictions

5.5.1 Medical Interventions

Medical interventions deemed necessary by the investigator for the health and well-being of the subject will not be excluded during this study.

5.5.2 Fluid and Food Intake

There are no restrictions on fluid and food intake. Subjects may continue their usual dietary regimens.

5.5.3 Activity

There are no activity restrictions. Subjects may continue their usual activity regimens.

5.6 Treatment Compliance

All doses of open-label DX-2930 administered at the investigational site will be under the direct supervision of the investigator or qualified study site personnel designated by the investigator.

Subjects are allowed to initiate self-administration at the subject's home or other agreed upon location after receiving the first 2 doses of DX-2930 at the study site. Once initiated, subjects may continue to self-administer subsequent doses of DX-2930 at the investigational site (when visits are scheduled study site visits) or the subject's home or other agreed upon location (when the study permits offsite dosing). Site personnel will call subjects within approximately 3 days after the planned off-site self-administrations to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented. See Study Activities Schedules (Table 1 and Table 2) for details. For all subjects, subsequent doses after the second dose require a minimum of 10 days and maximum of 18 days between administrations, and should fall within the accepted ±4 day window around study visits.

For rollover subjects, after the second DX-2930 dose is given either within the study window (±4 days) or an acceptable extra study visit, the 3rd dose must be administered at the next pre-defined study visit according to the schedule of assessments.

5.7 Packaging and Labeling

The open-label DX-2930 will be supplied by the Sponsor and prepackaged in a study kit for investigational studies. Each study kit will contain 1 vial (or pre-filled syringe, if available) of investigational product. Both the vials and carton (kit) will be appropriately labeled according to local regulations and bear the unique study drug kit number. The investigative site will provide ancillary supplies including syringes, needles, and alcohol wipes to subjects. The site has the option of using needles of a different gauge to aid subject comfort with each SC injection. Subjects who elect to self-administer investigational product will be provided the following supplies as applicable:

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

All used and unused vials should be returned to the study kit cartons/boxes and transported to the site for drug accountability. Written instructions on DX-2930 handling and self-administration procedures will be provided to trained subjects prior to initiating self-administration. Refer to the Pharmacy Manual for additional details on DX-2930 and its administration.

5.8 Storage and Accountability

All DX-2930 will be shipped refrigerated to the study site and must be stored at 2ºC to 8ºC/36ºF to 46ºF in the carton and protected from light. Storage must be in a securely locked area,

accessible to authorized persons only, until needed for dose preparation. See Section 5.7 and Section 6.15.1 for details.

5.9 Investigational Medicinal Product Retention at Study Site

The investigator (or designee) is responsible for maintaining accurate accountability records of DX-2930 throughout the clinical study. All DX-2930 received at the site must be inventoried and accounted for in an accountability log provided by the Sponsor. All dispensing and accountability records will be available for Sponsor review. Drug accountability will be verified during on-site monitoring visits.

Upon the completion or termination of the study, and upon written authorization from the Sponsor, or its representative, all unused and/or partially used DX-2930 should be returned or destroyed at the investigational site, as specified by Sponsor. It is the investigator's responsibility to ensure that the Sponsor, or its representative, has provided written authorization that procedures for proper disposal of DX-2930 have been established, and that appropriate records of the disposal are documented and maintained. No unused DX-2930 may be disposed until fully accounted for by the Sponsor monitor (or designee).

6. STUDY PROCEDURES

Please refer to the Study Activities Schedules (Table 1 and Table 2).

6.1 Informed Consent

The ICF must be executed prior to performing any study related activities and must be approved by the reviewing institutional review board (IRB), research ethics board (REB), or independent ethics committee (IEC). Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the investigator.

Subjects who are not rolling over from the double-blind DX-2930-03 study will provide informed consent at Screening. Subjects who are rolling over from the double-blind DX-2930-03 study will provide consent on or after Day 168 of Study DX-2930-03. Upon completion of the final assessments, the subjects will be discharged from the double-blind study and will start participation in the OLE study and receive their first open-label dose.

6.2 Eligibility Review

The investigator or qualified study site personnel will confirm that all Inclusion and Exclusion criteria have been met.

6.3 Demographics and Medical History

Demographics: date of birth (alternately age or year of birth, if full date is not allowed to be collected for legal reasons), sex, race, and ethnicity (where locally permitted) and medical history will be obtained at Screening from subjects not rolling over from Study DX-2930-03 and will be recorded on the source document and eCRF. Medical history will capture the subject's current medical status (current disease processes), past medical status (past disease processes), history of surgery, allergies and concomitant medications. For subjects rolling over from Study DX-2930-03, these data will be carried forward from that study.

6.4 HAE Attack Information Collection

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

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

At screening, HAE attack history will be collected for non-rollover subjects. Information collected will include any prior history of laryngeal attacks, attack frequency, average severity, predominant attack location(s), triggers, average duration, acute attack therapy use and history of LTP (including duration of LTP, medication(s) and dose used for LTP, and frequency of attacks

while receiving LTP). If available, information will also be collected on HAE diagnosis (year of confirmation, how many years after onset of symptoms was diagnosis confirmed, or if subject was misdiagnosed).

During the study, subjects (or caregivers) will be instructed to notify and report details to the study site within 72 hours of the onset of an attack. This includes the first attack experienced by rollover subjects following their first open-label dose. In the situation 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 experienced, but their use is not mandatory.

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 (work, school, social interactions) and whether any assistance or medical intervention was required, including hospitalizations, additional laboratory tests, or emergency department visits
- Any medications used to treat the attack (both prescription and over the counter)
- If the attack resolved, date and time the subject was no longer experiencing symptoms

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

Study site personnel will contact rollover subjects approximately every 7 days following the first dose of open-label until the subject has received their second open label dose. This is to ensure accurate reporting for any HAE attacks not already reported by the subject as required within 72 hours. During each study visit, study site personnel will solicit for any new HAE attack information that was not already provided to the site.

In this study, HAE attacks will be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to DX-2930, 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 EDC system within 24 hours of becoming aware of the event. For all adverse events that are reported as HAE attacks, the investigator or physician designee will review the event within 7 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 to receive additional information. Any subject-reported attack not confirmed by the investigator or physician designee must have an alternate AE diagnosis recorded. All subject-reported and investigator/ physician designee-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 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 or physician designee may still clinically determine that the event did not represent an attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (eg, urticaria), the reported event persists well beyond the typical time course of an HAE attack, or there is a likely alternate etiology for the event (eg, the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household).

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

6.5 Vital Signs

Vital signs prior to dosing and at 1 hour post-dosing (±15 min) will be assessed by the investigator or his/her qualified designee according to the Study Activities Schedules (Table 1 and Table 2) unless the subject has elected to self-administer off-site for that visit. 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. For subjects who rollover from Study DX-2930-03, vital signs taken during the final study visit in Study DX-2930-03 will serve as the Day 0 pre-dose vital signs in this study and will not be duplicated.

6.6 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 Schedules (Table 1 and Table 2). The physical examination will be performed in accordance with standards at the site.

For subjects who rollover from Study DX-2930-03, the physical exam taken during the final study visit in Study DX-2930-03 will serve as the Day 0 pre-dose physical exam in this study and will not be duplicated. Weight should be collected at every exam.

6.7 Electrocardiography (ECG)

A standard 12-lead ECG (single recording) will be performed according to the Study Activities Schedules (Table 1 and Table 2). 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 or will be assessed on site. For subjects who rollover from Study DX-2930-03, the ECG taken during the final study visit in Study DX-2930-03 will serve as the Day 0 pre-dose ECG in this study and will not be duplicated.

6.8 Clinical Laboratory Tests

6.8.1 Laboratory Parameters

Laboratory testing will be performed according to the Study Activities Schedules (Table 1 and Table 2).

Laboratory testing includes general safety parameters (hematology, coagulation, urinalysis, and serum chemistry), pregnancy tests (in females of childbearing potential), PK sampling, PD sampling, plasma anti-drug antibody testing, and biomarker testing. All laboratory tests will be performed using established and validated methods.

When multiple sample collection types are performed at the same assessment time point, the samples will be drawn in the following order (depending on what sample types are to be collected at that time point): laboratory safety samples (hematology, coagulation, serum chemistry), C1-INH, C4, C1q, PK, anti-drug antibodies, PD, and biomarker samples. Aliquots from the samples may be retained as back-up for additional parameter testing if necessary. Subjects will be in a seated or supine position during blood collection. For subjects who rollover from Study DX-2930-03, testing performed during the final study visit in Study DX-2930-03 will serve as the Day 0 pre-dose laboratory testing in this study and will not be duplicated.

6.8.1.1 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
-

6.8.1.2 Coagulation

- Prothrombin time (PT)

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

6.8.1.3 Chemistry

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

6.8.1.4 Urinalysis

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

Samples for urinalysis will be drawn during the study according to the Study Activities Schedules (Table 1 and Table 2).

6.8.1.5 Pregnancy Test

Pregnancy tests will be either serum or urine based according to the Study Activities Schedules (Table 1 and Table 2).

6.8.1.6 Biomarkers

EXPLORATORY BIOMARKERS

Samples for exploratory biomarker measurement will be drawn during the study according to the Study Activities Schedules (Table 1 and Table 2).

C1-INH FUNCTIONAL ASSAY

Results of a C1-INH functional assay are required for eligibility assessment and will be assessed during the study according to the Study Activities Schedules (Table 1 and Table 2).

Samples will be drawn at the Screening visit unless they were previously drawn in Study DX-2930-02 or Study DX-2930-03. Results of the C1-INH functional assay from DX-2930-02 or Study DX-2930-03 may be used to confirm diagnosis in this study. Subjects may be retested if results are incongruent with clinical history or believed by the investigator to be confounded by recent LTP use. Because C1-INH therapy may alter the lab results of C1-INH assessments, the investigator's discretion in collaboration with Medical Monitor is advised for proper documentation of eligibility.

C4 ASSAY

Results of a C4 assay may be required for eligibility assessment and will be assessed during the study according to the Study Activities Schedules (Table 1 and Table 2).

The C4 sample will be drawn at the same time as the C1-INH sample is drawn during the Screening visit unless previously drawn in Study DX-2930-02 or Study DX-2930-03. Results of the C4 assay from DX-2930-02 or Study DX-2930-03 may be used to confirm diagnosis in this study. Subjects may be retested if results are incongruent with clinical history or believed by the investigator to be confounded by recent LTP use.

C1Q ASSAY

Results of a C1q assay may be required for eligibility assessment. Any subject who requires C1-INH and C4 assay results for diagnostic confirmation in this study will have C1q assay results obtained as well. The C1q sample will be drawn at the same time as the C1 and C4 sample is drawn during the Screening visit.

6.8.1.7 PK Sample Collection

As outlined in Section 6.9.

6.8.1.8 PD Sample Collection

As outlined in Section 6.10.

6.8.1.9 Plasma Anti-Drug Antibody Testing

As outlined in Section 6.11.

6.8.2 Sample Collection, Storage, and Shipping

Blood samples for laboratory assessments will be collected at the site by a trained site staff designated and/or approved by the study investigator. Details for the collection, processing, storage and shipment of samples for all laboratory determinations will be provided in the Laboratory Manual.

Biological material will be stored and secured in a manner that assures that unauthorized access is prohibited and the samples are not lost, allowed to deteriorate, or accidentally or illegally destroyed.

6.9 Pharmacokinetic Assessments

Blood samples for the measurement of plasma DX-2930 concentration will be obtained as specified in the Study Activities Schedules (Table 1 and Table 2).

6.10 Pharmacodynamic Assessments

To evaluate the PD effects of DX-2930 upon plasma kallikrein activity, blood samples will be obtained as specified in the Study Activities Schedules.

6.11 Plasma Anti-Drug Antibody Testing

Plasma samples for testing for formation of antibodies to DX-2930 will be obtained as specified in the Study Activities Schedules. Additional testing may be required in patients who have positive ADA.

6.12 Prior and Concomitant Therapy

The Sponsor representatives and investigator at the site conducting the trial will review and evaluate prior (4 weeks prior to study screening) and concomitant medication usage on an ongoing basis. For subjects not rolling over from Study DX-2930-03, all prescription, over-the-counter medications, herbals, and supplements that are being taken or have been taken by subjects from 4 weeks prior to screening through the duration of the study will be regarded as concomitant medications and must be documented on the source document and eCRF following informed consent. For subjects rolling over from Study DX-2930-03, concomitant therapy use will be carried forward from that study and will continue to be collected through the duration of the study.

6.13 Investigational Medicinal Product Treatment

Instructions for safe handling of DX-2930, preparation of each subcutaneous dose and administration of DX-2930, are provided in the Pharmacy Manual. Preparation and dispensing of DX-2930 will be handled by qualified study site personnel or by subjects who are self-

administering after receiving appropriate training by the investigator or designee at the study site. The requirements for maintaining DX-2930 accountability are provided in Section 6.15.1 (for subjects self-administering) and Section 5.7 and Section 5.8 of this protocol.

6.14 Quality of Life Assessments

Quality of life (QoL) assessments will be conducted using the Angioedema Quality of Life Questionnaire (AE-QoL), EuroQoL 5-Dimensional 5-Level Measure (EQ-5D-5L), Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH), Hospital Anxiety and Depression Scale (HADS), and 12 Item Short Form Survey (SF-12). See Study Activities Schedules (Table 1 and Table 2). For subjects who rollover from Study DX-2930-03, quality of life assessments obtained during the final study visit in Study DX-2930-03 will serve as the Day 0 pre-dose quality of life assessments in this study and will not be duplicated.

6.14.1 Angioedema Quality of Life Questionnaire (AE-QoL)

The AE-QoL is a self-administered, symptom-specific tool developed and validated to assess quality of life (QoL) impairment in patients with recurrent angioedema (Weller et al. 2012). The AE-QoL consists of 17 questions covering four domains/dimensions (functioning, fatigue/mood, fear/shame, nutrition). Each of the 17 items has a five-point Likert-type response scale ranging from 1 (Never) to 5 (Very Often). The AE-QoL is scored to produce a score for each domain and a total score ranging from 0 to 100, with higher scores indicating stronger impairment. It takes 5 minutes to complete the AE-QoL.

6.14.2 EuroQoL 5-Dimensional 5-Level Measure (EQ-5D-5L)

The EQ-5D-5L is a self-administered standardized measure of health status comprised of a descriptive system and a Visual Analogue Scale (VAS). The descriptive system consists of five health related quality of life dimensions (ie, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is rated on a 5-point response scale (5 levels) indicating severity of problems, where 1 is “no problems” and 5 is “extreme problems”. The EQ-5D VAS is a measure of overall self-rated health status on a 20-cm vertical VAS with endpoints labelled “the best health you can imagine” and “the worst health you can imagine”. The VAS ranges from 0 to 100, with higher scores indicative of better overall health.

6.14.3 Work Productivity and Activity Impairment – General Health (WPAI-GH) Questionnaire

The WPAI-GH is a 6-item instrument assessing work and activity impairment due to health problems during the past 7 days. The instrument elicits four main scores in relation to general health specifically: absenteeism (the percentage of work time missed because of one's health in the past seven days), presenteeism (the percentage of impairment experienced while at work in the past seven days because of one's health), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and activity impairment (the percentage of impairment in daily activities because of one's health in the past seven days) (Reilly et al. 1993). Adolescent subjects should complete the WPAI questionnaire and use the term “school” instead of “work” when filling out this questionnaire. These data will be analyzed separately.

6.14.4 Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a self-assessment scale to detect states of depression, anxiety, and emotional distress amongst patients who were being treated for a variety of clinical problems (Zigmond and Snaith 1983). The scale has a total of 14 items. Seven of the items relate to anxiety and seven relate to depression. The responses are scored on a scale of 0–3 (3 indicates higher symptom frequencies). Scores for each subscale (anxiety and depression) range from 0 to 21 with scores categorized as follows: normal 0–7, mild 8–10, moderate 11–14, and severe 15–21. Scores for the entire scale (emotional distress) range from 0 to 42, with higher scores indicating more distress. This scale reflects how a subject has been feeling during the past week.

6.14.5 12 Item Short Form v2 Health Survey (SF-12v2)

The SF-12v2 Health Survey is a reliable and valid generic measure of functional health and well-being. The SF-12v2 consists of 12 questions, all selected from the SF-36 Health Survey (Ware et al. 1996). The SF-12v2 yields eight health domains (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, and mental health summary measures. Physical and Mental Health Composite Scores (PCS & MCS) can be computed using the scores of twelve questions and range from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health. The standard form of the instrument asks subjects to reply to questions according to how they have felt over the last 4 weeks.

6.14.6 Angioedema Control Test (AECT)

The Angioedema Control Test (AECT) is a patient reported outcome measure. The concept of the AECT is comparable to those of the well-established Asthma Control Test (ACT) and Urticaria Control Test (UCT) (Nathan et al. 2004; Weller et al. 2014). The AECT could be used to assess control of angioedema among patients with recurrent angioedema (including hereditary angioedema) and to aid treatment decisions. The AECT consists of up to 10 questions. Each question has 5 answer options (verbal rating scale) that are scored from 0 to 4 points, which ultimately comprise the total AECT score.

6.14.7 Treatment Satisfaction Questionnaire for Medication (TSQM-9)

The TSQM-9 is a validated 9-item questionnaire developed to measure subjects' satisfaction with their medication and includes three scale scores: effectiveness, convenience, and global satisfaction (Bharmal et al. 2009). Scale scores for each of the 3 scales, as well as a combined score are calculated separately. Scores are transformed to a 0 to 100 scale, where higher scores indicate greater treatment satisfaction. The TSQM-9 has been applied in clinical studies in several chronic conditions.

6.14.8 Global Impression of Treatment Response

The subjects' and investigators' global impression of treatment response will be assessed using a one-item question. The item will assess overall perception of treatment response. Assessment will be performed separately by the subject and investigator. The subjects and investigators will be asked to think of "today" while rating the question (or an appropriate translation, as

applicable): "Overall, how would you rate your response to the study medication?" There will be five response options; namely, poor; fair; good; very good, excellent.

6.14.9 Exit Interview

At the last follow-up visit, subjects will be asked about their overall experience with DX-2930 studies and any changes in signs and symptoms related to HAE and related impact on subjects health during the between-attack period in order to assess opportunities to improve the future studies. The exit interview will capture subject experience in general. These questions will ask about HAE control, changes pertaining to wellness between attacks, response to triggers, prodrome, and overall sense of vitality or energy level, or activity level.

6.15 DX-2930 Injection Report and Self-Administration and Subcutaneous Injection Survey

Assessments of subject experience with self-administration and SC injections of DX-2930 will be conducted.

6.15.1 DX-2930 Injection Report

The investigator or designee will train subjects who elect to self-administer DX-2930 on the following:

- Transportation and recommended storage conditions of investigational product from the study site to the offsite location.
- Maintenance of accurate records regarding each administration of investigational product including supply identification (ie, lot/kit number), date and time of injection, injection site location, infusion time, and if applicable, any reason the self-administration could not be completed as instructed.
- Retention of all used and unused vials of investigational product for drug accountability purposes.

After receiving appropriate training and demonstrating their understanding of self-administration, subjects are allowed to self-administer DX-2930 after receiving the first 2 doses of DX-2930 at the study site (administered by study personnel).

For those subjects who choose to self-administer or have a parent/legal guardian/caregiver administer DX-2930, subjects must complete an assessment of their experience with self-administration and subcutaneous injection for each dose received. Study personnel will document the subject's responses in the subjects' medical record and eCRF.

6.15.2 DX-2930 Self-administration and Subcutaneous Injection Survey

Subjects will complete an assessment on their overall experience with self-administration and experience with receiving SC injections of DX-2930 according to the Study Activities Schedules (Table 1 and Table 2) during the study. Subjects who received a PFS will be asked to describe the overall experience using the PFS including aspects of administration. For subjects who have previously received LTP with C1-INH products via IV administration, they will be asked to indicate the preferred route for medication administration. Study personnel will document the

subject's responses in the subjects' medical record and eCRF. In addition, investigators will be asked to indicate their preference (SC, IV, or no preference) on the route to administer medications to prevent angioedema attacks.

6.16 Adverse Event Reporting

Adverse events will be collected from signing of the informed consent through the last study visit.

6.16.1 Definitions

6.16.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical trial subject whether or not it appears to have a causal relationship with the treatment administered.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or participation in a clinical study, whether or not directly related to the medicinal product or study participation.

- AEs may be new events or may be pre-existing conditions that have become aggravated or have worsened in severity or frequency during the course of the study.
- AEs may be clinically significant changes from baseline in physical examination, laboratory tests, or other diagnostic investigation (eg, laboratory results, x-ray findings).

Laboratory abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. A clinically significant laboratory abnormality that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to DX-2930 interruption or discontinuation, will in itself, be considered an AE. Laboratory or diagnostic testing abnormalities that reflect or are part of a known underlying medical condition are not, in themselves, AEs; rather, the underlying medical condition leading to the abnormalities would be reported as the AE.

Pregnancy is not an AE; however, if a female subject becomes pregnant during the conduct of the study, the investigator must notify the Sponsor according to the procedures provided in Section 6.16.5.2.

6.16.1.2 Serious Adverse Event

A SAE is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening experience; Note: "Life-threatening" refers to a situation in which the subject was at risk of death at the time of the event; it does not refer to an event that might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization; Note: Does not include hospitalization for observation with release within 24 hours. A scheduled hospitalization for a pre-existing condition that has not worsened during participation in the study does not meet this criterion. Pre-planned hospitalizations for an elective medical/surgical procedure or routine check-ups do not meet this criterion.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is considered to be an important medical event defined as those that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

6.16.1.3 Overdose

An overdose is defined as a significant variation from the recommended/scheduled dosage for a product. The dosing for this study will be conducted in a controlled clinical setting and an overdose is not anticipated. However, in the event of an accident, for this study, an overdose of DX-2930 is considered a dose that is two-fold higher than the intended dose for the subject.

6.16.1.4 Planned Hospitalization

A hospitalization planned by the subject prior to the first dose of open-label DX-2930 is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the trial, it must be reported as an AE.

6.16.1.5 Treatment-Emergent Adverse Events (TEAE)

An AE is treatment-emergent if the onset time is after first administration of open-label DX-2930 through the final follow-up visit or, in the event that onset time precedes first DX-2930 administration, the AE increases in severity during the open-label treatment period.

For rollover subjects, any adverse event that started during the subject's participation in Study DX-2930-03 and was ongoing at the time of the first open-label dose in Study DX-2930-04 will not be counted as an AE in Study DX-2930-04 unless that event has worsened in severity or frequency following the first open-label dose. Adverse events that started during subject participation in Study DX-2930-03, resolved following the first open-label dose in Study DX-2930-04, and then subsequently reappeared in Study DX-2930-04 will be counted as a new TEAE in Study DX-2930-04.

6.16.1.6 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) will be captured and monitored during this study. Investigators will report all AESI to the Sponsor, regardless of causality, using the same timelines as described for SAE reporting. The following describe the AESI and the criteria for reporting AESI.

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.

6.16.2 Monitoring

6.16.2.1 Monitoring of Adverse Events

Each subject will be monitored for the occurrence of AEs, including SAEs and AESI, from signing of the ICF through the final follow-up visit.

- Subjects will be questioned and/or examined by the investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.
- Subjects having TEAEs will be monitored until resolution with relevant clinical assessments and laboratory tests, as determined by the investigator.
- AEs, actions taken as a result of AEs, and follow-up results must be recorded in the eCRF as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For any SAEs or AEs that require the subject to be discontinued from dosing, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s). Subjects will continue to be followed through completion of all scheduled visits.

6.16.2.2 Monitoring of Safety Laboratory Assessments

All safety laboratory assessments will be performed at a central laboratory. The clinical laboratory values will be reported to the investigator who will review them for clinical significance and consideration of abnormal values as potential AEs.

6.16.3 Assessment of Adverse Events

6.16.3.1 Assessment of Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

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) (Appendix 1, Appendix 2) 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) (Appendix 3). For abnormalities not specifically found in the Toxicity Tables, the following general scale will be used to estimate grade of severity:

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

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

All HAE attacks will be captured as AEs and assessed with DMID & HAE Attack Assessment and Reporting Procedures (HAARP) criteria.

6.16.3.2 Assessment of Causality

A medically qualified investigator must assess the relationship of any AE (including SAEs) to the use of DX-2930, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
- The temporal association between DX-2930 exposure and onset of the AE.

- Whether the manifestations of the AE are consistent with known actions or toxicity of DX-2930.
- The AE resolved or improved with decreasing the dose or stopping use of DX-2930 (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between DX-2930 and the AE will be assessed using one of the following categories:

Not Related: Factors consistent with an assessment of Not Related include:

- Temporal relationship is lacking (eg, the event did not occur within a reasonable time frame following administration of DX-2930); or
- Other causative factors more likely explain the event (eg, a pre-existing condition, other concomitant treatments).

Related: Factors consistent with an assessment of Related include:

- There is a positive temporal relationship (eg, the event occurred within a reasonable time frame following administration of DX-2930); or
- The AE is more likely explained by administration of DX-2930 than by another cause (ie, the AE shows a pattern consistent with previous knowledge of DX-2930 or the class of DX-2930).

6.16.3.3 Assessment of Clinical Significance

Clinical significance of individual AEs will be determined by the investigator, with discussion with the Medical Monitor as appropriate.

6.16.4 Clinical Laboratory Adverse Events

Laboratory abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. A clinically significant laboratory abnormality that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to DX-2930 interruption or discontinuation, will be considered an AE.

When laboratory abnormalities are considered to be AEs, the DMID Adult Toxicity Table (Appendix 2) or DMID Pediatric Toxicity Tables (Appendix 3) will be used to assess severity. Where discrepancies in the upper limit of normal (ULN) and lower limit of normal (LLN) of laboratory ranges occur between those included in the DMID tables and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade. Clinical significance of individual laboratory AEs will be determined by the investigator with input from the Medical Monitor as needed.

Following is an exception to defining clinically significant, abnormal laboratory values as AEs:

- APTT prolongation in the absence of any associated bleeding or other evidence of clinical relevance will not be considered a clinically significant laboratory abnormality or AE. In the appropriate physiologic setting, such as IV heparin therapy, aPTT can be used to monitor bleeding risk. However, as noted in the Investigators Brochure, aPTT prolongation due to plasma kallikrein inhibition is an artifactual *in vitro* phenomenon. Although plasma kallikrein drives fibrin formation in the aPTT assay, plasma kallikrein-driven coagulation does not appear to have hemostatic or other physiologically important functions *in vivo*. It is well documented that, in humans, deficiency of factor XII or prekallikrein (and thus plasma kallikrein) is not associated with abnormal bleeding, either spontaneous or during surgical procedures (Renne and Gruber 2012). Despite the lack of clinical effect, deficiency of either protein is associated with marked prolongation of the aPTT.

6.16.5 Reporting Investigator Safety Observations to the Sponsor

6.16.5.1 Reporting Non-serious Adverse Events

All AEs, regardless of seriousness, severity, or causal relationship to DX-2930, will be recorded on the AE page of the eCRF. In this study all HAE attacks reported by the subject, regardless of whether or not they are confirmed by the investigator, will be captured as AEs.

6.16.5.2 Reporting Pregnancies

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, the investigator must report the pregnancy to the Sponsor's Pharmacovigilance Department using the Pregnancy Reporting Form within 24 hours of becoming aware of the event. The investigator must obtain consent to collect pregnancy information (including the status of the newborn, if applicable).

If some of the information required for completion of the Pregnancy Reporting Form is unavailable at the time of the initial report, follow-up reports will be completed and submitted within 24 hours of becoming aware of the new information. The investigator is required to follow the pregnancy through delivery. The outcome of the pregnancy and the status of the newborn (if applicable) will be reported on the Pregnancy Reporting Form within 24 hours of becoming aware.

6.16.5.3 Safety Observations Requiring Expedited Reporting by the Investigator to the Sponsor

Any occurrence of the following events or outcomes in a subject in the trial must be reported expeditiously by the investigator or qualified designee to the Sponsor's Pharmacovigilance Department:

- SAE
- AESI
- Overdose
- Cancer

The investigator is to report any expedited safety observations from the list above to the Sponsor using the SAE Reporting Form in the EDC system within 24 hours of becoming aware of the event.

Any SAE reported to the Sponsor Pharmacovigilance Department using the SAE Reporting Form in the EDC system is to be recorded in the eCRF, as well as in the subject's source documentation along with any actions taken. If all required information on the form is not available at the time of the initial report, follow-up information will be completed in the EDC system.

The investigator is required to follow SAEs until resolution regardless of whether the subjects are still participating in the study. SAE resolution is defined as:

- Resolved with or without residual effects.
- A return to baseline for a pre-existing condition.
- Laboratory values have returned to baseline or stabilized.
- The investigator does not expect any further improvement or worsening of the event.
- Fatal outcome—if an autopsy is performed; the autopsy report is requested to be provided to the Sponsor as soon as it is available.

6.16.5.4 Expedited Reporting by the Sponsor to a Regulatory Health Authority

The Sponsor or designee will report relevant safety information to concerned health authorities in accordance with local laws and regulations.

6.16.5.5 Safety Contact Information

24-Hour Global Safety Contact: Pharmacovigilance Department
Email: [redacted]
Telephone (US) [redacted]

6.16.5.6 Safety Notifications by the Sponsor to the Investigator

Investigators will receive prompt notification of any adverse experience related to DX-2930 that is both serious and unexpected, or any finding that suggests a significant risk for subjects. The investigator will promptly inform his / her IRB/REB/IEC of the notification and insert the notification in the Investigator's Regulatory Binder in accordance with local regulations.

6.17 Subject Withdrawal

The investigator may withdraw a subject from DX-2930 treatment for any of the following reasons:

- In the opinion of the investigator, the subject is unable to comply with the requirements of the protocol for satisfactory completion or interpretation of study results (including use of prohibitive medications),
- A serious or intolerable AE occurs,

- A clinically significant change in a laboratory parameter occurs,
- The Sponsor or investigator terminates the study, or
- The subject requests to be discontinued from the study.

Subjects will continue to be followed through completion of all scheduled visits, unless the subject requests to be discontinued from the study.

6.18 Appropriateness of Measurements

This is a Phase 3 open-label extension study that is designed to evaluate the long-term safety and efficacy of DX-2930 in prophylactic therapy for angioedema attacks in subjects with HAE. DX-2930 is a recombinant, fully human IgG1, kappa light chain, monoclonal antibody. The open-label, non-controlled study design is a standard approach for extension studies that follow double-blind pivotal trials. Measures employed in this protocol are standard measures routinely used for the evaluation of the efficacy, safety and tolerability of an investigational product. Measures employed for rollover subjects between the first and second open-label doses are appropriate to characterize the outer bounds of dosing frequency for DX-2930.

7. STUDY ACTIVITIES

Study activities are summarized by study visit in Study Activities Schedules (Table 1 and Table 2).

7.1 Screening Visit (Up to Day −28)

For subjects not rolling over from Study DX-2930-03, the procedures and assessments described in the Study Activities Schedule (Table 1) should be followed:

- Informed consent (Section 6.1)
- Eligibility review (Section 6.2)
- Demographics and medical history (Section 6.3)
- C1-INH functional assay, C4 and C1q sample collection (Section 6.8)
- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including height and weight (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry, and urinalysis (Section 6.8)
- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16); pre-existing signs and symptoms

For subjects rolling over from the double-blind DX-2930-03 study, no Screening visit is required as subjects will enter the OLE on the same day that their last Study DX-2930-03 study visit is completed. Diagnostic test results and demographic and medical history for these subjects will be carried forward from that study.

7.2 Start of Treatment Period: Visit 1, Dose 1 (Day 0)

The following procedures and assessments are to be performed on Day 0 prior to the first dose of DX-2930. For subjects who rollover from Study DX-2930-03, all final assessments taken during the final study visit in Study DX-2930-03 will be used as the pre-dose results on Day 0 and will not be duplicated.

- Informed consent (for subjects rolling over from the double-blind DX-2930-03 study; this can be on or after Day 168 of that study) (Section 6.1)
- Eligibility review (Section 6.2)
- Urine pregnancy test (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- 12-Lead ECG (Section 6.7)

- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK baseline sample collection (Section 6.9)
- PD baseline sample collection (Section 6.10)
- Baseline anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- First dose of open-label DX-2930 (Section 5.1)

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2)
- AE collection (Section 6.16)

7.3 Interval between Dose 1 and Dose 2 for Rollover Subjects

Rollover subjects must adhere to the Study Activities Schedule (Table 1) for the entire duration of the study. Until a rollover subject reports their first HAE attack, study visits may be conducted via site check in calls, except for the following study visits which must be conducted at the investigative site:

- Day 14
- Day 28
- Day 56
- Day 98
- Day 126
- Day 154
- Day 182
- Day 224
- Day 266
- Day 308
- Day 364

The tests and assessments required at these visits are specified in the sections below.
Site check in calls may serve as any of the following study visits until the subject receives their second open-label dose:

- Day 42
- Day 70
- Day 84
- Day 112
- Day 140
- Day 168
- Day 196
- Day 210
- Day 238
- Day 252
- Day 280
- Day 294
- Day 322
- Day 336
- Day 350

Study site personnel will also contact rollover subjects approximately 7 days after each study visit (both site visits and check-in calls) until the subject receives their second open-label dose.

The following assessments are performed during all site calls:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.4 Dose 2 of DX-2930 for Rollover Subjects

The duration of time between Dose 1 and Dose 2 will vary by subject based on when their first HAE attack occurs following Dose 1. As a result, rollover subjects may not receive DX-2930 treatment at every dosing visit as outlined in the Study Activities Schedules (Table 1 and Table 2).

Once a rollover subject reports their first HAE attack they will present to the investigative site for their second open-label dose of DX-2930 as quickly as subject and site schedules allow. This treatment visit may be counted as a scheduled study visit, or as an acceptable extra study visit. For details on determining whether the second dose is counted as a scheduled or extra study visit, refer to Section 3.1.1.

Regardless of when the second dose is administered, the following tests and assessments will be conducted pre-dose on the day it is administered:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)

- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

The following tests and assessments will also be performed if the second dose occurs on a scheduled study visit for which they are required:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- 12-Lead ECG (Section 6.7)
- Quality of life assessments (Section 6.14)
- Long-term prophylactic therapy continuation (Section 3.1.1)

After the required pre-dose tests and assessments are completed:

- Second dose of open-label DX-2930 (Section 5.1)

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.5 Visit 2 (Day 14 ±4 days); Dose 2 of DX-2930 for Non-Rollover Subjects

On Day 14, the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1)

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.6 Continuation of Treatment Period: Visit 3 (Day 28 ±4 Days)

On Day 28, the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 3. At this visit, subjects have the option to self-administer at the investigational site.

After administration of DX-2930, the following post-treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.7 Continuation of Treatment Period: Visit 4 (Day 42 ±4 Days)

On Day 42 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 4. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.8 Continuation of Treatment Period: Visit 5 (Day 56 ±4 Days)

On Day 56 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 5. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.9 Continuation of Treatment Period: Visits 6 and 7 (Days 70 and 84, All ±4 Days)

On Days 70 and 84 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects these doses represent Dose 6 and Dose 7. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.10 Continuation of Treatment Period: Visit 8 (Day 98 ±4 Days)

On Day 98 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- 12-Lead ECG (Section 6.7)

- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 8. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2)
- AE collection (Section 6.16)

7.11 Continuation of Treatment Period: Visit 9 (Day 112 ±4 Days)

On Day 112 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 9. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.12 Continuation of Treatment Period: Visit 10 (Day 126 ±4 Days)

On Day 126 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 10. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.13 Continuation of Treatment Period: Visit 11 (Day 140 ±4 Days)

On Day 140 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 11. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.14 Continuation of Treatment Period: Visit 12 (Day 154 ±4 Days)

On Day 154 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 12. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.15 Continuation of Treatment Period: Visit 13 (Day 168 ±4 Days)

On Day 168 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 13. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.16 Continuation of Treatment Period: Visit 14 (Day 182 ±4 Days)

On Day 182, the following procedures and assessments will be performed:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, and serum chemistry (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Biomarker sample collection (6.8.1.6)
- Anti-drug antibody sample collection (Section 6.11)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 14. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2
- AE collection (Section 6.16)

7.17 Continuation of Treatment Period: Visit 15 (Day 196 ±4 Days)

On Day 196 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 15. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.18 Continuation of Treatment Period: Visit 16 (Day 210 ±4 Days)

On Day 210 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 16. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.19 Continuation of Treatment Period: Visit 17 (Day 224 ±4 Days)

On Day 224 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Laboratory testing including hematology, coagulation, and serum chemistry (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 17. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.20 Continuation of Treatment Period: Visit 18 (Day 238 ±4 Days)

On Day 238 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 18. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.21 Continuation of Treatment Period: Visit 19 (Day 252 ±4 Days)

On Day 252 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 19. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.22 Continuation of Treatment Period: Visit 20 (Day 266 ±4 Days)

On Day 266 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, and serum chemistry (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Biomarker sample collection (6.8.1.6)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 20. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2)
- AE collection (Section 6.16)

7.23 Continuation of Treatment Period: Visit 21 (Day 280 ±4 Days)

On Day 280 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 21. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.24 Continuation of Treatment Period: Visit 22 (Day 294 ±4 Days)

On Day 294 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 22. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.25 Continuation of Treatment Period: Visit 23 (Day 308 ±4 Days)

On Day 308 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Laboratory testing including hematology, coagulation, and serum chemistry (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 23. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.26 Continuation of Treatment Period: Visit 24 (Day 322 ±4 Days)

On Day 322 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 24. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.27 Continuation of Treatment Period: Visit 25 (Day 336 ±4 Days)

On Day 336 the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 25. At this visit, subjects have the option to self-administer DX-2930 at the investigational site or the subject's home or other agreed upon location.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)

- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.28 Continuation of Treatment Period: Visit 26 (Day 350 ±4 Days)

On Day 350, the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

7.29 Continuation of Treatment Period: Visit 27 (Day 364 ±4 Days)

On Day 364, the following procedures and assessments will be performed prior to DX-2930 treatment:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, and serum chemistry (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Biomarker sample collection (6.8.1.6)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)

- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)

After the preceding procedures and assessments are completed:

- Administer DX-2930 (Section 5.1). For non-rollover subjects this dose represents Dose 27. At this visit, subjects have the option to self-administer DX-2930 at the investigational site.

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 hour post-dose.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey (Section 6.15.2)
- AE collection (Section 6.16)

7.30 Continuation of Treatment Period: Visits 28 and 29 (Day 378 and 392 ±4 Days)

On Days 378 and 392, the following procedures and assessments will be performed prior to DX-2930 treatment:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

After the preceding procedures and assessments are completed:

- DX-2930 administration (Section 5.1)

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs, including body temperature, HR, BP, and RR (Section 6.5) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site.
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)
- Site Check In Call

7.31 Continuation of Treatment Period: On-Site Activities (Between Visit 30 and Visit 66)

At Visit 30 through Visit 66 *on-site* visits will occur every 8 weeks, although dosing will continue at intervals of 14 ± 4 days. On-site activities will include the following:

- Visit 30 (Day 406)
- Visit 34 (Day 462)
- Visit 38 (Day 518)
- Visit 42 (Day 574)
- Visit 46 (Day 630)
- Visit 50 (Day 686)
- Visit 54 (Day 742)
- Visit 58 (Day 798)
- Visit 62 (Day 854)
- Visit 66 (Day 910)

At these visits, the following procedures and assessments will be performed prior to DX-2930 treatment, per the Study Schedule of Activities:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs, including body temperature, HR, BP, and RR – prior to dosing and 1 hour after dosing (recommended ± 15-minute window). Monitoring of vital signs will not be performed for subjects who elect to self-administer away from the investigative site at optional off-site visits (indicated non-shaded columns). (Section 6.5)
- Physical examination, including weight (Section 6.6)
- Laboratory testing, including hematology, coagulation, serum chemistry, and urinalysis (urinalysis *is* performed as part of the clinical laboratory testing at Days 574, 742, 910/Visits 42, 54, 66) (Section 6.8)
- PK, PD, Anti-drug antibody, and Biomarker sample collection (Section 6.8, Section 6.9, Section 6.10 Section 6.11) – *only at Visits 34, 42, 50, 58, and 66 during this time range*
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments (Section 6.14)
  - AE-QoL
  - EQ-5D-5L
  - WPAI-GH

- HADS
- SF-12
- AECT
- TSQM-9 – *only at Visit 42 during this time range*

After the preceding procedures and assessments are completed:

- DX-2930 administration (Section 5.1)

After administration of DX-2930, the following post treatment procedures and assessments will be performed:

- Vital signs, including body temperature, HR, BP, and RR (Section x) at 1 hour post-dose. No monitoring of vital signs will be performed for subjects who elect to self-administer away from the investigational site. (Section 6.5)
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- DX-2930 Self-administration and Subcutaneous Injection Survey and Pre-filled Syringe Survey -- Collect subject's injection reports of their experience with DX-2930 self-administration, subcutaneous administration, and prefilled syringe (if relevant) for all doses. (Section 6.15.2)
- AE collection (Section 6.16)

Monitoring during the periods between on-site visits is described below in Section 7.32.

7.32 Continuation of Treatment Period: Potential Off-Site Activities (Between Visit 31 and Visit 65)

During the periods between the required on-site visits, subjects will have the option to self-administer DX-2930 *either* at the investigational site or the subject's home or other agreed upon location. For subjects who self-administer at home, site personnel will call within approximately 3 days after the planned self-administration to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.

Potential off-site visits will include the following (ie, visits at 2-week intervals between the visits that are on-site visits):

- Visits 31, 32, 33 (Days 420, 434, 448)
- Visits 35, 36, 37 (Days 476, 490, 504)
- Visits 39, 40, 41 (Days 532, 546, 560)
- Visits 43, 44, 45 (Days 588, 602, 616)
- Visits 47, 48, 49 (Days 644, 658, 672)

- Visits 51, 52, 53 (Days 700, 714, 728)
- Visits 55, 56, 57 (Days 756, 770, 784)
- Visits 59, 60, 61 (Days 812, 826, 840)
- Visits 63, 64, 65 (Days 868, 882, 896)

The assessments to be performed (regardless of whether the subject exercises the off-site option or not) will include the following, as shown on the Study Schedules of Events:

- DX-2930 administration (Section 5.1)
- HAE attack information (Section 6.4)
- Concomitant therapy (Section 6.12)
- DX-2930 Injection Report (Section 6.15.1)
- AE collection (Section 6.16)

If the subject is *off-site*, the following will also be performed:

- Site Check In Call

If the subject is *on-site*, the following will also be performed:

- Vital signs including body temperature, HR, BP, and RR (Section 6.5) – prior to dosing and 1 hour after dosing (recommended ± 15-minute window). Monitoring of vital signs will not be performed for subjects who elect to self-administer away from the investigative site at optional off-site visits (indicated non-shaded columns). (Section 6.5)

7.33 Completion of Treatment Period: Visit 67 (Day 924 ±4 Days)

On Day 924, the following procedures and assessments will be performed. Note that DX-2930 will not be administered during this visit:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Biomarker sample collection (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.34 Follow-up Period: Visit 68 (Day 938 ±4 Days)

On Day 938, all rollover and non-rollover subjects will receive a site check-in call. During this call, study site personnel will collect information shown in the Study Schedule of Activities:

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.35 Final Follow-up Visit: Visit 69 (Day 952 ±4 Days)

On Day 952, all rollover and non-rollover subjects will complete a final study visit at the investigative site, including the activities shown on the Study Schedule of Activities:

- Pregnancy test, serum or urine (females of childbearing potential) (Section 6.8)
- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Physical examination, including weight (Section 6.6)
- 12-Lead ECG (Section 6.7)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.8)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Anti-drug antibody sample collection (Section 6.11)
- Biomarker sample collection (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- Quality of life assessments
  - AE-QoL (Section 6.14)
  - EQ-5D-5L (Section 6.14)
  - WPAI-GH (Section 6.14)
  - HADS (Section 6.14)
  - SF-12 (Section 6.14)
  - AECT (Section 6.14.6)
  - TSQM-9 (Section 6.14.7)
  - Global Impression of Treatment Response (Section 6.14.8)
- AE collection (Section 6.16)

- Exit Interview (Section 6.14.9)

- Study Discharge: Subjects will be discharged at this study visit.

7.36 Early Termination

Subjects who terminate early from the study will undergo (if possible) all of the assessments and procedures scheduled for Day 952.

8. QUALITY CONTROL AND ASSURANCE

The Sponsor and the Contract Research Organization (CRO) conducting trial management services, Rho, Inc., will implement a system of quality assurance that includes all elements described in this protocol. Within this system, SOPs from the Sponsor and CRO will be implemented to ensure that the clinical trial is conducted in compliance with regulatory requirements and Good Clinical Practices (GCP). Quality control will be applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The site staff should assist in all aspects of audit/inspection.

9. DATA ANALYSIS / STATISTICAL METHODS

9.1 General Considerations

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

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, standard errors, and 95% confidence intervals for least squares means will be provided. Time-to-event data will be summarized using Kaplan-Meier estimates of the 25th, 50th (median), and 75th percentiles with associated two-sided 95% confidence intervals, as well as percentage of censored observations. Plots of the Kaplan-Meier curves and supporting data listings detailing each subject's contribution to the analysis will be provided.

Formal hypothesis testing will not be performed. Any hypothesis testing will be exploratory in nature and resulting p-values will be considered descriptive.

9.2 Sample Size Determination

No formal sample size calculation was performed. The sample size is not based on any statistical considerations. This study is designed to evaluate the safety and efficacy of open-label treatment with DX-2930 in subjects who participated in Study DX-2930-03 (rollover subjects) and individuals who were not otherwise able to participate in Study DX-2930-03 (non-rollover subjects).

9.3 Method of Assigning Study Subjects to Treatment

Subjects meeting all eligibility criteria will be enrolled in the study and sequentially assigned a unique site-based identification number.

9.4 Analysis Populations

9.4.1 Safety Population

The Safety Population will include all subjects who received any study drug after entering Study DX-2930-04 (ie, any exposure to open-label DX-2930). Unless otherwise specified, summary tabulations conducted with the Safety Population will be presented by the subject's study entry type (rollover or non-rollover) and overall.

9.4.2 Rollover Safety Population

The Rollover Safety Population is the subset of subjects who participated in Study DX-2930-03 and received any study drug after entering Study DX-2930-04 (ie, any exposure to open-label DX-2930). Unless otherwise specified, summary tabulations conducted with the Rollover Safety Population will be presented by the subject's prior treatment group from Study DX-2930-03

(DX-2930 300 mg every 2 weeks, DX-2930 300 mg every 4 weeks, DX-2930 150 mg every 4 weeks, and Placebo).

9.4.3 Non-rollover Safety Population

The Non-rollover Safety Population is the subset of subjects who directly entered Study DX-2930-04 and received any study drug after entering Study DX-2930-04 (ie, any exposure to open-label DX-2930). Unless otherwise specified, summary tabulations conducted with the Non-rollover Safety Population will be presented by subject's prior type of LTP therapy prior to study entry (C1-INH, androgens, anti-fibrinolytics, and not on LTP)..

9.5 Population Description and Exposure

9.5.1 Subject Disposition

The numbers of subjects treated with study drug, completed the study and discontinued prematurely by reason will be summarized for each analysis population.

9.5.2 Demographics and Other Baseline Characteristics

Baseline and demographic variables will be summarized for each analysis population.

9.5.3 Medical History

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

9.5.4 Treatment Exposure and Compliance

Treatment compliance and the extent of exposure to study drug 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 for each analysis population.

9.5.5 Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD). The number and percentage of subjects with prior or concomitant medications will be summarized by therapeutic class and preferred term for each analysis population. A separate, similar table will be provided for the subset of concomitant medications classified as rescue medications.

9.6 Analysis of Efficacy

9.6.1 Time to the First Investigator-confirmed HAE Attack

Time to the first investigator-confirmed HAE attack will be analyzed using the Rollover Safety Population.

Time to the first investigator-confirmed HAE attack (days) will be calculated from the date and time of the first open-label dose of DX-2930 to the date and time of the first investigator-confirmed HAE attack after the first open-label dose. Subjects who discontinue the study prior to experiencing their first on-study investigator-confirmed HAE attack will be censored at the date and time of study discontinuation. Time to the first investigator-confirmed HAE attack will be summarized using Kaplan-Meier methods.

Multivariate and univariate Cox proportional hazards regression models will be employed to examine the impact of baseline covariates on the time to the first investigator-confirmed HAE attack, including but not limited to: baseline attack rate prior to entering Study DX-2930-03, the treatment group in Study DX-2930-03, the time since the last dose given in Study DX-2930-03, the time since the last HAE attack, and the rate of attacks during Study DX-2930-03. Results of this exploratory analysis will be summarized.

9.6.2 Number of Investigator-confirmed HAE Attacks

The number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 924) expressed as a monthly HAE attack rate, will be analyzed using each analysis population.

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

The baseline investigator-confirmed HAE attack rate will be calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the pretreatment period for rollover subjects or historical reporting period for non-rollover subjects divided by the number of days the subject contributed to the pretreatment period for rollover subjects or historical reporting period for non-rollovers multiplied by 28 days.

The baseline, treatment period, and treatment period change from baseline in the investigator-confirmed HAE attack rate will be summarized for each analysis population. The summary will include the total number of investigator-confirmed HAE attacks reported during each period and subject-time in months that each subject contributed to each period. Figures will be created for each analysis population plotting the on-study investigator-confirmed HAE attacks reported during the treatment period relative to Day 0 for each subject.

In addition, the number of investigator-confirmed HAE attacks per month (defined as 28 days) will be summarized descriptively by month (per 28 day interval) for each analysis population. The summary will include the number, change from baseline, and percent change from baseline of investigator-confirmed HAE attacks. Investigator-confirmed HAE attacks will be grouped into 28-day intervals using the start date of the HAE attack. The date of the first exposure to study drug in this study will be used as the start of the first interval and end of the interval will be the date of first exposure to study drug in this study plus 28 days. Each successive interval will start the last day of the prior interval plus 1 day and end 28 days later.

Similar summary tables will be presented for the following efficacy endpoints for each analysis population:

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

9.7 Analysis of Safety

9.7.1 Adverse Events

Adverse events will be coded using the MedDRA coding dictionary. Separate summaries will be presented for each analysis population.

Treatment-emergent AEs are defined as AEs with onset at the time of or following the first exposure to open-label DX-2930 in this study, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. For AEs with partial onset times, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, then the AE will be classified as treatment-emergent.

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

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

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

- *Treatment Period AEs* will include all AEs starting at or after the first exposure to open-label DX-2930 in this study to those starting before or at the subject's last visit date during the treatment period in this study (AEs starting at or after treatment on Day 0 to the Day 924 visit).
- *Follow-up Period AEs* will include all AEs starting at or after the subject's last visit date of the treatment period in this study (AEs starting *after* the Day 924 visit).

For AEs with partial onset times, non-missing date parts will be used to determine if the AE falls within the period. If a determination cannot be made using the non-missing date parts as to if the AE falls within the period, the AE will be conservatively counted as a treatment-period AE.

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

The number and percentage of subjects with an AE, as well as the total number of AEs, will be summarized by SOC, and PT for each analysis period. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, related severe AEs, and investigator-reported AESI for treatment period and follow-up period AEs.

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

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

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

9.7.2 Laboratory Test Results

Laboratory test results will be summarized using the Safety Population.

Baseline is defined as the last non-missing value prior to the first exposure to DX-2930. For rollover subjects previously exposed to DX-2930, baseline is the last non-missing value prior to first exposure to study drug in Study DX-2930-03.

Actual values and change from baseline clinical laboratory tests will be summarized by study visit. If more than one laboratory result is reported per study visit per parameter, the last non-missing result will be selected for analysis.

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. The number of subjects with a non-missing result, and the number and percentage of subjects with a clinically significant result less than the lower limit of normal, non-clinically significant result less than the lower limit of normal, within the normal range, non-

clinically significant result more than the upper limit of normal, and clinically significant result more than the upper limit of normal will be summarized 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 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.

9.7.3 Vital Signs

Vital signs will be summarized using the Safety Population.

Baseline is defined as the last non-missing value prior to the first exposure to DX-2930. For rollover subjects previously exposed to DX-2930, baseline is the last non-missing value prior to first exposure to study drug in Study DX-2930-03.

Actual values and changes from baseline in vital signs will be summarized 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 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.

9.7.4 Electrocardiography

Electrocardiography results will be summarized using the Safety Population.

The number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECG results, or ECG no performed, will be summarized by study visit. Subjects with clinically significant ECG results will be listed. This listing will include all results for a subject across study time points to identify any trends.

9.8 Other Analyses

Additional analyses of pharmacokinetic (PK), pharmacodynamic (PD), biomarker data, and potential effect of ADA on PK, PD and biomarker 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.

9.8.1 Analysis of Pharmacokinetic Data

Plasma concentrations of DX-2930 will be summarized by nominal PK sampling time using the Safety Population.

9.8.2 Analysis of Pharmacodynamic Data

Plasma kallikrein activity will be summarized by nominal PD sampling time using the Safety Population.

9.8.3 Analysis of Biomarker Data

Additional biomarkers will be summarized by nominal sampling time using the Safety Population.

9.8.4 Analysis of Immunogenicity Data

Blood samples will be collected and tested for the presence of anti-drug antibody. Endpoint titers and assessment of in-vitro neutralization will be reported for samples testing positive. The number and percentage of negative, positive, and/or with neutralizing antibodies antibody samples will be reported and will be summarized by study visit and overall using the Safety Population.

9.8.5 Analysis of Quality of Life Assessments

Quality of life assessments will be summarized using the Safety Population.

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) will be summarized by study visit. In addition, the VAS score for the subject's self-rated health will be summarized by study visit.

The responses to the SF-12 for each item will be tabulated by study visit using the Safety Population. In addition, Physical and Mental Health Composite Scores (PCS & MCS) will be computed using the scores of twelve questions and range from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health.

Responses to the HADS for each item will be tabulated by study visit. In addition, continuous and categorical (0-7: normal, 8-10: mild, 11-14: moderate, 15-21: severe) total scores based on the items related to depression and anxiety, will be summarized by study visit. Each item in the questionnaire is scored from 0-3, with total scores between 0-21 for either depression or anxiety. Scores for the entire scale (emotional distress) will also be presented. Total score for the entire scale range from 0 to 42, with higher scores indicating more distress.

Responses to the WPAI-GH for each item will be summarized by study visit. In addition, four main scores in relation to general health will be summarized by study visit. Scores will be calculated as absenteeism (percentage work time missed due to health), presenteeism (percent impairment while working due to health), work productivity loss (percent overall work

impairment due to health), and activity impairment (percent activity impairment due to health). The scores are percentages, with higher values indicating greater percentage impairment. Only respondents who report being employed full-time or part-time will contribute data for absenteeism, presenteeism, and overall work productivity loss. All respondents contribute data for activity impairment.

Responses to the AE-QoL for each item will be tabulated by study visit. In addition, the domain scores (functioning, fatigue/mood, fears/shame, nutrition) and total score will be summarized by study visit. Each item in the questionnaire is scored from 0-4, with domain and total scores calculated using a linear transformation to a 0-100 scale.

The responses to the AECT for each item will be tabulated by study visit. In addition, total score will be computed using the scores of all questions.

The responses to the TSQM-9 for each item will be tabulated by study visit. In addition, total score will be computed using the scores of 9 questions and range from 0 to 100, where a zero score indicates the lowest level of treatment satisfaction and 100 indicates the highest level of treatment satisfaction.

Response to the Global Impression of Treatment Response question will be tabulated by study visit.

9.8.6 Analysis of Experience with Study Drug Self-administration

For each study population, the responses to each item of the Self-administration and subcutaneous injection survey will be tabulated by study visit.

The number and percentage of subjects who performed study drug administration via study staff administration in-clinic, self-administration in-clinic, and self-administration at home will be tabulated for each study population by study visit.

The number and percentage of subjects who had ever performed study drug administration via study staff administration in-clinic, self-administration in-clinic, or self-administration at home, as well as the total number of injections in each category, will be tabulated for each study population. Additionally, the number and percentage of subjects who received 0, 1-5, 6-10, 11-20, or >20 study staff administration in-clinic, self-administration in-clinic, or self-administration at home will be summarized for each study population.

9.8.7 Analysis of Subject Experience with Pre-filled Syringe Use (if Available)

For each study population, the responses to each item of the pre-filled syringe usage questionnaire will be tabulated by study visit.

9.8.8 Analysis of Subject Response to Rescue medication

For each study population, number and percentage of subjects receiving each type of rescue medication (icatibant [Firazyr®] and ecallantide [Kalbitor®]) will be summarized. In addition, the total number of doses they received will also be summarized by type of rescue medication.

The duration of HAE attacks treated with rescue medication will be summarized using descriptive statistics (n, median, 25% and 75% quartiles, and range) by type of rescue medication and rescue medication-treated attack number.

9.9 Statistical/Analytic Considerations

9.9.1 Interim Analyses and Data Monitoring

Interim analyses may be conducted to support administrative decisions and/or regulatory reporting when a reasonable number of subjects have completed 12 months of consecutive exposure to DX-2930 across the combined DX-2930-03 and DX-2930-04 studies, and only after database lock of Study DX-2930-03.

An independent Data Safety Monitoring Board (DSMB) has been established to provide an ongoing, independent review and assessment of the safety data for Study DX-2930-03. While an independent DSMB is not currently planned for this study, summary safety data from Study DX-2930-04 may be reviewed by the DSMB established for Study DX-2930-03 as part of the collection of safety information available on DX-2930.

9.9.2 Multiple Comparisons/Multiplicity

No adjustment for multiple comparisons will be performed. Any statistical testing will be considered exploratory.

9.9.3 Handling of Missing Data

All available data will be included in the analysis. No imputation of missing data will be performed.

9.9.4 Adjustment for Covariates

The impact of baseline covariates on the time to the first investigator-confirmed HAE attack will be explored to identify and assess the importance of potential prognostic factors.

9.9.5 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.

9.9.6 Subgroup Analyses

Subgroup analyses are planned for the number of investigator-confirmed HAE attacks during the treatment period and adverse events using the Safety Population. 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)
- Baseline HAE Attack Rate (1 to <2, 2 to <3, ≥3 attacks/month)
- HAE Type (Type I, Type II, Unspecified)
- Geographic Region (US, Canada, Jordan, Europe)
- DX-2930 Administration Type (Health Care Provider, Self-administration)
- History of laryngeal HAE attacks (history of laryngeal attack, no history of laryngeal attack)

9.9.7 Sensitivity Analyses

The following sensitivity analyses will be performed on the number of investigator-confirmed HAE attacks during the treatment period for each analysis population to evaluate the robustness of the results. Data summaries will parallel those described for the number of investigator-confirmed HAE attacks during the treatment period efficacy endpoint.

1. The analysis will be repeated counting HAE attacks occurring on Day 14 after administration of study drug through Day 924, instead of Day 0 to Day 924. For this analysis, the period of analysis would be a subset of the treatment period, defined as Day 14 to Day 924.

2. The analysis will be repeated counting HAE attacks occurring on Day 28 after administration of study drug through Day 924, instead of Day 0 to Day 924. For this analysis, the period of analysis would be a subset of the treatment period, defined as Day 28 to Day 924.

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

10. STUDY ADMINISTRATIVE STRUCTURE

The study administration structure is provided in Table 3.

Table 3 Study Administrative Structure

Sponsor Contact:	[redacted], MD [redacted], Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: [redacted]
Global Medical Monitor:	[redacted], MD 300 Shire Way, Lexington, MA 02421 USA Phone: [redacted]
Study Monitoring (US):	Rho, Inc. 6330 Quadrangle Drive, Chapel Hill, NC 27517 Phone: [redacted]
Study Monitoring (Jordan)	Triumpharma 07 Bldg., Al-Yarooty St. P.O. Box 2233, Amman 11941, Jordan Phone: [redacted], [redacted]
Study Monitoring (Canada)	Red Maple Trials Incorporated 1081 Carling Avenue, Suite 707 Ottawa, Ontario, Canada, K1Y4G2 Phone: [redacted]
Study Monitoring (Europe)	Dyax Corp., an indirect, wholly owned subsidiary of Shire plc. 300 Shire Way, Lexington, MA 02421 Phone: [redacted]

10.1 Institutional Review Board/ Research Ethics Board/Independent Ethics Committee

The protocol and all protocol amendments must be signed and dated by the investigator and approved in writing by the IRB/REB/IEC in accordance with GCP prior to implementation. In addition, the IRB/REB/IEC must approve the written informed consent form, any consent form updates, subject recruitment materials (eg, advertisements), and any written information to be provided to subjects prior to implementation. The investigator must provide an annual report to the IRB/REB/IEC on the progress of the study including number of subjects enrolled, discontinued, and SAEs. It is required that a yearly review of the protocol by the IRB/REB/IEC be documented in a letter from the IRB/REB/IEC. The investigator must provide notification to the IRB/REB/IEC of the completion, termination or discontinuation of the study.

10.2 Ethical Conduct of the Study

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the investigator abide by the principles of the International Conference on Harmonisation (ICH) guidelines on GCP, applicable local regulatory requirements, and the Declaration of Helsinki (Version 2008). The clinical study also will be carried out in keeping with national and local legal requirements [in accordance with United States Investigational New Drug (IND) regulations (21 CFR 56)].

10.3 Subject Information and Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained according to the regulatory and legal requirements of the participating country. As part of this procedure, the investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. Subjects who are under the age of 18 (or lower if age of consent is less than 18 in a specific country) and whose legal guardian or caretaker has provided written informed consent will provide their assent to participate. The investigator or designee will provide the Sponsor with a copy of the IRB/REB/IEC-approved informed consent form prior to the start of the study.

10.4 Subject Confidentiality

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number, initial or birth date (if allowed based on local data protection regulations), not by name. Documents that identify the subject (eg, the signed informed consent document) must be maintained in confidence by the investigator.

The investigator agrees not to use or disclose protected health information other than as permitted or required by the subject authorization or as required by law.

10.5 Study Monitoring

The Sponsor (or designee) will conduct a study initiation visit to verify the qualifications of the investigator, inspect the facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The investigator will make all appropriate safety assessments on an ongoing basis. The Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to GCP and SOPs for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the investigator.

10.6 Case Report Forms and Study Records

The investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the clinical sites by means of electronic or manual queries.

The investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each subject receiving randomized study drug.

The investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB/REB/IEC to have direct access to all documents pertaining to the study.

A Trial Master File will be maintained by the Sponsor (or designee). All documents and other materials that pertain to the conduct of the trial quality of the data, and compliance with GCPs will be collected in the Trial Master File.

10.7 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) has been established to provide ongoing, independent review and assessment of the safety data for Study DX-2930-03. While an independent DSMB is not currently planned for this study, summary safety data from Study DX-2930-04 may be reviewed by the DSMB established for Study DX-2930-03 as part of the collection of safety information available on DX-2930.

The DSMB will adhere to a prospectively determined Charter, which will be written by the Sponsor and approved by the DSMB. The Charter will define the responsibilities of the DSMB and Sponsor, the number and timing of the DSMB meetings, the conduct of the meetings, and the data sets to be reviewed by the DSMB. Further details regarding the DSMB can be found in the DSMB charter.

10.8 Protocol Violations/Deviations

The investigator will be instructed not to deviate from the protocol, except where necessary to eliminate an immediate hazard to study participants. Should other unexpected circumstances arise that will require deviation from protocol-specific procedures, the investigator should contact their Sponsor representative to discuss the appropriate course of action.

The investigator should document all protocol deviations/violations in the subject's eCRF and source documents or the Investigator Site File if appropriate. In the event of a significant deviation/violation, the investigator should notify the Sponsor representative. Significant deviations/violations include, but are not limited to those that increase the health risk to the subject, or confound interpretation of primary study assessments. The investigator will promptly report all changes in research activity and all unanticipated problems involving risks to human subjects or others to his or her IRB/REB/IEC.

10.9 Premature Closure of the Study

If the Sponsor, investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable subject risk, the study may be terminated overall or at a specific site after appropriate consultation between the Sponsor and the investigator(s). In addition, a decision on the part of the Sponsor to stop the study, or to suspend or discontinue development of the investigational product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to, the following:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- Failure of the investigator to comply with pertinent global regulations
- Submission of knowingly false information from the study site to the Sponsor or other pertinent regulatory authorities
- Insufficient adherence by the investigator to protocol requirements

10.10 Access to Source Documentation and On-Site Audits

Regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with country regulations. The investigator should immediately notify the Sponsor representative of any announced or unannounced regulatory agency inspections. An auditing inspection may also be conducted by the Sponsor representative or designee. Any aspect of the trial may be subject to audit by the Sponsor and/or inspection by regulatory authorities or the IRB/REB/IEC. Such audits/inspections may take place at the Sponsor's site(s), the CRO, or at the clinical sites, including laboratories, pharmacies and any other facilities used for the study.

The investigator will be responsible for the accuracy of the data entered in the eCRF. The investigator will permit the designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify data represented in the eCRF.

10.11 Data Generation and Analysis

This study will be performed in accordance with regulatory requirements outlined in Food and Drug Administration (FDA) 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 312 and 21 CFR Part 11 as well as the ICH GCP E6 Guidelines. The study monitors will meet with the investigators and staff shortly before the start of the trial to review the procedures for study conduct and documentation. During the study, the monitors will visit the sites to verify record keeping and adherence to the protocol. For this study, eCRFs will be used. The monitors will conduct 100% source document verification by comparing the eCRFs with the source documents to ensure accuracy and consistency. Edit check programs, other forms of electronic validation, manual listings and a query process will be executed to verify the accuracy of the database. The EDC system will maintain a full audit trail of electronic data changes. Access to all source documentation will be made available for monitoring and audit purposes.

10.12 Retention of Data

All source documents (eg, informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnosis and pharmacy records, and DX-2930 dispensing/disposition records) that support data in the eCRFs of each study subject must be retained in the files of the responsible investigator.

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the DX-2930. However, these documents should be retained for a longer period if required by the applicable legal requirements.

If the responsible investigator retires, relocates or for any other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor representative must be notified in writing of the name and address of the new custodian, prior to the transfer.

10.13 Financial Disclosure

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

10.14 Publication and Disclosure Policy

All information concerning DX-2930, Sponsor operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information, supplied to the investigator by a Sponsor representative and not previously published, is considered confidential and remains the sole property of the Sponsor. The investigator must agree to use this information only to accomplish this study, and must not use it for other purposes without the Sponsor's advanced written consent. A description of this clinical study may also be available on the externally facing public websites and registries. A summary of the study results may be potentially disclosed as per local and country specific requirements.

The information developed in this study will be used by the Sponsor in connection with the continued development of DX-2930 and thus may be disclosed as required to other clinical investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the Sponsor with all data obtained in the study.

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12. APPENDICES

Appendix 1	Protocol History
Appendix 2	National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Tables (Modified) (US National Institutes of Health; National Institute of Allergy and Infection Diseases)
Appendix 3	National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (Modified) (US National Institutes of Health; National Institute of Allergy and Infection Diseases)
Appendix 4	HAE Attack Assessment and Reporting Procedures (HAARP)
Appendix 5	Summary of Pivotal Study DX-2930-03 in Subjects with HAE

APPENDIX 1 Protocol History

Amendment Summary and Rationale

Amendment 1 to Protocol DX-2930-04 expanded upon the scope of the original protocol. Key revisions included extension of the study from 6 months to approximately 1 year, a corresponding increase in the number of study drug doses a subject may receive, allowance for subjects to elect self-administration both at and away from the site after completion and understanding of training, addition of 3 tertiary objectives, and revision of statistical methodology to accommodate changes in efficacy and other endpoints to allow for a more robust analysis.

Amendment 2 provided a number of clarifications and corrections.

Noteworthy changes to the protocol are captured in the tables below. Additional minor revisions in grammar, spelling, punctuation, and format have been made for clarity and are not reflected in the summary of changes.

Document	Date	Global/Country/Site Specific
Original Protocol	14 December 2015	Global
Amendment 1.0	27 June 2016	Global
Amendment 2.0	20 Jan 2017	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **27 June 2016**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Administrative updates related to changes in parties responsible for the study (eg, Sponsor, Sponsor Contact/Medical Director, and Medical Monitor) were made to reflect current information.		Title page, Protocol Signature Page, Section 10 Study Administrative Structure
Study location was updated to reflect study sites planned across regions rather than individual countries.		Synopsis Study Location
The tertiary objective to evaluate the effect of DX-2930 on health-related quality of life (QoL) was rephrased for clarity.		Synopsis Tertiary Objectives and Section 2.3 Tertiary Objectives
The tertiary objective to characterize the Pharmacokinetic (PK) and Pharmacodynamic (PD) profile of DX-2930 was clarified to indicate administration would be subcutaneous.		Synopsis Tertiary Objectives and Section 2.3 Tertiary Objectives
Three additional tertiary objectives were added to obtain more comprehensive information: • To evaluate safety and efficacy in the non-rollover population of switching from long-term prophylactic (LTP) treatment to DX-2930 • To evaluate breakthrough attack characteristics while receiving DX-2930 compared to historical baseline		Synopsis Tertiary Objectives and Section 2.3 Tertiary Objectives

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **27 June 2016**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
• To evaluate subject experience with self-administration of DX-2930 including ease of SC administration of DX-2930		
The number of non-rollover subjects allowed in DX-2930-04 was increased to at least 50 subjects with up to a maximum of 100 subjects.		Synopsis Study Design, Section 3.1.1 Overview
The number of non-rollover subjects was increased from at least 50 subjects up to a maximum of 100 subjects. Enrollment of subjects 12 to 17 years age was revised to be at least 15 including the estimated 10 rollover subjects from Study DX-2930-03. Therefore, the total enrollment for the study was updated to be at least 150, but not more than 250.		Synopsis Study Population and Section 4.1 Study Population
Revised to allow non-rollover subjects to continue long-term prophylactic HAE therapy with C1-INH, androgens or anti-fibrinolytics, for 2 weeks; initiation of tapering and discontinuation of LTP must occur within 3 weeks of receiving the first dose of DX-2930.		Synopsis Study Design, Section 3.1.1 Overview
Clarified that rollover subjects who experience their first attack outside the window of accepted scheduled visits are allowed to have an extra (unscheduled) study visit.		Synopsis Treatment Period, Section 3.1.1 Overview
The study has been extended in duration from 6 months to approximately one year and subsequently the number of doses of study drug a subject may receive has been increased.		Synopsis Duration of Treatment and Duration of Study for Individual Subjects, Study Activities Schedule
The study was expanded to allow subjects to self-administer doses of DX-2930 without supervision after receiving the first 2 doses of DX-2930 at the study site. Subjects must be considered suitable candidates; receive training; confirm understanding; and record specific information regarding subcutaneous administration and experience with self-administration. Subjects who elect to self-administer investigational product will be provided with supplies and be instructed on investigational product transport, storage, treatment compliance, and retention of all used and unused product vials for drug accountability purposes. Written instructions on DX-2930 handling and self-administration procedures will be provided to trained subjects prior to initiating self-administration. Vital signs will not be monitored for doses self-administered away from the investigational site.		Synopsis Self-Administration, Section 3.1.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **27 June 2016**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Since no data on embryo-fetal development toxicity are available for DX-2930, the clinical trial facilitation group's (CTFG) provided recommendations related to contraception and pregnancy testing. The inclusion criterion for contraception requirements was modified to emphasize the use of highly effective contraceptive measures and details for allowances (including stable estrogen doses) during treatment and until the end of relevant systemic exposure for women of childbearing potential. It was also clarified that the use of a male condom with or without spermicide or cervical cap, diaphragm, or sponge with spermicide or a combination (double-barrier methods) is not considered highly effective. Additional pregnancy tests (urine or serum) were also added for monitoring of pregnancy during treatment.		Synopsis Criteria for Inclusion, Section 4.2
Management of acute attacks was clarified to indicate that administration of the investigational product and study procedures will continue without alteration to the protocol-specified study schedule, even if the subject has HAE symptoms or receives treatment for an HAE attack.		Synopsis, Management of Acute Attacks, Section 5.4.1.1
Additional information was added to the study collection of data for HAE attacks to obtain more comprehensive information.		Section 6.4
Efficacy endpoints were revised from mean rates to number of attacks.		Synopsis Statistical Methodology, Section 9.6.2
Where appropriate, "Dyax" was replaced with the generic term of "the Sponsor."		Entire protocol Sections 1-10
A section on management of HAE attacks was added to Study Treatment(s).		Synopsis Management of Acute Attacks, Section 5.4.1.1
The study has been extended to incorporate an additional 6 months of treatment with DX-2930. Therefore the Study Activities Schedule has been revised to accommodate study assessments at dosing Visits 14-26. Follow-up visits (following end of treatment) are now occurring at Days 264, 378, and 392 (Visits 27, 28, and 29).		Study Activities Table, Section 7
The exclusion criterion prohibiting dosing with an investigational drug or exposure to an investigational device with 4 weeks prior to screening was clarified to not include DX-2930 or other HAE therapies.		Synopsis Exclusion Criteria, Section 4.3
The analysis population was clarified and is based on subjects who receive any exposure to DX-2930 in this study.		Synopsis Analysis Populations, Section 9.4
Data analysis and statistical methodology was revised to accommodate changes in efficacy or other study endpoints and to allow for more robust analyses.		Synopsis Statistical Methodology , Section 9.6
An interim analysis was added and will be conducted when at least 35 subjects complete 12 months of DX-2930 exposure.		Synopsis Interim Analysis and Data Monitoring, Section 9.9.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **27 June 2016**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
The efficacy evaluation period was updated to begin at Day 0 instead of Day 14 to be consistent with the intent-to-treat analysis principle.		Synopsis Statistical Methodology, Section 9.6.2
Quality of life assessments were revised and expanded to include EQ-5D-5L, SF-12, HADS, WPAI-GH and AE-QoL.		Synopsis Quality of Life Assessments, Section 6.14
An injection report and self-administration and SC injection survey were added to the study activities schedule and study procedures.		Synopsis DX-2930 Injection Report and Self-Administration and Subcutaneous Injection Survey, Section 6.15
Details on collection of prior medications were added to indicate documentation should extend to 4 weeks prior to study screening for non-rollover subjects.		Section 5.4
Information on packaging and labeling was expanded to detail the supplies for self-administration.		Section 5.7
Clarifying language was added to subject information and consent to indicate that subjects under 18 years will provide their assent to participate in the study if their legal guardian or caretaker has provided written informed consent.		Section 10.3 Subject Information and Consent
A new section was added for a Data Safety Monitoring Board (DSMB) who will provide an independent review of safety		Section 10.7 Data Safety Monitoring Board
To ensure subject safety, information on premature closure of the study was added to indicate some examples of conditions under which the study may be terminated overall or at a specific site after consultation between the Sponsor and investigators.		Section 10.9 Premature Closures of the Study
Financial disclosure language was updated to be consistent with 21 CFR 54 2(b) (1998).		Section 10.13 Financial Disclosure
Study Results/Publication Policy was updated to include language regarding posting of appropriate study information on applicable websites by the Sponsor. Additional detail on publication and disclosure of study information was added to indicate potential for public information.		Section 10.14 Publication and Disclosure Policy

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **20 Jan 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated administrative information to reflect current contact information, including contact information for the 24-Hour Global Medical Monitor and		Title Page, Section 6.16.5.5, Section 10

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **20 Jan 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Back-Up Global Medical Monitor and Sponsor Contact.		
Included clarifying note that female rollover subjects (those who previously participated in Study DX-2930-03) of childbearing potential may continue to use the effective birth control method used during Study DX-2930-03.		Synopsis
Introduced the international nonproprietary name "lanadelumab."		Section 4.2
Clarified that sites will call subjects within approximately 3 days of planned off-site self-administrations.		Synopsis, Section 5.1
Clarified that adolescent subjects should complete the WPAI-GH questionnaire and use the term "school" instead of "work" when filling out this questionnaire. These data will be analyzed separately.		Synopsis, Section 4.1, Section 5.1, Section 5.6
Refined language on interim analyses options to allow for interim analyses to be performed as appropriate for regulatory reporting and/or internal administrative decisions.		Section 6.14.3
The following editorial changes were made to remove inconsistencies in the text and to ensure all agreed changes from Amendment 1 and administrative letters are accurately presented across all sections		
Removed the duplicate Study Activities Schedule from Appendix 1 and changed in-text references/linking to the Study Activities Schedule from Appendix 1, to ensure a single location for the Study Activities Schedule.		Entire protocol
Corrected the numbers in Figure 1 to correctly present the length of treatment period.		Figure 1
Corrected text regarding the treatment period duration: the treatment period is 364 days, with the last dose of study drug administered on Day 350.		Synopsis, entire protocol
Added text from Section 3.1.1. to the synopsis for clarity; specifically, that the 3rd dose must be administered at the next pre-defined study visit according to the Study Activities Schedule.		Synopsis
Clarified that subjects in Study DX-2930-03 can be consented for enrollment in Study DX-2930-04 on or after Day 168 of Study DX-2930-03.		Synopsis, Table 1 (footnote "5"), Section 3.1.1, Section 6.1,Section 7.2
Revised text in Section 3.1.1 to match correct text in Synopsis, including text regarding standard of care treatment for subjects who experience an acute attack of HAE during the study.		Synopsis, Section 3.1.1
Updated wording regarding the enrollment number for non-rollover subjects from "up to a maximum of 100" to "approximately 100" in total.		Synopsis, Section 3.1.1, Section 4.1
Corrected text regarding the follow-up period: the follow-up period is 4 weeks from the last visit of the protocol-defined treatment period. Removed inconsistent text that erroneously mentioned an 8-week follow up period.		Synopsis,
Removed text indicating that the Sponsor would provide ancillary supplies to sites since the sites are responsible for sourcing them.		Section 3.1.1, Section 3.4, and Section 5.2
Clarified text to align with Study Activities Schedule; specifically, subject surveys on their experience with SC and self-administration injections of DX-		Section 5.7

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **20 Jan 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
2930 are to be completed by the subject during the study.		
Clarified text to align with Study Activities Schedule; specifically, that vital signs will be monitored both prior to dosing and at 1 hour post-dosing when dosing occurs at the investigational site, with a ±15 minutes window for all vital signs. Vital signs are not monitored when subjects elect to self-administer study drug away from the site.		Section 6.5, Section 7 itemization per visit
Clarified text to align with Study Activities Schedule; specifically, that weight is collected during each physical exam.		Table 1, Section 6.6, Section 7
Clarified text to align with Study Activities Schedule; specifically, that height is only collected at the Screening visit.		Table 1, Section 6.6, Section 7.1
Clarified text to align with Study Activities Schedule; specifically, that pregnancy tests performed on Day 0 must be urine-based to confirm eligibility prior to dosing while subsequent pregnancy tests can be urine or serum-based.		Section 6.8.1.5
Removed outdated contact information from safety reporting text.		Section 6.16.5.5
Removed remnant text regarding the requirement to complete a 2-week wash-out period before entering the treatment period for non-rollover subjects on LTP for HAE. Washout period does not exist for non-rollover subjects.		Section 7.1
Removed remnant text regarding the requirement for urinalysis for Visits 14, 17, 20, and 23. Urinalysis is not required at these visits.		Section 7.16, Section 7.19, Section 7.22, and Section 7.25
Removed text indicating a subject could self-administer study drug at their home or other agreed upon location and that no monitoring of vital signs will be performed for Visit 17 since this is a mandated investigational site visit.		Section 7.19
Removed safety analysis category called “pretreatment group” since a pretreatment period does not exist in this study.		Section 9.7.1

APPENDIX 2 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases)

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

Note: The following toxicity table is a DRAFT and designed to provide general guidance on parameters for monitoring safety in clinical trials. This toxicity table is not comprehensive and should not be applied directly to all trials.

When selecting a toxicity table, the following are some of the items that must be taken into consideration:

- The population being studied
  - Does the clinical trial evaluate healthy subjects, subjects with a particular disease or condition?
- The stage of test article development
  - Is the clinical trial a Phase I, II, III or IV?
- The type of test article
  - Does the clinical trial evaluate a drug, device, vaccine or other biologic agent?
- The prior human and preclinical experience with the test article
  - Are there any specific findings that require adjustment of the toxicity table?

Single site clinical trials evaluating healthy subjects should conform to the laboratory normal values at the single site. Multi-center clinical trials should reconcile among their laboratory normal values when evaluating a healthy volunteer population.

Please confer with the DMID protocol team and DMID's Office of Clinical Research Affairs when selecting or developing a toxicity table for a DMID-sponsored trial.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/mm^3	13,000-15,000/mm^3	15,000-30,000/mm^3	>30,000 or <1,000/mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

CHEMISTRIES (continued)

	Grade 1	Grade 2	Grade 3	Grade 4
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

RESPIRATORY				
	Grade 1	Grade 2	Grade 3	Grade 4
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

NEUROLOGICAL

	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

MUSCULOSKELATEL				
	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint distruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE NOVEMBER 2007 DRAFT

SKIN

	Grade 1	Grade 2	Grade 3	Grade 4
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC

	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25-50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

APPENDIX 3 National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (Modified) (US National Institutes of Health; National Institute of Allergy and Infectious Diseases

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

Note: The following toxicity table is a DRAFT and designed to provide general guidance on parameters for monitoring safety in clinical trials. This toxicity table is not comprehensive and should not be applied directly to all trials.

When selecting a toxicity table, the following are some of the items that must be taken into consideration:

- The population being studied
  - Does the clinical trial evaluate healthy subjects, subjects with a particular disease or condition?
- The stage of test article development
  - Is the clinical trial a Phase I (is it for the fisrt time in human subjects?) , II, III or IV?
- The type of test article
  - Does the clinical trial evaluate a drug, device, vaccine or other biologic agent?
- The prior human and preclinical experience with the test article
  - Are there any specific findings that require adjustment of the toxicity table?
  - Has it been approved for this indication in adult population?

Single site clinical trials evaluating healthy subjects should conform to the laboratory normal values at the single site. Multi-center clinical trials should reconcile among their laboratory normal values when evaluating a healthy volunteer population.

Please confer with the DMID protocol team and DMID's Office of Clinical Research Affairs when selecting or developing a toxicity table for a DMID-sponsored trial.

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ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
GRADE 5	**Death**	

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for spe ed criteria.

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(Selected Values for children less than or equal to 3 months of age – does not apply for preterm infants)

For all parameters not listed on this table, please refer to the DMID Toxicity Table for children > 3 months of age.

HEMATOLOGY				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin				
1-7 days old	13.0-14.0 gm/dL	12.0-12.9 gm/dL	<12 gm/dL	Cardiac Failure secondary to Anemia
8-21 days old	12.0-13.0 gm/dL	10.0-11.9 gm/dL	<10.0 gm/dL	Cardiac Failure secondary to Anemia
22-35 days old	9.5-10.5 gm/dL	8.0-9.4 gm/dL	<8.0 gm/dL	Cardiac Failure secondary to Anemia
36-60 days old	8.5-9.4 gm/dL	7.0-8.4 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
61-90 days old	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
Abs Neutrophil Ct				
1 day old	5000-7000/mm^3	3000-4999/mm^3	1500-2999/mm^3	<1500/mm^3
2-6 days old	1750-2500/mm^3	1250-1749/mm^3	750-1249/mm^3	<750/mm^3
7-60 days old	1200-1800/mm^3	900-1199/mm^3	500-899/mm^3	<500/mm^3
61-90 days old	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3
Bilirubin (Fractionated bilirubin test must be preformed when total bilirubin is elevated)				
<7 days old	.	20-25mg/dL	26-30 mg/dL	>30 mg/dL
7-60 days old	1.1-1.9xN	2.0-2.9Xn	3.0-7.5xN	>7.5xN
61-90 days old	1.1-1.9xN	2.0-2.9xN	3.0-7.5xN	>7.5xN

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(Selected Values for children less than or equal to 3 months of age)

HEMATOLOGY (continued)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Creatinine				
<7 days old	1.0-1.7 mg/dL	1.8-2.4 mg/dL	2.5-3.0 mg/dL	>3.0 mg/dL
7-60 days old	0.5-0.9 mg/dL	1.0-1.4 mg/dL	1.5-2.0 mg/dL	>2.0 mg/dL
61-90 days old	0.6-0.8 mg/dL	0.9-1.1 mg/dL	1.2-1.5 mg/dL	>1.5 mg/dL
Cr Clearance				
<7 days old	35-40 ml/min	30-34 ml/min	25-29 ml/min	<25 ml/min
7-60 days old	45-50 ml/min	40-44 ml/min	35-39 ml/min	<35 ml/min
61-90 days old	60-75 ml/min	50-59 ml/min	35-49 ml/min	<35 ml/min
Hypocalcemia				
<7 days old	6.5–6.9 mEq/L	6.0-6.4 mEq/L	5.5-5.9 mEq/L	<5.5 mEq/L
7-60 days old	7.6-8.0 mEq/L	7.0-7.5 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
61-90 days old	7.8-8.4 mEq/L	7.0-7.7 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
Hypercalcemia				
<7 days old	12.0-12.4 mEq/L	12.5-12.9 mEq/L	13.0-13.5 mEq/L	>13.5 mEq/L
7-60 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L
61-90 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L

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(Greater than 3 months of age)

LOCAL REACTIONS				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Induration	< 10mm	10-25 mm	26-50mm	>50mm
Erythema	< 10mm	10-25 mm	26-50mm	>50mm
Edema	< 10mm	10-25 mm	26-50mm	>50mm
Rash at Injection Site	< 10mm	10-25 mm	26-50mm	>50mm
Pruritus	Slight itching at injection site	Moderate itching at injection extremity	Itching at injection extremity and other sites	Itching over entire body

HEMATOLOGY				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin for children greater than months and less than 2 years of age	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to anemia
Hemoglobin for children greater that 2 years of age	10-10.9 gm/dL	7.0-9.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to anemia
Absolute Neutrophil Count	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3
Platelets	-------	50,000-75,000/mm^3	25,000-49,999/mm^3	<25,000/mm^3
Prothrombin Time (PT)	1.1-1.2 x ULN	1.3 -1.5 x ULN	1.6 -3.0 x ULN	>3.0 x ULN
Partial Thromboplastin Time (PTT)	1.1-1.6 x ULN	1.7-2.3 x ULN	2.4 -3.0 x ULN	>3.0 x ULN

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(Greater than 3 months of age)

GASTROINTESTINAL				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Bilirubin (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Bilirubin (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Pancreatic Amylase	1.1-1.4 x ULN	1.5-1.9 x ULN	2.0-3.0 x ULN	>3.0 x ULN
Uric Acid	7.5-9.9mg/dL	10-12.4 mg/dL	12.5-15.0 mg/dL	>15.0 mg/dL
CPK	See Neuromuscular Toxicity			
Appetite	----------	Decreased appetite	Appetite very decreased, no solid food taken	No solid or liquid taken
Abdominal Pain	Mild	Moderate- No Treatment Needed	Moderate- Treatment Needed	Severe- Hospitalized for treatment
Diarrhea	Slight change in consistency and/or frequency of stools	Liquid stools	Liquid stools greater that 4x the amount or number normal for this child	Liquid stools greater than 8x the amount or number normal for this child

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(Greater than 3 months of age)

GASTROINTESTINAL (continued)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Constipation	Slight change in the consistency/frequency of stool	Hard, dry stools with a change in frequency	Abdominal pain	Distention and Vomiting
Nausea	Mild	Moderate-Decreased oral intake	Severe-Little oral intake	Unable to ingest food or fluid for more than 24 hours
Vomiting	1 episode/day	2-3 episodes per day	4-6 episodes per day	Greater than 6 episodes per day or Intractable Vomiting

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(Greater than 3 months of age)

ELECTROLYTES				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
CREATININE				
3 Months -2 Years of age	0.6-0.8 x ULN	0.9-1.1 x ULN	1.2-1.5 x ULN	>1.5 x ULN
2 Years- 12 Years of age	0.7-1.0 x ULN	1.1-1.6 x ULN	1.7-2.0 x ULN	>2.0 x ULN
Greater than 12 Years of age	1.0-1.7 x ULN	1.8-2.4 x ULN	2.5-3.5 x ULN	>3.5 x ULN

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(Greater than 3 months of age)

ELECTROLYTES				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hypernatremia		<145-149 mEq/L	150-155 mEq/L	>155 mEq/L or abnormal sodium AND mental status changes
Hyponatremia		130-135 mEq/L	129-124 mEq/L	<124 mEq/L or abnormal sodium AND mental status changes
Hyperkalemia	5.0-5.9 mEq/L	6.0-6.4 mEq/L	6.5-7.0 mEq/L	>7.0 mEq/L or abnormal potassium AND cardiac arrhythamia
Hypokalemia	3.0-3-5 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L	<2.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypercalcemia	10.5-11.2mg/dL	11.3-11.9 mg/dL	12.0-12.9 mg/dL	>13.0 mg/dL
Hypocalcemia	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.0-6.9 mg/dL	<6.0 mg/dL
Hypomagnesemia	1.2-1.4 mEq/L	0.9-1.1 mEq/L	0.6-0.8 mEq/L	<0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia
Hypoglycemia	55-65 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose AND mental status changes
Hyperglycemia	116-159 mg/dL	160-249 mg/dL	250-400 mg/dL	>400 mg/dL or ketoacidosis
Proteinuria	Tr-1+ or <150 mg/day	2+ or 150-499 mg/day	3+ or 500-1000 mg/day	4+ or Nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25	Microsc >25		Gross hematuria

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	cells/hpf	cells/hpf		

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(Greater than 3 months of age)

CENTRAL NERVOUS SYSTEM (CNS)				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Generalized CNS Symptoms			Dizziness	Hypotonic, hyporesponsive episodes; Seizures; Apnea/Bradycardia; Inconsolable crying > 3 hrs;
Headache	Mild	Moderate, Responds to non-narcotic analgesia	Moderate to Severe, Responds to narcotic analgesia	Intractable
Level of Activity		Slightly irritable OR slightly subdued	Very irritable OR Lethargic	Inconsolable OR Obtunded
Visual		Blurriness, diplopia, or horizontal nystagmus of < 1 hour duration, with spontaneous resolution	More than 1 episode of Grade 2 symptoms per week, or an episode of Grade 2 symptoms lasting more than 1 hour with spontaneous resolution by 4 hours or vertical nystagmus	Decrease in visual acuity, visual field deficit, or oculogyric crisis
Myelopathy		None	None	Myelopathic/spinal cord symptoms, such as: pyramidal tract weakness and disinhibition, sensory level, loss of proprioception, bladder/bowel dysfunction

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(Greater than 3 months of age)

PERIPHERAL NERVOUS SYSTEM				
PARAMETER	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Neuropathy/ Lower Motor Neuropathy		Mild transient Paresthesia only	Persistent or progressive paresthesias, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss	Onset of significant weakness, decrease or loss of DTRs, sensory loss in "stocking glove" distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness.
Myopathy or Neuromuscular Junction Impairment	Normal or mild (<2 x ULN) CPK elevation	Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/- mild CPK elevation (<2 x ULN)	Proximal muscle weakness and/or atrophy affecting motor function +/- CPK elevation; or severe myalgias with CPK >2 x ULN;	Onset of myasthenia-like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms

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(Greater than 3 months of age)

OTHER				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
Allergy	Pruritus without Rash	Pruritic Rash	Mild Urticaria	Severe Urticaria Anaphylaxis, Angioedema
Drug Fever (Rectal)	.	38.5-40C 101.3 – 104.0F	Greater than 40.0C Greater than 104.0F	Sustained Fever: Equal or greater than 40C (104.0F) for longer than 5 days
Cutaneous	Localized rash	Diffuse maculopapular Rash	Generalized urticaria	Stevens-Johnson Syndrome or Erythema multiforme
Stomatitis	Mild discomfort	Painful, difficulty swallowing, but able to eat and drink	Painful: unable to swallow solids	Painful: unable to swallow liquids; requires IV fluids
Clinical symptoms *not otherwise specified* in this table	No therapy; monitor condition	May require minimal intervention and monitoring	Requires medical care and possible hospitalization	Requires active medical intervention, hospitalization, or hospice care
Laboratory values *not otherwise specified* in this table	Abnormal, but requiring no immediate intervention; follow	Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug	Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug	Life-threatening severity; Requires immediate evaluation, treatment, and usually hospitalization; Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism that study drug

APPENDIX 4 HAE Attack Assessment and Reporting Procedures (HAARP)

HAE Attack Assessment and Reporting Procedures (HAARP)

Title:	HAE Attack Assessment and Reporting Procedures (HAARP)
Product Name:	DX-2930
Indication:	Prevention of angioedema attacks in patients with HAE
Sponsor:	Dyax Corp. (an indirect, wholly owned subsidiary of Shire plc.) 300 Shire Way, Lexington, MA 02421
Original Date (v1.0):	14 September 2015
Version 2.0:	29 June 2017

TABLE OF CONTENTS

1 PURPOSE

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

2 DEFINITION OF AN ATTACK

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

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

Despite the presence of these symptoms, the investigator may still determine clinically that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an attack (e.g., urticaria), the reported event persists well beyond the typical time course of an attack (e.g., greater than 7 days), 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 their previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.

Attack resolution is defined as the subject no longer having symptoms of the attack.

Prodromal symptoms by themselves are not considered an attack.

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

3 REPORTING AND ASSESSMENT OF ATTACK DATA

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

During the relevant study periods, as defined in the applicable study protocol, subjects (or caregivers, for subjects < 18 years old) will be instructed to contact the site within 72 hours of the start of symptoms of an attack. In the situation that a subject is incapacitated and is

unable to contact the site, a family member or other individual with detailed knowledge of the event can provide the information. If desired by the subject, memory aids may be provided to assist in tracking any HAE attacks subject's experience. Any tools or devices the subject uses to track this information are not intended to serve as source documents for the study.

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

A designated individual at the site (the collector) will contact the subject or caregiver on a regular basis as defined in the study protocol, regardless of whether or not the subject has reported any attacks, in order to solicit for any attacks that may have occurred but were not reported. In addition, during each study visit, site personnel will solicit for any new attack information that was not provided through previous contact with the subject or caregiver.

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

3.1 Subject-Reported Symptoms

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

3.1.1 Attack Information

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

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

Subjects do not have to wait for their symptoms to completely resolve to report an attack. Information about ongoing symptoms can be obtained by the site during the check-in call and/ or at a scheduled study visit. Subjects should not withhold or delay any treatment they would normally receive to treat their attack in order contact the site.

3.1.2 Worsening Symptoms

The site may request the subject call them back if they experience worsening symptoms and/ or new symptoms for a reported attack. Otherwise, the new information will be captured during the next check-in call or scheduled study visit. Subjects may contact the site on their own to provide information about any worsening symptoms.

3.1.3 Subject Training

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

3.1.4 Reporting Multiple Attacks

If a subject experiences symptoms they attribute to more than one unique attack they can report this as multiple attacks to the site. Based on the definition of an attack as stated in Section 2, it will be the determination of the investigator or designee as to whether events reported as being separate are confirmed as separate attacks or not.

3.1.5 Caregiver Report

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

3.1.6 Subject Contact with Sites

Site personnel will establish a recommended method and time window for each subject to contact the site to report any symptoms of an attack. Sites will establish a primary contact person and, if possible, a back-up person, with contact information. Back-up plans, including call backs and/ or use of back-up contacts, should be established in case the subject is unable to reach someone at the site.

3.2 Site Contact with the Subject

Sites will establish a recommended day and time window for check-in calls between study visits, as outlined in the study protocol. The date and time for check-ins can be modified based on when the last contact with the subject was made. When the site is contacted by a subject reporting symptoms of an attack the site should make sure they have the ability to record the information provided in a complete and accurate way. Back-up plans should be

established in case the subject misses a call from the site. A study schedule for each subject's on-site visits will be provided to the subject by the site.

3.2.1 Review of subject report of symptoms

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

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

3.2.2 Documenting a Reported Attack

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

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

Additional probing questions about what the subject experienced to determine:

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

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

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

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

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

3.2.3 Site Training

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

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

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

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

3.3 HAE attacks as Adverse Events

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

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 Dyax using the SAE Reporting Form in the 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.

4 INVESTIGATOR ATTACK ASSESSMENT

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

The assessor must review the information and determine whether the event is an actual attack or not. If needed, the assessor can contact the subject and/or caregiver to clarify information or ask for any additional detail. The determination will be documented along with the date and time the determination was made. Any event deemed not an attack must be accompanied by an explanation and alternative diagnosis by the assessor.

When reviewing subject information, the assessor will follow the definitions of an attack as outlined in these procedures and, taking all available information about the event into consideration, will determine if it is a confirmed attack. The assessment of the attack is the Investigator or designee's own, and not the opinion of the subject, the subject's caregiver or any other site personnel. Assessors may consult with one another about a particular subject's attack but only one assessor makes the documented determination. It is possible for both the Principal Investigator and physician designee to assess different attacks for the same subject.

APPENDIX 5 Summary of Pivotal Study DX-2930-03 in Subjects with HAE

The proposed pivotal clinical study (Study DX-2930-03) is entitled "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)." This study will be a multi-center, double-blind, randomized, placebo-controlled parallel-arm study evaluating the efficacy of DX-2930 in preventing acute angioedema attacks in patients with Type I or Type II HAE. The double-blind study is planned to be followed by the study described in the present protocol, an open-label extension (OLE) study (DX-2930-04).

The primary objective of Study DX-2930-03 is to evaluate the efficacy of DX-2930 in preventing HAE attacks. The secondary objective is to evaluate the safety of repeated SC administrations of DX-2930. The tertiary objectives are to evaluate the pharmacodynamic effects of chronically administered DX-2930; to assess the immunogenicity of chronically administered DX-2930; to evaluate the pharmacokinetics of chronically administered DX-2930; and to evaluate the effect of DX-2930 upon quality of life assessments.

Subjects aged 12 years and over with a documented diagnosis of Type I or Type II HAE who experience at least 1 attack per 4 weeks will be eligible for the study. Up to 120 subjects are planned for enrollment across approximately 60 sites in the United States, Canada, Italy, Germany, United Kingdom and Jordan.

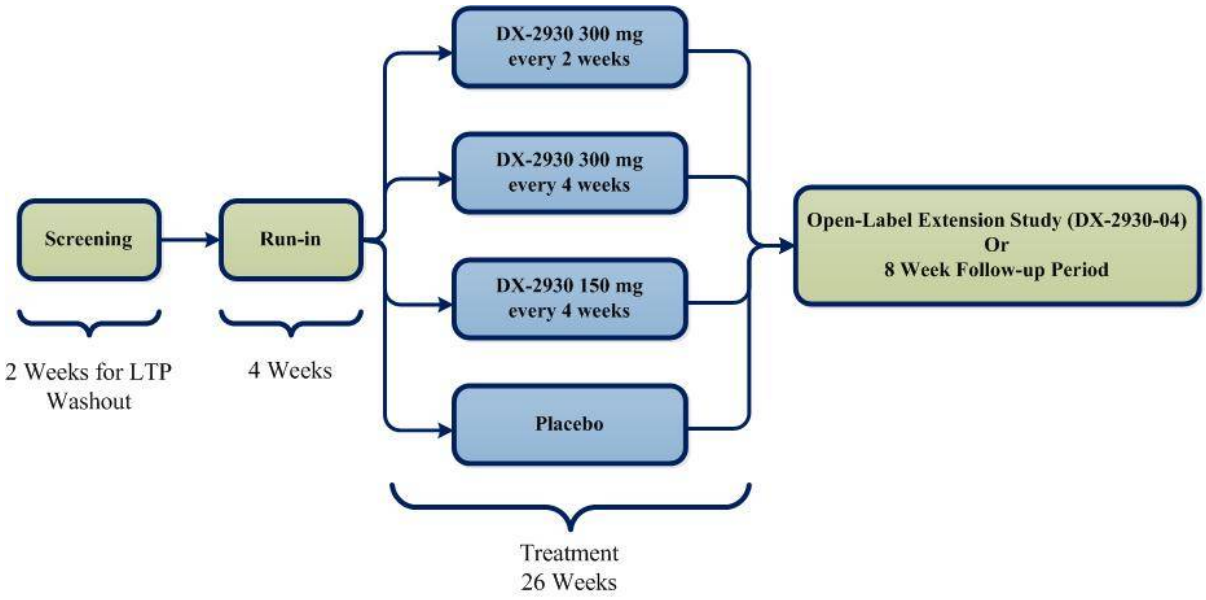
Following informed consent, subjects will undergo screening assessments. Subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. Subjects who are either not on long-term prophylactic therapy for HAE, or have completed the required washout period will enter a run-in period of 4 weeks to determine the baseline HAE attack rate. The run-in period may be extended to 8 weeks if the minimum baseline attack rate is not achieved in the first 4 weeks. HAE subjects will then 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 one of three dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks or 150 mg every 4 weeks. Each subject will undergo a treatment period consisting of 13 doses of blinded study drug, for a period of 26 weeks from the date of first dose on Day 0 through Day 182.

Subjects may consent to rollover into the OLE study (present protocol DX-2930-04) upon completion of their participation in the double-blind treatment period.

The primary endpoint will be to compare the number of investigator-confirmed HAE attacks observed in each DX-2930 treatment arm to that in the placebo arm during the efficacy assessment period (Day 0 through Day 182).

Figure 2 shows a schematic of the double-blind, pivotal study.

Figure 2 Overview of the Design of Pivotal Study DX-2930-03



Dose Rationale for Double-Blind, Pivotal Study DX-2930-03

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 while avoiding non-therapeutic or super-therapeutic doses and regimens.