Clinical Trial Protocol: DX-2930-03

Study Title:	HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)
Study Number:	DX-2930-03
Study Phase:	Phase 3
Product Name:	DX-2930
IND Number:	116647
EudraCT Number:	2015-003943-20
Indication:	Prevention of angioedema attacks in patients with HAE
Investigators:	Multicenter
Sponsor:	Dyax Corp. 55 Network Drive, Burlington, MA 01803 USA
Sponsor Contact:	Jennifer Schranz, MD PPD, Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: PPD
Medical Monitor US and Canada:	PPD, MD PPD, Clinical Development 300 Shire Avenue, MA 02421 USA Phone: PPD
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	Date:
Original Protocol	14 September 2015
Amendment 1.0	14 December 2015
Amendment 2.0	21 April 2016

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

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Study Number:	DX-2930-03
Amendment 2.0 Final Date:	21 April 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: PPD Date: PPD

Jennifer Schranz, MD PPD
PPD , Clinical Development
300 Shire Way, Lexington, MA 02421

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, 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. 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™: 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)
Study Number: DX-2930-03
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 efficacy of DX-2930 in preventing HAE attacks
Secondary Objective: To evaluate the safety of repeated subcutaneous administrations of DX-2930
Tertiary Objectives: • To evaluate the pharmacodynamic (PD) effects of chronically administered DX-2930 • To assess the immunogenicity of chronically administered DX-2930 • To evaluate the pharmacokinetics (PK) of chronically administered DX-2930 • To evaluate the effect of DX-2930 on health-related quality of life (QoL)
Study Design: This study is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of DX-2930 in preventing acute angioedema attacks in

patients with Type I and Type II HAE.

Long-Term Prophylactic (LTP) Therapy Washout:

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

Run-In Period:

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

Treatment Period:

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

Each subject will undergo a treatment period consisting of 13 doses of blinded Investigational Medicinal Product (IMP), for a period of 26 weeks from the date of first dose on Day 0 through two weeks after the final dose. Subjects randomized to one of the 4 treatment arms will either receive a DX-2930 or placebo dose according to the dosing schedule in Table 1.

Table 1. Treatment Period Dosing Schedule

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

Open-Label Extension (OLE) Study:

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

Follow-Up Period:

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

Study Population:

The study will enroll up to 120 subjects to provide 108 completed. Subjects will be 12 years of age and older with a confirmed diagnosis of HAE (Type I or II) who experience at least 1 Investigator-confirmed attack per 4 weeks during the run-in period. HAE diagnosis will be confirmed through documented clinical history consistent with HAE and diagnostic testing conducted during the screening visit. The study will aim to enroll at least 5 subjects who are 12 to 17 years of age.

Criteria for Inclusion:

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

1. Males and females 12 years of age or older at the time of screening.
2. Documented diagnosis of HAE (Type I or II) based upon 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 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 begin participating in the run-in period before these diagnostic results are available. 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. Experiencing a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks as confirmed during the run-in period.
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 provides informed consent, and 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 progestin-only oral contraceptive associated with inhibition of ovulation (oral, injectable, or implantable), 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) is 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 screening 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. 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.
2. Participation in a prior DX-2930 study.
3. Dosing with an investigational drug or exposure to an investigational device within 4 weeks prior to screening.
2. 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.
3. Exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 2 weeks prior to entering the run-in period.
4. Use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to entering the run-in period.
5. Use of short-term prophylaxis for HAE within 7 days prior to entering the run-in period. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or anti-fibrinolytics used to avoid angioedema complications from medically indicated procedures.
6. 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).
7. Pregnancy or breastfeeding.
8. 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, 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 vial contains a nominal concentration of 150 mg DX-2930 active ingredient in 1 mL solution. The test product will be administered subcutaneously into the upper arm in a blinded manner.

For each 300 mg dose of DX-2930, each subject will receive a total of 2 mL, divided into 2 separate 1.0 mL SC injections of DX-2930. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

For each 150 mg dose of DX-2930, each subject will receive a total of 2 mL, divided into 2 separate 1.0 mL SC injections, where one injection is DX-2930 and the other is

placebo. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

Placebo; Dose; and Mode of Administration:

Placebo consists of the inactive formulation of the test product: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, pH 6.0 with 0.01% Polysorbate 80.

Placebo doses will be administered to subjects randomized to the placebo treatment arm and in between doses of DX-2930 for subjects randomized to the 300 mg or 150 mg DX--2930 every 4 weeks treatment arms, according to the dosing schedule in Table 1.

For each placebo dose, each subject will receive a total of 2 mL, divided into 2 separate 1.0 mL SC injections of placebo. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

Duration of Treatment:

Subjects will receive a dose of blinded IMP every 2 weeks during the 26-week treatment period for a total of 13 doses. The first dose of IMP will be administered on Day 0 and the last dose of IMP will be administered on Day 168. There will be a ±3-day window around each study visit, with a maximum of 17 days or a minimum of 11 days between any 2 doses. Subjects will be monitored at the study site through 2 hours post-dose for the first 4 doses with the ability to reduce this time to 1 hour for the remaining doses based on the discretion of the Investigator and the absence of safety signals. A follow-up visit will occur on Day 182.

Duration of Study for Individual Subjects:

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of run-in. 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 last as long as 8 weeks in order to meet the minimum attack rate required for enrollment. Enrolled subjects will then undergo a 26-week treatment period. Subjects who do not participate in the OLE will be followed for an additional 8 weeks in the double-blind study.

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 is permitted if medically indicated.

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 prophylaxis. Administration of the investigational product and study procedures will continue without alteration to the protocol-specified study schedule, even if the patient receives any treatment for an HAE attack.

Safety Assessments:

The following assessments will be conducted according to the Study Activities Schedule:

- Adverse events (AEs), including serious adverse events (SAEs) and adverse events of special interest (AESI).
- 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).

Pharmacokinetic (PK) Assessments:

Blood samples will be collected for the measurement of plasma DX-2930 concentrations prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3 and 238±3 during the follow-up period for any subjects not entering OLE.

Pharmacodynamic (PD) Assessments:

Blood samples will be collected to evaluate the pharmacodynamic effects of DX-2930 through biomarker assays prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3 and 238±3 during the follow-up period for any subjects not entering OLE.

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 IMP administration on Day 0 and on Days 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Day 238±3 during the follow-up period for any subjects not entering OLE.

C1-INH, C4, and C1q Assessments:

Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment.

Quality of Life Assessments:

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

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). Site personnel will be trained on HAARP prior to screening subjects at their site.

During screening, 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, subject HAE attack history will be collected. 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 HAE attack. 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 subjects experience. Weekly communication between the patients and the site, including reports of HAE attacks, must be documented in the eCRF.

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

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

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

Site personnel will contact the subject or caregiver on a weekly basis or approximately 7 days after last contact with the subject throughout the run-in period. If the subject experiences 1 or more Investigator-confirmed HAE attacks by end of week 4, the subject will have fulfilled the run-in requirement and may proceed to enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks can exit the run-in period early and proceed to enrollment and randomization. If the subject

experiences no Investigator-confirmed HAE attacks by the end of week 4, the subject will remain in the run-in period for an additional 4 weeks. The maximum duration of the run-in period is 8 weeks. If run-in has been extended and the subject has 2 or more Investigator-confirmed HAE attacks by the end of week 8, the subject will have fulfilled the run-in requirement and may proceed to the double-blind treatment period. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in will be considered a screen fail.

During the treatment period site personnel will contact the subject or caregiver once between scheduled study visits or approximately 7 days after last contact to solicit for any HAE attack information not already reported.

Throughout the duration of the double-blind study, during each study visit at the investigative site, 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 IMP, 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 for additional information. Any subject-reported attack not confirmed by the Investigator must have an alternate AE diagnosis recorded. All subject-reported and Investigator-confirmed HAE attacks will be recorded in the eCRF.

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

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

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

Despite the presence of these symptoms, the Investigator may still clinically determine that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (e.g., urticaria), the reported event persists well beyond

the typical time course of an HAE attack, or there is a likely alternate etiology for the event (e.g., the subject's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household). To be counted as a unique attack distinct from the previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.
Interim Analysis and Data Safety Monitoring Board: No interim analysis is planned for this study. During the study, patient safety will be monitored on a continuous basis by the Medical Monitor until the last patient completes his or her last scheduled study assessment. An independent Data Safety Monitoring Board (DSMB) will also be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study. The ongoing review of SAEs and other responsibilities of the DSMB are described in the DSMB Charter.
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 completion of all scheduled visits, unless they request to be discontinued from the study. Subjects who are discontinued from further dosing will not be eligible to participate in the OLE.

Criteria for Evaluation:

Primary and secondary efficacy endpoints will be based on an efficacy evaluation period spanning Day 0 through Day 182.

Primary Efficacy Endpoint

- Number of Investigator-confirmed HAE attacks

Secondary Efficacy Endpoints (rank ordered)

1. Number of Investigator-confirmed HAE attacks requiring acute treatment
2. Number of moderate or severe Investigator-confirmed HAE attacks

Exploratory Efficacy Endpoints

- Time to first HAE attack after Day 14, i.e., duration that a subject is attack-free after Day 14
- Number of high-morbidity Investigator-confirmed HAE attacks during the efficacy evaluation 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 Measures:

- Adverse events (AEs) including serious adverse events (SAEs) and adverse events of special interest (AESI)
- Clinical laboratory testing (hematology, clinical chemistry, coagulation and urinalysis)
- Vitals signs including blood pressure, heart rate, body temperature and respiratory rate
- Physical examination
- 12-lead electrocardiogram (ECG)

Additional Measures:

- Pharmacodynamic (PD) effects
- Anti-drug antibody development
- Pharmacokinetics (PK)
- Health-related quality of life assessments

Analysis Populations:

Intent-to-treat (ITT) Population: will include all randomized subjects who are administered at least 1 dose of active IMP or placebo. The primary efficacy analyses will be carried out with the ITT Population.

Safety Population: will include all subjects who are administered at least 1 dose of active IMP or placebo. All safety analyses will use the Safety Population.

Sample Size Determination:

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

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

Statistical Methods:

The primary analysis will be to compare the primary endpoint, which is 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). For the primary endpoint, an analysis of all randomized subjects who have received at least 1 dose of IMP or placebo (ITT population) will be conducted.

The primary efficacy endpoint, number of Investigator-confirmed HAE attacks during the efficacy evaluation period (Day 0 through Day 182), will be compared for each active treatment group (DX-2930) to the placebo group using a generalized linear model for count data assuming a Poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential overdispersion. The model will include fixed effects for treatment group (categorical) and the normalized baseline attack rate (continuous), and the logarithm of time in days each subject was observed during the efficacy evaluation period will be used as an offset variable in the model.

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

The primary endpoint will be tested by the following hypothesis:

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

Where $\lambda_{DX\text{-}2930}$ refers to the mean Investigator-confirmed HAE attack rate in the DX-2930 group and $\lambda_{Placebo}$ refers to the mean Investigator-confirmed HAE attack rate in the placebo group. The null hypothesis is that the mean Investigator-confirmed HAE attack rate ratio is 1 (no difference between treatment groups), versus the alternative hypothesis that the HAE attack rate ratio is not 1. Estimated attack rate ratios less than one would

indicate that subjects treated with DX-2930, on average, have a lower incidence of Investigator-confirmed HAE attacks during the efficacy evaluation period. The hypothesis will be tested using the model-based least squares means estimate of the treatment difference using a Wald-based chi-square test.

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

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

The rank ordered secondary endpoints will be analyzed using the same method as described for the primary efficacy endpoint. To adjust for the potential of inflated overall type-I error rate, the rank ordered secondary endpoints will be tested in a fixed sequence for each active treatment group to placebo group comparison using a general gatekeeping approach consistent with the logical restrictions of the rank ordering of the endpoints. Secondary endpoints will not be declared statistically significant unless the primary endpoint for that active treatment group to placebo group comparison is found to be statistically significant.

Safety Analysis:

Treatment-emergent AEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. The number and percentage of subjects with TEAEs will be displayed for each treatment group by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries in terms of severity and relationship to study medication will also be provided. Serious AEs will be summarized separately in a similar fashion. Patient listings of AEs causing discontinuation of study medication, AEs leading to 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 for each of the treatment groups and the combined active treatment group.

Actual values and change from baseline in vital signs and clinical laboratory tests will be summarized for each treatment group 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.

Abnormal physical examination findings will be listed. The number and percentage of subjects with normal, abnormal-not clinically significant, and abnormal-clinically significant ECG findings will be displayed for each of the treatment groups. Additional analyses of AEs, SAEs, severe AEs, AESI, and abnormal findings will be based on the timing (Study Day) and number of prior doses of study medication. The incidence of AEs by month from the start of study medication will be examined and the incidence among the four treatment arms will be compared. The rate of study discontinuation among the four treatment arms will also be compared.
Date of Amendment 2.0: 21 April 2016

Study Activities Schedule

Study Activities Schedule

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

Study Activities Schedule

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

BP = Blood Pressure; C1-INH = C1 Inhibitor; C_{max} = Maximum Plasma Drug Concentration; ECG = Electrocardiogram; HAE = Hereditary Angioedema; HBsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; HR = Heart Rate; IMP = Investigational Medicinal Product; LTP = Long-Term Prophylactic; OLE = Open-Label Extension; PD = Pharmacodynamic; PK = Pharmacokinetic; RR = Resting Rate

1. Subjects will undergo a run-in period to determine their baseline HAE attack rate. Only subjects with a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 Investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 Investigator-confirmed attacks to proceed to enrollment and randomization. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered a screen fail.
2. Treatment Period visits have a ±3 day window, with a maximum of 17 days or a minimum of 11 days between any two doses, starting with Dose 2, Day 14 through Day 182.
3. For subjects who do not rollover into OLE (DX-2930-04). Follow-up visits have a ±3 day window.
4. Site personnel contact the subject to solicit for any attacks not already reported by the subject once between scheduled site visits or approximately 7 days after last contact with subject.
5. Subjects who are on long-term prophylactic (LTP) therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm that the subject has successfully completed the 2 week washout period before they can enter the run-in period.
6. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment.

7. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 and Day 182 must be urine-based. Tests performed at screening, Days 28, 56, 98, 126, 154, and Day 238 can be serum- or urine-based.
8. There is a ±15 minute window for all vital signs. At study visits in which IMP is administered, vital signs including sitting or supine BP, HR, body temperature, and RR, will be obtained prior to dosing, 1 hour after dosing, and 2 hours after dosing for the first 4 doses with the ability to eliminate the 2 hour vitals for the remaining doses based on the discretion of the Investigator and the absence of safety signals.
9. Height and weight will be collected at the Screening visit only.
10. ECGs (single recordings) are collected at screening, baseline prior to Dose 1, Day 56, Day 144±1 day to capture the estimated C_{max} and Day 182. The ECG assessment at C_{max} on Day 144±1 day may be performed via at-home nurse or technician in lieu of a subject visit to the study site.
11. Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis.
12. Historical attack information will be collected at screening. During the study subjects (or caregivers, in the event the subject is < 18 years old or is incapacitated) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. Site personnel will also contact the subject once a week or at approximately 7 days after last contact with the subject during the run-in period and once between study visits or approximately 7 days after last contact with the subject during the treatment period in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not given through prior subject contact with the site.
13. Quality of life data will be obtained using the EuroQoL Group 5-Dimension (EQ5D) Self-Report Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using the Angioedema Quality of Life Questionnaire (AE-QoL) at pre-dose on Days 0, 28±3, 56±3, 98±3, 126±3, 154±3, and 182±3. An additional quality of life assessment (EQ5D and AE-QoL) will be conducted on Day 238±3 for subjects not entering OLE.
14. Subjects who rollover into the Open-Label Extension protocol (DX-2930-04) will provide consent by Day 182 and receive their first open-label dose following the completion of all DX-2930-03 assessments scheduled on Day 182. At the completion of these assessments, the subject will be discharged from DX-2930-03 and roll into the DX-2930-04 study.
15. Subjects who terminate from the study early will undergo (if possible) all of the assessments and procedures as Day 182 at their final study visit.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

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
ANOVA	Analysis of variance
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
BLA	Biologics License Application
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C1-INH	C1 inhibitor
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CL/F	apparent total plasma clearance after extravascular administration
C_{max}	Maximum plasma drug concentration
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Clinical Research Organization
CSR	Clinical Study Report

DLT	Dose Limiting Toxicity
DMID	Division of Microbiology and Infectious Diseases
DP	Drug product
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ET	Early termination
EQ5D	EuroQoL Group 5-Dimension Report Questionnaire
FWER	family-wise type 1 error rate
FDA	Food and Drug Administration
FXI(a)	Factor XI (activated)
FXII(a)	Factor XII (activated)
GCP	Good Clinical Practice
GEE	Generalized estimating equation
GGT	Gamma-glutamyl transferase
HAE	Hereditary angioedema
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIPAA	Health Information Portability and Accountability Act
HIV	Human immunodeficiency virus
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
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
IWRS	Interactive Web-based Randomization System
K_i	inhibition constant
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LTP	Long-Term Prophylactic
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
OLE	Open-label extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
pKal	Plasma kallikrein
PT	Prothrombin time
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
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase (AST)

SGPT	Serum glutamic pyruvic transaminase (ALT)
SM	Safety Management
SMQ	Standard MedDRA query
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 high molecular weight

kininogen (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 and 1b 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 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, 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 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 a 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 and were followed for 15 weeks after the second dose.

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 suggest 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 are consisted with values obtained in healthy subjects in study DX-2930-01.

A Western blot assay showed pre-dose baseline levels of mean 2-chain high-molecular-weight kininogen (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, levels similar to that observed in healthy subjects. This outcome demonstrates 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 demonstrate 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 appears to be dose-proportional and consistent with the results obtained in healthy subjects in study DX-2930-01. Pharmacodynamic effect assays provide 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.

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objective

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

2.3 Tertiary Objectives

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

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Overview

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

Subjects aged 12 and over with a documented diagnosis of Type I or Type II HAE who experience at least 1 attack per 4 weeks during the run-in period will be eligible. Up to 120 subjects may be enrolled to provide 108 that complete. Subjects will be enrolled from sites in the United States, Canada, Italy, Germany, United Kingdom and Jordan.

3.1.1.1 Long-Term Prophylactic (LTP) Therapy Washout

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. These criteria ensure that patients who should remain on LTP do not washout for this study, but do allow the enrollment of appropriate patients with severe disease while minimizing their time off LTP. Current treatment guidelines recognize two different standard of care approaches to treating HAE, which include LTP and on-demand therapy (Cicardi et al., 2012; Craig et al., 2012; Zuraw et al., 2013). Throughout the study, subjects will be permitted to treat acute HAE attacks in accord with the Investigator's usual care of their patients. Thus, those subjects who stop their LTP to enter the study and are subsequently randomized to the placebo group will still be managed with no reduction in their standard of care. The Investigator must confirm that the subject has successfully completed the 2 week washout period before they can enter the run-in period.

3.1.1.2 Run-In Period

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

minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered a screen fail. Subjects who screen fail will not be allowed to rescreen into the study.

3.1.1.3 Treatment Period

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

Each subject will undergo a treatment period consisting of 13 doses of blinded Investigational Medicinal Product (IMP), for a period of 26 weeks from the date of first dose on Day 0 through two weeks after the final dose. Subjects randomized to one of the 4 treatment arms will either receive a DX-2930 or placebo dose according to the dosing schedule in Table 1.

Table 1. Treatment Period Dosing Schedule

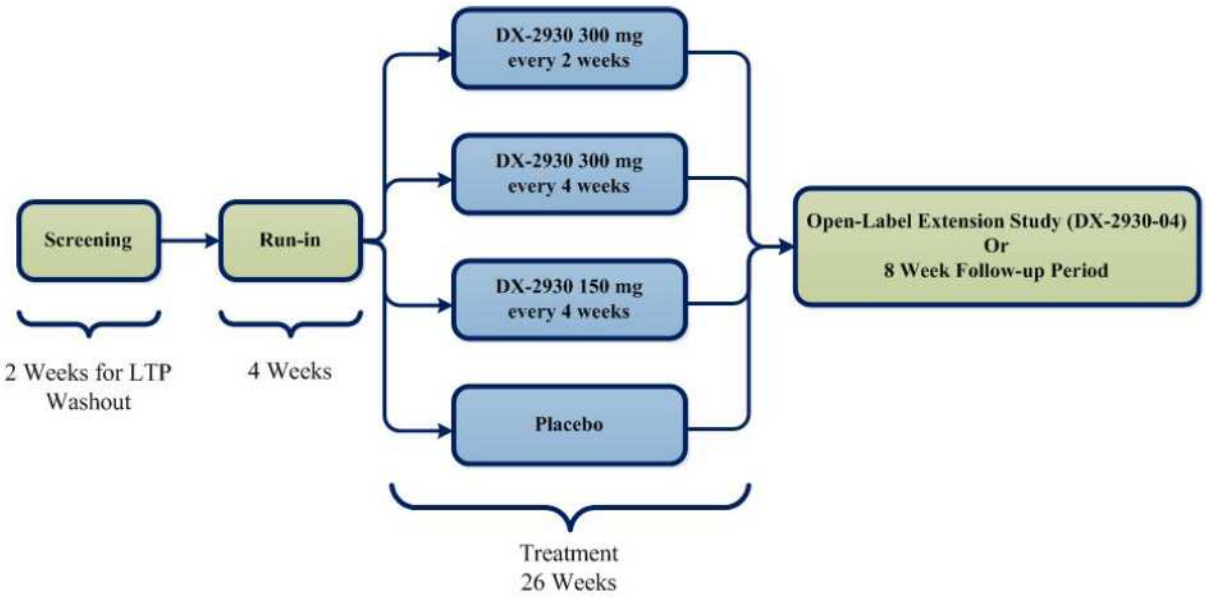
Treatment Period		Treatment Arms: DX-2930 or Placebo			
Dose Number	**Dose Day/Week**	**300 mg every 2 weeks**	**300 mg every 4 weeks**	**150 mg every 4 weeks**	**Placebo**
1	Day 0/Week 0	DX-2930	DX-2930	DX-2930	Placebo
2	Day 14/Week 2	DX-2930	Placebo	Placebo	Placebo
3	Day 28/Week 4	DX-2930	DX-2930	DX-2930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

3.1.1.4 Open-Label Extension (OLE)

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

Figure 1 shows a schematic of the study design.

Figure 1. Overview of the Study Design



3.1.1.5 Follow-Up Period

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

3.1.2 Safety Oversight and Stopping Rules

3.1.2.1 Interim Analysis and Data Safety Monitoring Board (DSMB)

No interim analysis is planned for this study. During the study, patient safety will be monitored on a continuous basis by the Medical Monitor until the last patient completes his or her last scheduled study assessment.

An independent data safety monitoring board (DSMB) will also be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study (see Section 10.7 for a description of the DSMB and its role). The ongoing review of SAEs and other responsibilities of the DSMB are described in the DSMB Charter.

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 for the duration of the 26 week treatment period, unless they request to be discontinued from the study. Subjects who are discontinued from further dosing will not be eligible to participate in the OLE.

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 Pivotal Dose Selection

The dose rationale is based on the pharmacodynamic bioactivity, PK, safety, and efficacy of DX-2930 from the Phase 1 clinical studies and nonclinical studies. Together, these attributes provide the rationale for the selected doses and regimens to achieve drug levels likely to prevent a majority of HAE attacks. Based on these considerations, 300 mg every 2 weeks, 300 mg every 4 weeks, and 150 mg every 4 weeks were identified as the dosing regimens for evaluation.

In study DX-2930-02, two DX-2930 doses of 300 mg or greater administered 2 weeks apart resulted in a normalization of plasma 2-chain HMWK levels and a maximal 91% reduction in HAE attacks (DX-2930 Investigators Brochure). Steady-state trough concentrations following DX-2930 administration every 2 weeks would be approximately 27,000 ng/mL. The maximum plasma concentration (C_{max}) obtained following ecallantide administration to treat an acute attack is similar to this trough concentration of DX-2930.

It is possible that lower drug levels would prevent attacks following prophylactic treatment than those required for acute attack treatment, since systemic drug exposure could attenuate contact system activation through the inhibition of plasma kallikrein-mediated FXII activation. As such, 2 dosing regimens of DX-2930 administered monthly are being evaluated. Doses of 300 mg or 150 mg DX-2930 administered every 4 weeks would result in a steady-state trough concentration of approximately 9,500 and 4,750 ng/mL, respectively. These trough levels bracket the C_{max} observed in the 100 mg dose group in study DX-2930-02, which demonstrated a slight, but not statistically significant, reduction in 2-chain HMWK levels.

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.

3.3 Individual Subject Dosing and Follow-Up

Subjects will receive a dose of blinded IMP every 2 weeks during the 26 week Treatment Period for a total of 13 doses. The first dose of IMP will be administered on Day 0 and the last dose of IMP will be administered on Day 168. There will be a ± 3 day window around each study visit, with a maximum of 17 days or a minimum of 11 days between any two doses. After each dose, subjects will be monitored at the study site through 2 hours post-dose for the first 4 doses with the ability to reduce this time to 1 hour for the remaining doses based on the discretion of the Investigator and the absence of safety signals. A follow-up visit will occur on Day 182.

3.4 Study Duration for Individual Subjects

Following informed consent, subjects will undergo screening assessments. Screened subjects who are on long-term prophylactic therapy for HAE are required to undergo a minimum 2 week wash-out period prior to the start of run-in. 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 last as long as 8 weeks in order to meet the minimum attack rate required for enrollment. Enrolled subjects will then undergo a 26-week treatment period. Subjects who do not participate in the OLE will be followed for an additional 8 weeks.

4 STUDY POPULATION SELECTION

4.1 Study Population

The study will enroll up to 120 subjects to provide 108 completed. Subjects will be 12 years of age and older with a confirmed diagnosis of HAE (Type I or II) who experience at least 1 Investigator-confirmed attack per 4 weeks during the run-in period. HAE diagnosis will be confirmed through documented clinical history consistent with HAE and diagnostic testing conducted during the screening visit.

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 5 subjects who are 12 to 17 years of age.

4.2 Inclusion Criteria

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

1. Males and females 12 years of age or older at the time of screening.
2. Documented diagnosis of HAE (Type I or II) based upon 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 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 begin participating in the run-in period before these diagnostic results are available. 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. Experiencing a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks as confirmed during the run-in period.
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 provides 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 progestin-only oral contraceptive associated with inhibition of ovulation (oral, injectable or implantable), intrauterine 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) is 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 screening 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. 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.
2. Participation in a prior DX-2930 study.
3. Dosing with an investigational drug or exposure to an investigational device within 4 weeks prior screening.
4. 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.
5. Exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 2 weeks prior to entering the run-in period.
6. Use of long-term prophylactic therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to entering the run-in period.
7. Use of short-term prophylaxis for HAE within 7 days prior to entering the run-in period. 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, 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 IMP administration, refer to the Pharmacy Manual.

5.1.1 DX-2930

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 vial contains a nominal concentration of 150 mg DX-2930 active ingredient in 1 mL solution. The test product will be administered by subcutaneous injection into the upper arm in a blinded manner.

For each 300 mg dose of DX-2930, each subject will receive a total of 2 mL, divided into 2 separate 1.0 mL SC injections of DX-2930. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

For each 150 mg dose of DX-2930, each subject will receive a total of 2 mL, divided into 2 separate 1.0 mL SC injections, where one injection is DX-2930 and the other is placebo. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

5.1.2 Placebo

Placebo consists of the inactive formulation of the test product: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, pH 6.0 with 0.01% Polysorbate 80.

Placebo doses will be administered to subjects randomized to the placebo treatment arm and in between doses of DX-2930 for subjects randomized to the 300 mg or 150 mg DX-2930 every 4 weeks treatment arms, according to the dosing schedule in Table 1.
For each placebo dose, each subject will receive a total of 2 mL, divided into 2 separate 1.0 mL SC injections of placebo. The 2 injections will be given in the same upper arm, with at least 2 cm separation between each injection site.

5.2 Dosing and Follow-Up Schedule

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

5.3 Method of Assigning Subjects to Treatment Groups

Subjects meeting all eligibility criteria will be enrolled in the study and sequentially assigned an identification number. Subjects will be assigned to one of the DX-2930 or placebo

treatment groups via an Interactive Web-based Randomization System (IWRS). Use of the IWRS will be outlined in the Operations Manual.

5.4 Blinding and Unblinding

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

The treatment code for an individual patient may only be broken by the Investigator or Sponsor or the DSMB for reasons of patient safety or in an emergency when knowledge of the study drug administered would be important for the treatment of the patient.

The Investigator must document the date, time and reason for the code break. The Investigator should follow the instructions within the IWRS System should a code break be required. In the case of a concerning drug-related safety event, the Investigator has the ability to contact and consult with the Medical Monitor. In emergency situations, the Investigator may break the treatment code immediately or as quickly as possible if he/she finds it is in the best interest of the trial subject. The Investigator has unrestricted and immediate access to break the treatment code through the IWRS System.

The Data and Safety Monitoring Board (DSMB), in consultation with the Medical Monitor, may also request unblinding of an individual patient's treatment assignment for reasons of safety.

In the event of a drug-related, serious, unexpected AE, the Sponsor's Pharmacovigilance Department will be provided with the treatment assignment for the subject for the purpose of regulatory reporting.

5.5 Prior and Concomitant Therapy

Reasonable efforts will be made to determine all relevant treatments received by the subject from the time of screening up to administration of the first dose of IMP.

All information on concomitant therapy from the time of first dose of IMP through the final study visit (including all prescription/non-prescription medications, herbal medications and vitamin supplements) must be recorded on the subject's electronic Case Report Form (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.

5.5.1 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 5.5.2. 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 prophylaxis. Administration of the investigational product and study procedures will continue without alteration to the protocol specified study schedule, even if the patient receives any treatment for an HAE attack.
- The use of short-term prophylactic treatment for HAE will be permitted if medically indicated.
- Therapies to treat any AEs the subject experiences during the study are permitted.

5.5.2 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.

5.6 Restrictions

5.6.1 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.

5.6.2 Fluid and Food Intake

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

5.6.3 Activity

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

5.7 Treatment Compliance

All doses of the IMP will be administered during clinic visits under the direct supervision of the Investigator or qualified site personnel designated by the Investigator.

5.8 Packaging and Labeling

The test products (DX-2930 and placebo) will be supplied by the Sponsor and packaged and labeled according to applicable local and regulatory requirements for investigational studies.

5.9 Storage and Accountability

All supplies of the investigational products (DX-2930 and placebo) must be stored refrigerated (2ºC to 8ºC/36ºF to 46ºF) in the original 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 investigational product received and will maintain records of disposition of the drug, including dates, quantity and use.

5.10 Investigational Medicinal Product Retention at Study Site

The Investigator (or designee) is responsible for maintaining accurate accountability records of the IMP throughout the clinical study. All IMP 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. IMP 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 IMP 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 IMP have been established, and that appropriate records of the disposal are documented and maintained. No unused IMP 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

Informed Consent and Assent forms must be approved for use by the reviewing institutional review board (IRB), research ethics board (REB) or independent ethics committee (IEC). Informed consent, and assent when applicable, must be obtained for all subjects participating in the study prior to performing any study related activities. 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.

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 (alternatively age or year of birth, if full date of birth is not allowed to be collected for legal reasons), sex, race and ethnicity (where locally permitted) and medical history will be obtained from the subject and recorded in source documents and the eCRF. Medical history will capture the subject's current relevant medical status (current disease processes), past relevant medical status (past disease processes), history of surgery, allergies and concomitant medications.

6.4 Efficacy Assessments

6.4.1 Primary and Secondary Endpoints

Primary and secondary efficacy endpoints will be based on an efficacy evaluation period spanning Day 0 through Day 182.

Primary Efficacy Endpoint

- Number of Investigator-confirmed HAE attacks

Secondary Efficacy Endpoints (rank ordered)

1. Number of Investigator-confirmed HAE attacks requiring acute treatment
2. Number of moderate or severe Investigator-confirmed HAE attacks

Exploratory Efficacy Endpoints

- Time to first HAE attack after Day 14, i.e., duration that a subject is attack-free after Day 14

- Number of high-morbidity Investigator-confirmed HAE attacks during the efficacy evaluation 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.

6.4.2 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) (Appendix 4). Site personnel will be trained on HAARP prior to screening subjects at their site.

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

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

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

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

Subjects washing out of LTP will be contacted by the site at the end of the 2 week washout period. The Investigator must confirm the subject has successfully completed the 2 week washout period before they can enter the run-in period. Confirmation of washout will be captured in the eCRF.

Site personnel will contact the subject or caregiver weekly, or approximately 7 days after their last contact with the subject, throughout the run-in period. If the subject experiences 1 or more Investigator confirmed HAE attacks by the end of week 4, the subject will have fulfilled the run-in requirement and may proceed to enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks can exit the run-in period early and proceed to enrollment and randomization. If the subject experiences no Investigator-confirmed HAE attacks the end of the subject will remain in the run-in period for an additional 4 weeks. The maximum duration of the run-in period is 8 weeks. If run-in has been extended and the subject has 2 or more Investigator-confirmed HAE attacks by the end of week 8, the subject will have fulfilled the run-in requirement and may proceed to the double-blind treatment period. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in will be considered a screen fail.

During the treatment period site personnel will contact the subject or caregiver once between scheduled study visits or approximately 7 days after their last contact to solicit for any HAE attack information not already reported.

Throughout the duration of the double-blind study, during each study visit at the investigative site, 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 study drug, will be recorded on the AE page of the eCRF. Any AE reported to the site meeting criteria for a serious adverse event must be reported to the Sponsor using the SAE Reporting Form in the EDC system within 24 hours of becoming aware of the event. For all serious adverse events that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 24 hours of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. For all non-serious AEs that are reported as HAE attacks, the Principal Investigator or physician designee will review the event within 3 days of initial notification and, in accordance with HAARP, evaluate if it represented a confirmed HAE attack. If necessary for the evaluation, the Investigator or designee may contact the subject for additional information. Any subject-reported attack not confirmed by the Investigator must have an alternate AE diagnosis recorded. All subject-reported and Investigator-confirmed HAE attacks will be recorded in the eCRF.

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

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

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

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

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

6.5 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. There is a ±15 minute window for all vital signs.

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 findings of each examination will be recorded on the source documents and eCRF. The physical examination will include the body systems listed below:

- Height and weight (at Screening visit only)
- General appearance
- Ears, nose, and throat
- Head and Neck
- Ophthalmological
- Respiratory

- Cardiovascular
- Abdomen
- Neurological
- Extremities
- Dermatological
- Lymphatic

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.

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), serology, pregnancy tests, C1-INH functional assay, C4 assay, C1q assay, PK samples, PD samples, and plasma anti-drug antibody testing. All laboratory tests will be performed using established and validated methods.

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 subject who does not rollover into the OLE will be approximately 271 mL. The total blood draw for each subject that does rollover into the OLE will be approximately 208 mL. Please refer to the Laboratory Manual for more information.

Laboratory testing will include the following as specified in the Study Activities Schedule (Appendix 1).

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 Serology

HBsAg, HCV, and HIV tests

6.8.1.6 Pregnancy Test

Serum or urine pregnancy test

6.8.1.7 C1-INH Functional Assay

Results of a C1-INH functional assay are required for eligibility assessment. Samples will be drawn at the screening visit. 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 C4 Assay

Results of a C4 assay may be required for eligibility assessment. Samples will be drawn at the screening visit. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.

6.8.1.9 C1q Assay

Results of a C1q assay may be required for eligibility assessment. Samples will be drawn at the screening visit. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use.

6.8.1.10 PK Sample Collection

As outlined in Section 6.9.

6.8.1.11 PD Sample Collection

As outlined in Section 6.10.

6.8.1.12 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 at pre-dose on Days 0, 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3 and 238±3 during the follow-up period for any subjects not entering OLE.

6.10 Pharmacodynamic Assessments

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

6.11 Plasma Anti-Drug Antibody Testing

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

6.12 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. All prescription, over-the-counter medications, herbals, and supplements that are being taken or have been taken by subjects from the time of screening through the duration of the study will be regarded as concomitant medications and must be documented in the source documents and eCRF.

6.13 Randomization

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

6.14 Investigational Medicinal Product Treatment

Instructions for safe handling of IMP, preparation of each subcutaneous dose, and administration of IMP are provided in the Pharmacy Manual. Preparation and dispensing of the IMP will be handled by qualified site personnel as directed by the Principal Investigator at the study site. The Principal Investigator or qualified site personnel will administer the assigned IMP. The requirements for maintaining IMP accountability are provided in Section 5.9 of this protocol.

6.15 Quality of Life Assessments

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

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 IMP 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 substantial 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 IMP 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 IMP through the final follow-up visit or, in the event that onset time precedes first IMP administration, the AE increases in severity during the follow-up period.

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, 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 the IMP, 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 IMP exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of the IMP.
- The AE resolved or improved with decreasing the dose or stopping use of the IMP (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between the study IMP 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 the IMP); 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 IMP); or
- The AE is more likely explained by the investigational product than by another cause (i.e., the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the IMP).

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, or by the DSMB for overall study AE review.

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 IMP 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 IMP, 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

Medical Safety Contact for US and Canada
PPD , MD
PPD , Clinical Development
300 Shire Avenue, MA 02421 USA
Phone: PPD
Email: PPD
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
PPD , MD, MBA
PPD
Phone: PPD
Email: PPD

Sponsor Pharmacovigilance Department
Email: PPD
Phone (US): PPD

6.16.5.6 Safety Notifications by the Sponsor to the Investigator

Investigators will receive prompt notification of any adverse experience related to IMP 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.

6.16.5.7 Unblinding a Subject's Treatment during the Trial

Requirements for emergency unblinding by the Investigator are detailed in Section 5.4. To assess an occurrence of a safety observation, the Sponsor Pharmacovigilance Department may unblind the treatment of any subject.

6.17 Subject Withdrawal

The Investigator may withdraw a subject from treatment with study drug for any of the reasons listed below.

- 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. The criteria used by the DSMB regarding dose administration suspension and/or study discontinuation are provided in Section 3.1.2.

6.18 Appropriateness of Measurements

This is a Phase 3 multi-center, randomized, double-blind, placebo-controlled study that is designed to evaluate the efficacy and safety of DX-2930 in prevention of HAE attacks in subjects with HAE. DX-2930 is a recombinant, fully human IgG1, kappa light chain, monoclonal antibody. The randomized, placebo controlled study design is a standard approach for differentiation between the efficacy and safety profiles of an active and placebo treatment when administered to subjects. All of the measures employed in this protocol are standard measures routinely used for the evaluation of the efficacy, safety and tolerability of an investigational product.

7 STUDY ACTIVITIES

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

7.1 Screening

The following procedures and assessments are to be performed during Screening:

- 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, serology, 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 2 week washout period, as confirmed by the Investigator, before entering the run-in period.
    - 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.

7.2 Run-in Period

Subjects who were on LTP may enter run-in after successfully completing a 2 week washout of their LTP. All subjects will undergo a run-in period of 4 weeks to determine the baseline HAE attack rate (Section 6.4). The run-in period may be shortened to less than 4 weeks for any subject who experiences 3 Investigator-confirmed attacks before the 4 weeks have ended. The run-in period may be expanded by an additional 4 weeks if the subject does not meet the minimum attack requirement during the first 4 weeks.

The following will be collected on an ongoing basis during the run-in period by subjects (or caregivers) reporting symptoms of an HAE attack to the site or through regular site contact with the subject (or caregiver):

- Prior and concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.3 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 IMP administration:

- Eligibility review (Section 6.2)
- Randomization to treatment (Section 6.13)
- 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 6.16)
- Quality of life assessments: EQ5D and AE-QoL (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.4 Site Contact with the Subject

Site personnel contact the subject once between scheduled study visits or approximately 7 days after their last contact with the subject to solicit for any HAE attack information not already reported by the subject.

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.5 Continuation of Treatment Period: Visit 2, Dose 2 (Day 14±3 Days)

On Day 14 the following procedures and assessments will be performed prior to IMP administration:

- 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 IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.6 Continuation of Treatment Period: Visit 3, Dose 3 (Day 28±3 Days)

On Day 28, the following procedures and assessments will be performed prior to IMP administration:

- 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)
- Pregnancy test, serum or urine (females) (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: AE-QoL (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.7 Continuation of Treatment Period: Visit 4, Dose 4 (Day 42 ±3 Days)

On Day 42, the following procedures and assessments will be performed prior to IMP administration:

- 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 IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.8 Continuation of Treatment Period: Visit 5, Dose 5 (Day 56±3 Days)

On Day 56, the following procedures and assessments will be performed prior to IMP administration:

- 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)
- Pregnancy test, serum or urine (females) (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: AE-QoL (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.9 Continuation of Treatment Period: Visits 6 and 7, Doses 6 and 7 (Days 70 and 84, All ±3 Days)

On Days 70 and 84, the following procedures and assessments will be performed prior to IMP administration:

- 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 IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.

- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.10 Continuation of Treatment Period: Visit 8, Dose 8 (Day 98±3 Days)

On Day 98, the following procedures and assessments will be performed prior to IMP administration:

- 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)
- Pregnancy test, serum or urine (females) (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: EQ5D and AE-QoL (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)

- AE collection (Section 6.16)

7.11 Continuation of Treatment Period: Visits 9 and 10, Doses 9 and 10 (Days 112 and 126, All ±3 Days)

On Days 112 and 126, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Pregnancy test, serum or urine (females) on Day 126±3 (Section 6.8)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: AE-QoL on Day 126±3 (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.12 Continuation of Treatment Period: Visit 11, Dose 11 (Day 140±3 Days)

On Day 140, the following procedures and assessments will be performed prior to IMP administration:

- 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 6.16)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.13 Continuation of Treatment Period (Day 144±1 Day)

This ECG assessment may be conducted through an at-home visit by a nurse or technician or at the study site. The date, time and collection location of this ECG and its results will be documented in the source documents and eCRF.

- 12-Lead ECG (Section 6.7)

7.14 Continuation of Treatment Period: Visits 12 and 13, Doses 12 and 13 (Days 154 and 168, All ±3 Days)

On Days 154 and 168, the following procedures and assessments will be performed prior to IMP administration:

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- Pregnancy test, serum or urine (females) on Day 154±3 (Section 6.8)

- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)
- Quality of life assessments: AE-QoL on Day 154±3 (Section 6.15)

After the preceding procedures and assessments are completed:

- Administer IMP (Section 6.14)

After administration of IMP, the following post treatment procedures and assessments will be performed:

- Vital signs including body temperature, HR, BP and RR (Section 6.5) at 1 and 2 hours post-dose. This 2 hour assessment of vitals may be dismissed if, based on the discretion of the Investigator and the absence of safety signals, the Investigator determines that the subject only needs to be monitored for 1 hour post dose. The post-dose monitoring period may be lengthened back to 2 hours at any time by the Sponsor based on DSMB recommendation.
- Concomitant therapy (Section 6.12)
- AE collection (Section 6.16)

7.15 Completion of Treatment Period: Visit 14, Day 182±3 Days

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

- 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)
- Urine pregnancy test (females) (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: EQ5D and AE-QoL (Section 6.15)
- Discharge from study:
  - Subjects will be offered the option of enrolling in the DX-2930-04 Open Label Extension (OLE) study for continued treatment and safety follow-up.
  - Informed Consent obtained for study DX-2930-04
  - Subjects who consent to participate in DX-2930-04 will receive their first OLE dose following the completion of all double-blind assessments scheduled on Day 182.

7.16 Follow-up Period (Subjects Not Continuing in Open-Label Extension Study): Visit 15, Day 210 ±3 Days

- Vital signs including body temperature, HR, BP and RR (Section 6.5)
- PK sample collection (Section 6.9)
- PD sample collection (Section 6.10)
- Concomitant therapy (Section 6.12)
- HAE attack information (Section 6.4)
- AE collection (Section 6.16)

7.17 Final Follow-up Visit (Subjects Not Continuing in Open-Label Extension Study): Visit 16, Day 238±3 Days

- 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)
- Pregnancy test, serum or urine (females) (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: EQ5D and AE-QoL (Section 6.15)

7.18 Early Termination (ET)

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 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, PPD, PPD, USA).

Unless otherwise specified, summary tabulations will be presented by treatment group. For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Where applicable, estimates from statistical model of least squares means, treatment differences, p-values, and 95% confidence intervals for least squares mean treatment differences 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 statistical hypothesis testing will be performed on the primary and rank ordered secondary efficacy endpoints with the global family-wise type I error rate (FWER) strongly controlled at two-sided 0.05 using a Bonferroni-based general gatekeeping procedure as described in Section 9.12.5.

9.2 Sample Size Determination

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

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

9.3 Method of Assigning Study Subjects to Treatment Groups

Subjects will be randomized after confirmation of study eligibility in a ratio of 2:1 via a computer-generated randomization schedule to receive repeated SC administrations of DX-2930 or placebo. Subjects who are randomized to DX-2930 will be assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 300 mg every 2 weeks, 300 mg every 4 weeks, or 150 mg every 4 weeks. Randomization will be performed centrally and stratified by the baseline attack rate observed during the run-in period into the following groups: 1 to < 2 attacks per 4 weeks, 2 to < 3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks. Permuted blocks will be used to ensure that approximately equal numbers of subjects are assigned each treatment within strata.

9.4 Analysis Populations

The analysis populations will be defined as follows:

Intent-to-treat (ITT) Population: will include all randomized subjects who are administered at least 1 dose of active IMP or placebo. Subjects will be analyzed according to their randomized treatment assignment regardless of the treatment actually received. The primary efficacy analyses will be carried out with the ITT Population.

Safety Population: will include all subjects who are administered at least 1 dose of active IMP or placebo. Subjects will be analyzed according to the treatment they actually received. All safety analyses will use the Safety Population.

9.5 Analysis of Disposition

The numbers of subjects randomized, completing, or withdrawing, along with reasons for withdrawal, will be tabulated by treatment group and overall for the ITT and safety populations.

9.6 Demographics and Baseline Characteristics Analyses

Baseline and demographic variables will be descriptively summarized by treatment group and overall for the ITT and safety populations.

9.7 Treatment Compliance and Extent of Exposure

Treatment compliance and extent of exposure will be described by calculating the percentage of planned doses received by the subject and the total number of doses received by the subject and summarized by treatment group for the ITT and safety populations.

9.8 Analysis of Primary and Secondary Efficacy Endpoints

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint, number of Investigator-confirmed HAE attacks during the efficacy evaluation period (Day 0 through Day 182), will be compared for each active treatment group (DX-2930) to the placebo group using a generalized linear model for count data assuming a Poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential overdispersion. The model will include fixed effects for treatment group (categorical) and the normalized baseline attack rate (continuous), and the logarithm of time in days each subject was observed during the efficacy evaluation period will be used as an offset variable in the model.

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

The primary endpoint will be tested by the following hypothesis:

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

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

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

All efficacy analyses will be conducted using the ITT population.

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

9.8.2 Secondary Efficacy Endpoints

The rank-ordered secondary efficacy endpoints are as follows:

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

The secondary endpoints will be analyzed using the same method as described for the primary efficacy endpoint.

To adjust for the potential of inflated overall Type I error rate, the rank ordered secondary endpoints will be tested in a fixed sequence for each active treatment group to placebo group comparison using a general gatekeeping approach consistent with the logical restrictions of the rank ordering of the endpoints. Secondary endpoints will not be declared statistically significant unless the primary endpoint for that active treatment group to placebo group comparison is found to be statistically significant. The testing procedure is detailed in Section 9.12.5.

9.8.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include:

- Time to first HAE attack after Day 14, i.e., duration that a subject is attack-free after Day 14
- Number of high-morbidity Investigator-confirmed HAE attacks during the efficacy evaluation 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.

The exploratory efficacy endpoints are considered supportive and any statistical tests comparing treatments will be made without adjustment for multiplicity. The resulting p-values from these supportive analyses will be interpreted descriptively as summarizing the weight of evidence for a treatment effect.

9.9 Analysis of Pharmacokinetic and Pharmacodynamic Endpoints

9.9.1 Pharmacokinetic Assessments:

Blood samples will be collected for the measurement of plasma DX-2930 concentrations prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3 and 182±3. Additional samples will be collected on Days 210±3, and 238±3 during the follow-up period for any subjects not entering OLE.

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

9.9.2 Pharmacodynamic Assessments:

Blood samples will be collected to evaluate the pharmacodynamic effects of DX-2930 through biomarker assays prior to IMP administration on Day 0 and on Days 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Days 210±3, and 238±3 during the follow-up period for any subjects not entering OLE.

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

9.9.3 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 IMP administration on Day 0 and on Days 56±3, 98±3, 140±3, and 182±3. Additional samples will be collected on Day 238±3 during the follow-up period for any subjects not entering OLE

9.9.4 C1-INH and C4 Assessments:

Samples will be obtained for C1-INH, C4 and C1q assays at screening for eligibility assessment.

9.10 Safety Analysis

Treatment-emergent AEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. The number and percentage of subjects with TEAEs will be displayed for each treatment group by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries in terms of severity and relationship to study medication will also be provided. Serious AEs will be summarized separately in a similar fashion. Patient listings of AEs causing discontinuation of study medication, AEs leading to 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 for each of the treatment groups and the combined active treatment group.

Actual values and change from screening in vital signs and clinical laboratory tests will be summarized for each treatment group 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.

Abnormal physical examination findings will be listed.

The number and percentage of subjects with normal, abnormal-not clinically significant, and abnormal-clinically significant ECG findings will be displayed for each of the treatment groups.

Additional analyses of AEs, SAEs, severe AEs, AESI, and abnormal findings will be based on the timing (Study Day) and number of prior doses of study medication. The incidence of AEs by month from the start of study medication will be examined and the incidence among the four treatment arms will be compared. The rate of study discontinuation among the four treatment arms will also be compared.

9.11 Analysis of Quality of Life Assessments

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

9.12 Statistical/Analytic Issues

9.12.1 Adjustment for Covariates

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

9.12.2 Handling of Dropouts or Missing Data

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

9.12.3 Interim Analysis and Data Monitoring

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

9.12.4 Multicenter Studies

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

9.12.5 Multiple Comparisons/Multiplicity

The global family-wise Type I error rate (FWER) for the statistical tests of the primary and rank ordered secondary efficacy endpoints (rank specified in Section 6.4.1) will be controlled at 0.05. To strongly control the global FWER at this level, a general gatekeeping approach with branches for each active treatment group to placebo group comparison will be utilized in which each family of statistical tests will be conducted in a sequential manner. Specifically, a three-branch general gatekeeping procedure with three families of hypotheses will be defined as follows:

- Family 1 (F_1): Hypothesis tests for the primary efficacy endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{11}, H_{12}, and H_{13}).
- Family 2 (F_2): Hypothesis tests for the first ranked secondary endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{21}, H_{22}, and H_{23}).
- Family 3 (F_3): Hypothesis tests for the second ranked secondary endpoint, one test for each active treatment to placebo comparison ordered by highest total monthly dose (H_{31}, H_{32}, and H_{33}).

The 3 sets of hypotheses in F1, F2, and F3 will be tested in a fixed sequence within each active treatment group to placebo group comparison or branch. Testing within a branch will continue in sequence until the first test that the null hypothesis cannot be rejected; statistical significance cannot be declared for that test or for any of the remaining tests within the branch.

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

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

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

9.12.6 Sensitivity Analyses

Sensitivity analyses will be performed on the primary efficacy endpoint to evaluate the robustness of the results from the primary analysis method. These analyses will be described in the statistical analysis plan.

10 STUDY ADMINISTRATIVE STRUCTURE

The study administration structure is provided in Table 2.

Table 2. Study Administrative Structure

Sponsor Contact/Sponsor Medical Director:	Jennifer Schranz, MD PPD, Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: PPD
Medical Monitor (US, Canada):	PPD, MD PPD, Clinical Development 300 Shire Way, Lexington, MA 02421 USA Phone: PPD Email: PPD
Medical Monitor (Jordan, Europe)	PPD, MD, MBA Voisin Consulting PPD, PPD PPD, France Phone: PPD Email: PPD
Study Monitoring (US):	Rho, Inc. PPD, PPD, PPD Phone: PPD
Study Monitoring (Jordan)	Triumpharma PPD, PPD PPD, PPD PPD, Jordan Phone: PPD
Study Monitoring (Canada)	Red Maple Trials Incorporated PPD, PPD PPD, PPD, Canada, PPD Phone: PPD
Study Monitoring (Europe)	Dyax Corp. 55 Network Drive, Burlington, MA 01803 Phone: PPD

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 and assent forms, any consent or assent form updates, subject recruitment procedures (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 and assent forms 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 and 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, source 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 Data Safety Monitoring Board

An independent DSMB will be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study.

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, DSMB, 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 Data Handling Considerations

Data that may potentially unblind the treatment assignment (i.e., investigational product serum concentrations, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

10.13 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 IMP 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 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.

10.14 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).

10.15 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 other 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

Bennett G, Craig T. Hereditary angioedema with a focus on the child. Allergy Asthma Proc. 2015;36(1):70-3.

Bork K, Hardt J, Schicketanz K-H, Ressel N. Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to C1 esterase inhibitor deficiency. Arch Int Med. 2003;163:1229-1235.

Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol. 2012;130(3):692-7.

Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: New findings concerning symptoms, affected organs, and course. Am J Med. 2006;119(3):267-274.

Bork K, Siedlecki K, Bosch S, Schopf RE, Kreuz W. Asphyxiation by laryngeal edema in patients with hereditary angioedema. Mayo Clin Proc. 2000;75(4):349-54.

Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. Br J Dermatol. 2009;161(5):1153-8.

Cicardi M, Bork K, Caballero T, Craig T, Li HH, Longhurst H, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. Allergy. 2012;67(2):147-57.

Craig T, Pursun EA, Bork K, Bowen T, Boysen H, Farkas H, et al. WAO Guideline for the Management of Hereditary Angioedema. World Allergy Organ J. 2012;5(12):182-199.

Davis AE, 3rd. Mechanism of angioedema in first complement component inhibitor deficiency. Immunol Allergy Clin North Am. 2006;26(4):633-51.

Farkas H. Pediatric hereditary angioedema due to C1-inhibitor deficiency. Allergy Asthma Clin Immunol. 2010;6(1):18.

Goring HD, Bork K, Spath PJ, Bauer R, Ziemer A, Hintner H, et al. [Hereditary angioedema in the German-speaking region]. Hautarzt. 1998;49(2):114-22.

KALBITOR® (ecallantide) [package insert] Burlington, MA: Dyax Corp.; 2015.

Kaplan AP, Joseph K. The bradykinin-forming cascade and its role in hereditary angioedema. Ann Allergy Asthma Immunol. 2010;104(3):193-204.

Kenniston JA, Faucette RR, Martik D, Comeau SR, Lindberg AP, Kopacz KJ, et al. Inhibition of plasma kallikrein by a highly specific active site blocking antibody. J Biol Chem. 2014;289(34):23596-608.

Lei WT, Shyur SD, Huang LH, Kao YH, Lo CY. Type I hereditary angioedema in Taiwan -- clinical, biological features and genetic study. Asian Pac J Allergy Immunol. 2011;29(4):327-31.

Nordenfelt P, Dawson S, Wahlgren CF, Lindfors A, Mallbris L, Bjorkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. Allergy Asthma Proc. 2014;35(2):185-90.

Renne T, Gruber A. Plasma kallikrein: novel functions for an old protease. Thromb Haemost. 2012;107(6):1012-3.

Roche O, Blanch A, Caballero T, Sastre N, Callejo D, Lopez-Trascasa M. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. Ann Allergy Asthma Immunol. 2005;94(4):498-503.

Zuraw BL. Clinical practice. Hereditary angioedema. N Engl J Med. 2008;359(10):1027-36.

Zuraw BL, Banerji A, Bernstein JA, Busse PJ, Christiansen SC, Davis-Lorton M, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 Recommendations for the Management of Hereditary Angioedema Due to C1 Inhibitor Deficiency. J Allergy Clin Immunol Pract. 2013;1(5):458-67.

Zuraw BL, Bernstein JA, Lang DM, Craig T, Dreyfus D, Hsieh F, et al. A focused parameter update: Hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. J Allergy Clin Immunol. 2013;131(6):1491-1493 e25.

12 APPENDICES

Appendix 1 Study Activities Schedule

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

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

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

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

8. There is a ± 15 minute window for all vital signs. At study visits in which IMP is administered, vital signs including sitting or supine BP, HR, body temperature, and RR, will be obtained prior to dosing, 1 hour after dosing, and 2 hours after dosing for the first 4 doses with the ability to eliminate the 2 hour vitals for the remaining doses based on the discretion of the Investigator and the absence of safety signals.
9. Height and weight will be collected at the Screening visit only.
10. ECGs (single recordings) are collected at screening, baseline prior to Dose 1, Day 56, Day 144±1 day to capture the estimated C_{max} and Day 182. The ECG assessment at C_{max} on Day 144±1 day may be performed via at-home nurse or technician in lieu of a subject visit to the study site.
11. Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis.
12. Historical attack information will be collected at screening. During the study subjects (or caregivers, in the event the subject is < 18 years old or is incapacitated) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. Site personnel will also contact the subject once a week or at approximately 7 days after last contact with the subject during the run-in period and once between study visits or approximately 7 days after last contact with the subject during the treatment period in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not given through prior subject contact with the site.
13. Quality of life data will be obtained using the EuroQoL Group 5-Dimension (EQ5D) Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using the Angioedema-Quality of Life (AE-QoL) Questionnaire at pre-dose on Days 0, 28±3, 56±3, 98±3, 126±3, 154±3, and 182±3. An additional quality of life assessment (EQ5D and AE-QoL) will be conducted on Day 238±3 for subjects not entering OLE.
14. Subjects who rollover into the Open-Label Extension protocol (DX-2930-04) will provide consent by Day 182 and receive their first open-label dose following the completion of all DX-2930-03 assessments scheduled on Day 182. At the completion of these assessments, the subject will be discharged from DX-2930-03 and roll into the DX-2930-04 study.
15. Subjects who terminate from the study early will undergo (if possible) all of the assessments and procedures as Day 182 at their final study visit.

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
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.

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

	cells/hpf	cells/hpf		

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

(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.