Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

This supplement contains the following items:
1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.
Clinical Trial Protocol: DX-2930-02

Study Title: A Phase 1b, Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX-2930 in Hereditary Angioedema Subjects

Study Number: DX-2930-02

Study Phase: Phase 1b

Product Name: DX-2930

IND Number: 116647

EudraCT Number: 2013-005066-18

Indication: Hereditary Angioedema

Investigators: Multicenter

Sponsor: Dyax Corp.

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Date:

Original Protocol: 24 February 2014

Confidentiality Statement

This document is the property of Dyax Corp. The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed without the express written permission of Dyax unless required by federal or state law or regulations. Any person to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.
PROTOCOL SIGNATURE PAGE

Study Title: A Phase 1b, Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX-2930 in Hereditary Angioedema Subjects

Study Number: DX-2930-02

Final Date: 24 February 2014

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

Signed: ___________________________  Date: ___________________
Ryan Iarrobino
Senior Director, Clinical Development
55 Network Drive, Burlington, MA 01803

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in compliance with the Declaration of Helsinki, 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) or Ethics Committee (EC) and will fulfill all responsibilities for submitting pertinent information to the IRB/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: ___________________________

Confidential  Page 2 of 73
SYNOPSIS

Sponsor:
Dyax Corp

Name of Finished Product:
DX-2930 Drug Product (DP)

Name of Active Ingredient:
DX-2930 is a recombinant, Chinese hamster ovary (CHO) cell-expressed, fully human immunoglobulin G subclass 1 (IgG1), kappa light chain, monoclonal antibody.

Names of Inactive Ingredients:
Sodium phosphate, citric acid, histidine, sodium chloride, and Tween 80

Study Title:
A Phase 1b, Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX-2930 in Hereditary Angioedema

Study Number:
DX-2930-0

Study Phase: Phase 1

Study Location:
Approximately 12 study sites planned for U.S., Italy, and Jordan

Primary Objective(s):
To assess the safety and tolerability of multiple subcutaneous administrations of DX-2930 at different dose levels in hereditary angioedema (HAE) subjects.

Secondary Objective(s):
To characterize the pharmacokinetics (PK) of DX-2930 following multiple subcutaneous administrations at different dose levels.

Tertiary Objective(s):
- To assess the immunogenicity of DX-2930
- To evaluate pharmacodynamic (PD) effects of DX-2930 through exploratory biomarker assessments
- To conduct an exploratory assessment of the indirect effects of plasma kallikrein inhibition upon endogenous C1-inhibitor activity
- To conduct exploratory assessments to characterize HAE attacks and acute attack therapy usage during the study

Study Design:
This study is a Phase 1b, multi-center, randomized, double-blind, placebo-controlled, multiple ascending dose trial of subcutaneous administrations of DX-2930 in HAE subjects. Eligible subjects will be randomized to receive either active study drug or placebo within 3 dose cohorts (30, 100, and 300 mg), with each cohort consisting of 6 subjects. Cohorts will be dosed in a staggered, dose ascending fashion. For each dosing cohort, 4 subjects will be randomized to receive active drug and 2 subjects will be randomized to receive placebo.
Each subject within a dosing cohort will receive 2 doses of study drug, administered subcutaneously into the upper arm. The second dose will be administered 14 days following the first dose. When a cohort has completed dosing (including after the final nominal cohort of 300mg), a review will be conducted of the safety data from screening through 14 days after the second dose. Cumulative safety data from any earlier cohort will also be included in the review. This safety evaluation will be conducted by a dose escalation committee (DEC) and will include a review of all adverse events, vital signs, physical examinations, laboratories, and electrocardiograms (ECGs). Escalation to the next highest dosing cohort will proceed if there are no concerning safety signals.

A flexible dose escalation scheme will be used in this study that allows for modification of dose escalation if necessary to further characterize DX-2930 (such as for safety, PK, or exploratory assessments) and if supported by review of safety data from previous cohorts. This flexible dose escalation scheme allows for expansion of a current or prior cohort or intermediate doses higher or lower than the preceding dose to be studied in a subsequent cohort. This may result in adding subjects to receive specific dose levels and an increase in the total number of cohorts and/or subjects enrolled in the study. The flexible dose escalation scheme also allows further escalation to doses higher than 300 mg (up to a maximum of 400 mg) if necessary and if supported by cumulative safety results. This would require additional cohort(s), increasing the total number of subjects enrolled and extending the total study duration.

If subjects experience acute HAE attacks during the study, they will be permitted standard of care treatment as prescribed by their physician. Any subject experiencing an HAE attack (even if resolving or limited to prodromal symptoms) on Day 1 will have their scheduled visit postponed for at least 72 hours after their attack has resolved.

**Study Population:**
Eighteen (18) HAE subjects (4 active and 2 placebo subjects per cohort) will be enrolled nominally across 3 dosing cohorts. If necessary, the flexible dose escalation scheme will allow up to 18 additional subjects (12 active, 6 placebo) to be enrolled, for a maximum of 36 subjects treated in the study. Subjects will be enrolled only once and will not be included in subsequent dosing cohorts. Subjects who do not receive both doses of study drug may be replaced.

**Criteria for Inclusion:**
Each subject must meet the following criteria to be enrolled in this study:
1. At least 18 years of age 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).
   - C1 inhibitor (C1-INH) antigen or functional level < 40% of the normal level. Subjects with antigen or functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range and a family history consistent with HAE Type I or II. Test results must have been obtained within 5 years of enrollment.
   - Age at reported onset of first angioedema symptoms ≤ 30 years or a family history consistent with HAE Type I or II.
3. Experiencing ≥2 HAE attacks per year, with at least 1 attack in the past 6 months reported by the subject.
4. Willing and able to read, understand, and sign an informed consent form.
5. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception from the Screening Period through 30 days after the final study visit: progestin-only oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. Female subjects must agree to practice the above birth control methods for 30 days after the final study visit as a safety precaution.
6. 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.
7. Males with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study visit. All male subjects, including males who are surgically sterile (post vasectomy), must agree to practice the above birth control methods for 60 days from the final study visit as a safety precaution.

Criteria for Exclusion:
Subjects who meet any of the following criteria will be excluded from the study:
1. Any exposure to an investigational drug or device within 90 days prior to initial study treatment.
2. Any prior history of exposure within the past 5 years to a monoclonal antibody or recombinant protein bearing an Fc domain (such as a soluble receptor-Fc fusion protein).
3. Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1 inhibitor deficiency, HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or angioedema associated with urticaria.
4. Use of long-term prophylaxis for HAE (C1-INH used for long-term prophylaxis, attenuated androgens, or anti-fibrinolytics) within 90 days prior to initial study treatment.
5. Use of C1-INH for short-term prophylaxis and/or on-demand treatment for an HAE attack that exceeds a total of 30 days within the past 90 days prior to initial study treatment; any use of C1-INH within 7 days prior to initial study treatment.
6. Any exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 90 days prior to initial study treatment.
7. Any exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 90 days prior to initial study treatment.
8. Presence of an indwelling catheter.
9. Diagnosis of HIV.
10. Active liver disease (e.g., Acute or chronic hepatitis B or C, alcoholic or non-alcoholic steatohepatitis).
11. 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 > 1.5x upper limit of normal (unless subject has known Gilbert’s Syndrome).
12. History of substance abuse or dependence.
13. Pregnancy or breastfeeding.
14. Subject has any condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of study results).

**Test Product; Dose; and Mode of Administration:**
DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated in 30 mM sodium phosphate, 8.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Tween 80. All formulation components are compendial. Each vial contains a nominal concentration of 100 mg DX-2930 active ingredient in 1 mL solution. The test product will be administered by subcutaneous injection into the upper arm.

**Placebo; Dose; and Mode of Administration:**
Placebo consists of the inactive formulation of the test product: 30 mM sodium phosphate, 8.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, pH 6.0 with 0.01% Tween 80. For subjects randomized to receive placebo, the volume of placebo administered will be the same as the total volume for an active dose within the placebo subjects’ assigned dose cohort. Placebo will be administered by subcutaneous injection into the upper arm.

**Duration of Treatment:**
Subjects will receive a dose of blinded study drug on Study Day 1 and will be monitored at the study site through 4 hours post-dose. Subjects will receive their second administration of blinded study drug at the same dose on Study Day 15 and will be monitored again at the study site through 4 hours post-dose. Follow-up visits will occur through 15 weeks (105 ± 3 days) after the second dosing.

**Duration of Study:**
The total duration of study participation for each individual subject will be approximately 120 days from the time of enrollment.

**Prohibited Concomitant Treatments:**
Use of the following treatments will not be permitted during the study:
- Long-term prophylaxis for HAE (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 investigational drug or device.

**Safety Assessments:**
Safety assessments will include the following:
- Adverse events (AEs), including serious adverse events (SAEs).
- Vital signs, including sitting or supine blood pressure (BP), heart rate (HR), oral body temperature, and respiratory rate (RR).
- Physical examination.
- Clinical laboratory testing (hematology, clinical chemistry, coagulation and urinalysis).
• 12-Lead electrocardiogram (ECG).

**Pharmacokinetic Variables:**

Blood samples will be collected for the measurement of plasma DX-2930 concentration prior to study drug administration on Day 1 and on Days 2, 4 and 8. Additional blood samples will be obtained on Day 15 (prior to administration of the second dose of study drug) and on Days 16, 18, 22, 29±1, 36±1, 50±2, 64±2, 92±3 and 120±3. DX-2930 non-compartmental PK variable determinations will include maximum concentration in plasma (C\text{max}), time to reach C\text{max} in plasma (t\text{max}), and area under the curve from time 0 to last sample (AUC_{0-t}). Compartmental PK modeling will describe the PK of DX-2930 and generate underlying C\text{max}, t\text{max}, AUC, apparent clearance (CL/F), apparent volume of distribution (Vd/F) and terminal elimination half-life (t\text{\frac{1}{2}}).

**Immunogenicity Assessments:**

DX-2930 plasma anti-drug antibody determinations will be performed using blood samples collected at pre-dose on Day 1 and on Days 36±1, 64±2, 92±3, and 120±3.

**C1-INH Functional Assessments:**

As an exploratory assessment of the indirect effects of plasma kallikrein inhibition upon endogenous C1-INH activity, samples will be obtained for C1-INH functional testing. Blood samples will be collected at pre-dose on Day 1 and Day 15 (prior to treatment with the second dose of study drug). Additional blood samples will be obtained on Days 29±1, 36±1, 64±2, 92±3 and 120±3.

**Exploratory Biomarker Assessments:**

Samples will be obtained to evaluate the pharmacodynamic effects of treatment on plasma kallikrein activity. Blood samples will be collected at pre-dose on Day 1 and on Days 2, 4 and 8. Additional blood samples will be obtained on Day 15 (prior to treatment with the second dose of study drug) and on Days 16, 18, 22, 29±1, 36±1, 50±2, 64±2, 92±3 and 120±3.

**Exploratory Assessments to Characterize HAE Attacks and Acute Attack Treatment Usage:**

Prior to enrollment, HAE attack history will be collected by the Investigator. Information collected will include any prior history of laryngeal attacks, attack frequency, severity, location, duration, and acute attack therapy use.

In addition, subjects will be asked to report to their Investigator any HAE attacks they experience during the course of the study. Collection of clinical information regarding any such attacks will include attack location, severity, time of onset, duration, and treatment with any acute attack therapy. In addition, subjects will be encouraged, but not required, to come into the study site (maximum of 4 visits during the study, of which no more than 1 can be within the first 36 days following enrollment unless they occur at the same time as a planned study visit) for such attacks in order to have blood drawn for biomarker, C1-INH functional level, and PK testing. Subjects will be eligible to undergo this blood sample collection as long as they are assessed within 24 hours of symptom onset irrespective of any treatment they may have received for their attack. If the subject presents to the study site for an acute HAE attack during the study and it coincides with a scheduled study visit, the additional exploratory assessments and procedures (including blood draws) beyond what is already is scheduled will not be necessary for that visit.

Subjects will also be asked to report to their Investigator any use of acute attack treatment during the course of the study.

**Dose Escalation Rules:**
Adverse events will be reviewed in a blinded manner and graded using the 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). Dose-limiting toxicity (DLT) will be defined generally as clinically significant, severe (Grade 3) AEs occurring in ≥2 subjects that are determined to be related to DX-2930.

The following general rules regarding assessment of AEs and dose escalation will be followed:

a. If 1 subject in the cohort (6 total subjects) has a Grade 3 AE, no unblinding is necessary and escalation to the next dose cohort may proceed.

b. If 2 or more subjects in the cohort (6 total subjects) have Grade 3 AEs that are determined to be clinically significant and related to study drug, the Sponsor may break the blind to determine if the events occurred in DX-2930 recipients. Determination of clinical significance and relatedness and decisions regarding breaking the blind will be based on clinical judgment and experience. If the AEs occurred in subjects that received DX-2930, then the current dosing cohort may be expanded by an additional 3 (2 active + 1 placebo) or 6 (4 active + 2 placebo) subjects for further evaluation. If it is determined that it would not be safe to proceed with further treatments at that same dose level of DX-2930, then DLT is declared and no further treatments at that dose level may be recommended. Subsequent dosing may be modified to an intermediate dose that is lower than the current dosing cohort but higher than the prior cohort. Alternatively, depending on the nature of the AEs (i.e. degree of clinical significance, organ or system involved), escalation to a dose intermediate between the current and next planned dose level may be recommended. Otherwise, if there are no major safety concerns (e.g., both subjects with the Grade 3 AEs had received placebo), the dose escalation may proceed as planned.

c. If any subject experiences a life-threatening AE (Grade 4) that is study drug-related, and unblinding reveals that the subject had received DX-2930, any further dosing may be suspended pending thorough data review.

**Study Stopping Rules:**

The occurrence of a study drug-related SAE in any subject who is shown by unblinding to have received DX-2930 (see Section 5.4) may result in suspension of any further dosing in the study by the Medical Monitor until the DEC has evaluated the event and determined the next appropriate course of action. At any time during the study, the study may be discontinued if the DEC determines that further drug exposure would pose an undue risk to subjects.

**Individual Stopping Rules:**

Dosing for any individual subject will be discontinued (i.e. further treatment with the study medication will not be given) if the subject experiences a DX-2930-related SAE or a DX-2930-related, clinically significant non-serious AE that, in the opinion of the Investigator and Medical Monitor, warrants discontinuation from further dosing for that subject’s well-being. Any occurrence of a DX-2930-related clinically significant, severe (or Grade 3) toxicity may also terminate further dosing in a subject at the discretion of the Investigator and the Medical Monitor.

**Statistical Methods:**

All demographic, safety and PK data will be listed and summarized in tabular format using descriptive statistics for continuous variables and frequency and percentages for discrete variables. Missing data will not be imputed. Descriptive data will be tabulated to best represent
the baseline characteristics of the two prospectively enrolled randomized groups. Additional exploratory analyses may be performed. Non-compartmental methods will be used to generate actual $C_{\text{max}}$, $t_{\text{max}}$ and $AUC_{0-t}$. Compartmental PK methods will be used to generate predictions of $C_{\text{max}}$, $t_{\text{max}}$, $AUC$, $\text{CL/F}$, $V_d/F$, and $t^{1/2}$.

**Interim Analysis:**
An interim analysis of all subject data through at least Day 36 of the final cohort is planned by the Sponsor. This interim analysis will include all safety and subject information as well as any available and relevant PK, anti-drug antibody, and exploratory assessment data collected across all dosing cohorts. The final cohort is presumed to be the 300 mg cohort, unless the final dose level evaluated in the study is lower or higher than 300 mg. Unblinded, aggregate safety data will be reviewed across all dosing cohorts and by individual cohort to identify any safety signals. Available PK data, safety data, and results of exploratory analyses will be evaluated to guide selection of dose levels for the Phase 2 study. A blinded medical monitor will be retained to assess safety for the remainder of the study follow-up period.

**Date of Original Protocol:** 24 February 2014
# Study Activities Schedule

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<th>Days 29±1, 36±1, 50±2, 64±2, &amp; 92±3*</th>
<th>Final Visit Day 120±3 or ET Visit</th>
<th>Optional Study Site Visit(s) for Acute HAE Attack(s) During Study&lt;sup&gt;11&lt;/sup&gt;</th>
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### Tests and Assessments

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</table>

ECG = electrocardiogram; PK = pharmacokinetic; ET = early termination

*Note: During this outlined period (Day 29 through Day 92), physical examination, vital signs, and safety laboratory tests (hematology, coagulation, serum chemistry, and urinalysis) will occur on Days 29±1, 36±1, 64±2, and 92±3. During this period laboratory test for C1-INH Function will occur on Days 29±1, 36±1, 64±2 and 92±3. During this period, anti-drug antibody testing will be conducted on samples obtained on Days 36±1, 64±2, and 92±3. 12-lead ECG will be performed at Day36±1 during this outlined period.

1. Height, weight and calculation of BMI will be additional assessments conducted at this time point.
2. This physical examination will be abbreviated and include General, Skin, Cardiovascular, Pulmonary, Abdomen, and Extremities. (For Day 1 post-dosing and Day 15 post-dosing, this examination will occur at 4 hours ±15 minutes).
3. Documentation of vital signs including oral body temperature, HR, BP, and RR. On Day 1 post-dosing and Day 15 post-dosing, oral body temperature will not be collected.
4. Documentation of vital signs; HR , BP, and RR only at 1, 2, and 4 hours ±15 minutes.
5. CBC with differential
6. Includes INR, aPTT and PT
7. Includes total protein, albumin, glucose, alkaline phosphatase, bilirubin (total and direct), AST, ALT, GGT, LDH, uric acid, BUN, creatinine, calcium, sodium, potassium, chloride, CO2, phosphate, magnesium, cholesterol, triglycerides, CPK
8. Includes pH, glucose, ketones, blood, specific gravity, nitrite, protein, bilirubin and microscopy
9. C1 inhibitor (C1-INH) antigen or functional level < 40% of the normal level is required for entry into the study. Subjects with antigen or functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range and a family history consistent with HAE Type I or II. Test results must have been obtained within 5 years of enrollment. Following enrollment into the study, C1-INH functional levels will be collected at the outlined time points.
10. Serum or urine pregnancy test to be obtained at screening, prior to first dosing, and at Day 120 final visit or ET
11. Prior concomitant medications and procedures will be documented before dose administration. Concomitant medications and procedures will be assessed on a continual basis throughout the study
12. Pre-existing signs and symptoms will be captured prior to dosing. AEs will be assessed on a continual basis from the signing of the consent form and throughout the study
13. Clinical information related to historical HAE attacks will be obtained prior to dosing on Day 1. Clinical information related to any HAE attacks as well as any acute attack treatments occurring during the study will be obtained throughout the study
14. If the subject presents to the study site for an acute HAE attack during the study and it coincides with a scheduled study visit, the additional exploratory assessments and procedures (including blood draws), beyond what is already scheduled will not be necessary for that visit.
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Confidential
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<tr>
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<th>Definition</th>
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<tr>
<td>ACE</td>
<td>Angiotensin converting enzyme</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>aPTT</td>
<td>Activated partial thromboplastin time</td>
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<td>AST</td>
<td>Aspartate aminotransferase</td>
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<td>AUC</td>
<td>Area under the plasma concentration-time curve</td>
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<td>AUC(_{0-t})</td>
<td>AUC from time zero to the last quantifiable concentration in plasma at time t</td>
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<td>Body mass index</td>
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<td>BUN</td>
<td>Blood urea nitrogen</td>
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<td>C1-INH</td>
<td>C1 inhibitor</td>
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<td>CFR</td>
<td>Code of Federal Regulations</td>
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<td>CHO</td>
<td>Chinese hamster ovary</td>
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<td>CL/F</td>
<td>apparent total plasma clearance after extravascular administration</td>
</tr>
<tr>
<td>C(_{\text{max}})</td>
<td>Maximum plasma drug concentration</td>
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<tr>
<td>CO(_{2})</td>
<td>Carbon dioxide</td>
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<td>CPK</td>
<td>Creatine phosphokinase</td>
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<td>Clinical Trial Management System</td>
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<td>Electrocardiogram</td>
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<td>Electronic case report form</td>
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<tr>
<td>EDC</td>
<td>Electronic data capture</td>
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ET Early termination
FDA Food and Drug Administration
GCP Good Clinical Practice
GGT Gamma-glutamyl transferase
HAE Hereditary angioedema
HBsAg Hepatitis B surface antigen
HCV Hepatitis C virus
HED Human Equivalent Dose
HIPAA Health Information Portability and Accountability Act
HIV Human immunodeficiency virus
HR Heart rate
ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC Independent Ethics Committee
IgG1 Immunoglobulin G subclass 1
IMP Investigational medicinal product
IND Investigational New Drug
INR International normalized ratio
IRB Institutional Review Board
IUD Intrauterine device
IWRS Interactive Web-based Randomization System
Ki inhibition constant
LDH Lactate dehydrogenase
MABEL Minimum Anticipated Biological Effect Level
MCH Mean corpuscular hemoglobin
MCHC Mean corpuscular hemoglobin concentration
MCV Mean corpuscular volume
MedDRA Medical Dictionary for Regulatory Activities
MTD Maximum tolerated dose
PAP Pharmacokinetic Analysis Plan
<table>
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<td>Respiratory rate</td>
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<td>Serious adverse event</td>
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<td>SOP</td>
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<td>$t_{\frac{1}{2}}$</td>
<td>Terminal elimination half-life</td>
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<td>$t_{\max}$</td>
<td>Time to maximum plasma concentration</td>
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<td>TEAE</td>
<td>Treatment-Emergent Adverse Event</td>
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<tr>
<td>TT</td>
<td>Thrombin time</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>Vd/F</td>
<td>Apparent volume of distribution during terminal phase after extravascular administration</td>
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<tr>
<td>WBC</td>
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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 an autosomal dominant disorder that manifests clinically as intermittent, self-limited attacks of subcutaneous (SC or submucosal edema affecting the face, larynx, gastrointestinal tract, limbs or genitalia (Bork et al, 2006). Laryngeal attacks are the most serious as they are life-threatening due to the potential for airway compromise. HAE mortality has been estimated to be as high as 30% in undiagnosed individuals (Bork and Ressel, 2003). Abdominal attacks are often accompanied by severe pain and, in fact, can be mistaken for an acute abdomen with patients often undergoing unnecessary surgery due to their clinical presentation (Zuraw, 2008). Peripheral attacks can frequently be associated with considerable dysfunction and pain (Kusuma et al., 2012).

1.3 Therapeutic Rationale for DX-2930

Plasma kallikrein plays a critical role in the pathogenesis of HAE attacks (Morgan, 2010). In normal physiology, C1-inhibitor (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. 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 that is thought to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. Intervening to prevent bradykinin production with a plasma kallikrein inhibitor would therefore represent 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 the short-acting inhibitor, ecallantide, in the treatment of acute HAE attacks (KALBITOR® U.S. Package Insert).

DX-2930 is a highly potent (Ki = 125 pM) and specific inhibitor of plasma kallikrein. Furthermore, preclinical data in nonhuman primates suggest that DX-2930 will have a long half-life in humans. PK data from a Phase 1a clinical study involving single dose administration in healthy subjects corroborates these data. The mean half-life following a single subcutaneous dose of DX-2930 at 3 mg/kg was approximately 20 days (DX-2930 Investigator’s Brochure). Due to a potentially long half-life in HAE patients, DX-2930 might provide a long-acting and sustained pharmacologic effect. As a result, treatment with DX-2930 potentially may enable the suppression of plasma kallikrein activity to be maintained indefinitely and thereby prevent HAE attacks from even developing.

The DX-2930 development program will determine the safety and efficacy of DX-2930 in providing effective long-term prophylaxis against attacks of HAE. Data are available from a Phase 1a study of single subcutaneous doses of DX-2930 in healthy subjects. The present Phase 1b study will evaluate the safety, tolerability, and PK profile of multiple subcutaneous administrations of DX-2930 across a range of doses in HAE subjects.
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 clinical study support a wide safety margin in conjunction with data from the nonclinical toxicity studies. The mean $C_{\text{max}}$ for human subjects treated at the highest dose of 3 mg/kg was approximately 14.5 μg/ml. As comparison, a mean $C_{\text{max}}$ of 1310 μg/ml was observed following dosing of monkeys with 50 mg/kg DX-2930 SC weekly for 28 days. No toxicologically significant findings were observed in these treated animals or in any other nonclinical toxicity study to date. Thus, the drug exposure in the Phase 1b clinical study following two administrations of DX-2930 (up to a maximum of 400 mg) is predicted to be substantially less than that attained and evaluated in the nonclinical toxicity studies.

In addition, current knowledge regarding plasma kallikrein biology does not appear \textit{a priori} to predict any toxicity from plasma kallikrein inhibition. Plasma kallikrein is a drug target that has already been validated in humans through the clinical experience with ecallantide, a product approved by the FDA for treating HAE attacks in the United States. The safety of plasma kallikrein inhibition is further supported by the clinical presentation of Fletcher Factor Deficiency, a congenital condition characterized by a severe prekallikrein deficiency. As prekallikrein is the precursor from which plasma kallikrein is generated, plasma kallikrein is also severely deficient in cases of Fletcher Factor Deficiency. Individuals with this condition do not appear to suffer any clinical complications attributable to the defect (Renne et al, 2012).

The possibility of off-target effects with DX-2930 also appears unlikely. Experience with monoclonal antibodies overall indicates that off-target effects are rare and that toxicity from such therapeutic agents is usually related to on-target pharmacology (Muller et al, 2009). DX-2930 possesses high specificity for plasma kallikrein. \textit{In vitro} studies demonstrated that DX-2930 does not inhibit prekallikrein, the precursor for plasma kallikrein. DX-2930 does not inhibit numerous other serine proteases (tested at a maximum concentration of at least 1 μM) that are also resident in the extracellular environment.

For a summary of findings from the single dose, clinical study in healthy subjects and further details on the nonclinical findings, please refer to the DX-2930 Investigator’s Brochure.

1.5 Rationale for Multiple Dose Study of DX-2930 in HAE Subjects

The planned range of DX-2930 dosing for the clinical development program is based upon estimation of the level of plasma kallikrein inhibition necessary to attain effective prophylaxis against HAE attacks. The planned nominal doses in this Phase 1b study of 30, 100, and 300 mg (with a flexible dose escalation scheme up to a maximum of 400 mg) are believed to encompass the range of possibilities for which DX-2930 is anticipated to be therapeutically active.

Evaluation of this dose range in the Phase 1b study is necessary to assess the safety of multiple administrations of DX-2930 in HAE subjects prior to proceeding with the Phase 2 study, a parallel arm, dose-ranging study with long-term drug administration. The absence of dose-limiting toxicities observed in the single dose study support the progression to this multiple
ascending dose study. Pharmacokinetic and exploratory assessment data, including pharmacodynamic data, from the Phase 1b study will further refine the design of the dosing regimen in the Phase 2 study.

Information regarding the rationale for the study design, including selection of the starting dose is in Section 3.2.
2 STUDY OBJECTIVES

2.1 Primary Objective

To assess the safety and tolerability of multiple, subcutaneous administrations of DX-2930 at different dose levels in HAE subjects.

2.2 Secondary Objective

To characterize the pharmacokinetics (PK) of DX-2930 following multiple, subcutaneous administrations at different dose levels.

2.3 Tertiary Objectives

• To assess the immunogenicity of DX-2930

• To evaluate the pharmacodynamic (PD) effects of DX-2930 through exploratory biomarker assessments

• To conduct an exploratory assessment of the indirect effects of plasma kallikrein inhibition upon endogenous C1-inhibitor activity

• To conduct exploratory assessments to characterize HAE attacks and acute attack therapy usage during the study
3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Overview

This study is a Phase 1b, multi-center, randomized, double-blind, placebo-controlled, multiple ascending dose trial of subcutaneous administrations of DX-2930 in HAE subjects. Eligible subjects will be randomized 2:1 to receive either active study drug or placebo within a cohort. The study consists of 3 dose cohorts (30, 100, and 300 mg), with each cohort consisting of 6 subjects.

Cohorts will be dosed in a staggered, dose ascending fashion. For each dosing cohort, 4 subjects will be randomized to receive active drug and 2 subjects will be randomized to receive placebo. Each subject within a dosing cohort will receive 2 doses of study drug, administered subcutaneously into the upper arm. The second dose will be administered 14 days following the first dose. When a cohort has completed dosing, a review will be conducted of the safety data through 14 days after the second dose. Cumulative safety data from any earlier cohort will also be included in the review. This safety evaluation will be conducted by a dose escalation committee (DEC) and will include a review of all adverse events, vital signs, physical examinations, laboratories, and electrocardiograms (ECGs). Escalation to the next highest dosing cohort will proceed if there are no concerning safety signals.

A flexible dose escalation scheme will be used in this study that (based on review of safety data from previous cohorts) allows for expansion of a current or prior cohort or intermediate doses higher or lower than the preceding dose to be studied in a subsequent cohort. This may result in adding of subjects to receive specific dose levels and in an increase in the total number of cohorts and/or subjects enrolled in the study.

Blood samples for the measurement of plasma DX-2930 concentration will be obtained prior to administration of study drug and at specific time points following study drug administration (see Study Activities Schedule, Appendix 1).

If subjects experience acute HAE attacks during the study, they will be permitted standard of care treatment as prescribed by their physician. Any subject experiencing an HAE attack (even if resolving or limited to prodromal symptoms) on Day 1 will have their visit postponed for at least 72 hours after their attack has resolved.

3.1.2 Flexible Dose Escalation Scheme

The nominal dose escalation scheme will be 30, 100, and 300 mg. To facilitate efficient selection of the therapeutic dose(s) of DX-2930 to be studied in subsequent clinical trials and to make optimal use of the cohorts of subjects in this study while protecting their safety, a flexible scheme of dose escalation will be used. The flexible dose escalation approach requires that the safety data through the Day 29 visit for all subjects in a cohort be available for review by the Dose Escalation Committee (DEC) prior to escalation to the next highest dose. This review will be done using blinded data.

The flexible dose escalation scheme allows for modification of dose escalation if necessary to further characterize DX-2930 (such as for safety, PK, or exploratory assessments) and if
supported by review of safety data from previous cohorts. This scheme will allow for expansion of a current or prior dosing cohort, escalation to intermediate doses higher than the preceding dose, or de-escalation to intermediate doses lower than the preceding dose for evaluation in subsequent cohorts based on safety assessments by the DEC (Section 3.1.3). This strategy may require addition of subjects at specific dose levels, which may result in an increase in the total number of cohorts and/ or subjects enrolled in the study.

The flexible dose escalation scheme also allows further escalation to doses higher than 300 mg (up to a maximum of 400 mg) if necessary due to PK or PD reasons and if supported by safety results from an interim data review. This scheme also allows for expansion of the 300 mg cohort (or lower dose cohort) if necessary to further characterize DX-2930 (such as for safety, PK, or exploratory assessments) and if supported by review of safety data from previous cohorts. This safety review will be conducted after all subjects in the 300 mg cohort have been assessed through at least Day 29. Cumulative safety data from earlier cohorts will also be included in the review. In addition, any available and relevant PK or exploratory data, together with available PK data from the Phase 1a study, will be used to assess if a need exists to escalate beyond 300 mg and to confirm that the nonclinical toxicity data provide adequate safety margins.

3.1.3 Dose Escalation Committee (DEC) Safety Review

The DEC will consist of the Medical Monitor and the Dyax Medical Director. To assist in the safety assessments, the DEC may request that Investigators, other experts, or members within their organizations review the data and participate in the discussions.

Blinded safety data will be evaluated by the DEC at each dose escalation stage (safety data through 14 days after the second dose is administered [Day 29] to all subjects in the current cohort). This evaluation will include a review of AE/SAE reports, vital signs assessments, physical examinations, 12-lead ECGs and clinical laboratory testing. The seriousness, severity, and relatedness of adverse events (AEs)/serious adverse events (SAEs) will also be considered in the safety evaluation. (For definitions of AE, SAE, severe AE, and relatedness, please refer to Section 6.13). Cumulative safety data from any earlier cohort(s) will also be included in the review as needed.

Escalation to the next highest dosing cohort (Section 3.1.4) will only proceed if there are no safety concerns at the lower dose as determined by the DEC.

The DEC will also review the safety data, and any available and relevant PK or exploratory data, after all subjects in the 300 mg cohort have completed at least Day 29 follow-up to determine if escalation to doses higher than 300 mg or expansion of the 300 mg (or lower) dosing cohort is warranted.

3.1.4 Dose Escalation Rules

Adverse events will be reviewed in a blinded manner and graded using the 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). Dose-limiting toxicity (DLT) will generally be defined as clinically significant, severe (Grade 3) AEs occurring in ≥2 subjects that are determined to be related to DX-2930.
The following general rules regarding assessment of AEs and dose escalation will be followed:

a) If 1 subject in the cohort (6 total subjects) has a Grade 3 AE, no unblinding is necessary and escalation to the next dose cohort may proceed.

b) If 2 or more subjects in the cohort (6 total subjects) have Grade 3 AEs that are determined to be clinically significant and related to study drug, the Sponsor may break the blind to determine if the events occurred in DX-2930 recipients. Determination of clinical significance and relatedness and decisions regarding breaking the blind will be based on clinical judgment and experience. If the AEs occurred in subjects that received DX-2930, then the current dosing cohort may be expanded by an additional 3 (2 active + 1 placebo) or 6 (4 active + 2 placebo) subjects for further evaluation. If it is determined that it would not be safe to proceed with further treatments at that same dose level of DX-2930, then DLT is declared and no further treatments at that dose level may be recommended. Subsequent dosing may be modified to an intermediate dose that is lower than the current dosing cohort but higher than the prior cohort. Alternatively, depending on the nature of the AEs (i.e. degree of clinical significance, organ or system involved), escalation to a dose intermediate between the current and next planned dose level may be recommended. Otherwise, if there are no major safety concerns (e.g., both subjects with the Grade 3 AEs had received placebo), the dose escalation may proceed as planned.

c) If any subject experiences a life-threatening AE (Grade 4) that is study drug-related, and unblinding reveals that the subject had received DX-2930, any further dosing may be suspended pending thorough data review.

3.1.5 Study Stopping Rules

The occurrence of a study drug-related SAE in any subject who is shown by unblinding to have received DX-2930 (see Section 5.4) may result in suspension of any further dosing in the study by the Medical Monitor until the DEC has evaluated the event and determined the next appropriate course of action. At any time during the study, the study may be discontinued if the DEC determines that further drug exposure would pose an undue risk to subjects.

3.1.6 Individual Stopping Rules

Dosing for any individual subject will be discontinued (i.e. further treatment with the study medication will not be given) if the subject experiences a DX-2930-related SAE or a DX-2930-related, significant non-serious AE that, in the opinion of the Investigator and Medical Monitor, warrants discontinuation from further dosing for that subject’s well-being. Any occurrence of a DX-2930-related clinically significant, severe (or Grade 3) toxicity may also terminate further dosing in a subject at the discretion of the Investigator and the Medical Monitor.

3.1.7 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 Study Design and Control Group

The planned range of DX-2930 dosing for the clinical development program is based upon estimation of the level of plasma kallikrein inhibition necessary to attain effective prophylaxis against HAE attacks. It is hypothesized that the necessary molar concentration of DX-2930 will correspond to the average $C_{\text{max}}$ attained followed administration of Kalbitor (ecallantide) in treating acute HAE attacks. The EDEMA3 and EDEMA4 clinical trials demonstrated that a 30 mg SC dose of ecallantide is effective in the treatment of acute HAE attacks (KALBITOR® U.S. Package Insert). In principle, maintaining this level of plasma kallikrein inhibition continuously may prevent HAE attacks from occurring. According to this hypothesis, DX-2930 dosing to maintain steady state plasma concentrations above 80 nM will be necessary for HAE attack prophylaxis. Alternatively, a lower DX-2930 dose may be necessary if blockade of plasma kallikrein at an early stage when levels of plasma kallikrein activity are low could conceivably prevent the activation of a positive feedback loop. Conversely, a higher dose may be necessary if DX-2930 is not as potent as ecallantide in vivo in HAE patients.

As typical of most Phase 1 multiple dose studies, evaluation across a dose range that encompasses the anticipated therapeutic dose is planned for this DX-2930 multiple dose study in HAE subjects. Safety and PK data, together with PD and other exploratory data, will inform the design of a subsequent Phase 2 study to evaluate DX-2930 for long-term HAE prophylaxis.

A conservative starting dose of 30 mg per dose is planned for the present study, with escalation to 100 and then 300 mg in a flexible dose escalation scheme. Dose escalations will occur only after safety and tolerability data through 14 days after the second dose for all subjects in a cohort have been reviewed and after the DEC has confirmed that it would be safe to proceed to a higher dose. The study uses a placebo control for comparison of safety and other effects of DX-2930.

It is theoretically possible that 300 mg may still not provide adequate plasma kallikrein inhibition relevant to what is hypothesized as necessary as for HAE prophylaxis, either on a PK or PD basis. The flexible dose escalation scheme therefore allows escalation to doses higher than 300 mg (up to a maximum of 400 mg) if necessary and if supported by the cumulative safety results.

3.3 Study Duration

The duration of individual subject participation, from enrollment until final follow-up, will be approximately 120 days (17 weeks). Eligibility screening will be performed up to 28 days prior to Day 1 enrollment and first dosing. Subjects will receive the second dose on Day 15. After the second dose, follow-up visits for safety assessments and anti-drug antibody, PK, C1-INH and biomarker sampling will occur at regular intervals until the final study visit on Day 120.
4 STUDY POPULATION SELECTION

4.1 Study Population

Eighteen (18) HAE subjects (4 active and 2 placebo subjects per cohort) will be enrolled across 3 dosing cohorts. The flexible dose escalation scheme will allow, if necessary, enrollment of up to 18 additional subjects (12 active, 6 placebo) for a maximum of 36 subjects treated in the study. Subjects will be enrolled only once in the study and will not be included in subsequent dosing cohorts. Subjects who do not receive both doses of study drug may be replaced. Subjects who do not receive both doses of study drug will still continue to be followed through completion of all scheduled visits.

4.2 Inclusion Criteria

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

1. At least 18 years of age 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).
   - C1 inhibitor (C1-INH) antigen or functional level < 40% of the normal level. Subjects with C1-INH antigen or functional level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range and a family history consistent with HAE Type I or II. Test results must have been obtained within 5 years of enrollment.
   - Age at reported onset of first angioedema symptoms ≤ 30 years or a family history consistent with HAE Type I or II.
3. Experiencing ≥2 HAE attacks per year, with at least 1 attack in the past 6 months reported by the subject.
4. Willing and able to read, understand, and sign an informed consent form (ICF).
5. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception from the Screening Period through 30 days after the final study visit: progestin-only oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. Female subjects must agree to practice the above birth control methods for 30 days after the final study visit as a safety precaution.
6. 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.
7. Males with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study visit. All male subjects, including males who are surgically sterile (post
vasectomy), must agree to practice the above birth control methods for 60 days from the final study visit as a safety precaution.

4.3 Exclusion Criteria

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

1. Any exposure to an investigational drug or device within 90 days prior to initial study treatment.
2. Any prior history of exposure within the past 5 years to a monoclonal antibody or recombinant protein bearing an Fc domain (such as a soluble receptor-Fc fusion protein).
3. Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1 inhibitor deficiency, HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or angioedema associated with urticaria.
4. Use of long-term prophylaxis for HAE (use of C1-INH for long-term prophylaxis, attenuated androgens, or anti-fibrinolytics) within 90 days prior to initial study treatment.
5. Use of C1-INH for short-term prophylaxis and/or on-demand treatment for an HAE attack that exceeds a total of 30 days within the past 90 days prior to initial study treatment; any use of C1-INH within 7 days prior to initial study treatment.
6. Any exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 90 days prior to initial study treatment.
7. Any exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 90 days prior to initial study treatment.
8. Presence of an indwelling catheter.
9. Diagnosis of HIV.
10. Active liver disease (e.g., Acute or chronic hepatitis B or C, alcoholic or non-alcoholic steatohepatitis).
11. 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 > 1.5x upper limit of normal (unless subject has known Gilbert’s Syndrome).
12. History of substance abuse or dependence.
13. Pregnancy or breastfeeding.
14. Subject has any condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of study results).
5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

For detailed information regarding study drug 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 in 30 mM sodium phosphate, 8.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Tween 80. All formulation components are compendial. Each vial contains a nominal concentration of 100 mg DX-2930 active ingredient in 1 mL solution. The test product will be administered by subcutaneous injection into the upper arm.

Subjects randomized to receive active study drug will receive one of the pre-defined fixed doses (30, 100, or 300 mg) or an intermediate dose as defined by the DEC following a cohort safety evaluation (Section 3.1.3). If necessary and if supported by the DEC’s review of the cumulative safety data, dose escalation beyond 300 mg may occur (up to a maximum of 400 mg).

For the 30 mg cohort, each subject will receive 0.3 mL in a single SC injection; for the 100 mg cohort, each subject will receive 1 mL in a single SC injection; and for the 300 mg cohort, each subject will receive 3 mL, which may be divided into 2 separate SC injections. The vehicle for the solution will be the placebo (Section 5.1.2). If escalation to doses above 300 mg occurs, the doses will be divided such that no single SC injection consists of more than 2 mL. When more than one injection is required, the injections will be given in the same arm.

5.1.2 Placebo

Placebo consists of the inactive formulation of the test product: 30 mM sodium phosphate, 8.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, pH 6.0 with 0.01% Tween 80. For subjects randomized to receive placebo, the volume of placebo administered will be the same as the total volume for an active dose within the placebo subjects’ assigned dose cohort. Placebo will be administered by subcutaneous injection into the upper arm. When more than one injection is required, the injections will be given in the same arm.

5.2 Cohort Dosing

Eligibility screening will be performed up to 28 days prior to Day 1 enrollment and first dosing. Any subject experiencing an HAE attack (even if resolving or limited to prodromal symptoms) on Day 1 will have their visit postponed for at least 72 hours after their attack has resolved. Eligible subjects will be randomized to receive two doses of DX-2930 or placebo within one of the following sequential, ascending dose cohorts: 30, 100, or 300 mg. Subjects in this study can only be enrolled once and will not be included in subsequent dosing cohorts.

Subjects will receive the first dose of blinded study drug on Day 1 and will be monitored at the treatment site through 4 hours post-dose. Follow-up visits after the first dose will be made on Days 2, 4 and 8. Subjects will receive the second dose of study drug at the same dose on Day 15 and will be monitored at the treatment site through 4 hours post-dose. Follow-up visits after the second dose will occur on Days 16, 18, 22, 29±1, 36 ±1, 50 ±2, 64 ±2, 92 ±3, and 120 ±3. The
total duration of study participation for each individual subject will be up to 120±3 days from enrollment until the final follow-up visit (Study Activities Schedule, Appendix 1). Optional visits to the clinic (up to a maximum of 4 per subject, of which no more than 1 can be within the first 36 days following enrollment unless they occur at the same time as a planned study visit) may occur for evaluation of acute HAE attacks.

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 either 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

This is a randomized, double-blinded, placebo-controlled trial. Subjects will be randomized to receive either DX-2930 or placebo within each cohort. Subjects will be blinded to the treatment administered until enrollment is complete and the database is locked. Investigators and site personnel will be blinded to subject treatment until enrollment is complete and the database is locked. The sponsor will be blinded to the treatment administered through the completion of at least the Day 36 follow-up visit for the last subject in the final (300 mg) dosing cohort. At that point, an interim analysis of data through at least Day 36 will be conducted (Section 9.9). The sponsor will review the data in an unblinded fashion but a blinded medical monitor will be retained to assess safety for the remainder of the study follow-up period. If escalation to dose(s) higher than 300 mg occurs, the interim analysis may be deferred until all of the subjects at the highest dose complete through at least Day 36.

If necessary for the DEC’s safety evaluation, the Sponsor may break the blind to determine if adverse events occurred in DX-2930 recipients.

In the event of a drug-related SAE, the Investigator will contact and consult with the Medical Monitor regarding emergency unblinding of treatment assignment for the subject. The Investigator or the Medical Monitor can obtain the treatment assignment for the subject through the IWRS. In the event of a drug-related, serious, unexpected AE, the Dyax Pharmacovigilance Department may 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 within 30 days before administration of the first dose of study drug.

All information on concomitant therapy (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.
- 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 (use of C1-INH therapy 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 investigational drug or device

5.6 Restrictions

5.6.1 Medical Interventions

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

5.6.2 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

The two doses of study drug will be administered under the direct supervision of the Investigator or qualified site personnel designated by the Investigator.

5.8 Packaging and Labeling

The test products (active and placebo) will be supplied by Dyax Corp. 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 (2°C to 8°C/36°F to 46°F) in the carton and protected from light, in a securely locked area, accessible to authorized persons only, until needed for dose preparation. Qualified site personnel will inventory the investigational product received and will maintain records of disposition of the drug, including dates, quantity and use.

5.10 Investigational Product Retention at Study Site

The Investigator (or designee) is responsible for maintaining accurate accountability records of the investigational product throughout the clinical study. All study drug 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. Study drug accountability will be verified during on-site monitoring visits.

Upon the completion or termination of the study, and upon written authorization from the Sponsor, or its representative, all unused and/or partially used study drug 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 study drug have been established, and that appropriate records of the disposal are documented and maintained. No unused study drug may be disposed until fully accounted for by the Sponsor monitor (or designee).
6 STUDY PROCEDURES

6.1 Informed Consent

The ICF must be executed prior to performing any study related activities and must be approved by the reviewing institutional review board (IRB) or independent ethics committee (IEC). Informed consent 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 Demographics and Medical History

6.2.1 Demographics and General Medical History

Demographics (age, gender, race and ethnicity) and medical history will be obtained from the subject and recorded on the source document and eCRF. Medical history will capture the subject’s current medical status (current disease processes), past medical status (past disease processes), history of surgery, allergies and concomitant medications.

6.2.2 HAE Attack Information

Prior to enrollment, HAE attack history will be collected and recorded in the eCRF. Information collected by the Investigator will include any prior history of laryngeal attacks, attack frequency, severity, location, duration, and acute attack therapy use.

In addition, subjects will be asked to report to their Investigator any HAE attacks they experience during the course of the study. Collection of clinical information regarding any such attacks will include attack location, severity, time of onset, duration, and treatment with any acute attack therapy. In addition, subjects will be encouraged, but not required, to come into the study site (maximum of 4 visits during the study, of which no more than 1 can be within the first 36 days following enrollment unless they occur at the same time as a planned study visit) for such attacks in order to have blood drawn for biomarker, C1-INH functional level, and PK testing. Subjects will be eligible to undergo this blood sample collection as long as they are assessed within 24 hours of symptom onset irrespective of if they have received any treatment for their attack. If the subject presents to the study site for an acute HAE attack during the study and it coincides with a scheduled study visit, the additional exploratory assessments and procedures (including blood draws) beyond what is already is scheduled will not be necessary for that visit.

Subjects will also be asked to report to their Investigator any use of acute attack treatment during the course of the study.

6.3 Physical Examination

A complete physical examination including height, weight and calculation of Body Mass Index (BMI) will be performed by the Investigator or his/her qualified designee according to the Study Activities Schedule (Appendix 1. The findings of each examination will be recorded on the
source documents and eCRF. The physical examination will include the following body systems:

- General appearance
- Head, eyes, ears, nose, and throat
- Neck
- Respiratory
- Cardiovascular
- Abdomen
- Neurologic
- Extremities
- Dermatologic
- Lymphatic

### 6.4 Vital Signs

Vital signs will be performed 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 oral 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.

### 6.5 Electrocardiography (ECG)

#### 6.5.1 12-Lead Electrocardiograms

A standard 12-lead ECG 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.

### 6.6 Clinical Laboratory Tests

#### 6.6.1 Laboratory Parameters

Laboratory testing (hematology, coagulation, urinalysis, serum chemistry, serologies, pregnancy tests, C1-INH antigen, C1-INH functional assay, C4, PK samples, and plasma anti-drug antibody testing) will be performed using established methods. In addition, blood samples will be obtained for exploratory laboratory biomarker assays to evaluate PD effects upon plasma kallikrein activity. Laboratory testing will be performed according to the Study Activities Schedule (Appendix 1). 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, PK, exploratory biomarker, anti-drug antibodies. Aliquots from the PK, biomarker 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 completes the study at Day 120, without any optional
study site visits for acute HAE attacks, will be 400.1 mL. Up to an additional 81.6 mL could be
drawn for any subject who agrees to come to the study site for an acute HAE attack (up to a
maximum of 4 times during the study, of which no more than 1 can be within the first 36 days
following enrollment unless they occur at the same time as a planned study visit). Please refer to
the Laboratory Manual for more information.

Laboratory testing will include the following as in the Study Activities Schedule (Appendix 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

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

**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)
- Gamma-glutamyl transferase (GGT)
• Glucose
• Lactate dehydrogenase (LDH)
• Phosphate
• Magnesium
• Potassium
• Sodium
• Total cholesterol
• Total protein
• Triglycerides
• Uric acid

**Urinalysis**
• Bilirubin
• Glucose
• Ketones
• Blood
• Nitrite
• pH
• Protein
• Specific gravity
• Microscopy (if urinalysis is abnormal)

**Serologies**
• HBsAg, HCV, and HIV

**Pregnancy Test**
• Serum or urine pregnancy test

**C1-INH Antigen and Functional Assay**
• Results of a C1-INH antigen or functional assay are required for eligibility assessment (test results must have been obtained within 5 years of enrollment). In addition, C1-INH functional levels will be collected during the study as an exploratory assessment of the indirect effects of plasma kallikrein inhibition upon endogenous C1-inhibitor activity (Section 6.9).

**C4 Assay**
• C4 is required for eligibility assessment (must be lower than the normal range and obtained within 5 years of enrollment) for subjects with C1-INH antigen or functional level 40-50% of the normal level and a family history consistent with HAE Type I or II (Section 6.10).

**PK Sample Collection**

• As outlined in Section 6.8.

**Plasma Anti-Drug Antibody Testing**

• As outlined in Section 6.11.

**Exploratory Biomarker Sample Collection**

• As outlined in Section 6.12.

6.6.2 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.

6.7 Dispensing Study Drug

Instructions for preparation of each subcutaneous dose of study drug are provided in the Pharmacy Manual. The Principal Investigator or qualified site personnel will administer the assigned study drug. Information regarding administration of study drug is provided in the Pharmacy Manual.

Preparation and dispensing of the study drug will be handled by qualified site personnel as directed by the Principal Investigator at the study site. Instructions for safe handling of the study drug are provided in the Pharmacy Manual. The requirements for maintaining drug accountability are provided in Section 5.9 of this protocol.

6.8 Pharmacokinetic Assessments

Blood samples for the measurement of plasma DX-2930 concentration will be obtained according to the schedule in Table 1.
### Table 1: Schedule of PK Sample Collection

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Study Drug Administration</th>
<th>PK Collection Timepoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Day 1</td>
<td>Single SC dose of DX-2930 or placebo</td>
<td>Pre-dose</td>
</tr>
<tr>
<td>Study Day 2</td>
<td>No dosing</td>
<td>Once at 24 ±2 hours post-dose</td>
</tr>
<tr>
<td>Study Day 4</td>
<td>No dosing</td>
<td>Once at 72 ±4 hours post-dose</td>
</tr>
<tr>
<td>Study Day 8</td>
<td>No dosing</td>
<td>Once on Study Day 8, 7 days ±6 hours from time of dosing on Day 1</td>
</tr>
<tr>
<td>Study Day 15</td>
<td>Single SC dose of DX-2930 or placebo</td>
<td>Pre-dose</td>
</tr>
<tr>
<td>Study Day 16</td>
<td>No further dosing</td>
<td>Once at 24 ±2 hours post-dose</td>
</tr>
<tr>
<td>Study Day 18</td>
<td>No further dosing</td>
<td>Once at 72 ±4 hours post-dose</td>
</tr>
<tr>
<td>Study Day 22</td>
<td>No further dosing</td>
<td>Once on Study Day 22, 7 days ±6 hours from time of dosing on Day 15</td>
</tr>
<tr>
<td>Study Days 29-92</td>
<td>No further dosing</td>
<td>Days 29 ±1, 36 ±1, 50 ±2, 64 ±2, and 92 ±3</td>
</tr>
<tr>
<td>Study Day 120 or ET</td>
<td>No further dosing</td>
<td>Day 120 ±3 or ET visit</td>
</tr>
</tbody>
</table>

DX-2930 PK non-compartmental parameter determinations following dosing on Days 1 and 15 will include:
- $C_{\text{max}}$
- $t_{\text{max}}$
- $AUC_{0-t}$

DX-2930 PK compartmental modeling parameter determinations following dosing on Days 1 and 15 will include:
- $C_{\text{max}}$
- $t_{\text{max}}$
- $AUC$
- $t_{1/2}$
- $Vd/F$
- $CL/F$

The PK analysis will be described in a separate Pharmacokinetic Analysis Plan.
6.9  **C1-INH Antigen and Functional Assay**

Results of a C1-INH antigen or functional assay are required at Screening for eligibility assessment. Test results must have been obtained within 5 years of enrollment or a new assay must be performed for Screening.

In addition, blood samples for an exploratory assessment of the indirect effects of plasma kallikrein inhibition upon endogenous C1-INH activity will be obtained by assaying C1-INH functional levels during the study. Blood samples for assay will be collected at pre-dose on Day 1 and Day 15 (prior to treatment with the second dose of study drug). Additional blood samples will be obtained on Days 29±1, 36±1, 64±2, 92±3 and 120±3. See the Study Activities Schedule (Appendix 1).

6.10  **C4 Assay**

Results of C4 assay are required at Screening for eligibility assessment for subjects with C1-INH antigen or functional level 40-50% of normal level and a family history consistent with HAE Type I or Type II. Test results must have been obtained within 5 years of enrollment or a new assay must be performed for Screening. See the Study Activities Schedule (Appendix 1).

6.11  **Plasma Anti-Drug Antibody Testing**

Plasma samples for testing for formation of antibodies to DX-2930 will be obtained at pre-dose on Day 1 and on Days 36 ±1, 64 ±2, 92 ±3, and the final study visit at Day 120 ±3 (or early termination).

6.12  **Exploratory Biomarker Testing**

To evaluate the pharmacodynamic effects of DX-2930 upon plasma kallikrein activity, blood samples will be collected at timepoints prior to and after study drug administration for exploratory biomarker assessments. These blood samples will be collected on the same schedule as for PK sample collection shown in Table 1 (Section 6.8).

6.13  **Adverse Event Reporting**

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

6.13.1  **Definitions**

6.13.1.1  **Adverse Event**

An AE is any untoward medical occurrence in a clinical trial subject that does not necessarily have a causal relationship with the treatment administered. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.
• AEs may be new events or may be pre-existing conditions that have become aggravated or have worsened in severity or frequency.
• 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 study drug interruption or discontinuation, will be considered an 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 6.13.5.2.

6.13.1.2 Serious Adverse Event

A SAE is any adverse experience occurring at any dose that results in any of the following outcomes:
• Death
• Life-threatening experience; Note: “Life-threatening” refers to a situation in which the subject was at risk of death at the time of the event; it does not refer to an event that might have caused death if it were more severe.
• Requires inpatient hospitalization or prolongation of existing hospitalization; Note: Does not include hospitalization for observation with release within 24 hours. A scheduled hospitalization for a pre-existing condition that has not worsened during participation in the study does not meet this criterion. Pre-planned hospitalizations for an elective medical/surgical procedure or routine check-ups do not meet this criterion.
• Results in persistent or significant disability or incapacity.
• Is a congenital anomaly or birth defect.
• Is considered to be an important medical event; Note: Important medical events are 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.

6.13.1.3 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.
6.13.1.4 Planned Hospitalization

A hospitalization planned by the subject prior to the first dose of study medication 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.

6.13.1.5 Treatment-Emergent Adverse Events (TEAE)

An AE is treatment-emergent if the onset time is after administration of study drug through the Day 120 post dose final follow-up visit or, in the event that onset time precedes study drug administration, the AE increases in severity during the 120 day post dose follow-up period.

6.13.2 Monitoring

6.13.2.1 Monitoring of Adverse Events

Each subject will be monitored for the occurrence of AEs, including SAEs, from signing of the ICF through final follow-up on Day 120 ±3 days post dose.

- 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.

6.13.2.2 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.

6.13.3 Assessment of Adverse Events

6.13.3.1 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). 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 (<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

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.

6.13.3.2 Assessment of Causality

A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product, 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 drug exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of the investigational product.
- The AE resolved or improved with decreasing the dose or stopping use of the investigational product (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between the study medication 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 study medication); 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 study medication); 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 investigational product).

### 6.13.3.3 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 DEC for overall study AE review. Before each escalation to the next highest dosing cohort, a review of all safety data through 14 days following the second dose of study drug (Day 29) will be conducted by the DEC. Dose escalation will only proceed if the DEC has determined that it would be safe and appropriate to do so.

### 6.13.4 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 study drug interruption or discontinuation, will be considered an AE.

When laboratory abnormalities are considered to be AEs, the DMID Adult Toxicity Table (Appendix 2) 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, 2012). Despite the lack of clinical effect, deficiency of either protein is associated with marked prolongation of the aPTT.

6.13.5 Reporting Investigator Safety Observations to the Sponsor

6.13.5.1 Reporting Non-serious Adverse Events

All AEs, regardless of seriousness, severity, or causal relationship to study medication, will be recorded on the AE page of the eCRF.

6.13.5.2 Reporting Pregnancies

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

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

6.13.5.3 Safety Observations Requiring Expedited Reporting by the Investigator to Dyax

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

- SAE
- Overdose
- Cancer

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

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

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

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

6.13.5.4 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.

6.13.5.5 Safety Contact Information

24-Hour Medical Safety Contact
J. Gordon Still, MD, PhD
Medical Monitor
Phone (US): (919) 245-5531
Email: gordon.still@aptivsolutions.com

Dyax Pharmacovigilance Department
Contacts: Marianne Reardon or Aimee Jackman
Email: drugsafety@dyax.com
Phone (US): (617) 250-5588

6.13.5.6 Safety Notifications by the Sponsor to the Investigator

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

6.13.5.7 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 Dyax Pharmacovigilance Department may
unblind the treatment of any subject.

6.14 Prior and Concomitant Medication Assessments

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 within 30 days before study entry and during the study will be regarded as concomitant
medications and must be documented on the source document and eCRF following informed
consent.
6.15 Subject Withdrawal

Subjects who do not receive both doses of study drug may be replaced. The Investigator may withdraw a subject from the trial for any of the following reasons:

- A protocol violation occurs,
- 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.

The criteria used by the DEC regarding dose administration suspension and/or study discontinuation as well as the DEC criteria for dose escalation suspension and/or discontinuation are provided in Section 3.1.

6.16 Appropriateness of Measurements

This is a Phase 1b double-blind, randomized, placebo-controlled multiple ascending dose study that is designed to evaluate the safety, tolerability and PK of multiple doses of DX-2930 in HAE subjects. 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 safety profiles of an active and placebo treatment when administered to subjects. All of the safety measures employed in this protocol are standard measures routinely used for the evaluation of the 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 Visit (Day -28 to Day -1)

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

- Informed consent (Section 6.1)
- Eligibility review (Section 4.2 and Section 4.3)
- Demographics and medical history (Section 6.2)
- Complete physical examination (Section 6.3) including documentation of height, weight and calculation of BMI
- Vital signs including oral body temperature, HR, BP and RR (Section 6.4)
- 12-Lead ECG (Section 6.5)
- Laboratory testing including HBsAg, HCV, and HIV screening, serum or urine pregnancy test (females), hematology, coagulation, serum chemistry and urinalysis (Section 6.6)
- If historical results are not within the past 5 years, C1-INH antigen or functional assay sample collection (Section 6.9)
- If historical results are not within the past 5 years, C4 assay sample collection (results of C4 assay are required for eligibility assessment only for subjects with C1-INH antigen or functional level 40-50% of the normal level and a family history consistent with HAE Type I or II) (Section 6.10)
- Prior and concomitant therapy (Section 6.14)
- AE Collection (Section 6.13); pre-existing signs and symptoms

7.2 Enrollment and First Treatment (Day 1)

The following procedures and assessments are to be performed at Enrollment on Day 1 prior to the first dose of study drug administration:

- Eligibility review (Section 4.2 and Section 4.3)
- Complete physical examination (Section 6.3)
- Vital signs including oral body temperature, HR, BP and RR (Section 6.4)
- 12-Lead ECG (Section 6.5)
- Laboratory testing including serum or urine pregnancy test (females), hematology, coagulation, serum chemistry and urinalysis (Section 6.6)
- C1-INH functional assay sample collection (Section 6.9)
• PK baseline sample collection (Section 6.8)
• Exploratory biomarker sample collection (Section 6.12)
• Plasma anti-drug antibody testing (Section 6.11)
• Prior and concomitant therapy (Section 6.14)
• AE collection (Section 6.13)
• HAE attack information (Section 6.2)
• Randomization to DX-2930 or placebo

After the preceding procedures and assessments are completed:
• Administer study drug (Section 5.2)

After administration of study drug, the following post treatment procedures and assessments will be performed:
• Abbreviated physical examination to include general, skin, cardiovascular, pulmonary, abdomen and extremities (Section 6.3) at 4 hours ±15 minutes post-dose
• Vital signs including HR, BP and RR (Section 6.4) at 1, 2, and 4 hours ±15 minutes post-dose
• Concomitant therapy (Section 6.14)
• AE collection (Section 6.13)

7.3 Follow-up: Day 2

On Day 2, the following procedures and assessments will be performed at approximately 24 ±2 hours following administration of study drug on Day 1:
• Concomitant therapy (Section 6.14)
• AE collection (Section 6.13)
• HAE attack information (Section 6.2)
• PK sample collection (Section 6.8)
• Exploratory biomarker sample collection (Section 6.12)

7.4 Follow-up: Day 4

On Day 4, the following procedures and assessments will be performed at approximately 72 ±4 hours following administration of study drug on Day 1:
• Concomitant therapy (Section 6.14)
• AE collection (Section 6.13)
• HAE attack information (Section 6.2)
PK sample collection (Section 6.8)

Exploratory biomarker sample collection (Section 6.12)

7.5 Follow-up: Day 8

On Day 8, the following procedures and assessments will be performed at approximately 7 days ±6 hours from the time of dosing on Day 1:

- Complete physical examination (Section 6.3)
- Vital signs including oral body temperature, HR, BP and RR (Section 6.4)
- 12-Lead ECG (Section 6.5)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.6)
- PK sample collection (Section 6.8)
- Exploratory biomarker sample collection (Section 6.12)
- Concomitant therapy (Section 6.14)
- AE collection (Section 6.13)
- HAE attack information (Section 6.2)

7.6 Day 15 Second Dosing

The following procedures and assessments are to be performed on Day 15 prior to the dose of study drug administration:

- Complete physical examination (Section 6.3)
- Vital signs including oral body temperature, HR, BP and RR (Section 6.4)
- 12-Lead ECG (Section 6.5)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.6)
- C1-INH functional assay sample collection (Section 6.9)
- PK sample collection (Section 6.8)
- Exploratory biomarker sample collection (Section 6.12)
- Concomitant therapy (Section 6.14)
After the preceding procedures and assessments are completed:

- Administer study drug (Section 5.2)

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

- Abbreviated physical examination to include general, skin, cardiovascular, pulmonary, abdomen and extremities (Section 6.3) at 4 hours ±15 minutes post-dose
- Vital signs including HR, BP and RR (Section 6.4) at 1, 2, and 4 hours ±15 minutes post-dose
- Concomitant therapy (Section 6.14)
- AE collection (Section 6.13)

### 7.7 Follow-up: Day 16

On Day 16, the following procedures and assessments will be performed at approximately 24 ±2 hours following administration of study drug on Day 15:

- Concomitant therapy (Section 6.14)
- AE collection (Section 6.13)
- HAE attack information (Section 6.2)
- PK sample collection (Section 6.8)
- Exploratory biomarker sample collection (Section 6.12)

### 7.8 Follow-up: Day 18

On Day 18, the following procedures and assessments will be performed at approximately 72 ±4 hours following administration of study drug on Day 15:

- Concomitant therapy (Section 6.14)
- AE collection (Section 6.13)
- HAE attack information (Section 6.2)
- PK sample collection (Section 6.8)
- Exploratory biomarker sample collection (Section 6.12)
7.9 **Follow-up: Day 22**

On Day 22, the following procedures and assessments will be performed at approximately 7 days ±6 hours from the time of dosing on Day 15:

- Complete physical examination (*Section 6.3*)
- Vital signs including oral body temperature, HR, BP and RR (*Section 6.4*)
- 12-Lead ECG (*Section 6.5*)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (*Section 6.6*)
- PK sample collection (*Section 6.8*)
- Exploratory biomarker sample collection (*Section 6.12*)
- Concomitant therapy (*Section 6.14*)
- AE collection (*Section 6.13*)
- HAE attack information (*Section 6.2*)

7.10 **Follow-up Visits: Days 29 ±1, 36 ±1, 50 ±2, 64 ±2, and 92 ±3**

The following procedures and assessments will be performed during the subject’s scheduled study visit:

- Complete physical examination only on Days 29 ±1, 36 ±1, 64 ±2, and 92 ±3 (*Section 6.3*)
- Vital signs including oral body temperature, HR, BP and RR only on 29 ±1, 36 ±1, 64 ±2, and 92 ±3 (*Section 6.4*)
- 12-Lead ECG only on Day 36 ±1 (*Section 6.5*)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis only on Days 29 ±1, 36 ±1, 64 ±2, and 92 ±3 (*Section 6.6*)
- C1-INH functional assay sample collection only on Days 29 ±1, 36 ±1, 64 ±2, and 92 ±3 (*Section 6.9*)
- PK sample collection on Days 29 ±1, 36 ±1, 50 ±2, 64 ±2, and 92 ±3 (*Section 6.8*)
- Exploratory biomarker sample collection on Days 29±1, 36±1, 50±2, 64±2, and 92±3 (*Section 6.12*)
- Plasma anti-drug antibody testing on Days 36±1, 64±2, and 92±3 (*Section 6.11*)
• Concomitant therapy (Section 6.14)

• AE collection (Section 6.13)

• HAE attack information (Section 6.2)

7.11 Optional Study Site Visit for Acute HAE Attack(s) During Study

If the subject presents to the study site for an acute HAE attack during the study and it coincides with a scheduled study visit, the additional exploratory assessments and procedures (including blood draws) beyond what is already is scheduled will not be necessary for that visit. The following procedures and assessments will be performed during the subject’s optional study visit:

• Abbreviated physical examination to include general, skin, cardiovascular, pulmonary, abdomen and extremities (Section 6.3)

• Vital signs including oral body temperature, HR, BP and RR (Section 6.4)

• C1-INH functional assay sample collection (Section 6.9)

• PK sample collection (Section 6.8)

• Exploratory biomarker sample collection (Section 6.12)

• Concomitant therapy (Section 6.14)

• AE collection (Section 6.13)

• HAE attack information (Section 6.2)

7.12 Final Follow-up Visit: Day 120 ±3 or Early Termination Visit

The following procedures and assessments will be performed during the subject’s final follow-up or early termination (ET) visit:

• Complete physical examination (Section 6.3)

• Vital signs including oral body temperature, HR, BP, and RR (Section 6.4)

• 12-Lead ECG (Section 6.5)

• Laboratory testing including serum or urine pregnancy test (females), hematology, coagulation, serum chemistry and urinalysis (Section 6.6)

• C1-INH Functional assay sample collection (Section 6.9)

• PK sample collection (Section 6.8)
• Exploratory biomarker sample collection (Section 6.12)
• Plasma anti-drug antibody testing (Section 6.11)
• Concomitant therapy (Section 6.14)
• AE collection (Section 6.13)
• HAE attack information (Section 6.2)
• Discharge from study
8 QUALITY CONTROL AND ASSURANCE

The Sponsor (Dyax) and the Contract Research Organization (CRO) conducting trial management services (Aptiv Solutions) will implement a system of quality assurance that includes all elements described in this protocol. Within this system, SOPs from the Sponsor and Aptiv Solutions 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 PLANNED STATISTICAL METHODS

This is a Phase 1b safety, tolerability, and PK study of DX-2930 in HAE subjects. The study includes exploratory analyses of PD effects of DX-2930 on plasma kallikrein concentrations, indirect effects of plasma kallikrien inhibition on endogenous C1-INH activity and characterization of HAE attacks and acute therapy use by subjects while on study. A Statistical Analysis Plan (SAP) and a Pharmacokinetic Analysis Plan (PAP) will be finalized prior to database lock.

9.1 General Considerations

Data will be described and analyzed using the SAS System, Version 9.3 or greater (SAS Institute Inc., Cary, NC, SAS System). Individual subject data will be presented in subject data listings. Descriptive statistics including number of subjects (N), mean, standard deviation (SD), median, and minimum and maximum will be presented for continuous data. For categorical data, frequency and percentage of subjects in each category will be presented.

All demographic and safety data will be listed and summarized in tabular format using descriptive statistics for continuous variables and frequency and percentages for discrete variables. Missing data will not be imputed. Descriptive data will be tabulated to best represent the baseline characteristics of the prospectively enrolled randomized treatment groups. Additional exploratory analyses may be performed.

9.2 Determination of Sample Size

Approximately 18 to 36 HAE subjects will be enrolled across multiple clinical sites according to the flexible dose escalation scheme (Section 3.1.2). The estimated sample size has been chosen to provide adequate numbers of subjects to characterize the safety, tolerability, and PK of DX-2930. Overall, the total number of subjects evaluated will depend on the emerging DX-2930 safety and PK profile as determined by the DEC. Depending on DEC findings, the number of subjects may be expanded by the addition of subjects within a dosing cohort or inclusion of additional dose cohorts at intermediate doses or at dose(s) higher than 300 mg in order to further characterize DX-2930.

9.3 Analysis Populations

All safety analyses will be based on the Safety Population, which includes randomized subjects who received at least one dose of study drug.

The PK data analysis will be based on the PK Population, which includes the subjects in the Safety Population who have sufficient blood samples to obtain a plasma concentration vs. time profile.

9.4 Disposition of Subjects

The number and percentage of subjects entering and completing the clinical study will be presented, stratified by dose group.
9.5 Demographics and Baseline Characteristics

All demographic and baseline characteristic data will be listed and summarized in tabular format using descriptive statistics for continuous variables and frequency and percentages for discrete variables.

9.6 Statistical Analysis of PK Variables

DX-2930 plasma level determinations will be performed using blood samples collected at pre- and post-dosing through the final follow-up visit (Day 120). These determinations will be used to calculate the multiple dose PK profiles for each dose level administered. Non-compartmental methods will allow calculation of $C_{\text{max}}$, $t_{\text{max}}$, and $AUC_{0-t}$ during the sample collection period. Compartmental PK models will be generated to describe the underlying PK behavior of DX-2930 based on data after both doses. Compartmental PK predictions will include $C_{\text{max}}$, $t_{\text{max}}$, AUC, $Vd/F$, $CL/F$, and $t\frac{1}{2}$ as appropriate. Individual and summary PK parameters will be listed and summarized in tabular format using descriptive statistics for continuous variables and frequency and percentages for discrete variables. Missing data will not be imputed.

9.7 Safety Analysis

Safety measures include AEs, clinical laboratory tests, physical examinations, ECG determinations and vital signs. The Medical Dictionary for Regulatory Activities (MedDRA) (most recent version) coding system will be used for System Organ Class (SOC) and preferred term classification of AEs. All safety data will be listed and summarized in tabular format using descriptive statistics for continuous variables and frequency and percentages for discrete variables.

9.7.1 Adverse Events

The proportion of participants experiencing AEs and SAEs for DX-2930 or placebo will be computed by dose received and overall. Proportions will be computed for all events and for related events only, and for both AEs and SAEs separately and together.

9.7.2 Clinical Laboratory Tests

Individual data listings of laboratory results will be presented for each subject. Flags will be attached to values outside of the laboratory’s reference limits along with the Investigator’s assessment. Clinically significant worsening from baseline or new clinically significant laboratory test abnormalities that were considered AEs by the Investigator will be presented in the AE analyses. Clinical laboratory tests (observed values) will be summarized descriptively in tabular format. Shift tables will be presented for select laboratory parameters (chemistry and hematology).

9.7.3 Physical Examinations

Abnormal physical examination findings will be listed. Clinically significant worsening from baseline or new clinically significant physical examination abnormalities that were considered AEs by the Investigator will be presented in the AE analyses.
9.7.4 Vital Signs

Individual data listings of vital signs (observed and change from baseline) will be presented for each subject. Clinically significant worsening from baseline or new clinically significant vital sign findings that were considered AEs by the Investigator will be presented in the AE analyses. Observed values as well as change from baseline data will be summarized descriptively in tabular format.

9.7.5 Electrocardiogram

Twelve-lead ECG data (observed and change from baseline) will be listed for each subject and time point. Observed values as well as change from baseline will be summarized descriptively in tabular format. Clinically significant worsening from baseline or new clinically significant ECG abnormalities that were considered AEs by the Investigator will be presented in the AE analyses.

9.7.6 Anti-drug Antibody Testing

DX-2930 plasma anti-drug antibody data will be listed and summarized in tabular format using descriptive statistics.

9.8 Other Assessments or Analyses

Exploratory analyses may be performed to evaluate PD effects of DX-2930 through exploratory biomarkers and to characterize HAE attacks and acute attack therapy usage occurring during the study. In addition, an exploratory assessment of the indirect effects of plasma kallikrein inhibition upon endogenous C1-INH activity may be performed.

9.9 Interim Analysis

In preparation for a subsequent Phase 2 study (dose-ranging and proof of concept study in HAE subjects), an interim analysis of all subject data through at least Day 36 of the final cohort is planned by the Sponsor. This interim analysis will include all safety and subject information as well as any available and relevant PK, anti-drug antibody, and exploratory assessment data collected across all dosing cohorts. The final cohort is presumed to be the 300 mg cohort, unless the final dose level evaluated in the study is lower or higher than 300 mg.

Aggregate, unblinded safety data will be reviewed across all dosing cohorts and by individual cohort to identify any safety signals. Available plasma concentrations of DX-2930 and results of exploratory analyses will be evaluated to guide selection of dose levels for the Phase 2 study. A blinded medical monitor will be retained to assess safety for the remainder of the study follow-up period.
10 STUDY ADMINISTRATION

10.1 Study Administrative Structure

The study administration structure is provided in Table 2.

Table 2: Study Administrative Structure

| Sponsor Contact:                      | Ryan Iarrobino                                      |
|                                      | Senior Director, Clinical Development                |
|                                      | 55 Network Drive, Burlington, MA 01803              |
|                                      | Phone: 617-250-5574                                  |
|                                      | Email: riarrobino@dyax.com                           |
| Sponsor Medical Director:            | Yung Chyung, MD                                      |
|                                      | Senior Medical Director                              |
|                                      | 55 Network Drive, Burlington, MA 01803              |
|                                      | Phone: 617-250-5549                                  |
|                                      | Email: ychyung@dyax.com                              |
| Medical Monitor:                     | J. Gordon Still, MD, PhD                            |
|                                      | Aptiv Solutions                                     |
|                                      | 4505 Emperor Boulevard, Suite 400                   |
|                                      | Durham, NC 27703                                    |
|                                      | Phone: 919-245-5531                                  |
|                                      | Email: gordon.still@aptivsolutions.com               |
| Study Monitoring (US and Italy):     | Aptiv Solutions                                     |
|                                      | 4505 Emperor Boulevard, Suite 400                   |
|                                      | Durham, NC 27703                                    |
|                                      | Phone (Main): 919-401-1800                          |
|                                      | Email: dyaxclinops@aptivsolutions.com                |
| Study Monitoring (Jordan):           | Triumpharma                                         |
|                                      | 07 Bldg., Al-Yarooty St.                            |
|                                      | P.O. Box 2233, Amman                                |
|                                      | 11941, Jordan                                       |
|                                      | Phone: +962 6 5350582, 5358733                       |
|                                      | Email: ahmad@triumpharma.com                         |

10.2 Institutional Review 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/IEC in accordance with GCP prior to implementation. In addition, the IRB/IEC must approve the written informed consent form, any consent 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/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/IEC be documented in a
letter from the IRB/IEC. The Investigator must provide notification to the IRB/IEC of the completion, termination or discontinuation of the study.

10.3 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)].

10.4 Subject Information and Consent

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

10.5 Subject Confidentiality

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number, initial or birth date, 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.

10.6 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 Sponsor’s 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.

10.7 Case Report Forms and Study Records

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

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

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

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB/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.

10.8 Dose Escalation Committee

The DEC will be responsible for confirming the safety of the investigative product prior to dose escalation. In addition, over the course of the study, the DEC will review any drug-related SAEs to determine if modifications to the study or other measures are necessary to ensure the safety of the subjects. The DEC will consist of the Dyax Medical Director and the Medical Monitor. To assist in the safety assessments, the DEC may request that investigators, other experts, or members within their organizations review the data and participate in the discussions.

10.9 Protocol Violations/Deviations

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

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

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/IEC. Such audits/inspections may take place at the Sponsor’s site(s), Aptiv Solutions, 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 consistency. Edit check programs, other forms of electronic validation, manual listings and a query process will be executed to verify the accuracy of the database. The EDC system will maintain a full audit trail of electronic data changes. Access to all source documentation will be made available for monitoring and audit purposes.

10.12 Retention of Data

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

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

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

10.13 Financial Disclosure

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

10.14 Publication and Disclosure Policy

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

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


The Common Terminology Criteria for Adverse Events (CTCAE) v4.0; National Cancer Institute 2013.


## Appendix 1  Study Activities Schedule

| Tests and Assessments | Screening | Day 1 Prior to Dosing | Day 1 Dosing | Day 1 Post Dosing | Day 2 | Day 4 | Day 8 | Day 15 Prior to Dosing | Day 15 Dosing | Day 16 | Day 18 | Day 22 | Days 29±1: 36±1, 50±2, 64±2, & 92±3 | Final Visit Day 120±3 or ET Visit | Optional Study Site Visit(s) for Acute HAE Attack(s) During Study* |
|-----------------------|-----------|----------------------|--------------|------------------|------|------|------|-----------------------|--------------|-------|-------|-------|-------|------------------------------------|--------------------------|----------------------------------|
| Informed Consent      | X         |                      |              |                  |      |      |      |                      |              |       |       |       |       |                                    |                          |                                  |
| Eligibility Review    | X         | X                    |              |                  |      |      |      |                      |              |       |       |       |       |                                    |                          |                                  |
| Demographics and Medical History | X |                      |              |                  |      |      |      |                      |              |       |       |       |       |                                    |                          |                                  |
| Physical Examination  | X¹        | X                    | X²           |                  | X    | X    |      | X²                   |              |       |       |       |       |                                    |                          |                                  |
| Vital Signs           | X         | X                    | X³           |                  | X    | X    |      | X³                   |              |       |       |       |       |                                    |                          |                                  |
| 12-Lead ECG           | X         | X                    |              |                  | X    | X    |      | X                    |              |       |       |       |       |                                    |                          |                                  |
| Hematology           | X         | X                    | X³           |                  | X    | X    |      | X³                   |              |       |       |       |       |                                    |                          |                                  |
| Coagulation           | X         | X                    | X³           |                  | X    | X    |      | X³                   |              |       |       |       |       |                                    |                          |                                  |
| Serum Chemistry       | X         | X                    | X³           |                  | X    | X    |      | X³                   |              |       |       |       |       |                                    |                          |                                  |
| Urinalysis           | X         | X                    | X³           |                  | X    | X    |      | X³                   |              |       |       |       |       |                                    |                          |                                  |
| C1-INH levels        | X         | X                    |              |                  | X    | X    |      | X                    |              |       |       |       |       |                                    |                          |                                  |
| C4 Assay              | X         |                      |              |                  |      |      |      |                      |              |       |       |       |       |                                    |                          |                                  |
| Serum or Urine Pregnancy Test (females) | X | X | | | | | | | | | | | | |
| HBsAg, HCV, and HIV Screening | X | | | | | | | | | | | | |
### Tests and Assessments

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<th>Screening</th>
<th>Day 1 Prior to Dosing</th>
<th>Day 1 Dosing</th>
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<th>Day 4</th>
<th>Day 8</th>
<th>Day 15 Prior to Dosing</th>
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<th>Day 15 Post Dosing</th>
<th>Day 16</th>
<th>Day 18</th>
<th>Day 22</th>
<th>Days 29±1, 36±1, 64±2, &amp; 92±3</th>
<th>Final Visit Day 120±3 or ET Visit</th>
<th>Optional Study Site Visit(s) for Acute HAE Attack(s) During Study</th>
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ECG = electrocardiogram; PK = pharmacokinetic; ET = early termination

*Note: During this outlined period (Day 29 through Day 92), physical examination, vital signs, and safety laboratory tests (hematology, coagulation, serum chemistry, and urinalysis) will occur on Days 29±1, 36±1, 64±2, and 92±3. During this period laboratory test for C1-INH Function will occur on Days 29±1, 36±1, 64±2 and 92±3. During this period, anti-drug antibody testing will be conducted on samples obtained on Days 36±1, 64±2, and 92±3. 12-lead ECG will be performed at Day 36±1 during this outlined period.

1. Height, weight and calculation of BMI will be additional assessments conducted at this timepoint.
2. This physical examination will be abbreviated and include General, Skin, Cardiovascular, Pulmonary, Abdomen, and Extremities. (For Day 1 post-dosing and Day 15 post-dosing, this examination will occur at 4 hours ±15 minutes).
3. Documentation of vital signs including oral body temperature, HR, BP, and RR. On Day 1 post-dosing and Day 15 post-dosing, oral body temperature will not be collected.
4. Documentation of vital signs; HR, BP, and RR only at 1, 2, and 4 hours ±15 minutes.
5. CBC with differential.
6. Includes INR, aPTT and PT.
7. Includes total protein, albumin, glucose, alkaline phosphatase, bilirubin (total and direct), AST, ALT, GGT, LDH, uric acid, BUN, creatinine, calcium, sodium, potassium, chloride, CO2, phosphate, magnesium, cholesterol, triglycerides, CPK.
8. Includes pH, glucose, ketones, blood, specific gravity, nitrite, protein, bilirubin and microscopy.
9. C1 inhibitor (C1-INH) antigen or function level < 40% of the normal level is required for entry into the study. Subjects with C1-INH antigen or functional level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range and a family history consistent with HAE Type I or II. Test results must have been obtained within 5 years of enrollment. Following enrollment into the study, C1-INH functional levels will be collected at the outlined time points.
10. Serum or urine pregnancy test to be obtained at screening, prior to first dosing, and at Day 120 final visit or ET.
11. Prior concomitant medications and procedures will be documented before dose administration. Concomitant medications and procedures will be assessed on a continual basis throughout the study.
12. Pre-existing signs and symptoms will be captured prior to dosing. AEs will be assessed on a continual basis from the signing of the consent form and throughout the study.
13. Clinical information related to historical HAE attacks will be obtained prior to dosing on Day 1. Clinical information related to any HAE attacks as well as any acute attack treatments occurring during the study will be obtained throughout the study.
14. If the subject presents to the study site for an acute HAE attack during the study and it coincides with a scheduled study visit, the additional exploratory assessments and procedures (including blood draws), beyond what is already scheduled will not be necessary for that 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)

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ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal  LLN = Lower Limit of Normal  
Rx = 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.

LABORATORY RANGES

Where discrepancies in the ULN and LLN of laboratory ranges occur between those included in this document and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade.
### HEMATOLOGY

<table>
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<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
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<td>8.0 - 9.4 gm/dL</td>
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<td>% Polymorphonuclear Leucocytes + Band Cells</td>
<td>&gt; 80%</td>
<td>90 – 95%</td>
<td>&gt;95%</td>
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</tr>
<tr>
<td>Activated Partial Thromboplastin (APTT)</td>
<td>1.01 - 1.66 × ULN</td>
<td>1.67 - 2.33 × ULN</td>
<td>2.34 - 3 × ULN</td>
<td>&gt; 3 × ULN</td>
</tr>
</tbody>
</table>

### CHEMISTRIES

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>130-135 mEq/L</td>
<td>123-129 mEq/L</td>
<td>116-122 mEq/L</td>
<td>&lt; 116 mEq/L or abnormal sodium with mental status changes or seizures</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>146-150 mEq/L</td>
<td>151-157 mEq/L</td>
<td>158-165 mEq/L</td>
<td>&gt; 165 mEq/L or abnormal sodium with mental status changes or seizures</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3.0 - 3.4 mEq/L</td>
<td>2.5 - 2.9 mEq/L</td>
<td>2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required</td>
<td>&lt; 2.0 mEq/L or abnormal potassium with paresis, ileus or life-threatening arrhythmia</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>5.6 - 6.0 mEq/L</td>
<td>6.1 - 6.5 mEq/L</td>
<td>6.6 - 7.0 mEq/l</td>
<td>&gt; 7.0 mEq/L or abnormal potassium with life-threatening arrhythmia</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>55-64 mg/dL</td>
<td>40-54 mg/dL</td>
<td>30-39 mg/dL</td>
<td>&lt;30 mg/dL or abnormal glucose with mental status changes or coma</td>
</tr>
<tr>
<td>Hyperglycemia (nonfasting and no prior diabetes)</td>
<td>116 - 160 mg/dL</td>
<td>161 - 250 mg/dL</td>
<td>251 - 500 mg/dL</td>
<td>&gt; 500 mg/dL or abnormal glucose with ketoacidosis or seizures</td>
</tr>
<tr>
<td>Hypocalcemia(corrected for albumin)</td>
<td>8.4 - 7.8 mg/dL</td>
<td>7.7 - 7.0 mg/dL</td>
<td>6.9 - 6.1 mg/dL</td>
<td>&lt; 6.1 mg/Dl or abnormal calcium with life threatening arrhythmia or tetany</td>
</tr>
<tr>
<td>Hypercalcemia (correct for albumin)</td>
<td>10.6 - 11.5 mg/dL</td>
<td>11.6 - 12.5 mg/dL</td>
<td>12.6 - 13.5 mg/dL</td>
<td>&gt; 13.5 mg/dL or abnormal calcium with life threatening arrhythmia</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>1.4 - 1.2 mEq/L</td>
<td>1.1 - 0.9 mEq/L</td>
<td>0.8 - 0.6 mEq/L</td>
<td>&lt; 0.6 mEq/L or abnormal magnesium with life-threatening arrhythmia</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>2.0 - 2.4 mg/dL</td>
<td>1.5 -1.9 mg/dL or replacement Rx required</td>
<td>1.0 -1.4 mg/dL intensive therapy or hospitalization required</td>
<td>&lt; 1.0 mg/dL or abnormal phosphate with life-threatening arrhythmia</td>
</tr>
</tbody>
</table>
### Hyperbilirubinemia
- **(when accompanied by any increase in other liver function test)**
  - 1.1 - <1.25 x ULN
  - 1.25 - <1.75 x ULN
  - > 1.75 x ULN

- **(when other liver function are in the normal range)**
  - 1.1 - <1.5 x ULN
  - 1.5 - <2.0 x ULN
  - > 2.0 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

### ENZYMES

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (SGOT)</td>
<td>1.1 - &lt;2.0 x ULN</td>
<td>2.0 – &lt;3.0 x ULN</td>
<td>3.0 – 8.0 x ULN</td>
<td>&gt; 8 x ULN</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>1.1 - &lt;2.0 x ULN</td>
<td>2.0 – &lt;3.0 x ULN</td>
<td>3.0 – 8.0 x ULN</td>
<td>&gt; 8 x ULN</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>1.1 - &lt;2.0 x ULN</td>
<td>2.0 – &lt;3.0 x ULN</td>
<td>3.0 – 8.0 x ULN</td>
<td>&gt; 8 x ULN</td>
</tr>
</tbody>
</table>

### URINALYSIS

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>1+ or 200 mg - 1 gm loss/day</td>
<td>2-3+ or 1- 2 gm loss/day</td>
<td>4+ or 2-3.5 gm loss/day</td>
<td>nephrotic syndrome or &gt; 3.5 gm loss/day</td>
</tr>
<tr>
<td>Hematuria</td>
<td>microscopic only &lt;10 rbc/hpf</td>
<td>gross, no clots &gt;10 rbc/hpf</td>
<td>gross, with or without clots, OR red blood cell casts</td>
<td>obstructive or required transfusion</td>
</tr>
</tbody>
</table>

### CARDIOVASCULAR

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Rhythm</td>
<td>asymptomatic, transient signs, no Rx required</td>
<td>recurrent/persistent symptomatic Rx required</td>
<td>unstable dysrhythmia; hospitalization and treatment required</td>
<td>end organ damage or hospitalization required</td>
</tr>
<tr>
<td>Hypertension</td>
<td>transient increase &gt; 20 mm/Hg; no treatment</td>
<td>recurrent, chronic increase &gt; 20mm/Hg. /treatment required</td>
<td>acute treatment required; outpatient treatment or hospitalization possible</td>
<td>end organ damage or hospitalization required</td>
</tr>
<tr>
<td>Hypotension</td>
<td>transient orthostatic hypotension with heart rate increased by &lt;20 beat/min or decreased by &lt;10 mm Hg systolic BP, No treatment required</td>
<td>symptoms due to orthostatic hypotension or BP decreased by &lt;20 mm Hg systolic; correctable with oral fluid treatment</td>
<td>requires IV fluids; no hospitalization required</td>
<td>mean arterial pressure &lt;60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment</td>
</tr>
</tbody>
</table>
### 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

### RESPIRATORY

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>transient-no treatment</td>
<td>persistent cough; treatment responsive</td>
<td>Paroxysmal cough; uncontrolled with treatment</td>
<td>---------</td>
</tr>
<tr>
<td>Bronchospasm, Acute</td>
<td>transient; no treatment; 70% - 80% FEV$_1$ of peak flow</td>
<td>requires treatment; normalizes with bronchodilator; FEV$_1$ 50% - 70% (of peak flow)</td>
<td>no normalization with bronchodilator; FEV$_1$ 25% - 50% of peak flow; or retractions present</td>
<td>cyanosis; FEV$_1$ &lt; 25% of peak flow or intubation necessary</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>dyspnea on exertion</td>
<td>dyspnea with normal activity</td>
<td>dyspnea at rest</td>
<td>Dyspnea requiring oxygen therapy</td>
</tr>
</tbody>
</table>

### GASTROINTESTINAL

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>mild or transient; maintains reasonable intake</td>
<td>moderate discomfort; intake decreased significantly; some activity limited</td>
<td>no significant intake; requires IV fluids</td>
<td>hospitalization required;</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 episode in 24 hours</td>
<td>2-5 episodes in 24 hours</td>
<td>&gt;6 episodes in 24 hours or needing IV fluids</td>
<td>physiologic consequences requiring hospitalization or requiring parenteral nutrition</td>
</tr>
<tr>
<td>Constipation</td>
<td>requiring stool softener or dietary modification</td>
<td>requiring laxatives</td>
<td>obstipation requiring manual evacuation or enema</td>
<td>obstruction or toxic megacolon</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>mild or transient; 3-4 loose stools/day or mild diarrhea last &lt;1 week</td>
<td>moderate or persistent; 5-7 loose stools/day or diarrhea lasting &gt;1 week</td>
<td>&gt;7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or &gt;2L IV fluids required</td>
<td>hypotensive shock or physiologic consequences requiring hospitalization</td>
</tr>
<tr>
<td>Oral Discomfort/Dysphagia</td>
<td>mild discomfort; no difficulty swallowing</td>
<td>some limits on eating/drinking</td>
<td>eating/talking very limited; unable to swallow solid foods</td>
<td>unable to drink fluids; requires IV fluids</td>
</tr>
</tbody>
</table>

### NEUROLOGICAL

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>Neuro-Cerebellar</th>
<th>slight incoordination dysdiadochokinesis</th>
<th>intention tremor, dysmetria, slurred speech; nystagmus</th>
<th>locomotor ataxia</th>
<th>incapacitated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric</td>
<td>mild anxiety or depression</td>
<td>moderate anxiety or depression; therapy required; change in normal routine</td>
<td>severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation</td>
<td>acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations</td>
</tr>
<tr>
<td>Muscle Strength</td>
<td>subjective weakness, no objective symptoms/ signs</td>
<td>mild objective signs/symptoms no decrease in function</td>
<td>objective weakness function limited</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Paresthesia (burning, tingling, etc.)</td>
<td>mild discomfort; no treatment required</td>
<td>moderate discomfort; non-narcotic analgesia required</td>
<td>severe discomfort; or narcotic analgesia required with symptomatic improvement</td>
<td>incapacitating; or not responsive to narcotic analgesia</td>
</tr>
<tr>
<td>Neuro-sensory</td>
<td>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</td>
<td>moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical</td>
<td>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)</td>
<td>sensory loss involves limbs and trunk; paralysis; or seizures</td>
</tr>
</tbody>
</table>

### MUSCULOSKELETAL

<table>
<thead>
<tr>
<th>Arthralgia (joint pain)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>mild pain not interfering with function</td>
<td>moderate pain, analgesics and/or pain interfering with function but not with activities of daily living</td>
<td>severe pain; pain and/or analgesics interfering with activities of daily living</td>
<td>disabling pain</td>
<td></td>
</tr>
</tbody>
</table>

<p>| 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 destruction |</p>
<table>
<thead>
<tr>
<th></th>
<th>Myalgia with no limitation of activity</th>
<th>muscle tenderness (at other than injection site) or with moderate impairment of activity</th>
<th>severe muscle tenderness with marked impairment of activity</th>
<th>frank myonecrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>erythema; pruritus</td>
<td>diffuse, maculo papular rash, dry desquamation</td>
<td>vesiculation or moist desquamation or ulceration</td>
<td>exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery</td>
</tr>
<tr>
<td>Induration</td>
<td>&lt; 15mm</td>
<td>15-30 mm</td>
<td>&gt;30mm</td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>&lt; 15mm</td>
<td>15-30 mm</td>
<td>&gt;30mm</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>&lt; 15mm</td>
<td>15-30 mm</td>
<td>&gt;30mm</td>
<td></td>
</tr>
<tr>
<td>Rash at Injection Site</td>
<td>&lt; 15mm</td>
<td>15-30 mm</td>
<td>&gt;30mm</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>slight itching at injection site</td>
<td>moderate itching at injection extremity</td>
<td>itching over entire body</td>
<td></td>
</tr>
<tr>
<td>SYSTEMIC</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Allergic Reaction</td>
<td>pruritus without rash</td>
<td>localized urticaria</td>
<td>generalized urticaria; angioedema</td>
<td>anaphylaxis</td>
</tr>
<tr>
<td>Headache</td>
<td>mild, no treatment required</td>
<td>transient, moderate; treatment required</td>
<td>severe; responds to initial narcotic therapy</td>
<td>intractable; requires repeated narcotic therapy</td>
</tr>
<tr>
<td>Fever: oral</td>
<td>37.7 - 38.5 °C or 100.0 - 101.5 °F</td>
<td>38.6 - 39.5 °C or 101.6 - 102.9 °F</td>
<td>39.6 - 40.5 °C or 103 - 105 °F</td>
<td>&gt; 40 °C or &gt; 105 °F</td>
</tr>
<tr>
<td>Fatigue</td>
<td>normal activity reduced &lt; 48 hours</td>
<td>normal activity decreased 25-50% &gt; 48 hours</td>
<td>normal activity decreased &gt; 50% can’t work</td>
<td>unable to care for self</td>
</tr>
</tbody>
</table>
Clinical Trial Protocol: DX-2930-02

Study Title: A Phase 1b, Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX-2930 in Hereditary Angioedema Subjects

Study Number: DX-2930-02

Study Phase: Phase 1b

Product Name: DX-2930

IND Number: 116647

EudraCT Number: 2013-005066-18

Indication: Hereditary Angioedema

Investigators: Multicenter

Sponsor: Dyax Corp.

55 Network Drive, Burlington, MA 01803

Sponsor Contact: Ryan Iarrobino

55 Network Drive, Burlington, MA 01803

Phone: 617-250-5574

Mobile: 617-803-6069

Medical Monitor: Yung Chyung, MD

55 Network Drive, Burlington, MA 01803

Phone: 617-250-5549

Mobile: 617-417-9114

Date:

Original Protocol: 24 February 2014

Amendment 1.0: 07 January 2015

Confidentiality Statement

This document is the property of Dyax Corp. The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed without the express written permission of Dyax unless required by federal or state law or regulations. Any person to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.
PROTOCOL SIGNATURE PAGE

Study Title: A Phase 1b, Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX-2930 in Hereditary Angioedema Subjects

Study Number: DX-2930-02
Original Protocol: 24 February 2014
Amendment 1.0: 07 January 2015

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

Signed: ___________________________ Date: ______________________
Ryan Iarrobino
Senior Director, Clinical Development
55 Network Drive, Burlington, MA 01803

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in compliance with the Declaration of Helsinki, 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) or Ethics Committee (EC) and will fulfill all responsibilities for submitting pertinent information to the IRB/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.

<table>
<thead>
<tr>
<th>Name of Finished Product:</th>
<th>DX-2930 Drug Product (DP)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Name of Active Ingredient:</th>
</tr>
</thead>
<tbody>
<tr>
<td>DX-2930 is a recombinant, Chinese hamster ovary (CHO) cell-expressed, fully human immunoglobulin G subclass 1 (IgG1), kappa light chain, monoclonal antibody.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Names of Inactive Ingredients:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium phosphate, citric acid, histidine, sodium chloride, and Tween 80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Title:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Phase 1b, Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX-2930 in Hereditary Angioedema</td>
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<tr>
<th>Study Number:</th>
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<tbody>
<tr>
<td>DX-2930-02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Phase:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Location:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximately 12 study sites planned for U.S., Italy, and Jordan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Objective(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>To assess the safety and tolerability of multiple subcutaneous administrations of DX-2930 at different dose levels in hereditary angioedema (HAE) subjects.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Objective(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>To characterize the pharmacokinetics (PK) of DX-2930 following multiple subcutaneous administrations at different dose levels.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tertiary Objective(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• To assess the immunogenicity of DX-2930</td>
</tr>
<tr>
<td>• To evaluate pharmacodynamic (PD) effects of DX-2930 through exploratory biomarker assessments</td>
</tr>
<tr>
<td>• To conduct an exploratory assessment of the indirect effects of plasma kallikrein inhibition upon endogenous C1-inhibitor activity</td>
</tr>
<tr>
<td>• To conduct exploratory assessments to characterize HAE attacks and acute attack therapy usage during the study</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Design:</th>
</tr>
</thead>
<tbody>
<tr>
<td>This study is a Phase 1b, multi-center, randomized, double-blind, placebo-controlled, multiple ascending dose trial of subcutaneous administrations of DX-2930 in HAE subjects. Eligible subjects will be randomized to receive either active study drug or placebo within 3 dose cohorts (30, 100, and 300 mg), with each cohort consisting of 6 subjects. Cohorts will be dosed in a staggered, dose ascending fashion. For each dosing cohort, 4 subjects will be randomized to receive active drug and 2 subjects will be randomized to...</td>
</tr>
</tbody>
</table>
receive placebo. Each subject within a dosing cohort will receive 2 doses of study drug, administered subcutaneously into the upper arm. The second dose will be administered 14 days following the first dose. When a cohort has completed dosing (including after the final nominal cohort of 300 mg), a review will be conducted of the safety data from screening through 14 days after the second dose. Cumulative safety data from any earlier cohort will also be included in the review. This safety evaluation will be conducted by a dose escalation committee (DEC) and will include a review of all adverse events, vital signs, physical examinations, laboratories, and electrocardiograms (ECGs). Escalation to the next highest dosing cohort will proceed if there are no concerning safety signals.

A flexible dose escalation scheme will be used in this study that allows for modification of dose escalation if necessary to further characterize DX-2930 (such as for safety, PK, or exploratory assessments) and if supported by review of safety data from previous cohorts. This flexible dose escalation scheme allows for expansion of a current or prior cohort or intermediate doses higher or lower than the preceding dose to be studied in a subsequent cohort. This may result in adding subjects to receive specific dose levels and an increase in the total number of cohorts and/or subjects enrolled in the study. The flexible dose escalation scheme also allows further escalation to doses higher than 300 mg (up to a maximum of 400 mg) if necessary and if supported by cumulative safety results. This would require additional cohort(s), increasing the total number of subjects enrolled and extending the total study duration.

If subjects experience acute HAE attacks during the study, they will be permitted standard of care treatment as prescribed by their physician. Any subject experiencing an HAE attack (even if resolving or limited to prodromal symptoms) on Day 1 will have their scheduled visit postponed for at least 72 hours after their attack has resolved.

**Study Population:**
Eighteen (18) HAE subjects (4 active and 2 placebo subjects per cohort) will be enrolled nominally across 3 dosing cohorts. If necessary, the flexible dose escalation scheme will allow up to 18 additional subjects (12 active, 6 placebo) to be enrolled, for a maximum of 36 subjects treated in the study. Subjects will be enrolled only once and will not be included in subsequent dosing cohorts. Subjects who do not receive both doses of study drug may be replaced.

**Criteria for Inclusion:**
Each subject must meet the following criteria to be enrolled in this study:

1. At least 18 years of age 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).
   - C1 inhibitor (C1-INH) antigen or functional level < 40% of the normal level. Subjects with antigen or functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range and a family history consistent with HAE Type I or II. Test results must have been obtained within 5 years of enrollment.
   - Age at reported onset of first angioedema symptoms ≤ 30 years or a family history consistent with HAE Type I or II.
3. Experiencing ≥2 HAE attacks per year, with at least 1 attack in the past 6 months reported by the subject.
4. Willing and able to read, understand, and sign an informed consent form.
5. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception from the Screening Period through 30 days after the final study visit: progestin-only oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. Female subjects must agree to practice the above birth control methods for 30 days after the final study visit as a safety precaution.
6. 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.
7. Males with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study visit. All male subjects, including males who are surgically sterile (post vasectomy), must agree to practice the above birth control methods for 60 days from the final study visit as a safety precaution.

Criteria for Exclusion:
Subjects who meet any of the following criteria will be excluded from the study:
1. Any exposure to an investigational drug or device within 90 days prior to initial study treatment.
2. Any prior history of exposure within the past 5 years to a monoclonal antibody or recombinant protein bearing an Fc domain (such as a soluble receptor-Fc fusion protein).
3. Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1 inhibitor deficiency, HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or angioedema associated with urticaria.
4. Use of long-term prophylaxis for HAE (C1-INH used for long-term prophylaxis, attenuated androgens, or anti-fibrinolytics) within 90 days prior to initial study treatment.
5. Use of C1-INH for short-term prophylaxis and/or on-demand treatment for an HAE attack that exceeds a total of 30 days within the past 90 days prior to initial study treatment; any use of C1-INH within 7 days prior to initial study treatment.
6. Any exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 90 days prior to initial study treatment.
7. Any exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 90 days prior to initial study treatment.
8. Presence of an indwelling catheter.
9. Diagnosis of HIV.
10. Active liver disease (e.g., Acute or chronic hepatitis B or C, alcoholic or non-alcoholic steatohepatitis).
11. Any of the following liver function test abnormalities: alanine aminotransferase (ALT)
11. Aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 1.5x upper limit of normal (unless subject has known Gilbert’s Syndrome).

12. History of substance abuse or dependence.

13. Pregnancy or breastfeeding.

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

**Test Product; Dose; and Mode of Administration:**

DX-2930 is a sterile, preservative-free solution for injection, pH 6.0. The active ingredient, DX-2930, is formulated in 30 mM sodium phosphate, 8.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Tween 80. All formulation components are compendial. Each vial contains a nominal concentration of 100 mg DX-2930 active ingredient in 1 mL solution. The test product will be administered by subcutaneous injection into the upper arm.

**Placebo; Dose; and Mode of Administration:**

Placebo consists of the inactive formulation of the test product: 30 mM sodium phosphate, 8.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, pH 6.0 with 0.01% Tween 80. For subjects randomized to receive placebo, the volume of placebo administered will be the same as the total volume for an active dose within the placebo subjects’ assigned dose cohort. Placebo will be administered by subcutaneous injection into the upper arm.

**Duration of Treatment:**

Subjects will receive a dose of blinded study drug on Study Day 1 and will be monitored at the study site through 4 hours post-dose. Subjects will receive their second administration of blinded study drug at the same dose on Study Day 15 and will be monitored again at the study site through 4 hours post-dose. Follow-up visits will occur through 15 weeks (105 ± 3 days) after the second dosing.

**Duration of Study:**

The total duration of study participation for each individual subject will be approximately 120 days from the time of enrollment.

**Prohibited Concomitant Treatments:**

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

- Long-term prophylaxis for HAE (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 investigational drug or device.

**Safety Assessments:**

Safety assessments will include the following:
• Adverse events (AEs), including serious adverse events (SAEs).
• Vital signs, including sitting or supine blood pressure (BP), heart rate (HR), oral body temperature, and respiratory rate (RR).
• Physical examination.
• Clinical laboratory testing (hematology, clinical chemistry, coagulation and urinalysis).
• 12-Lead electrocardiogram (ECG).

**Pharmacokinetic Variables:**
Blood samples will be collected for the measurement of plasma DX-2930 concentration prior to study drug administration on Day 1 and on Days 2, 4 and 8. Additional blood samples will be obtained on Day 15 (prior to administration of the second dose of study drug) and on Days 16, 18, 22, 29±1, 36±1, 50±2, 64±2, 92±3 and 120±3. DX-2930 non-compartmental PK variable determinations will include maximum concentration in plasma (C_{max}), time to reach C_{max} in plasma (t_{max}), and area under the curve from time 0 to last sample (AUC_{0-t}). Compartmental PK modeling will describe the PK of DX-2930 and generate underlying C_{max}, t_{max}, AUC, apparent clearance (CL/F), apparent volume of distribution (Vd/F) and terminal elimination half-life (t½).

**Immunogenicity Assessments:**
DX-2930 plasma anti-drug antibody determinations will be performed using blood samples collected at pre-dose on Day 1 and on Days 36±1, 64±2, 92±3, and 120±3.

**C1-INH Functional Assessments:**
As an exploratory assessment of the indirect effects of plasma kallikrein inhibition upon endogenous C1-INH activity, samples will be obtained for C1-INH functional testing. Blood samples will be collected at pre-dose on Day 1 and Day 15 (prior to treatment with the second dose of study drug). Additional blood samples will be obtained on Days 29±1, 36±1, 64±2, 92±3 and 120±3.

**Exploratory Biomarker Assessments:**
Samples will be obtained to evaluate the pharmacodynamic effects of treatment on plasma kallikrein activity. Blood samples will be collected at pre-dose on Day 1 and on Days 2, 4 and 8. Additional blood samples will be obtained on Day 15 (prior to treatment with the second dose of study drug) and on Days 16, 18, 22, 29±1, 36±1, 50±2, 64±2, 92±3 and 120±3.

**Exploratory Assessments to Characterize HAE Attacks and Acute Attack Treatment Usage:**
Prior to enrollment, HAE attack history will be collected by the Investigator. Information collected will include any prior history of laryngeal attacks, attack frequency, severity, location, duration, and acute attack therapy use.
In addition, subjects will be asked to report to their Investigator any HAE attacks they experience during the course of the study. Collection of clinical information regarding any such attacks will include attack location, severity, time of onset, duration, and treatment with any acute attack therapy. In addition, subjects will be encouraged, but not required, to come into the study site (maximum of 4 visits during the study, of which no more than 1 can be within the first 36 days following enrollment unless they occur at the same time as a planned study visit) for such attacks in order to have blood drawn for biomarker, C1-INH functional
level, and PK testing. Subjects will be eligible to undergo this blood sample collection as long as they are assessed within 24 hours of symptom onset irrespective of any treatment they may have received for their attack. If the subject presents to the study site for an acute HAE attack during the study and it coincides with a scheduled study visit, the additional exploratory assessments and procedures (including blood draws) beyond what is already is scheduled will not be necessary for that visit.

Subjects will also be asked to report to their Investigator any use of acute attack treatment during the course of the study.

**Dose Escalation Rules:**

Adverse events will be reviewed in a blinded manner and graded using the 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). Dose-limiting toxicity (DLT) will be defined generally as clinically significant, severe (Grade 3) AEs occurring in ≥2 subjects that are determined to be related to DX-2930. The following general rules regarding assessment of AEs and dose escalation will be followed:

a. If 1 subject in the cohort (6 total subjects) has a Grade 3 AE, no unblinding is necessary and escalation to the next dose cohort may proceed.

b. If 2 or more subjects in the cohort (6 total subjects) have Grade 3 AEs that are determined to be clinically significant and related to study drug, the Sponsor may break the blind to determine if the events occurred in DX-2930 recipients. Determination of clinical significance and relatedness and decisions regarding breaking the blind will be based on clinical judgment and experience. If the AEs occurred in subjects that received DX-2930, then the current dosing cohort may be expanded by an additional 3 (2 active + 1 placebo) or 6 (4 active + 2 placebo) subjects for further evaluation. If it is determined that it would not be safe to proceed with further treatments at that same dose level of DX-2930, then DLT is declared and no further treatments at that dose level may be recommended. Subsequent dosing may be modified to an intermediate dose that is lower than the current dosing cohort but higher than the prior cohort. Alternatively, depending on the nature of the AEs (i.e. degree of clinical significance, organ or system involved), escalation to a dose intermediate between the current and next planned dose level may be recommended. Otherwise, if there are no major safety concerns (e.g., both subjects with the Grade 3 AEs had received placebo), the dose escalation may proceed as planned.

c. If any subject experiences a life-threatening AE (Grade 4) that is study drug-related, and unblinding reveals that the subject had received DX-2930, any further dosing may be suspended pending thorough data review.

**Study Stopping Rules:**

The occurrence of a study drug-related SAE in any subject who is shown by unblinding to have received DX-2930 (see Section 5.4) may result in suspension of any further dosing in the study by the Medical Monitor until the DEC has evaluated the event and determined the next appropriate course of action. At any time during the study, the study may be discontinued if the DEC determines that further drug exposure would pose an undue risk to subjects.
**Individual Stopping Rules:**
Dosing for any individual subject will be discontinued (i.e. further treatment with the study medication will not be given) if the subject experiences a DX-2930-related SAE or a DX-2930-related, clinically significant non-serious AE that, in the opinion of the Investigator and Medical Monitor, warrants discontinuation from further dosing for that subject’s well-being. Any occurrence of a DX-2930-related clinically significant, severe (or Grade 3) toxicity may also terminate further dosing in a subject at the discretion of the Investigator and the Medical Monitor.

**Statistical Methods:**
All demographic, safety and PK data will be listed and summarized in tabular format using descriptive statistics for continuous variables and frequency and percentages for discrete variables. Missing data will not be imputed. Descriptive data will be tabulated to best represent the baseline characteristics of the two prospectively enrolled randomized groups. Additional exploratory analyses may be performed. Non-compartmental methods will be used to generate actual $C_{\text{max}}$, $t_{\text{max}}$ and $\text{AUC}_{0-t}$. Compartmental PK methods will be used to generate predictions of $C_{\text{max}}$, $t_{\text{max}}$, AUC, CL/F, Vd/F, and $t/2$.

**Interim Analysis:**
An interim analysis after at least 6 subjects have reached Day 36 of the 300 mg cohort is planned by the Sponsor, unless the highest dose level in the study is lower than 300 mg, in which case the interim analysis will be conducted after at least 6 subjects at the highest dose cohort have reached Day 36. This interim analysis will include all safety and subject information as well as any available and relevant PK, anti-drug antibody, and exploratory assessment data collected across all dosing cohorts leading up to and including the highest dose cohort. Unblinded, aggregate safety data will be reviewed across all dosing cohorts and by individual cohort to identify any safety signals. Available PK data, safety data, and results of exploratory analyses will be evaluated to guide selection of dose levels for the Phase 2 study. In accordance with the flexible dose schema, additional cohorts may be added following a DEC review and/ or interim analysis. Additional interim analyses may be conducted following the initial interim analysis. A blinded medical monitor will be retained to assess safety for the remainder of the study follow-up period.

**Date of Original Protocol:** 24 February 2014
**Date of Amendment 1.0:** 07 January 2015
### Study Activities Schedule

<table>
<thead>
<tr>
<th>Tests and Assessments</th>
<th>Screening</th>
<th>Day 1 Prior to Dosing</th>
<th>Day 1 Dosing</th>
<th>Day 1 Post Dosing</th>
<th>Day 2</th>
<th>Day 4</th>
<th>Day 8</th>
<th>Day 15 Prior to Dosing</th>
<th>Day 15 Dosing</th>
<th>Day 15 Post Dosing</th>
<th>Day 16</th>
<th>Day 18</th>
<th>Day 22</th>
<th>Days 29±1 36±1, 50±2, 64±2, 92±3</th>
<th>*</th>
<th>Final Visit Day 120±3 or ET Visit</th>
<th>Optional Study Site Visit(s) for Acute HAE Attack(s) During Study(\text{a})</th>
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<tr>
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\(\text{a}\) Includes visits up to and including the Final Visit Day 120±3 or ET Visit.
<table>
<thead>
<tr>
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<th>Days 29±1, 36±1, 50±2, 64±2, &amp; 92±3 *</th>
<th>Final Visit Day 120±3 or ET Visit</th>
<th>Optional Study Site Visit(s) for Acute HAE Attack(s) During Study 21</th>
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<td>Days 29±1, 36±1, 50±2, 64±2, &amp; 92±3 *</td>
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<td>Optional Study Site Visit(s) for Acute HAE Attack(s) During Study 21</td>
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<td>Optional Study Site Visit(s) for Acute HAEAttack(s) During Study 21</td>
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<td>Optional Study Site Visit(s) for Acute HAE Attack(s) During Study 21</td>
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<td>Days 29±1, 36±1, 50±2, 64±2, &amp; 92±3 *</td>
<td>Final Visit Day 120±3 or ET Visit</td>
<td>Optional Study Site Visit(s) for Acute HAE Attack(s) During Study 21</td>
</tr>
</tbody>
</table>

ECG = electrocardiogram; PK = pharmacokinetic; ET = early termination

*Note: During this outlined period (Day 29 through Day 92), physical examination, vital signs, and safety laboratory tests (hematology, coagulation, serum chemistry, and urinalysis) will occur on Days 29±1, 36±1, 64±2, and 92±3. During this period laboratory test for C1-INH Function will occur on Days 29±1, 36±1, 64±2 and 92±3. During this period, anti-drug antibody testing will be conducted on samples obtained on Days 36±1, 64±2, and 92±3. 12-lead ECG will be performed at Day 36±1 during this outlined period.

1. Height, weight and calculation of BMI will be additional assessments conducted at this time point.
2. This physical examination will be abbreviated and include General, Skin, Cardiovascular, Pulmonary, Abdomen, and Extremities. (For Day 1 post-dosing and Day 15 post-dosing, this examination will occur at 4 hours ±15 minutes).
3. Documentation of vital signs including oral body temperature, HR, BP, and RR. On Day 1 post-dosing and Day 15 post-dosing, oral body temperature will not be collected.
4. Documentation of vital signs; HR, BP, and RR only at 1, 2, and 4 hours ±15 minutes
5. CBC with differential
Includes INR, aPTT and PT
Includes total protein, albumin, glucose, alkaline phosphatase, bilirubin (total and direct), AST, ALT, GGT, LDH, uric acid, BUN, creatinine, calcium, sodium, potassium, chloride, CO2, phosphate, magnesium, cholesterol, triglycerides, CPK
Includes pH, glucose, ketones, blood, specific gravity, nitrite, protein, bilirubin and microscopy
C1 inhibitor (C1-INH) antigen or functional level < 40% of the normal level is required for entry into the study. Subjects with antigen or functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range and a family history consistent with HAE Type I or II. Test results must have been obtained within 5 years of enrollment. Following enrollment into the study, C1-INH functional levels will be collected at the outlined time points.
Serum or urine pregnancy test to be obtained at screening, prior to first dosing, and at Day 120 final visit or ET
Prior concomitant medications and procedures will be documented before dose administration. Concomitant medications and procedures will be assessed on a continual basis throughout the study
Pre-existing signs and symptoms will be captured prior to dosing. AEs will be assessed on a continual basis from the signing of the consent form and throughout the study
Clinical information related to historical HAE attacks will be obtained prior to dosing on Day 1. Clinical information related to any HAE attacks as well as any acute attack treatments occurring during the study will be obtained throughout the study
If the subject presents to the study site for an acute HAE attack during the study and it coincides with a scheduled study visit, the additional exploratory assessments and procedures (including blood draws), beyond what is already scheduled will not be necessary for that visit.
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<td>Angiotensin converting enzyme</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>aPTT</td>
<td>Activated partial thromboplastin time</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the plasma concentration-time curve</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>AUC from time zero to the last quantifiable concentration in plasma at time t</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt;</td>
<td>AUC from time 0 to infinity</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
</tr>
<tr>
<td>C1-INH</td>
<td>C1 inhibitor</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CHO</td>
<td>Chinese hamster ovary</td>
</tr>
<tr>
<td>CL/F</td>
<td>apparent total plasma clearance after extravascular administration</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma drug concentration</td>
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<tr>
<td>CO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Carbon dioxide</td>
</tr>
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<td>CPK</td>
<td>Creatine phosphokinase</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CRO</td>
<td>Clinical Research Organization</td>
</tr>
<tr>
<td>CTMS</td>
<td>Clinical Trial Management System</td>
</tr>
<tr>
<td>DEC</td>
<td>Dose Escalation Committee</td>
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<tr>
<td>DLT</td>
<td>Dose Limiting Toxicity</td>
</tr>
<tr>
<td>DMID</td>
<td>Division of Microbiology and Infectious Diseases</td>
</tr>
<tr>
<td>DP</td>
<td>Drug product</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
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<td>eCRF</td>
<td>Electronic case report form</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic data capture</td>
</tr>
<tr>
<td>ET</td>
<td>Early termination</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma-glutamyl transferase</td>
</tr>
<tr>
<td>HAE</td>
<td>Hereditary angioedema</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
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<tr>
<td>HED</td>
<td>Human Equivalent Dose</td>
</tr>
<tr>
<td>HIPAA</td>
<td>Health Information Portability and Accountability Act</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IgG1</td>
<td>Immunoglobulin G subclass 1</td>
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<tr>
<td>IMP</td>
<td>Investigational medicinal product</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>INR</td>
<td>International normalized ratio</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>IUD</td>
<td>Intrauterine device</td>
</tr>
<tr>
<td>IWRS</td>
<td>Interactive Web-based Randomization System</td>
</tr>
<tr>
<td>Ki</td>
<td>inhibition constant</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>MABEL</td>
<td>Minimum Anticipated Biological Effect Level</td>
</tr>
<tr>
<td>MCH</td>
<td>Mean corpuscular hemoglobin</td>
</tr>
<tr>
<td>MCHC</td>
<td>Mean corpuscular hemoglobin concentration</td>
</tr>
<tr>
<td>MCV</td>
<td>Mean corpuscular volume</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MTD</td>
<td>Maximum tolerated dose</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>PAP</td>
<td>Pharmacokinetic Analysis Plan</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamic(s)</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic(s)</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin time</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cell (count)</td>
</tr>
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<td>RR</td>
<td>Respiratory rate</td>
</tr>
<tr>
<td>RSI</td>
<td>Reference Safety Information</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
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<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SC</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SGOT</td>
<td>Serum glutamic oxaloacetic transaminase (AST)</td>
</tr>
<tr>
<td>SGPT</td>
<td>Serum glutamic pyruvic transaminase (ALT)</td>
</tr>
<tr>
<td>SM</td>
<td>Safety Management</td>
</tr>
<tr>
<td>SOC</td>
<td>System Organ Class</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard operating procedure</td>
</tr>
<tr>
<td>t½</td>
<td>Terminal elimination half-life</td>
</tr>
<tr>
<td>t_max</td>
<td>Time to maximum plasma concentration</td>
</tr>
<tr>
<td>TEAE</td>
<td>Treatment-Emergent Adverse Event</td>
</tr>
<tr>
<td>TT</td>
<td>Thrombin time</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>Vd/F</td>
<td>Apparent volume of distribution during terminal phase after extravascular administration</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cell (count)</td>
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</table>
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 an autosomal dominant disorder that manifests clinically as intermittent, self-limited attacks of subcutaneous (SC or submucosal edema affecting the face, larynx, gastrointestinal tract, limbs or genitalia (Bork et al, 2006). Laryngeal attacks are the most serious as they are life-threatening due to the potential for airway compromise. HAE mortality has been estimated to be as high as 30% in undiagnosed individuals (Bork and Ressel, 2003). Abdominal attacks are often accompanied by severe pain and, in fact, can be mistaken for an acute abdomen with patients often undergoing unnecessary surgery due to their clinical presentation (Zuraw, 2008). Peripheral attacks can frequently be associated with considerable dysfunction and pain (Kusuma et al., 2012).

1.3 Therapeutic Rationale for DX-2930

Plasma kallikrein plays a critical role in the pathogenesis of HAE attacks (Morgan, 2010). In normal physiology, C1-inhibitor (C1-INH) regulates the activity of plasma kallikrein as well as a variety of other proteases, such as C1r, C1s, factor Xla and factor XIIa. 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 that is thought to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. Intervening to prevent bradykinin production with a plasma kallikrein inhibitor would therefore represent 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 the short-acting inhibitor, ecallantide, in the treatment of acute HAE attacks (KALBITOR® U.S. Package Insert).

DX-2930 is a highly potent (Ki = 125 pM) and specific inhibitor of plasma kallikrein. Furthermore, preclinical data in nonhuman primates suggest that DX-2930 will have a long half-life in humans. PK data from a Phase 1a clinical study involving single dose administration in healthy subjects corroborates these data. The mean half-life following a single subcutaneous dose of DX-2930 at 3 mg/kg was approximately 20 days (DX-2930 Investigator’s Brochure). Due to a potentially long half-life in HAE patients, DX-2930 might provide a long-acting and sustained pharmacologic effect. As a result, treatment with DX-2930 potentially may enable the suppression of plasma kallikrein activity to be maintained indefinitely and thereby prevent HAE attacks from even developing.
The DX-2930 development program will determine the safety and efficacy of DX-2930 in providing effective long-term prophylaxis against attacks of HAE. Data are available from a Phase 1a study of single subcutaneous doses of DX-2930 in healthy subjects. The present Phase 1b study will evaluate the safety, tolerability, and PK profile of multiple subcutaneous administrations of DX-2930 across a range of doses in HAE subjects.

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 clinical study support a wide safety margin in conjunction with data from the nonclinical toxicity studies. The mean $C_{\text{max}}$ for human subjects treated at the highest dose of 3 mg/kg was approximately 14.5 $\mu$g/ml. As comparison, a mean $C_{\text{max}}$ of 1310 $\mu$g /ml was observed following dosing of monkeys with 50 mg/kg DX-2930 SC weekly for 28 days. No toxicologically significant findings were observed in these treated animals or in any other nonclinical toxicity study to date. Thus, the drug exposure in the Phase 1b clinical study following two administrations of DX-2930 (up to a maximum of 400 mg) is predicted to be substantially less than that attained and evaluated in the nonclinical toxicity studies.

In addition, current knowledge regarding plasma kallikrein biology does not appear a priori to predict any toxicity from plasma kallikrein inhibition. Plasma kallikrein is a drug target that has already been validated in humans through the clinical experience with ecallantide, a product approved by the FDA for treating HAE attacks in the United States. The safety of plasma kallikrein inhibition is further supported by the clinical presentation of Fletcher Factor Deficiency, a congenital condition characterized by a severe prekallikrein deficiency. As prekallikrein is the precursor from which plasma kallikrein is generated, plasma kallikrein is also severely deficient in cases of Fletcher Factor Deficiency. Individuals with this condition do not appear to suffer any clinical complications attributable to the defect (Renne et al, 2012).

The possibility of off-target effects with DX-2930 also appears unlikely. Experience with monoclonal antibodies overall indicates that off-target effects are rare and that toxicity from such therapeutic agents is usually related to on-target pharmacology (Muller et al, 2009). DX-2930 possesses high specificity for plasma kallikrein. In vitro studies demonstrated that DX-2930 does not inhibit prekallikrein, the precursor for plasma kallikrein. DX-2930 does not inhibit numerous other serine proteases (tested at a maximum concentration of at least 1 $\mu$M) that are also resident in the extracellular environment.

For a summary of findings from the single dose, clinical study in healthy subjects and further details on the nonclinical findings, please refer to the DX-2930 Investigator’s Brochure.
1.5 Rationale for Multiple Dose Study of DX-2930 in HAE Subjects

The planned range of DX-2930 dosing for the clinical development program is based upon estimation of the level of plasma kallikrein inhibition necessary to attain effective prophylaxis against HAE attacks. The planned nominal doses in this Phase 1b study of 30, 100, and 300 mg (with a flexible dose escalation scheme up to a maximum of 400 mg) are believed to encompass the range of possibilities for which DX-2930 is anticipated to be therapeutically active. Evaluation of this dose range in the Phase 1b study is necessary to assess the safety of multiple administrations of DX-2930 in HAE subjects prior to proceeding with the Phase 2 study, a parallel arm, dose-ranging study with long-term drug administration. The absence of dose-limiting toxicities observed in the single dose study support the progression to this multiple ascending dose study. Pharmacokinetic and exploratory assessment data, including pharmacodynamic data, from the Phase 1b study will further refine the design of the dosing regimen in the Phase 2 study.

Information regarding the rationale for the study design, including selection of the starting dose is in Section 3.2.
2 STUDY OBJECTIVES

2.1 Primary Objective

To assess the safety and tolerability of multiple, subcutaneous administrations of DX-2930 at different dose levels in HAE subjects.

2.2 Secondary Objective

To characterize the pharmacokinetics (PK) of DX-2930 following multiple, subcutaneous administrations at different dose levels.

2.3 Tertiary Objectives

- To assess the immunogenicity of DX-2930
- To evaluate the pharmacodynamic (PD) effects of DX-2930 through exploratory biomarker assessments
- To conduct an exploratory assessment of the indirect effects of plasma kallikrein inhibition upon endogenous C1-inhibitor activity
- To conduct exploratory assessments to characterize HAE attacks and acute attack therapy usage during the study
3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Overview

This study is a Phase 1b, multi-center, randomized, double-blind, placebo-controlled, multiple ascending dose trial of subcutaneous administrations of DX-2930 in HAE subjects. Eligible subjects will be randomized 2:1 to receive either active study drug or placebo within a cohort. The study consists of 3 dose cohorts (30, 100, and 300 mg), with each cohort consisting of 6 subjects.

Cohorts will be dosed in a staggered, dose ascending fashion. For each dosing cohort, 4 subjects will be randomized to receive active drug and 2 subjects will be randomized to receive placebo. Each subject within a dosing cohort will receive 2 doses of study drug, administered subcutaneously into the upper arm. The second dose will be administered 14 days following the first dose. When a cohort has completed dosing, a review will be conducted of the safety data through 14 days after the second dose. Cumulative safety data from any earlier cohort will also be included in the review. This safety evaluation will be conducted by a dose escalation committee (DEC) and will include a review of all adverse events, vital signs, physical examinations, laboratories, and electrocardiograms (ECGs). Escalation to the next highest dosing cohort will proceed if there are no concerning safety signals.

A flexible dose escalation scheme will be used in this study that (based on review of safety data from previous cohorts) allows for expansion of a current or prior cohort or intermediate doses higher or lower than the preceding dose to be studied in a subsequent cohort. This may result in adding of subjects to receive specific dose levels and in an increase in the total number of cohorts and/or subjects enrolled in the study.

Blood samples for the measurement of plasma DX-2930 concentration will be obtained prior to administration of study drug and at specific time points following study drug administration (see Study Activities Schedule, Appendix 1).

If subjects experience acute HAE attacks during the study, they will be permitted standard of care treatment as prescribed by their physician. Any subject experiencing an HAE attack (even if resolving or limited to prodromal symptoms) on Day 1 will have their visit postponed for at least 72 hours after their attack has resolved.

3.1.2 Flexible Dose Escalation Scheme

The nominal dose escalation scheme will be 30, 100, and 300 mg. To facilitate efficient selection of the therapeutic dose(s) of DX-2930 to be studied in subsequent clinical trials and to make optimal use of the cohorts of subjects in this study while protecting their safety, a flexible scheme of dose escalation will be used. The flexible dose escalation approach requires that the safety data through the Day 29 visit for all subjects in a cohort be available
for review by the Dose Escalation Committee (DEC) prior to escalation to the next highest dose. This review will be done using blinded data.

The flexible dose escalation scheme allows for modification of dose escalation if necessary to further characterize DX-2930 (such as for safety, PK, or exploratory assessments) and if supported by review of safety data from previous cohorts. This scheme will allow for expansion of a current or prior dosing cohort, escalation to intermediate doses higher than the preceding dose, or de-escalation to intermediate doses lower than the preceding dose for evaluation in subsequent cohorts based on safety assessments by the DEC (Section 3.1.3). This strategy may require addition of subjects at specific dose levels, which may result in an increase in the total number of cohorts and/ or subjects enrolled in the study.

The flexible dose escalation scheme also allows further escalation to doses higher than 300 mg (up to a maximum of 400 mg) if necessary due to PK or PD reasons and if supported by safety results from an interim data review. This scheme also allows for expansion of the 300 mg cohort (or lower dose cohort) if necessary to further characterize DX-2930 (such as for safety, PK, or exploratory assessments) and if supported by review of safety data from previous cohorts. This safety review will be conducted after all subjects in the 300 mg cohort have been assessed through at least Day 29. Cumulative safety data from earlier cohorts will also be included in the review. In addition, any available and relevant PK or exploratory data, together with available PK data from the Phase 1a study, will be used to assess if a need exists to escalate beyond 300 mg and to confirm that the nonclinical toxicity data provide adequate safety margins.

3.1.3 Dose Escalation Committee (DEC) Safety Review

The DEC will consist of the Medical Monitor and the Dyax Medical Director. To assist in the safety assessments, the DEC may request that Investigators, other experts, or members within their organizations review the data and participate in the discussions.

Blinded safety data will be evaluated by the DEC at each dose escalation stage (safety data through 14 days after the second dose is administered [Day 29] to all subjects in the current cohort). This evaluation will include a review of AE/SAE reports, vital signs assessments, physical examinations, 12-lead ECGs and clinical laboratory testing. The seriousness, severity, and relatedness of adverse events (AEs)/serious adverse events (SAEs) will also be considered in the safety evaluation. (For definitions of AE, SAE, severe AE, and relatedness, please refer to Section 6.13). Cumulative safety data from any earlier cohort(s) will also be included in the review as needed.

Escalation to the next highest dosing cohort (Section 3.1.4) will only proceed if there are no safety concerns at the lower dose as determined by the DEC.

The DEC will also review the safety data, and any available and relevant PK or exploratory data, after all subjects in the 300 mg cohort have completed at least Day 29 follow-up to determine if escalation to doses higher than 300 mg or expansion of the 300 mg (or lower) dosing cohort is warranted.
3.1.4 Dose Escalation Rules

Adverse events will be reviewed in a blinded manner and graded using the 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). Dose-limiting toxicity (DLT) will generally be defined as clinically significant, severe (Grade 3) AEs occurring in ≥2 subjects that are determined to be related to DX-2930.

The following general rules regarding assessment of AEs and dose escalation will be followed:

a) If 1 subject in the cohort (6 total subjects) has a Grade 3 AE, no unblinding is necessary and escalation to the next dose cohort may proceed.

b) If 2 or more subjects in the cohort (6 total subjects) have Grade 3 AEs that are determined to be clinically significant and related to study drug, the Sponsor may break the blind to determine if the events occurred in DX-2930 recipients. Determination of clinical significance and relatedness and decisions regarding breaking the blind will be based on clinical judgment and experience. If the AEs occurred in subjects that received DX-2930, then the current dosing cohort may be expanded by an additional 3 (2 active + 1 placebo) or 6 (4 active + 2 placebo) subjects for further evaluation. If it is determined that it would not be safe to proceed with further treatments at that same dose level of DX-2930, then DLT is declared and no further treatments at that dose level may be recommended. Subsequent dosing may be modified to an intermediate dose that is lower than the current dosing cohort but higher than the prior cohort. Alternatively, depending on the nature of the AEs (i.e. degree of clinical significance, organ or system involved), escalation to a dose intermediate between the current and next planned dose level may be recommended. Otherwise, if there are no major safety concerns (e.g., both subjects with the Grade 3 AEs had received placebo), the dose escalation may proceed as planned.

c) If any subject experiences a life-threatening AE (Grade 4) that is study drug-related, and unblinding reveals that the subject had received DX-2930, any further dosing may be suspended pending thorough data review.

3.1.5 Study Stopping Rules

The occurrence of a study drug-related SAE in any subject who is shown by unblinding to have received DX-2930 (see Section 5.4) may result in suspension of any further dosing in the study by the Medical Monitor until the DEC has evaluated the event and determined the next appropriate course of action. At any time during the study, the study may be discontinued if the DEC determines that further drug exposure would pose an undue risk to subjects.
3.1.6 Individual Stopping Rules

Dosing for any individual subject will be discontinued (i.e. further treatment with the study medication will not be given) if the subject experiences a DX-2930-related SAE or a DX-2930-related, significant non-serious AE that, in the opinion of the Investigator and Medical Monitor, warrants discontinuation from further dosing for that subject’s well-being. Any occurrence of a DX-2930-related clinically significant, severe (or Grade 3) toxicity may also terminate further dosing in a subject at the discretion of the Investigator and the Medical Monitor.

3.1.7 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 Study Design and Control Group

The planned range of DX-2930 dosing for the clinical development program is based upon estimation of the level of plasma kallikrein inhibition necessary to attain effective prophylaxis against HAE attacks. It is hypothesized that the necessary molar concentration of DX-2930 will correspond to the average $C_{\text{max}}$ attained following administration of Kalbitor (ecallantide) in treating acute HAE attacks. The EDEMA3 and EDEMA4 clinical trials demonstrated that a 30 mg SC dose of ecallantide is effective in the treatment of acute HAE attacks (KALBITOR® U.S. Package Insert). In principle, maintaining this level of plasma kallikrein inhibition continuously may prevent HAE attacks from occurring. According to this hypothesis, DX-2930 dosing to maintain steady state plasma concentrations above 80 nM will be necessary for HAE attack prophylaxis. Alternatively, a lower DX-2930 dose may be necessary if blockade of plasma kallikrein at an early stage when levels of plasma kallikrein activity are low could conceivably prevent the activation of a positive feedback loop. Conversely, a higher dose may be necessary if DX-2930 is not as potent as ecallantide in vivo in HAE patients.

As typical of most Phase 1 multiple dose studies, evaluation across a dose range that encompasses the anticipated therapeutic dose is planned for this DX-2930 multiple dose study in HAE subjects. Safety and PK data, together with PD and other exploratory data, will inform the design of a subsequent Phase 2 study to evaluate DX-2930 for long-term HAE prophylaxis.

A conservative starting dose of 30 mg per dose is planned for the present study, with escalation to 100 and then 300 mg in a flexible dose escalation scheme. Dose escalations will occur only after safety and tolerability data through 14 days after the second dose for all
subjects in a cohort have been reviewed and after the DEC has confirmed that it would be safe to proceed to a higher dose. The study uses a placebo control for comparison of safety and other effects of DX-2930.

It is theoretically possible that 300 mg may still not provide adequate plasma kallikrein inhibition relevant to what is hypothesized as necessary as for HAE prophylaxis, either on a PK or PD basis. The flexible dose escalation scheme therefore allows escalation to doses higher than 300 mg (up to a maximum of 400 mg) if necessary and if supported by the cumulative safety results.

3.3 Study Duration

The duration of individual subject participation, from enrollment until final follow-up, will be approximately 120 days (17 weeks). Eligibility screening will be performed up to 28 days prior to Day 1 enrollment and first dosing. Subjects will receive the second dose on Day 15. After the second dose, follow-up visits for safety assessments and anti-drug antibody, PK, C1-INH and biomarker sampling will occur at regular intervals until the final study visit on Day 120.
4 STUDY POPULATION SELECTION

4.1 Study Population

Eighteen (18) HAE subjects (4 active and 2 placebo subjects per cohort) will be enrolled across 3 dosing cohorts. The flexible dose escalation scheme will allow, if necessary, enrollment of up to 18 additional subjects (12 active, 6 placebo) for a maximum of 36 subjects treated in the study. Subjects will be enrolled only once in the study and will not be included in subsequent dosing cohorts. Subjects who do not receive both doses of study drug may be replaced. Subjects who do not receive both doses of study drug will still continue to be followed through completion of all scheduled visits.

4.2 Inclusion Criteria

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

1. At least 18 years of age 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).
   - C1 inhibitor (C1-INH) antigen or functional level < 40% of the normal level. Subjects with C1-INH antigen or functional level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range and a family history consistent with HAE Type I or II. Test results must have been obtained within 5 years of enrollment.
   - Age at reported onset of first angioedema symptoms ≤ 30 years or a family history consistent with HAE Type I or II.
3. Experiencing ≥2 HAE attacks per year, with at least 1 attack in the past 6 months reported by the subject.
4. Willing and able to read, understand, and sign an informed consent form (ICF).
5. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception from the Screening Period through 30 days after the final study visit: progestin-only oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. Female subjects must agree to practice the above birth control methods for 30 days after the final study visit as a safety precaution.
6. 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.
7. Males with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through
60 days after the final study visit. All male subjects, including males who are surgically sterile (post vasectomy), must agree to practice the above birth control methods for 60 days from the final study visit as a safety precaution.

4.3 Exclusion Criteria

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

1. Any exposure to an investigational drug or device within 90 days prior to initial study treatment.

2. Any prior history of exposure within the past 5 years to a monoclonal antibody or recombinant protein bearing an Fc domain (such as a soluble receptor-Fc fusion protein).

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

4. Use of long-term prophylaxis for HAE (use of C1-INH for long-term prophylaxis, attenuated androgens, or anti-fibrinolytics) within 90 days prior to initial study treatment.

5. Use of C1-INH for short-term prophylaxis and/or on-demand treatment for an HAE attack that exceeds a total of 30 days within the past 90 days prior to initial study treatment; any use of C1-INH within 7 days prior to initial study treatment.

6. Any exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 90 days prior to initial study treatment.

7. Any exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 90 days prior to initial study treatment.

8. Presence of an indwelling catheter.

9. Diagnosis of HIV.

10. Active liver disease (e.g., Acute or chronic hepatitis B or C, alcoholic or non-alcoholic steatohepatitis).

11. 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 > 1.5x upper limit of normal (unless subject has known Gilbert’s Syndrome).

12. History of substance abuse or dependence.

13. Pregnancy or breastfeeding.

14. Subject has any condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of study results).
5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

For detailed information regarding study drug 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 in 30 mM sodium phosphate, 8.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Tween 80. All formulation components are compendial. Each vial contains a nominal concentration of 100 mg DX-2930 active ingredient in 1 mL solution. The test product will be administered by subcutaneous injection into the upper arm.

Subjects randomized to receive active study drug will receive one of the pre-defined fixed doses (30, 100, or 300 mg) or an intermediate dose as defined by the DEC following a cohort safety evaluation (Section 3.1.3). If necessary and if supported by the DEC’s review of the cumulative safety data, dose escalation beyond 300 mg may occur (up to a maximum of 400 mg).

For the 30 mg cohort, each subject will receive 0.3 mL in a single SC injection; for the 100 mg cohort, each subject will receive 1 mL in a single SC injection; and for the 300 mg cohort, each subject will receive 3 mL, which may be divided into 2 separate SC injections. The vehicle for the solution will be the placebo (Section 5.1.2). If escalation to doses above 300 mg occurs, the doses will be divided such that no single SC injection consists of more than 2 mL. When more than one injection is required, the injections will be given in the same arm.

5.1.2 Placebo

Placebo consists of the inactive formulation of the test product: 30 mM sodium phosphate, 8.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, pH 6.0 with 0.01% Tween 80. For subjects randomized to receive placebo, the volume of placebo administered will be the same as the total volume for an active dose within the placebo subjects’ assigned dose cohort. Placebo will be administered by subcutaneous injection into the upper arm. When more than one injection is required, the injections will be given in the same arm.

5.2 Cohort Dosing

Eligibility screening will be performed up to 28 days prior to Day 1 enrollment and first dosing. Any subject experiencing an HAE attack (even if resolving or limited to prodromal symptoms) on Day 1 will have their visit postponed for at least 72 hours after their attack has resolved. Eligible subjects will be randomized to receive two doses of DX-2930 or placebo within one of the following sequential, ascending dose cohorts: 30, 100, or 300 mg. Subjects in this study can only be enrolled once and will not be included in subsequent dosing cohorts.
Subjects will receive the first dose of blinded study drug on Day 1 and will be monitored at the treatment site through 4 hours post-dose. Follow-up visits after the first dose will be made on Days 2, 4 and 8. Subjects will receive the second dose of study drug at the same dose on Day 15 and will be monitored at the treatment site through 4 hours post-dose. Follow-up visits after the second dose will occur on Days 16, 18, 22, 29±1, 36 ±1, 50 ±2, 64 ±2, 92 ±3, and 120 ±3. The total duration of study participation for each individual subject will be up to 120±3 days from enrollment until the final follow-up visit (Study Activities Schedule, Appendix 1). Optional visits to the clinic (up to a maximum of 4 per subject, of which no more than 1 can be within the first 36 days following enrollment unless they occur at the same time as a planned study visit) may occur for evaluation of acute HAE attacks.

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 either 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

This is a randomized, double-blinded, placebo-controlled trial. Subjects will be randomized to receive either DX-2930 or placebo within each cohort. Subjects will be blinded to the treatment administered until enrollment is complete and the database is locked. Investigators and site personnel will be blinded to subject treatment until enrollment is complete and the database is locked. The sponsor will be blinded to the treatment administered through the completion of at least the Day 36 follow-up visit for the last subject in the 300 mg dosing cohort (or highest dosing cohort if the highest dose is lower than 300 mg). At that point, an interim analysis of data through at least Day 36 will be conducted (Section 9.9). In accordance with the flexible dose schema, additional cohorts may be added following a DEC review and/ or interim analysis. Additional interim analyses may be conducted following the initial interim analysis. The sponsor will review interim analysis data in an unblinded fashion but a blinded medical monitor will be retained to assess safety for the remainder of the study follow-up period.

If necessary for the DEC’s safety evaluation, the Sponsor may break the blind to determine if adverse events occurred in DX-2930 recipients.

In the event of a drug-related SAE, the Investigator will contact and consult with the Medical Monitor regarding emergency unblinding of treatment assignment for the subject. The Investigator or the Medical Monitor can obtain the treatment assignment for the subject through the IWRS. In the event of a drug-related, serious, unexpected AE, the Dyax Pharmacovigilance Department may 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 within 30 days before administration of the first dose of study drug.

All information on concomitant therapy (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.
- 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 (use of C1-INH therapy 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 investigational drug or device

5.6 **Restrictions**

5.6.1 **Medical Interventions**

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

5.6.2 **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

The two doses of study drug will be administered under the direct supervision of the Investigator or qualified site personnel designated by the Investigator.

5.8 Packaging and Labeling

The test products (active and placebo) will be supplied by Dyax Corp. 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 (2°C to 8°C/36°F to 46°F) in the carton and protected from light, in a securely locked area, accessible to authorized persons only, until needed for dose preparation. Qualified site personnel will inventory the investigational product received and will maintain records of disposition of the drug, including dates, quantity and use.

5.10 Investigational Product Retention at Study Site

The Investigator (or designee) is responsible for maintaining accurate accountability records of the investigational product throughout the clinical study. All study drug 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. Study drug accountability will be verified during on-site monitoring visits.

Upon the completion or termination of the study, and upon written authorization from the Sponsor, or its representative, all unused and/or partially used study drug 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 study drug have been established, and that appropriate records of the disposal are documented and maintained. No unused study drug may be disposed until fully accounted for by the Sponsor monitor (or designee).
6 STUDY PROCEDURES

6.1 Informed Consent

The ICF must be executed prior to performing any study related activities and must be approved by the reviewing institutional review board (IRB) or independent ethics committee (IEC). Informed consent 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 Demographics and Medical History

6.2.1 Demographics and General Medical History

Demographics (age, gender, race and ethnicity) and medical history will be obtained from the subject and recorded on the source document and eCRF. Medical history will capture the subject’s current medical status (current disease processes), past medical status (past disease processes), history of surgery, allergies and concomitant medications.

6.2.2 HAE Attack Information

Prior to enrollment, HAE attack history will be collected and recorded in the eCRF. Information collected by the Investigator will include any prior history of laryngeal attacks, attack frequency, severity, location, duration, and acute attack therapy use.

In addition, subjects will be asked to report to their Investigator any HAE attacks they experience during the course of the study. Collection of clinical information regarding any such attacks will include attack location, severity, time of onset, duration, and treatment with any acute attack therapy. In addition, subjects will be encouraged, but not required, to come into the study site (maximum of 4 visits during the study, of which no more than 1 can be within the first 36 days following enrollment unless they occur at the same time as a planned study visit) for such attacks in order to have blood drawn for biomarker, C1-INH functional level, and PK testing. Subjects will be eligible to undergo this blood sample collection as long as they are assessed within 24 hours of symptom onset irrespective of if they have received any treatment for their attack. If the subject presents to the study site for an acute HAE attack during the study and it coincides with a scheduled study visit, the additional exploratory assessments and procedures (including blood draws) beyond what is already is scheduled will not be necessary for that visit.

Subjects will also be asked to report to their Investigator any use of acute attack treatment during the course of the study.

6.3 Physical Examination

A complete physical examination including height, weight and calculation of Body Mass Index (BMI) will be performed by the Investigator or his/her qualified designee according to
the Study Activities Schedule (Appendix 1). The findings of each examination will be recorded on the source documents and eCRF. The physical examination will include the following body systems:

- General appearance
- Head, eyes, ears, nose, and throat
- Neck
- Respiratory
- Cardiovascular
- Abdomen
- Neurologic
- Extremities
- Dermatologic
- Lymphatic

### 6.4 Vital Signs

Vital signs will be performed 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 oral 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.

### 6.5 Electrocardiography (ECG)

#### 6.5.1 12-Lead Electrocardiograms

A standard 12-lead ECG 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.

### 6.6 Clinical Laboratory Tests

#### 6.6.1 Laboratory Parameters

Laboratory testing (hematology, coagulation, urinalysis, serum chemistry, serologies, pregnancy tests, C1-INH antigen, C1-INH functional assay, C4, PK samples, and plasma anti-drug antibody testing) will be performed using established methods. In addition, blood samples will be obtained for exploratory laboratory biomarker assays to evaluate PD effects upon plasma kallikrein activity. Laboratory testing will be performed according to the Study Activities Schedule (Appendix 1). 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, PK, exploratory biomarker, anti-drug antibodies. Aliquots from the PK, biomarker 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 completes the study at Day 120, without any optional study site visits for acute HAE attacks, will be 400.1 mL. Up to an additional 81.6 mL could be drawn for any subject who agrees to come to the study site for an acute HAE attack (up to a maximum of 4 times during the study, of which no more than 1 can be within the first 36 days following enrollment unless they occur at the same time as a planned study visit). Please refer to the Laboratory Manual for more information.

Laboratory testing will include the following as in the Study Activities Schedule (Appendix 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

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

**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)
- Gamma-glutamyl transferase (GGT)
- Glucose
- Lactate dehydrogenase (LDH)
- Phosphate
- Magnesium
- Potassium
- Sodium
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid

**Urinalysis**

- Bilirubin
- Glucose
- Ketones
- Blood
- Nitrite
- pH
- Protein
- Specific gravity
- Microscopy (if urinalysis is abnormal)

**Serologies**

- HBsAg, HCV, and HIV

**Pregnancy Test**

- Serum or urine pregnancy test

**C1-INH Antigen and Functional Assay**

- Results of a C1-INH antigen or functional assay are required for eligibility assessment (test results must have been obtained within 5 years of enrollment). In addition, C1-INH functional levels will be collected during the study as an exploratory assessment of the
indirect effects of plasma kallikrein inhibition upon endogenous C1-inhibitor activity (Section 6.9).

**C4 Assay**

- C4 is required for eligibility assessment (must be lower than the normal range and obtained within 5 years of enrollment) for subjects with C1-INH antigen or functional level 40-50% of the normal level and a family history consistent with HAE Type I or II (Section 6.10).

**PK Sample Collection**

- As outlined in Section 6.8.

**Plasma Anti-Drug Antibody Testing**

- As outlined in Section 6.11.

**Exploratory Biomarker Sample Collection**

- As outlined in Section 6.12.

### 6.6.2 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.

### 6.7 Dispensing Study Drug

Instructions for preparation of each subcutaneous dose of study drug are provided in the Pharmacy Manual. The Principal Investigator or qualified site personnel will administer the assigned study drug. Information regarding administration of study drug is provided in the Pharmacy Manual.

Preparation and dispensing of the study drug will be handled by qualified site personnel as directed by the Principal Investigator at the study site. Instructions for safe handling of the study drug are provided in the Pharmacy Manual. The requirements for maintaining drug accountability are provided in Section 5.9 of this protocol.

### 6.8 Pharmacokinetic Assessments

Blood samples for the measurement of plasma DX-2930 concentration will be obtained according to the schedule in Table 1.
Table 1: Schedule of PK Sample Collection

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Study Drug Administration</th>
<th>PK Collection Timepoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Day 1</td>
<td>Single SC dose of DX-2930 or placebo</td>
<td>Pre-dose</td>
</tr>
<tr>
<td>Study Day 2</td>
<td>No dosing</td>
<td>Once at 24 ±2 hours post-dose</td>
</tr>
<tr>
<td>Study Day 4</td>
<td>No dosing</td>
<td>Once at 72 ±4 hours post-dose</td>
</tr>
<tr>
<td>Study Day 8</td>
<td>No dosing</td>
<td>Once on Study Day 8, 7 days ±6 hours from time of dosing on Day 1</td>
</tr>
<tr>
<td>Study Day 15</td>
<td>Single SC dose of DX-2930 or placebo</td>
<td>Pre-dose</td>
</tr>
<tr>
<td>Study Day 16</td>
<td>No further dosing</td>
<td>Once at 24 ±2 hours post-dose</td>
</tr>
<tr>
<td>Study Day 18</td>
<td>No further dosing</td>
<td>Once at 72 ±4 hours post-dose</td>
</tr>
<tr>
<td>Study Day 22</td>
<td>No further dosing</td>
<td>Once on Study Day 22, 7 days ±6 hours from time of dosing on Day 1</td>
</tr>
<tr>
<td>Study Days 29-92</td>
<td>No further dosing</td>
<td>Days 29 ±1, 36 ±1, 50 ±2, 64 ±2, and 92 ±3</td>
</tr>
<tr>
<td>Study Day 120 or ET</td>
<td>No further dosing</td>
<td>Day 120 ±3 or ET visit</td>
</tr>
</tbody>
</table>

DX-2930 PK non-compartmental parameter determinations following dosing on Days 1 and 15 will include:
- \( C_{\text{max}} \)
- \( t_{\text{max}} \)
- \( \text{AUC}_{0-t} \)

DX-2930 PK compartmental modeling parameter determinations following dosing on Days 1 and 15 will include:
- \( C_{\text{max}} \)
- \( t_{\text{max}} \)
- \( \text{AUC} \)
- \( t_{\frac{1}{2}} \)
- \( \text{Vd/F} \)
- \( \text{CL/F} \)

The PK analysis will be described in a separate Pharmacokinetic Analysis Plan.
6.9  **C1-INH Antigen and Functional Assay**

Results of a C1-INH antigen or functional assay are required at Screening for eligibility assessment. Test results must have been obtained within 5 years of enrollment or a new assay must be performed for Screening.

In addition, blood samples for an exploratory assessment of the indirect effects of plasma kallikrein inhibition upon endogenous C1-INH activity will be obtained by assaying C1-INH functional levels during the study. Blood samples for assay will be collected at pre-dose on Day 1 and Day 15 (prior to treatment with the second dose of study drug). Additional blood samples will be obtained on Days 29±1, 36±1, 64±2, 92±3 and 120±3. See the Study Activities Schedule (Appendix 1).

6.10  **C4 Assay**

Results of C4 assay are required at Screening for eligibility assessment for subjects with C1-INH antigen or functional level 40-50% of normal level and a family history consistent with HAE Type I or Type II. Test results must have been obtained within 5 years of enrollment or a new assay must be performed for Screening. See the Study Activities Schedule (Appendix 1).

6.11  **Plasma Anti-Drug Antibody Testing**

Plasma samples for testing for formation of antibodies to DX-2930 will be obtained at pre-dose on Day 1 and on Days 36 ±1, 64 ±2, 92 ±3, and the final study visit at Day 120 ±3 (or early termination).

6.12  **Exploratory Biomarker Testing**

To evaluate the pharmacodynamic effects of DX-2930 upon plasma kallikrein activity, blood samples will be collected at timepoints prior to and after study drug administration for exploratory biomarker assessments. These blood samples will be collected on the same schedule as for PK sample collection shown in Table 1 (Section 6.8).

6.13  **Adverse Event Reporting**

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

6.13.1  **Definitions**

6.13.1.1  **Adverse Event**

An AE is any untoward medical occurrence in a clinical trial subject that does not necessarily have a causal relationship with the treatment administered. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or
disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

- AEs may be new events or may be pre-existing conditions that have become aggravated or have worsened in severity or frequency.
- 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 study drug interruption or discontinuation, will be considered an 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 6.13.5.2.

6.13.1.2 Serious Adverse Event

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

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

6.13.1.3 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.

6.13.1.4 Planned Hospitalization

A hospitalization planned by the subject prior to the first dose of study medication 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.

6.13.1.5 Treatment-Emergent Adverse Events (TEAE)

An AE is treatment-emergent if the onset time is after administration of study drug through
the Day 120 post dose final follow-up visit or, in the event that onset time precedes study
drug administration, the AE increases in severity during the 120 day post dose follow-up
period.

6.13.2 Monitoring

6.13.2.1 Monitoring of Adverse Events

Each subject will be monitored for the occurrence of AEs, including SAEs, from signing of
the ICF through final follow-up on Day 120 ±3 days post dose.

- 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.

6.13.2.2 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.
6.13.3 Assessment of Adverse Events

6.13.3.1 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). 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 (<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

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.

6.13.3.2 Assessment of Causality

A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product, 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 drug exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of the investigational product.
- The AE resolved or improved with decreasing the dose or stopping use of the investigational product (dechallenge). Judgment should be used if multiple products are discontinued at the same time.
The causal relationship between the study medication 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 study medication); 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 study medication); 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 investigational product).

6.13.3.3 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 DEC for overall study AE review. Before each escalation to the next highest dosing cohort, a review of all safety data through 14 days following the second dose of study drug (Day 29) will be conducted by the DEC. Dose escalation will only proceed if the DEC has determined that it would be safe and appropriate to do so.

6.13.4 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 study drug interruption or discontinuation, will be considered an AE.

When laboratory abnormalities are considered to be AEs, the DMID Adult Toxicity Table (Appendix 2) 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 \textit{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 \textit{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, 2012). Despite the lack of clinical effect, deficiency of either protein is associated with marked prolongation of the aPTT.

6.13.5 Reporting Investigator Safety Observations to the Sponsor

6.13.5.1 Reporting Non-serious Adverse Events

All AEs, regardless of seriousness, severity, or causal relationship to study medication, will be recorded on the AE page of the eCRF.

6.13.5.2 Reporting Pregnancies

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, the Investigator must report the pregnancy to the Dyax Pharmacovigilance Department using the \textbf{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.

6.13.5.3 Safety Observations Requiring Expedited Reporting by the Investigator to Dyax

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

• SAE
• Overdose
• Cancer

The Investigator is to report any expedited safety observations from the list above to Dyax using the \textbf{SAE Reporting Form in the EDC system} within 24 hours of becoming aware of the event.
Any SAE reported to the Dyax Pharmacovigilance Department using the SAE Reporting Form in the EDC system is to be recorded in the eCRF, as well as in the subject's source documentation along with any actions taken. If all required information on the form is not available at the time of the initial report, follow-up information will be completed in the EDC system.

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

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

6.13.5.4 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.

6.13.5.5 Safety Contact Information

24-Hour Medical Safety Contact
Yung Chyung, MD
Medical Monitor
Phone (US): (617) 417-9114
Email: ychyung@dyax.com

Dyax Pharmacovigilance Department
Contacts: Marianne Reardon or Aimee Jackman
Email: drugsafety@dyax.com
Phone (US): (617) 250-5588

6.13.5.6 Safety Notifications by the Sponsor to the Investigator

Investigators will receive prompt notification of any adverse experience related to study medication that is both serious and unexpected, or any finding that suggests a significant risk for subjects. The Investigator will promptly inform his / her IRB/IEC of the notification and insert the notification in the Investigator’s Regulatory Binder in accordance with local regulations.
6.13.5.7 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 Dyax Pharmacovigilance Department may unblind the treatment of any subject.

6.14 Prior and Concomitant Medication Assessments

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 within 30 days before study entry and during the study will be regarded as concomitant medications and must be documented on the source document and eCRF following informed consent.

6.15 Subject Withdrawal

Subjects who do not receive both doses of study drug may be replaced. The Investigator may withdraw a subject from the trial for any of the following reasons:

- A protocol violation occurs,
- 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.

The criteria used by the DEC regarding dose administration suspension and/or study discontinuation as well as the DEC criteria for dose escalation suspension and/or discontinuation are provided in Section 3.1.

6.16 Appropriateness of Measurements

This is a Phase 1b double-blind, randomized, placebo-controlled multiple ascending dose study that is designed to evaluate the safety, tolerability and PK of multiple doses of DX-2930 in HAE subjects. 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 safety profiles of an active and placebo treatment when administered to subjects. All of the safety measures employed in this protocol are standard measures routinely used for the evaluation of the 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 Visit (Day -28 to Day -1)

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

- Informed consent (Section 6.1)
- Eligibility review (Section 4.2 and Section 4.3)
- Demographics and medical history (Section 6.2)
- Complete physical examination (Section 6.3) including documentation of height, weight and calculation of BMI
- Vital signs including oral body temperature, HR, BP and RR (Section 6.4)
- 12-Lead ECG (Section 6.5)
- Laboratory testing including HBsAg, HCV, and HIV screening, serum or urine pregnancy test (females), hematology, coagulation, serum chemistry and urinalysis (Section 6.6)
- If historical results are not within the past 5 years, C1-INH antigen or functional assay sample collection (Section 6.9)
- If historical results are not within the past 5 years, C4 assay sample collection (results of C4 assay are required for eligibility assessment only for subjects with C1-INH antigen or functional level 40-50% of the normal level and a family history consistent with HAE Type I or II) (Section 6.10)
- Prior and concomitant therapy (Section 6.14)
- AE Collection (Section 6.13); pre-existing signs and symptoms

7.2 Enrollment and First Treatment (Day 1)

The following procedures and assessments are to be performed at Enrollment on Day 1 prior to the first dose of study drug administration:

- Eligibility review (Section 4.2 and Section 4.3)
- Complete physical examination (Section 6.3)
- Vital signs including oral body temperature, HR, BP and RR (Section 6.4)
- 12-Lead ECG (Section 6.5)
• Laboratory testing including serum or urine pregnancy test (females), hematology,
coagulation, serum chemistry and urinalysis (Section 6.6)
• C1-INH functional assay sample collection (Section 6.9)
• PK baseline sample collection (Section 6.8)
• Exploratory biomarker sample collection (Section 6.12)
• Plasma anti-drug antibody testing (Section 6.11)
• Prior and concomitant therapy (Section 6.14)
• AE collection (Section 6.13)
• HAE attack information (Section 6.2)
• Randomization to DX-2930 or placebo

After the preceding procedures and assessments are completed:
• Administer study drug (Section 5.2)

After administration of study drug, the following post treatment procedures and
assessments will be performed:
• Abbreviated physical examination to include general, skin, cardiovascular, pulmonary,
abdomen and extremities (Section 6.3) at 4 hours ±15 minutes post-dose
• Vital signs including HR, BP and RR (Section 6.4) at 1, 2, and 4 hours ±15 minutes post-
dose
• Concomitant therapy (Section 6.14)
• AE collection (Section 6.13)

7.3 Follow-up: Day 2

On Day 2, the following procedures and assessments will be performed at approximately
24 ±2 hours following administration of study drug on Day 1:
• Concomitant therapy (Section 6.14)
• AE collection (Section 6.13)
• HAE attack information (Section 6.2)
• PK sample collection (Section 6.8)
• Exploratory biomarker sample collection (Section 6.12)

7.4 Follow-up: Day 4

On Day 4, the following procedures and assessments will be performed at approximately
72 ±4 hours following administration of study drug on Day 1:
• Concomitant therapy (Section 6.14)
- AE collection (Section 6.13)
- HAE attack information (Section 6.2)
- PK sample collection (Section 6.8)
- Exploratory biomarker sample collection (Section 6.12)

7.5 Follow-up: Day 8

On Day 8, the following procedures and assessments will be performed at approximately 7 days ±6 hours from the time of dosing on Day 1:

- Complete physical examination (Section 6.3)
- Vital signs including oral body temperature, HR, BP and RR (Section 6.4)
- 12-Lead ECG (Section 6.5)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.6)
- PK sample collection (Section 6.8)
- Exploratory biomarker sample collection (Section 6.12)
- Concomitant therapy (Section 6.14)
- AE collection (Section 6.13)
- HAE attack information (Section 6.2)

7.6 Day 15 Second Dosing

The following procedures and assessments are to be performed on Day 15 prior to the dose of study drug administration:

- Complete physical examination (Section 6.3)
- Vital signs including oral body temperature, HR, BP and RR (Section 6.4)
- 12-Lead ECG (Section 6.5)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.6)
- C1-INH functional assay sample collection (Section 6.9)
- PK sample collection (Section 6.8)
• Exploratory biomarker sample collection (Section 6.12)
• Concomitant therapy (Section 6.14)
• AE collection (Section 6.13)
• HAE attack information (Section 6.2)

**After the preceding procedures and assessments are completed:**

• Administer study drug (Section 5.2)

**After administration of study drug, the following post-treatment procedures and assessments will be performed:**

• Abbreviated physical examination to include general, skin, cardiovascular, pulmonary, abdomen and extremities (Section 6.3) at 4 hours ±15 minutes post-dose
• Vital signs including HR, BP and RR (Section 6.4) at 1, 2, and 4 hours ±15 minutes post-dose
• Concomitant therapy (Section 6.14)
• AE collection (Section 6.13)

### 7.7 Follow-up: Day 16

On Day 16, the following procedures and assessments will be performed at approximately 24 ±2 hours following administration of study drug on Day 15:

• Concomitant therapy (Section 6.14)
• AE collection (Section 6.13)
• HAE attack information (Section 6.2)
• PK sample collection (Section 6.8)
• Exploratory biomarker sample collection (Section 6.12)

### 7.8 Follow-up: Day 18

On Day 18, the following procedures and assessments will be performed at approximately 72 ±4 hours following administration of study drug on Day 15:

• Concomitant therapy (Section 6.14)
• AE collection (Section 6.13)
• HAE attack information (Section 6.2)
• PK sample collection (Section 6.8)
• Exploratory biomarker sample collection (Section 6.12)
7.9 Follow-up: Day 22

On Day 22, the following procedures and assessments will be performed at approximately 7 days ±6 hours from the time of dosing on Day 15:

- Complete physical examination (Section 6.3)
- Vital signs including oral body temperature, HR, BP and RR (Section 6.4)
- 12-Lead ECG (Section 6.5)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis (Section 6.6)
- PK sample collection (Section 6.8)
- Exploratory biomarker sample collection (Section 6.12)
- Concomitant therapy (Section 6.14)
- AE collection (Section 6.13)
- HAE attack information (Section 6.2)

7.10 Follow-up Visits: Days 29 ±1, 36 ±1, 50 ±2, 64 ±2, and 92 ±3

The following procedures and assessments will be performed during the subject’s scheduled study visit:

- Complete physical examination only on Days 29 ±1, 36 ±1, 64 ±2, and 92 ±3 (Section 6.3)
- Vital signs including oral body temperature, HR, BP and RR only on Days 29 ±1, 36 ±1, 64 ±2, and 92 ±3 (Section 6.4)
- 12-Lead ECG only on Day 36 ±1 (Section 6.5)
- Laboratory testing including hematology, coagulation, serum chemistry and urinalysis only on Days 29 ±1, 36 ±1, 64 ±2, and 92 ±3 (Section 6.6)
- C1-INH functional assay sample collection only on Days 29 ±1, 36 ±1, 64 ±2, and 92 ±3 (Section 6.9)
- PK sample collection on Days 29 ±1, 36 ±1, 50 ±2, 64 ±2, and 92 ±3 (Section 6.8)
- Exploratory biomarker sample collection on Days 29±1, 36±1, 50±2, 64±2, and 92 ±3 (Section 6.12)
• Plasma anti-drug antibody testing on Days 36±1, 64±2, and 92±3 (Section 6.11)
• Concomitant therapy (Section 6.14)
• AE collection (Section 6.13)
• HAE attack information (Section 6.2)

7.11 Optional Study Site Visit for Acute HAE Attack(s) During Study

If the subject presents to the study site for an acute HAE attack during the study and it coincides with a scheduled study visit, the additional exploratory assessments and procedures (including blood draws) beyond what is already is scheduled will not be necessary for that visit. The following procedures and assessments will be performed during the subject’s optional study visit:

• Abbreviated physical examination to include general, skin, cardiovascular, pulmonary, abdomen and extremities (Section 6.3)
• Vital signs including oral body temperature, HR, BP and RR (Section 6.4)
• C1-INH functional assay sample collection (Section 6.9)
• PK sample collection (Section 6.8)
• Exploratory biomarker sample collection (Section 6.12)
• Concomitant therapy (Section 6.14)
• AE collection (Section 6.13)
• HAE attack information (Section 6.2)

7.12 Final Follow-up Visit: Day 120 ±3 or Early Termination Visit

The following procedures and assessments will be performed during the subject’s final follow-up or early termination (ET) visit:

• Complete physical examination (Section 6.3)
• Vital signs including oral body temperature, HR, BP, and RR (Section 6.4)
• 12-Lead ECG (Section 6.5)
• Laboratory testing including serum or urine pregnancy test (females), hematology, coagulation, serum chemistry and urinalysis (Section 6.6)
• C1-INH Functional assay sample collection (Section 6.9)
- PK sample collection (Section 6.8)
- Exploratory biomarker sample collection (Section 6.12)
- Plasma anti-drug antibody testing (Section 6.11)
- Concomitant therapy (Section 6.14)
- AE collection (Section 6.13)
- HAE attack information (Section 6.2)
- Discharge from study
8 QUALITY CONTROL AND ASSURANCE

The Sponsor (Dyax) and the Contract Research Organization (CRO) conducting trial management services (Aptiv Solutions) will implement a system of quality assurance that includes all elements described in this protocol. Within this system, SOPs from the Sponsor and Aptiv Solutions 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 PLANNED STATISTICAL METHODS

This is a Phase 1b safety, tolerability, and PK study of DX-2930 in HAE subjects. The study includes exploratory analyses of PD effects of DX-2930 on plasma kallikrein concentrations, indirect effects of plasma kallikrein inhibition on endogenous C1-INH activity and characterization of HAE attacks and acute therapy use by subjects while on study. A Statistical Analysis Plan (SAP) and a Pharmacokinetic Analysis Plan (PAP) will be finalized prior to database lock.

## 9.1 General Considerations

Data will be described and analyzed using the SAS System, Version 9.3 or greater (SAS Institute Inc., Cary, NC, SAS System). Individual subject data will be presented in subject data listings. Descriptive statistics including number of subjects (N), mean, standard deviation (SD), median, and minimum and maximum will be presented for continuous data. For categorical data, frequency and percentage of subjects in each category will be presented.

All demographic and safety data will be listed and summarized in tabular format using descriptive statistics for continuous variables and frequency and percentages for discrete variables. Missing data will not be imputed. Descriptive data will be tabulated to best represent the baseline characteristics of the prospectively enrolled randomized treatment groups. Additional exploratory analyses may be performed.

## 9.2 Determination of Sample Size

Approximately 18 to 36 HAE subjects will be enrolled across multiple clinical sites according to the flexible dose escalation scheme (Section 3.1.2). The estimated sample size has been chosen to provide adequate numbers of subjects to characterize the safety, tolerability, and PK of DX-2930. Overall, the total number of subjects evaluated will depend on the emerging DX-2930 safety and PK profile as determined by the DEC. Depending on DEC findings, the number of subjects may be expanded by the addition of subjects within a dosing cohort or inclusion of additional dose cohorts at intermediate doses or at dose(s) higher than 300 mg in order to further characterize DX-2930.

## 9.3 Analysis Populations

All safety analyses will be based on the Safety Population, which includes randomized subjects who received at least one dose of study drug.

The PK data analysis will be based on the PK Population, which includes the subjects in the Safety Population who have sufficient blood samples to obtain a plasma concentration vs. time profile.

## 9.4 Disposition of Subjects

The number and percentage of subjects entering and completing the clinical study will be presented, stratified by dose group.
9.5 **Demographics and Baseline Characteristics**

All demographic and baseline characteristic data will be listed and summarized in tabular format using descriptive statistics for continuous variables and frequency and percentages for discrete variables.

9.6 **Statistical Analysis of PK Variables**

DX-2930 plasma level determinations will be performed using blood samples collected at pre-and post-dosing through the final follow-up visit (Day 120). These determinations will be used to calculate the multiple dose PK profiles for each dose level administered. Non-compartmental methods will allow calculation of $C_{\text{max}}$, $t_{\text{max}}$ and $AUC_{0-t}$ during the sample collection period. Compartmental PK models will be generated to describe the underlying PK behavior of DX-2930 based on data after both doses. Compartmental PK predictions will include $C_{\text{max}}$, $t_{\text{max}}$, AUC, Vd/F, CL/F, and $t\frac{1}{2}$ as appropriate. Individual and summary PK parameters will be listed and summarized in tabular format using descriptive statistics for continuous variables and frequency and percentages for discrete variables. Missing data will not be imputed.

9.7 **Safety Analysis**

Safety measures include AEs, clinical laboratory tests, physical examinations, ECG determinations and vital signs. The Medical Dictionary for Regulatory Activities (MedDRA) (most recent version) coding system will be used for System Organ Class (SOC) and preferred term classification of AEs. All safety data will be listed and summarized in tabular format using descriptive statistics for continuous variables and frequency and percentages for discrete variables.

9.7.1 **Adverse Events**

The proportion of participants experiencing AEs and SAEs for DX-2930 or placebo will be computed by dose received and overall. Proportions will be computed for all events and for related events only, and for both AEs and SAEs separately and together.

9.7.2 **Clinical Laboratory Tests**

Individual data listings of laboratory results will be presented for each subject. Flags will be attached to values outside of the laboratory’s reference limits along with the Investigator’s assessment. Clinically significant worsening from baseline or new clinically significant laboratory test abnormalities that were considered AEs by the Investigator will be presented in the AE analyses. Clinical laboratory tests (observed values) will be summarized descriptively in tabular format. Shift tables will be presented for select laboratory parameters (chemistry and hematology).
9.7.3 Physical Examinations

Abnormal physical examination findings will be listed. Clinically significant worsening from baseline or new clinically significant physical examination abnormalities that were considered AEs by the Investigator will be presented in the AE analyses.

9.7.4 Vital Signs

Individual data listings of vital signs (observed and change from baseline) will be presented for each subject. Clinically significant worsening from baseline or new clinically significant vital sign findings that were considered AEs by the Investigator will be presented in the AE analyses. Observed values as well as change from baseline data will be summarized descriptively in tabular format.

9.7.5 Electrocardiogram

Twelve-lead ECG data (observed and change from baseline) will be listed for each subject and time point. Observed values as well as change from baseline will be summarized descriptively in tabular format. Clinically significant worsening from baseline or new clinically significant ECG abnormalities that were considered AEs by the Investigator will be presented in the AE analyses.

9.7.6 Anti-drug Antibody Testing

DX-2930 plasma anti-drug antibody data will be listed and summarized in tabular format using descriptive statistics.

9.8 Other Assessments or Analyses

Exploratory analyses may be performed to evaluate PD effects of DX-2930 through exploratory biomarkers and to characterize HAE attacks and acute attack therapy usage occurring during the study. In addition, an exploratory assessment of the indirect effects of plasma kallikrein inhibition upon endogenous C1-INH activity may be performed.

9.9 Interim Analysis

In preparation for a subsequent Phase 2 study (dose-ranging and proof of concept study in HAE subjects), an interim analysis after at least 6 subjects have reached Day 36 of the 300 mg cohort is planned by the Sponsor, unless the highest dose level in the study is lower than 300 mg, in which case the interim analysis will be conducted after at least 6 subjects at the highest dose cohort have reached Day 36. This interim analysis will include all safety and subject information as well as any available and relevant PK, anti-drug antibody, and exploratory assessment data collected across all dosing cohorts leading up to and including the highest dose cohort.

Unblinded, aggregate safety data will be reviewed across all dosing cohorts and by individual cohort to identify any safety signals. Available PK data, safety data, and results of
exploratory analyses will be evaluated to guide selection of dose levels for the Phase 2 study. In accordance with the flexible dose schema, additional cohorts may be added following a DEC review and/or interim analysis.

Additional interim analyses may be conducted following the initial interim analysis.

A blinded medical monitor will be retained to assess safety for the remainder of the study follow-up period.
10 STUDY ADMINISTRATION

10.1 Study Administrative Structure

The study administration structure is provided in Table 2.

Table 2: Study Administrative Structure

| Sponsor Contact: | Ryan Iarrobino  
Senior Director, Clinical Development  
55 Network Drive, Burlington, MA 01803  
Phone: 617-250-5574  
Email: riarrobino@dyax.com |
|------------------|--------------------------------------------------|
| Sponsor Medical Director and Medical Monitor*: | Yung Chyung, MD  
Vice President, Medical Research  
55 Network Drive, Burlington, MA 01803  
Phone: 617-250-5549  
Email: ychyung@dyax.com |
| Blinded Medical Monitor: | Christopher Stevens, MD  
Dyax Corp.  
55 Network Drive, Burlington, MA 01803  
Phone: 617-250-5732  
Email: cstevens@dyax.com |
| Study Monitoring (US and Italy): | Aptiv Solutions  
4505 Emperor Boulevard, Suite 400  
Durham, NC 27703  
Phone (Main): 919-401-1800  
Email: dyaxclinops@aptivsolutions.com |
| Study Monitoring (Jordan): | Triumpharma  
07 Bldg., Al-Yarooty St.  
P.O. Box 2233, Amman  
11941, Jordan  
Phone: +962 6 5350582, 5358733  
Email: ahmad@triumpharma.com |

*Yung Chyung assumed the Medical Monitor role on 01 January 2015 following the departure of the previous Medical Monitor from Aptiv Solutions.

10.2 Institutional Review 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/IEC in accordance with GCP prior to implementation. In addition, the IRB/IEC must approve the written informed consent form, any consent 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/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/IEC be documented in a letter from the IRB/IEC. The Investigator must provide notification to the IRB/IEC of the completion, termination or discontinuation of the study.

10.3 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)].

10.4 Subject Information and Consent

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

10.5 Subject Confidentiality

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number, initial or birth date, 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.

10.6 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 Sponsor’s 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.

10.7 Case Report Forms and Study Records

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

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

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

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB/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.

10.8 Dose Escalation Committee

The DEC will be responsible for confirming the safety of the investigative product prior to dose escalation. In addition, over the course of the study, the DEC will review any drug-related SAEs to determine if modifications to the study or other measures are necessary to ensure the safety of the subjects. The DEC will consist of the Dyax Medical Director and the Medical Monitor. To assist in the safety assessments, the DEC may request that investigators, other experts, or members within their organizations review the data and participate in the discussions.
10.9 Protocol Violations/Deviations

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

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

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/IEC. Such audits/inspections may take place at the Sponsor’s site(s), Aptiv Solutions, 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 consistency. Edit check programs, other forms of electronic validation, manual listings and a query process will be executed to verify the accuracy of the database. The EDC system will maintain a full audit trail of electronic data changes. Access to all source documentation will be made available for monitoring and audit purposes.
10.12 Retention of Data

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

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

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

10.13 Financial Disclosure

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

10.14 Publication and Disclosure Policy

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

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


The Common Terminology Criteria for Adverse Events (CTCAE) v4.0; National Cancer Institute 2013.


## Appendix 1  
### Study Activities Schedule

<table>
<thead>
<tr>
<th>Tests and Assessments</th>
<th>Screening</th>
<th>Day 1 Prior to Dosing</th>
<th>Day 1 Dosing</th>
<th>Day 1 Post Dosing</th>
<th>Day 2</th>
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<th>Day 8</th>
<th>Day 15 Prior to Dosing</th>
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<th>Day 15 Post Dosing</th>
<th>Day 16</th>
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<th>Day 22</th>
<th>Days 29±1, 36±1, 50±2, 64±2, &amp; 92±3</th>
<th>Final Visit Day 120±3 or ET Visit</th>
<th>Optional Study Site Visit(s) for Acute HAE Attack(s) During Study14</th>
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EGC = electrocardiogram; PK = pharmacokinetic; ET = early termination

*Note: During this outlined period (Day 29 through Day 92), physical examination, vital signs, and safety laboratory tests (hematology, coagulation, serum chemistry, and urinalysis) will occur on Days 29±1, 36±1, 64±2, and 92±3. During this period laboratory test for C1-INH Function will occur on Days 29±1, 36±1, 64±2 and 92±3. During this period, anti-drug antibody testing will be conducted on samples obtained on Days 36±1, 64±2, and 92±3. 12-lead ECG will be performed at Day 36±1 during this outlined period.

1 Height, weight and calculation of BMI will be additional assessments conducted at this timepoint.
2 This physical examination will be abbreviated and include General, Skin, Cardiovascular, Pulmonary, Abdomen, and Extremities. (For Day 1 post-dosing and Day 15 post-dosing, this examination will occur at 4 hours ±15 minutes).
3 Documentation of vital signs including oral body temperature, HR, BP, and RR. On Day 1 post-dosing and Day 15 post-dosing, oral body temperature will not be collected.
4. Documentation of vital signs; HR, BP, and RR only at 1, 2, and 4 hours ±15 minutes.

5. CBC with differential.

6. Includes INR, aPTT and PT.

7. Includes total protein, albumin, glucose, alkaline phosphatase, bilirubin (total and direct), AST, ALT, GGT, LDH, uric acid, BUN, creatinine, calcium, sodium, potassium, chloride, CO2, phosphate, magnesium, cholesterol, triglycerides, CPK.

8. Includes pH, glucose, ketones, blood, specific gravity, nitrite, protein, bilirubin and microscopy.

9. C1 inhibitor (C1-INH) antigen or function level < 40% of the normal level is required for entry into the study. Subjects with C1-INH antigen or functional level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range and a family history consistent with HAE Type I or II. Test results must have been obtained within 5 years of enrollment. Following enrollment into the study, C1-INH functional levels will be collected at the outlined time points.

10. Serum or urine pregnancy test to be obtained at screening, prior to first dosing, and at Day 120 final visit or ET.

11. Prior concomitant medications and procedures will be documented before dose administration. Concomitant medications and procedures will be assessed on a continual basis throughout the study.

12. Pre-existing signs and symptoms will be captured prior to dosing. AEs will be assessed on a continual basis from the signing of the consent form and throughout the study.

13. Clinical information related to historical HAE attacks will be obtained prior to dosing on Day 1. Clinical information related to any HAE attacks as well as any acute attack treatments occurring during the study will be obtained throughout the study.

14. If the subject presents to the study site for an acute HAE attack during the study and it coincides with a scheduled study visit, the additional exploratory assessments and procedures (including blood draws), beyond what is already scheduled will not be necessary for that 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)

NOVEMBER 2007 - DRAFT

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal  LLN = Lower Limit of Normal
Rx  = 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.

LABORATORY RANGES

Where discrepancies in the ULN and LLN of laboratory ranges occur between those included in this document and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade.
## HEMATOLOGY

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>9.5 - 10.5 gm/dL</td>
<td>8.0 - 9.4 gm/dL</td>
<td>6.5 - 7.9 gm/dL</td>
<td>&lt; 6.5 gm/dL</td>
</tr>
<tr>
<td>Absolute Neutrophil Count</td>
<td>1000-1500/mm³</td>
<td>750-999/mm³</td>
<td>500-749/mm³</td>
<td>&lt;500/mm³</td>
</tr>
<tr>
<td>Platelets</td>
<td>75,000-99,999/mm³</td>
<td>50,000-74,999/mm³</td>
<td>20,000-49,999/mm³</td>
<td>&lt;20,000/mm³</td>
</tr>
<tr>
<td>WBCs</td>
<td>11,000-13,000/mm³</td>
<td>13,000-15,000/mm³</td>
<td>15,000-30,000/mm³</td>
<td>&gt;30,000 or &lt;1,000 mm³</td>
</tr>
<tr>
<td>% Polymorphonuclear Leucocytes + Band Cells</td>
<td>&gt; 80%</td>
<td>90 – 95%</td>
<td>&gt;95%</td>
<td>&lt;---------</td>
</tr>
<tr>
<td>Activated Partial Thromboplastin (APTT)</td>
<td>1.01 -1.66 × ULN</td>
<td>1.67 - 2.33 × ULN</td>
<td>2.34 - 3 × ULN</td>
<td>&gt; 3 × ULN</td>
</tr>
</tbody>
</table>

## CHEMISTRIES

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>130-135 mEq/L</td>
<td>123-129 mEq/L</td>
<td>116-122 mEq/L</td>
<td>&lt; 116 mEq/L or abnormal sodium with mental status changes or seizures</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>146-150 mEq/L</td>
<td>151-157 mEq/L</td>
<td>158-165 mEq/L</td>
<td>&gt; 165 mEq/L or abnormal sodium with mental status changes or seizures</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3.0 - 3.4 mEq/L</td>
<td>2.5 - 2.9 mEq/L</td>
<td>2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required</td>
<td>&lt; 2.0 mEq/L or abnormal potassium with paresis, ileus or life-threatening arrhythmia</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>5.6 - 6.0 mEq/L</td>
<td>6.1 - 6.5 mEq/L</td>
<td>6.6 - 7.0 mEq/l</td>
<td>&gt; 7.0 mEq/L or abnormal potassium with life-threatening arrhythmia</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>55-64 mg/dL</td>
<td>40-54 mg/dL</td>
<td>30-39 mg/dL</td>
<td>&lt;30 mg/dL or abnormal glucose with mental status changes or coma</td>
</tr>
<tr>
<td>Hyperglycemia (nonfasting and no prior diabetes)</td>
<td>116 -160 mg/dL</td>
<td>161- 250 mg/dL</td>
<td>251 - 500 mg/dL</td>
<td>&gt; 500 mg/dL or abnormal glucose with ketoacidosis or seizures</td>
</tr>
<tr>
<td>Hypocalcemia(corrected for albumin)</td>
<td>8.4 - 7.8 mg/dL</td>
<td>7.7 - 7.0 mg/dL</td>
<td>6.9 - 6.1 mg/dL</td>
<td>&lt; 6.1 mg/Dl or abnormal calcium with life threatening arrhythmia or tetany</td>
</tr>
<tr>
<td>Hypercalcemia (correct for albumin)</td>
<td>10.6 - 11.5 mg/dL</td>
<td>11.6 - 12.5 mg/dL</td>
<td>12.6 - 13.5 mg/dL</td>
<td>&gt; 13.5 mg/dL or abnormal calcium with life threatening arrhythmia</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>1.4 - 1.2 mEq/L</td>
<td>1.1 - 0.9 mEq/L</td>
<td>0.8 - 0.6 mEq/L</td>
<td>&lt; 0.6 mEq/L or abnormal magnesium with life-threatening arrhythmia</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>2.0 - 2.4 mg/dL or replacement Rx required</td>
<td>1.5 -1.9 mg/dL or replacement Rx required</td>
<td>1.0 -1.4 mg/dL intensive therapy or hospitalization required</td>
<td>&lt; 1.0 mg/Dl or abnormal phosphate with life-threatening arrhythmia</td>
</tr>
</tbody>
</table>
### 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

- **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

### ENZYMES

<table>
<thead>
<tr>
<th>ENZYME</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (SGOT)</td>
<td>1.1 - &lt;2.0 x ULN</td>
<td>2.0 – &lt;3.0 x ULN</td>
<td>3.0 – 8.0 x ULN</td>
<td>&gt; 8 x ULN</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>1.1 - &lt;2.0 x ULN</td>
<td>2.0 – &lt;3.0 x ULN</td>
<td>3.0 – 8.0 x ULN</td>
<td>&gt; 8 x ULN</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>1.1 - &lt;2.0 x ULN</td>
<td>2.0 – &lt;3.0 x ULN</td>
<td>3.0 – 8.0 x ULN</td>
<td>&gt; 8 x ULN</td>
</tr>
</tbody>
</table>

### URINALYSIS

<table>
<thead>
<tr>
<th>URINARY INDICATOR</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>1+ or 200 mg - 1 gm loss/day</td>
<td>2-3+ or 1- 2 gm loss/day</td>
<td>4+ or 2-3.5 gm loss/day</td>
<td>nephrotic syndrome or &gt; 3.5 gm loss/day</td>
</tr>
<tr>
<td>Hematuria</td>
<td>microscopic only &lt;10 rbc/hpf</td>
<td>gross, no clots &gt;10 rbc/hpf</td>
<td>gross, with or without clots, OR red blood cell casts</td>
<td>obstructive or required transfusion</td>
</tr>
</tbody>
</table>

### CARDIOVASCULAR

<table>
<thead>
<tr>
<th>CARDIOVASCULAR INDICATOR</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Rhythm</td>
<td>asymptomatic, transient signs, no Rx required</td>
<td>recurrent/persistent symptomatic Rx required</td>
<td>unstable dysrhythmia; hospitalization and treatment required</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>transient increase &gt; 20 mm/Hg; no treatment</td>
<td>recurrent, chronic increase &gt; 20mm/Hg, /treatment required</td>
<td>acute treatment required; outpatient treatment or hospitalization possible</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>transient orthostatic hypotension with heart rate increased by &lt;20 beat/min or decreased by &lt;10 mm Hg systolic BP, No treatment required</td>
<td>symptoms due to orthostatic hypotension or BP decreased by &lt;20 mm Hg systolic; correctable with oral fluid treatment</td>
<td>requires IV fluids; no hospitalization required</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mean arterial pressure &lt;60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Pericarditis</strong></td>
<td>minimal effusion</td>
<td>mild/moderate asymptomatic effusion, no treatment</td>
<td>symptomatic effusion; pain; EKG changes</td>
<td>tamponade; pericardiocentesis or surgery required</td>
</tr>
<tr>
<td><strong>Hemorrhage, Blood Loss</strong></td>
<td>microscopic/occult</td>
<td>mild, no transfusion</td>
<td>gross blood loss; 1-2 units transfused</td>
<td>massive blood loss; &gt; 3 units transfused</td>
</tr>
<tr>
<td><strong>RESPIRATORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>transient- no treatment</td>
<td>persistent cough; treatment responsive</td>
<td>Paroxysmal cough; uncontrolled with treatment</td>
<td></td>
</tr>
<tr>
<td>Bronchospasm, Acute</td>
<td>transient; no treatment; 70% - 80% FEV₁ of peak flow</td>
<td>requires treatment; normalizes with bronchodilator; FEV₁ 50% - 70% (of peak flow)</td>
<td>no normalization with bronchodilator; FEV₁ 25% - 50% of peak flow; or retractions present</td>
<td>cyanosis: FEV₁ &lt; 25% of peak flow or intubation necessary</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>dyspnea on exertion</td>
<td>dyspnea with normal activity</td>
<td>dyspnea at rest</td>
<td>Dyspnea requiring oxygen therapy</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>mild or transient; maintains reasonable intake</td>
<td>moderate discomfort; intake decreased significantly; some activity limited</td>
<td>no significant intake; requires IV fluids</td>
<td>hospitalization required;</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 episode in 24 hours</td>
<td>2-5 episodes in 24 hours</td>
<td>&gt;6 episodes in 24 hours or needing IV fluids</td>
<td>physiologic consequences requiring hospitalization or requiring parenteral nutrition</td>
</tr>
<tr>
<td>Constipation</td>
<td>requiring stool softener or dietary modification</td>
<td>requiring laxatives</td>
<td>obstipation requiring manual evacuation or enema</td>
<td>obstruction or toxic megacolon</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>mild or transient; 3-4 loose stools/day or mild diarrhea last &lt; 1 week</td>
<td>moderate or persistent; 5-7 loose stools/day or diarrhea lasting &gt;1 week</td>
<td>&gt;7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or &gt;2L IV fluids required</td>
<td>hypotensive shock or physiologic consequences requiring hospitalization</td>
</tr>
</tbody>
</table>
**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

**NEUROLOGICAL**

<table>
<thead>
<tr>
<th>Category</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuro-Cerebellar</td>
<td>slight incoordination dysdiadochokinesis</td>
<td>intention tremor, dysmetria, slurred speech; nystagmus</td>
<td>locomotor ataxia</td>
<td>incapacitated</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>mild anxiety or depression</td>
<td>moderate anxiety or depression; therapy required; change in normal routine</td>
<td>severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation</td>
<td>acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations</td>
</tr>
<tr>
<td>Muscle Strength</td>
<td>subjective weakness, no objective symptoms/ signs</td>
<td>mild objective signs/symptoms no decrease in function</td>
<td>objective weakness function limited</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Paresthesia (burning, tingling, etc.)</td>
<td>mild discomfort; no treatment required</td>
<td>moderate discomfort; non-narcotic analgesia required</td>
<td>severe discomfort; or narcotic analgesia required with symptomatic improvement</td>
<td>incapacitating; or not responsive to narcotic analgesia</td>
</tr>
</tbody>
</table>

**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

**MUSCULOSKELETAL**

<table>
<thead>
<tr>
<th>Category</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia (joint pain)</td>
<td>mild pain not interfering with function</td>
<td>moderate pain, analgesics and/or pain interfering with function but not with activities of daily living</td>
<td>severe pain; pain and/or analgesics interfering with activities of daily living</td>
<td>disabling pain</td>
</tr>
<tr>
<td>Arthritis</td>
<td>mild pain with inflammation, erythema or joint swelling – but not interfering with function</td>
<td>moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living</td>
<td>severe pain with inflammation, erythema or joint swelling – and interfering with activities of daily living</td>
<td>permanent and/or disabling joint destruction</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Myalgia with no limitation of activity</td>
<td>muscle tenderness (at other than injection site) or with moderate impairment of activity</td>
<td>severe muscle tenderness with marked impairment of activity</td>
<td>frank myonecrosis</td>
</tr>
<tr>
<td>SKIN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>Grade 1: erythema; pruritus</td>
<td>Grade 2: diffuse, maculo papular rash, dry desquamation</td>
<td>Grade 3: vesiculation or moist desquamation or ulceration</td>
<td>Grade 4: exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery</td>
</tr>
<tr>
<td>Induration</td>
<td>&lt; 15mm to 15-30 mm</td>
<td>&gt; 30mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>&lt; 15mm to 15-30 mm</td>
<td>&gt; 30mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>&lt; 15mm to 15-30 mm</td>
<td>&gt; 30mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash at Injection Site</td>
<td>&lt; 15mm to 15-30 mm</td>
<td>&gt; 30mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>slight itching at injection site</td>
<td>moderate itching at injection extremity</td>
<td>itching over entire body</td>
<td></td>
</tr>
<tr>
<td>SYSTEMIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic Reaction</td>
<td>Grade 1: pruritus without rash</td>
<td>Grade 2: localized urticaria</td>
<td>Grade 3: generalized urticaria; angioedema</td>
<td>Grade 4: anaphylaxis</td>
</tr>
<tr>
<td>Headache</td>
<td>mild, no treatment required</td>
<td>transient, moderate; treatment required</td>
<td>severe; responds to initial narcotic therapy</td>
<td>intractable; requires repeated narcotic therapy</td>
</tr>
<tr>
<td>Fever: oral</td>
<td>37.7 - 38.5 °C or 100.0 - 101.5 °F</td>
<td>38.6 - 39.5 °C or 101.6 - 102.9 °F</td>
<td>39.6 - 40.5 °C or 103 - 105 °F</td>
<td>&gt; 40 °C or &gt; 105 °F</td>
</tr>
<tr>
<td>Fatigue</td>
<td>normal activity reduced &lt; 48 hours</td>
<td>normal activity decreased 25 - 50% &gt; 48 hours</td>
<td>normal activity decreased &gt; 50% can’t work</td>
<td>unable to care for self</td>
</tr>
</tbody>
</table>
Protocol Amendment DX-2930-02

Summary of Changes

Original Study Title: A Phase 1b, Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX-2930 in Hereditary Angioedema Subjects

Study Number: DX-2930-02
Study Phase: 1b
Product Name: DX-2930
IND Number: 116647
EudraCT Number: 2013-005066-18
Description: Recombinant Fully Human Antibody Inhibitor of Plasma Kallikrein

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Medical Monitor: Yung Chyung, MD
55 Network Drive, Burlington, MA 01803
Phone: 617-250-5549
Mobile: 617-417-9114

Date:

<table>
<thead>
<tr>
<th>Original Protocol:</th>
<th>24 February 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment 1.0</td>
<td>07 January 2015</td>
</tr>
</tbody>
</table>

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2. INDIVIDUAL CHANGES ........................................................................4
1 SUMMARY AND JUSTIFICATION OF CHANGES

This amendment includes changes to the original protocol, summarized as follows:

- As per Administrative Letter dated 19 March 2014, misprints in the footnotes (*Note) of Study Activities Schedules table on pages 11 and 68 of 75 were corrected. These corrections were related to the “±” symbol used for study visit days for specific study assessments. Additional corrections to the numbering of the footnotes on page 68 were made.

- As per Administrative Letter dated 10 September 2014, the timing of the planned interim analysis defined in Section 9.9 was clarified to occur after at least 6 subjects reached Day 36 of the 300 mg cohort.

- The ability of Dyax to perform additional interim analyses following the initial interim analysis has been added.

- The role of Medical Monitor was assumed by Yung Chyung, VP of Medical Research for Dyax Corp. on 01 January 2015 and for the remainder of the trial following the departure of the Aptiv Solutions Medical Monitor.
2 INDIVIDUAL CHANGES

Unless otherwise specified, the page numbers and section numbers provided below refer to the original protocol dated 24 February 2014.

Page 1, Study Title Page

Yung Chung replaces J. Gordon Still as Medical Monitor for the trial.

Page 9, Study Synopsis and Page 59, Section 9.9 Interim Analysis

Revised Text:

“…an interim analysis after at least 6 subjects have reached Day 36 of the 300 mg cohort is planned by the Sponsor, unless the highest dose level in the study is lower than 300 mg, in which case the interim analysis will be conducted after at least 6 subjects at the highest dose cohort have reached Day 36. This interim analysis will include all safety and subject information as well as any available relevant PK, anti-drug antibody, and exploratory assessment data collected across all dosing cohorts leading up to and including the highest dose cohort. Unblinded, aggregate safety data will be reviewed across all dosing cohorts and by individual cohort to identify any safety signals. Available PK data, safety data, and results of exploratory analyses will be evaluated to guide selection of dose levels for the Phase 2 study. In accordance with the flexible dose schema, additional cohorts may be added following a DEC review and/or interim analysis. Additional interim analyses may be conducted following the initial interim analysis. A blinded medical monitor will be retained to assess safety for the remainder of the study follow-up period.

Pages 11 and 68, Study Activities Schedule table footnotes

Footnote (*Note):

This note should read “During this outlined period (Day 29 through Day 92), physical examination, vital signs, and safety laboratory tests (hematology, coagulation, serum chemistry, and urinalysis) will occur on Days 29±1, 36±1, 64±2, and 92±3. During this period laboratory test for C1-INH Function will occur on Days 29±1, 36±1, 64±2 and 92±3. During this period, anti-drug antibody testing will be conducted on samples obtained on Days 36±1, 64±2, and 92±3. 12-lead ECG will be performed at Day36±1 during this outlined period.” The correction is that ± applies to each visit date cited in the note.

Numbered Footnotes:

On page 68 the numbering of footnotes should be corrected so as to include two footnotes that were listed but were inadvertently not numbered. This correction results in the numbered footnotes being numbered consistently with page 11 as follows:

1 Height, weight and calculation of BMI will be additional assessments conducted at this timepoint.
This physical examination will be abbreviated and include General, Skin, Cardiovascular, Pulmonary, Abdomen, and Extremities. (For Day 1 post-dosing and Day 15 post-dosing, this examination will occur at 4 hours ±15 minutes).

Documentation of vital signs including oral body temperature, HR, BP, and RR. On Day 1 post-dosing and Day 15 post-dosing, oral body temperature will not be collected.

Documentation of vital signs; HR, BP, and RR only at 1, 2, and 4 hours ±15 minutes.

CBC with differential.

Includes INR, aPTT and PT.

Includes total protein, albumin, glucose, alkaline phosphatase, bilirubin (total and direct), AST, ALT, GGT, LDH, uric acid, BUN, creatinine, calcium, sodium, potassium, chloride, CO2, phosphate, magnesium, cholesterol, triglycerides, CPK.

Includes pH, glucose, ketones, blood, specific gravity, nitrite, protein, bilirubin and microscopy.

C1 inhibitor (C1-INH) antigen or function level < 40% of the normal level is required for entry into the study. Subjects with C1-INH antigen or functional level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range and a family history consistent with HAE Type I or II. Test results must have been obtained within 5 years of enrollment. Following enrollment into the study, C1-INH functional levels will be collected at the outlined time points.

Serum or urine pregnancy test to be obtained at screening, prior to first dosing, and at Day 120 final visit or ET.

Prior concomitant medications and procedures will be documented before dose administration. Concomitant medications and procedures will be assessed on a continual basis throughout the study.

Pre-existing signs and symptoms will be captured prior to dosing. AEs will be assessed on a continual basis from the signing of the consent form and throughout the study.

Clinical information related to historical HAE attacks will be obtained prior to dosing on Day 1. Clinical information related to any HAE attacks as well as any acute attack treatments occurring during the study will be obtained throughout the study.

If the subject presents to the study site for an acute HAE attack during the study and it coincides with a scheduled study visit, the additional exploratory assessments and procedures (including blood draws), beyond what is already scheduled will not be necessary for that visit.

**Page 32, Section 5.4 Blinding and Unblinding**

Revised Text:

This is a randomized, double-blinded, placebo-controlled trial. Subjects will be randomized to receive either DX-2930 or placebo within each cohort. Subjects will be blinded to the treatment administered until enrollment is complete and the database is locked. Investigators and site personnel will be blinded to subject treatment until enrollment is complete and the database is locked. The sponsor will be blinded to the treatment administered through the completion of at least the Day 36 follow-up visit for the last subject in the 300 mg dosing cohort (or highest dosing cohort if the highest dose is lower than 300 mg). At that point, an interim analysis of data through at least Day 36 will be conducted (Section 9.9). In accordance with the flexible dose schema, additional cohorts may be added following a DEC review and/ or interim analysis. Additional interim analyses may be conducted following the initial interim analysis. The sponsor will review interim analysis data in an unblinded fashion but a blinded medical monitor will be retained to assess safety for the remainder of the study follow-up period.
Page 47, Section 6.13.5.5 Safety Contact Information

24-Hour Medical Safety Contact Information provided for Yung Chyung, replacing J. Gordon Still:

24-Hour Medical Safety Contact
Yung Chyung, MD
Medical Monitor
Phone (US): (617) 417-9114
Email: ychyung@dyax.com

Page 61, Section 10.1 Table 2 Study Administrative Structure

Yung Chyung listed as Sponsor Medical Director and Medical Monitor.

Christopher Stevens is the Blinded Medical Monitor:

Christopher Stevens, MD
Dyax Corp.
55 Network Drive, Burlington, MA 01803
Phone: 617-250-5732
Email: cstevens@dyax.com
<table>
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<tr>
<td>Title Page, Medical Monitor</td>
<td>J. Gordon Still, MD, PhD 4505 Emperor Boulevard, Suite 400, Durham, NC 27703 Phone: 919-245-5531 Mobile: 919-749-5992</td>
<td>Yung Chyung, MD 55 Network Drive, Burlington, MA 01803 Phone: 617-250-5549 Mobile: 617-417-9114</td>
<td>Departure of Aptiv Solutions’ Medical Monitor</td>
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### Table 1. Summary of Individual Changes

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<tr>
<td>Study Synopsis, Page 9 and Section 9.9, Interim Analysis, page 59</td>
<td>“…an interim analysis of all subject data through at least Day 36 of the final cohort is planned by the Sponsor. This interim analysis will include all safety and subject information as well as any available and relevant PK, anti-drug antibody, and exploratory assessment data collected across all dosing cohorts. The final cohort is presumed to be the 300 mg cohort, unless the final dose level evaluated in the study is lower or higher than 300 mg. Aggregate, unblinded safety data will be reviewed across all dosing cohorts and by individual cohort to identify any safety signals. Available plasma concentrations of DX-2930 and results of exploratory analyses will be evaluated to guide selection of dose levels for the Phase 2 study. A blinded medical monitor will be retained to assess safety for the remainder of the study follow-up period.</td>
<td>“…an interim analysis after at least 6 subjects have reached Day 36 of the 300 mg cohort is planned by the Sponsor, unless the highest dose level in the study is lower than 300 mg, in which case the interim analysis will be conducted after at least 6 subjects at the highest dose cohort have reached Day 36. This interim analysis will include all safety and subject information as well as any available and relevant PK, anti-drug antibody, and exploratory assessment data collected across all dosing cohorts leading up to and including the highest dose cohort. Unblinded, aggregate safety data will be reviewed across all dosing cohorts and by individual cohort to identify any safety signals. Available PK data, safety data, and results of exploratory analyses will be evaluated to guide selection of dose levels for the Phase 2 study. In accordance with the flexible dose schema, additional cohorts may be added following a DEC review and/ or interim analysis. Additional interim analyses may be conducted following the initial interim analysis. A blinded medical monitor will be retained to assess safety for the remainder of the study follow-up period.</td>
<td>Clarifies timing of initial interim analysis as per Administrative Letter dated 10 September 2014. Specifies that Dyax may run additional interim analyses following the initial interim analysis.</td>
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<td>Study Activities Schedule table footnote (*Note) pages 11 and 68</td>
<td>*Note: During this outlined period (Day 29 through Day 92), physical examination, vital signs, and safety laboratory tests (hematology, coagulation, serum chemistry, and urinalysis) will occur on Days 29±1, 36±1, 64±2, and 92±3. During this period laboratory test for C1-INH Function will occur on Days 29±1, 36±1, 64±2 and 92±3. During this period, anti-drug antibody testing will be conducted on samples obtained on Days 36±1, 64±2, and 92±3. 12-lead ECG will be performed at Day36±1 during this outlined period.</td>
<td>*Note: During this outlined period (Day 29 through Day 92), physical examination, vital signs, and safety laboratory tests (hematology, coagulation, serum chemistry, and urinalysis) will occur on Days 29±1, 36±1, 64±2, and 92±3. During this period laboratory test for C1-INH Function will occur on Days 29±1, 36±1, 64±2 and 92±3. During this period, anti-drug antibody testing will be conducted on samples obtained on Days 36±1, 64±2, and 92±3. 12-lead ECG will be performed at Day36±1 during this outlined period.</td>
<td>Corrects the ± symbol used for study visit days for specific assessments as per Administrative Letter dated 19 March 2014. Additional correction to the numbering of footnotes on page 68 to be consistent with page 11.</td>
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<td>receive either DX-2930 or placebo within each cohort.</td>
<td>receive either DX-2930 or placebo within each cohort.</td>
<td>initial interim</td>
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<td>Subjects will be blinded to the treatment administered until enrollment is complete and the database is locked. Investigators and site personnel will be blinded to subject treatment until enrollment is complete and the database is locked. The sponsor will be blinded to the treatment administered through the completion of at least the Day 36 follow-up visit for the last subject in the final (300 mg) dosing cohort. At that point, an interim analysis of data through at least Day 36 will be conducted (Section 9.9) The sponsor will review the data in an unblinded fashion but a blinded medical monitor will be retained to assess safety for the remainder of the study follow-up period. If escalation to dose(s) higher than 300 mg occurs, the interim analysis may be deferred until all of the subjects at the highest dose complete through at least Day 36.</td>
<td>Subjects will be blinded to the treatment administered until enrollment is complete and the database is locked. Investigators and site personnel will be blinded to subject treatment until enrollment is complete and the database is locked. The sponsor will be blinded to the treatment administered through the completion of at least the Day 36 follow-up visit for the last subject in the final (300 mg) dosing cohort. At that point, an interim analysis of data through at least Day 36 will be conducted (Section 9.9). In accordance with the flexible dose schema, additional cohorts may be added following a DEC review and/ or interim analysis. Additional interim analyses may be conducted following the initial interim analysis. The sponsor will review interim analysis data in an unblinded fashion but a blinded medical monitor will be retained to assess safety for the remainder of the study follow-up period.</td>
<td>analysis and the point at which the sponsor is unblinded as per Administrative Letter dated 10 September 2014 as well as for any additional interim analyses conducted.</td>
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| Section 6.13.5.5, |                  | 24-Hour Medical Safety Contact | Departure of Aptiv |
| Safety Contact    | J. Gordon Still, MD, PhD | Yung Chyung, MD | Solutions’ Medical |
| Information,      | Medical Monitor      | Medical Monitor | Monitor |
| page 47           | Phone (US): (919) 245-5531 | Phone (US): (617) 417-9114 |                  |
|                  | Email: gordon.still@aptivsolutions.com | Email: ychyung@dyax.com |                  |
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</table>
| Section 10.1, Table 2 Study Administrative Structure, page 61 | **Sponsor Medical Director:** Yung Chyung, MD  
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55 Network Drive, Burlington, MA 01803  
Phone: 617-250-5549  
Email: ychyung@dyax.com  
**Medical Monitor:** J. Gordon Still, MD, PhD  
Aptiv Solutions  
4505 Emperor Boulevard, Suite 400  
Durham, NC 27703  
Phone: 919-245-5531  
Email: gordon.still@aptivsolutions.com                                                                 | **Sponsor Medical Director and Medical Monitor**: Yung Chyung, MD  
Vice President, Medical Research  
55 Network Drive, Burlington, MA 01803  
Phone: 617-250-5549  
Email: ychyung@dyax.com  
*Yung Chyung assumed the Medical Monitor role on 01 January 2015 following the departure of the previous Medical Monitor from Aptiv Solutions.*  
**Blinded Medical Monitor:**  
Christopher Stevens, MD  
Dyax Corp.  
55 Network Drive, Burlington, MA 01803  
Phone: 617-250-5732  
Email: cstevens@dyax.com                                                                 | Departure of Aptiv Solutions’ Medical Monitor                                                                                           |
Statistical Analysis Plan: DX-2930-02

(Based on Protocol DX-2930 Amendment 1)

Study Title: A Phase 1b, Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX-2930 in Hereditary Angioedema Subjects

Study Number: DX-2930-02

Study Phase: 1b

Product Name: DX-2930

Indication: Hereditary Angioedema

Statistician: Audrey Moreau
Senior Biostatistician
Aptiv Solutions
5 rue du Talus, 67400 Illkirch, France

Sponsor: Dyax Corp.
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Final Date: 29 January 2015

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LIST OF APPENDICES

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2 SIGNATURE PAGE

Study Title: A Phase 1b, Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX-2930 in Hereditary Angioedema Subjects

Study Number: DX-2930-02

Statisticians: Audrey Moreau

Prepared by: ________________________________ Date: ______________________
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Senior Biostatistician
Aptiv Solutions

Approved by: ________________________________ Date: ______________________
Scott Mollan
Senior Biostatistician
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Ryan Iarrobino
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Approved by: ________________________________ Date: ______________________
Robert Mensah
Senior Director, Biometrics
Dyax Corp.

Approved by: ________________________________ Date: ______________________
Yung Chyung
VP, Medical Research
Dyax Corp.
2 SIGNATURE PAGE

Study Title: A Phase 1b, Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX-2930 in Hereditary Angioedema Subjects

Study Number: DX-2930-02

Statisticians: Audrey Moreau

Prepared by: Audrey Moreau
Senior Biostatistician
Aptiv Solutions

Date: 23 JAN 2015

Approved by: Scott Mollan
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Date: 02 Feb 2015

Approved by: Ryan Jarrobin
Senior Director, Clinical Development
Dyax Corp.

Date: 03 Feb 2015

Approved by: Robert Mensah
Senior Director, Biometrics
Dyax Corp.

Date: 03 Feb 2015

Approved by: Yung Chyung
VP, Medical Research
Dyax Corp.

Date: 3 Feb 2015
3 ABBREVIATIONS

AE  Adverse event
ALT  Alanine aminotransferase
aPTT  Activated partial thromboplastin time
AST  Aspartate aminotransferase
AUC  Area under the plasma concentration-time curve
AUC\textsubscript{0-t}  AUC from time zero to the last quantifiable concentration in plasma at time t
AUC\textsubscript{0-∞}  AUC from time 0 to infinity
BMI  Body mass index
BP  Blood pressure
BUN  Blood urea nitrogen
C1-INH  C1 inhibitor
CO\textsubscript{2}  Carbon dioxide
CPK  Creatine phosphokinase
CL/F  Apparent clearance
C\textsubscript{max}  Maximum plasma concentration
DEC  Dose Escalation Committee
DMID  Division of Microbiology and Infectious Diseases
ECG  Electrocardiogram
eCRF  Electronic case report form
GEE  Generalized Estimating Equation
GGT  Gamma-glutamyl transferase
HAE  Hereditary angioedema
HBsAg  Hepatitis B surface antigen
HCV  Hepatitis C virus
HIV  Human immunodeficiency virus
HR  Heart rate
ICF  Informed consent form
INR  International normalized ratio
IWRS  Interactive Web-based Randomization System
LDH  Lactate dehydrogenase
LLN  Lower Limit of Normal
Lsmean  Least-squares means
MCH  Mean corpuscular hemoglobin
MCHC  Mean corpuscular hemoglobin concentration
MCV  Mean corpuscular volume
MedDRA  Medical Dictionary for Regulatory Activities
PD  Pharmacodynamic(s)
PK  Pharmacokinetic(s)
PT  Prothrombin time
RBC  Red blood cell (count)
RR  Respiratory rate
SAE  Serious adverse event
SAP  Statistical Analysis Plan
SD  Standard deviation
SE  Standard Error
SGOT  Serum glutamic oxaloacetic transaminase (AST)
SGPT  Serum glutamic pyruvic transaminase (ALT)
SOC  System Organ Class
$t_\frac{1}{2}$  Terminal elimination half-life
$t_{\text{max}}$  Time to maximum plasma concentration
TEAE  Treatment Emergent Adverse Event
ULN  Upper Limit of Normal
USA  United States of America
US  United States
Vd/F  Apparent volume of distribution during terminal phase after extravascular administration
WBC  White blood cell (count)
WHODD  WHO Drug Dictionary
4  INTRODUCTION

This statistical analysis plan (SAP) describes the planned interim and final analysis from study DX-2930-02. A detailed description of the planned tables, figures and listings (TFLs) to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL template document. A separate Pharmacokinetic (PK) Analysis Plan details the pharmacokinetic analysis.

The intent of this document is to provide guidance for the analysis of data related to safety and other exploratory endpoints and to describe any applicable statistical procedures. A limited amount of information concerning this study (e.g., objectives, study design) is summarized to help the reader interpret the accompanying TFL templates. Attached signatures indicate approval of the safety and exploratory statistical analyses sections of the SAP. These sections must be agreed upon prior to database lock. When the SAP and TFL templates are agreed upon and finalized, they will serve as the template for generation of the TFLs that will be the basis of the safety and other exploratory results described in the clinical study report.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are different, they will be so identified and a rationale for the change provided. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the appropriate section of the CSR. Any substantial deviations from this SAP will be agreed upon between Dyax Corp. and Aptiv Solutions Inc. and documented in an Amendment to the SAP. All deviations from the SAP and/or TFL templates will be documented in a running Addendum to the SAP document and finalized with signoff as an addendum to the SAP prior to database lock. Deviations from this SAP, both substantial and non-substantial, will be documented in the CSR.

5  STUDY OBJECTIVES

5.1  Study Objectives

5.1.1  Primary Objective

To assess the safety and tolerability of multiple, subcutaneous administrations of DX-2930 at different dose levels in HAE subjects.

5.1.2  Secondary Objective

To characterize the pharmacokinetics (PK) of DX-2930 following multiple, subcutaneous administrations at different dose levels.
5.1.3  Tertiary Objectives

- To assess the immunogenicity of DX-2930
- To evaluate the pharmacodynamic (PD) effects of DX-2930 through exploratory biomarker assessments
- To conduct an exploratory assessment of the indirect effects of plasma kallikrein inhibition upon endogenous C1-inhibitor activity
- To conduct exploratory assessments to characterize HAE attacks and acute attack therapy usage during the study

6  STUDY DESIGN AND CONDUCT CONSIDERATIONS

6.1  Study Design

This study is a Phase 1b, multi-center, randomized, double-blind, placebo-controlled, multiple ascending dose trial of subcutaneous administrations of DX-2930 in HAE subjects. Eligible subjects will be randomized 2:1 to receive either active study drug or placebo within a cohort.

The study consists of 3 dose cohorts (30, 100, and 300 mg), with each cohort nominally consisting of 6 subjects.

For each dosing cohort, 4 subjects will be randomized to receive active drug and 2 subjects will be randomized to receive placebo.

Each subject within a dosing cohort will receive 2 doses of study drug, administered subcutaneously into the upper arm. The second dose will be administered 14 days following the first dose. When a cohort has completed dosing, a review will be conducted of the safety data through 14 days after the second dose. Cumulative safety data from any earlier cohort will also be included in the review. This safety evaluation will be conducted by a dose escalation committee (DEC) and will include a review of all adverse events, vital signs, physical examinations, laboratories, and electrocardiograms (ECGs). Escalation to the next highest dosing cohort will proceed if there are no concerning safety signals.

A flexible dose escalation scheme will be used in this study that allows for expansion of a current or prior cohort or intermediate doses higher or lower than the preceding dose to be studied in a subsequent cohort. This may result in adding of subjects to receive specific dose levels and in an increase in the total number of cohorts and/or subjects enrolled in the study.

The flexible dose escalation scheme also allows further escalation to a maximum of 400 mg if necessary due to PK or PD reasons and if supported by safety results from an interim data review. This scheme also allows for expansion cohorts to further characterize DX-2930 (such as for safety, PK, or exploratory assessments) and if supported by review of safety data from
previous cohorts. This safety review will be conducted after all subjects in the 300 mg cohort have been assessed through at least Day 29. Cumulative safety data from earlier cohorts will also be included in the review. In addition, any available and relevant PK or exploratory data, together with available PK data from the Phase 1a study, will be used to assess if a need exists to escalate beyond 300 mg and to confirm that the nonclinical toxicity data provide adequate safety margins.

An interim analysis will be conducted after at least 6 subjects have reached Day 36 in the 300 mg cohort unless the highest dose level in the study is lower than 300 mg, in which case the interim analysis will be conducted after at least 6 subjects at the highest dose cohort have reached the Day 36 time point. Additional interim analyses may be conducted following the initial interim analysis at the discretion of the Sponsor. The details of the interim analysis are described in Section 8.3 of this SAP.

6.2 Sample Size

Approximately 18 to 36 HAE subjects will be enrolled across multiple clinical sites according to the flexible dose escalation scheme. The estimated sample size has been chosen to provide adequate numbers of subjects to characterize the safety, tolerability, and PK of DX-2930. Depending on DEC findings, the number of subjects may be expanded by the addition of subjects within a dosing cohort or inclusion of additional dose cohorts at intermediate doses or at dose(s) higher than 300 mg (up to a maximum of 400 mg) in order to further characterize DX-2930.

6.3 Randomization Procedure

Subjects meeting all eligibility criteria will be enrolled in the study and sequentially assigned an identification number. Subjects will be assigned to either DX-2930 or placebo treatment groups via an Interactive Web-based Randomization System (IWRS).

6.4 Schedule of Visits and Procedures

The duration of individual subject participation, from enrollment until final follow-up, will be approximately 120 days (17 weeks). Eligibility screening will be performed up to 28 days prior to Day 1 enrollment and first dosing. Subjects will receive the second dose on Day 15. After the second dose, follow-up visits for safety assessments and anti-drug antibody, PK, C1-INH and biomarker sampling will occur at regular intervals until the final study visit on Day 120. All scheduled assessments are listed in the Study Activities Schedule found in Appendix 1 of this SAP.
6.5 Study Endpoints

6.5.1 Safety Endpoints

Safety measures include the following:

- Adverse events (AEs) including serious adverse events (SAEs)
- Clinical laboratory testing (hematology, clinical chemistry, coagulation and urinalysis)
- Plasma anti-drug antibody development
- Vital signs, including sitting or supine blood pressure (BP), heart rate (HR), oral body temperature, and respiratory rate (RR).
- Physical examination
- 12-lead electrocardiogram (ECG)

6.5.1.1 Adverse Events

Recording of AEs and SAEs will begin after the subject signs the informed consent form (ICF), and will continue until the end of study Day 120 post-dosing ±3 days.

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 study drug interruption or discontinuation, will be considered an AE. Clinical significance of individual AEs, including laboratory AEs, will be determined by the Investigator with input from the Medical Monitor as needed. APTT prolongation in the absence of any associated bleeding or other evidence of clinical relevance will not be considered a clinically significant event. Pregnancy is not an AE laboratory abnormality or adverse event.

An AE will be considered treatment emergent if the onset time is after administration of study drug through the Day 120 post dose final follow-up visit, or if a pre-existing AE increases in severity during the 120 day post dose follow-up period compared to the pre-dose severity. If the start date/time of the AE is unknown, it will be assumed to be after the start of study drug.

6.5.1.2 Laboratory Tests

Laboratory testing will include those outlined in the protocol according to Study Activities Schedule, Appendix 1 of this SAP.
6.5.1.3 Anti-drug Antibody Testing

DX-2930 plasma anti-drug antibody determinations will be performed using blood samples collected at pre-dose on Day 1 and on Days 36±1, 64±2, 92±3, and 120±3.

6.5.1.4 Vital Signs

Vital signs will be performed 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 oral 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.

6.5.1.5 Physical Examinations

A complete physical examination including height, weight and calculation of Body Mass Index (BMI) will be performed by the Investigator or his/her qualified designee according to the Study Activities Schedule (Appendix 1). The findings of each examination will be recorded on the source documents and eCRF. The physical examination will include the following body systems:

- General appearance
- Dermatologic
- Musculoskeletal
- Head, eyes, ears, nose, throat
- Neurological
- Endocrine
- Respiratory
- Gastrointestinal
- Cardiovascular
- Genito-urinary

6.5.1.6 Electrocardiogram

A standard 12-lead ECG 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.

6.5.1.7 Prior and Concomitant Therapies

The Sponsor representatives and Investigator at the site conducting the trial will review and evaluate prior and concomitant medication usage on an ongoing basis. All prescription, over-the-counter medications, herbals, and supplements that are being taken or have been taken by subjects within 30 days before study entry and during the study will be regarded as concomitant medications and must be documented on the source document and eCRF following informed consent.
6.5.2 Pharmacokinetic Endpoints

Blood samples will be collected for the measurement of plasma DX-2930 concentration prior to study drug administration on Day 1 and on Days 2, 4 and 8. Additional blood samples will be obtained on Day 15 (prior to administration of the second dose of study drug) and on Days 16, 18, 22, 29 ± 1, 36 ± 1, 50 ± 2, 64 ± 2, 92 ± 3 and 120 ± 3 (or early termination).

PK parameter determinations will include the following:

- Maximum plasma concentration (C_max)
- Time to maximum concentration (t_max)
- Area under the plasma concentration-time curve (AUC): AUC_{0-∞} after a single dose or AUC_{0-τ} at steady state
- Apparent clearance (CL/F)
- Apparent volume of distribution (Vd/F)
- Terminal elimination half-life (t_{1/2})

Refer to the PK Analysis Plan for more information about the PK analyses.

6.5.3 Other Endpoints

6.5.3.1 Exploratory Biomarkers

Samples will be obtained to evaluate the pharmacodynamic effects of treatment on plasma kallikrein activity. Blood samples will be collected at pre-dose on Day 1 and on Days 2, 4 and 8. Additional blood samples will be obtained on Day 15 (prior to treatment with the second dose of study drug) and on Days 16, 18, 22, 29 ± 1, 36 ± 1, 50 ± 2, 64 ± 2, 92 ± 3 and 120 ± 3 (or early termination).

6.5.3.2 C1-INH Functional Assay

As an exploratory assessment of the indirect effects of plasma kallikrein inhibition upon endogenous C1-INH activity, samples will be obtained for C1-INH functional testing. Blood samples will be collected at pre-dose on Day 1 and Day 15 (prior to treatment with the second dose of study drug). Additional blood samples will be obtained on Days 29 ± 1, 36 ± 1, 64 ± 2, 92 ± 3 and 120 ± 3 (or early termination).

6.5.3.3 C4 Assay

C4 is required for eligibility assessment (must be lower than the normal range and obtained within 5 years of enrollment) for subjects with C1-INH antigen or functional level 40-50% of the normal level and a family history consistent with HAE Type I or II. Other exploratory analyses based on C4 levels following dosing may be conducted using blood samples.
collected for C1-INH functional testing at pre-dose on Day 1 and Day 15 (prior to treatment with the second dose of study drug) and on Days 29 ± 1, 36 ± 1, 64 ± 2, 92 ± 3 and 120 ± 3 (or early termination).

6.5.3.4 Efficacy Endpoints

This exploratory efficacy analysis will evaluate subjects treated with placebo, 300 mg and/or 400 mg DX-2930 with a historical baseline attack rate of at least 2 attacks over the past 3 months prior to enrollment.

- Primary efficacy endpoint:
  - Number of HAE attacks per week from Day 8 to Day 50
- Secondary efficacy endpoints:
  - Number of HAE attacks per week from Day 1 to Day 50
  - Number of HAE attacks per week from Day 8 to Day 64
  - Number of HAE attacks per week from Day 8 to Day 92

The endpoints are repeated measures of the number of distinct HAE attacks reported in a 7-day period (168 hours) for each subject. All reports of HAE attacks on study and for the historical baseline rate are subject-provided.

6.5.3.5 HAE Attacks

Prior to enrollment, HAE attack history will be collected by the Investigator. Information collected will include any prior history of laryngeal attacks, attack frequency, severity, location, duration, and acute attack therapy use.

In addition, subjects will be asked to report to their Investigator any HAE attacks they experience during the course of the study. Collection of clinical information regarding any such attacks will include attack location, severity, time of onset, duration, and treatment with any acute attack therapy. In addition, subjects will be encouraged, but not required, to come into the study site (maximum of 4 visits during the study, of which no more than 1 can be within the first 36 days following enrollment unless they occur at the same time as a planned study visit) for such attacks in order to have blood drawn for biomarker, C1-INH functional level, and PK testing. Subjects will be eligible to undergo this blood sample collection as long as they are assessed within 24 hours of symptom onset irrespective of any treatment they may have received for their attack. If the subject presents to the study site for an acute HAE attack during the study and it coincides with a scheduled study visit, the additional exploratory assessments and procedures (including blood draws) beyond what is already scheduled will not be necessary for that visit.

Subjects will also be asked to report to their Investigator any use of acute attack treatment during the course of the study.
When analyzing the severity of HAE attacks the following definitions will be utilized:

- Mild HAE attacks are those where symptoms are noticeable but do not impair activities of daily living.
- Moderate HAE attacks are those where symptoms affect activities of daily living.
- Severe HAE attacks are those where symptoms prevent the subject from performing activities of daily living.

In this trial each HAE attack experienced by a subject is recorded as an Adverse Event with complete start date and time and end date and time on the AE eCRF. Efficacy endpoints described in Section 6.5.3.4 and their efficacy analyses described in Section 13.3 will be calculated based on HAE attacks from the Adverse Event dataset. Specific rules pertaining to counting reported HAE attack in a specific 7-day period are listed below.

It is important to determine if two consecutive HAE events are overlapping and thus count as one HAE attack or two separate, HAE attacks. Overlapping attacks are attacks that have overlapping start and stop dates and times. There must be at least 24 hours between the stop date/time of the first event and the start date/time of the next event, for attacks to be considered two new and separate HAE attacks. If there is less than 24 hours between the stop date/time of the first event and the start date/time of the next event, the events will be counted as one attack.

If an HAE attack worsens, the new higher severity of attack is not counted as a new HAE attack. If an HAE attack extends longer than one 7-day period and extends into the second 7-day period, then the HAE attack is numbered as an attack in the first period and not as a new attack in the second period.

If an attack begins prior to first study drug administration (i.e., on Day 1) and ends after drug administration begins, then this attack is not counted as an attack in the first 7-day period or overall efficacy analysis.

Any attack for which all or part of the start date and time or end date and time are unknown will be assigned to a 7-day period as follows:

- If the start time and/or end time are not known and the dates fall within a defined 7-day period then the attack will be counted in that period.
- If the start time is not known and the start date falls on a period transition day, i.e., a day on which one period ends and the next period begins, the attack will be counted in only the period ending on that day.
- If the start time is not known and the start date falls on the day of first dose, the attack will be counted in the first 7-day period.
- If the start date is not known and the end date is known, the attack will be counted in the 7-day period the end date falls in.
• Any attack with both an unknown start and end date will be excluded from the analyses.
• Any unknown end date will be assumed to be the last day of the same period as the start date.
• If the end time is not known and a second HAE attack is recorded on the next calendar day, the second HAE attack will be considered a new HAE attack.

The first 7-day period starts on the date and time of the first study drug treatment. Consecutive periods begin exactly in multiples of 168 hours after the start of the first drug treatment and last until the end of the last multiple of 168 hours within the particular time interval being assessed for efficacy. Any part of a 7-day period will last until the end of the period. For the final period, if the subject completes the study prior to an elapsed time of a full 168 hours, then the number of attacks reported in that period will be equal to the number of observed attacks and the week will be counted with the observed number of attacks without prorating.

6.6 Completion and Discontinuation

Subjects who do not receive both doses of study drug may be replaced. The Investigator may withdraw a subject from the trial for any of the following reasons:

• A protocol violation occurs,
• 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.

The criteria used by the DEC regarding dose administration suspension and/or study discontinuation as well as the DEC criteria for dose escalation suspension and/or discontinuation are provided in Protocol Section 3.1.

7 STUDY POPULATIONS

7.1 Subject Disposition

All subjects entered in the study will be accounted for in the disposition summarization report. The number and percentage of subjects belonging to each analysis population will be displayed and individual information will be listed. A subject’s end of study status and reason for any early discontinuation will be summarized and listed.
7.2 Analysis Populations

The All Subjects Population includes all subjects with informed consent date.

The Randomized Population includes all subjects who have been randomized.

All safety analyses will be based on the Safety Population, which includes randomized subjects who received at least one dose of study drug.

The PK data analysis will be based on the PK Population, which includes the subjects in the Safety Population who have sufficient blood samples to obtain a plasma concentration vs. time profile. A separate Pharmacokinetic (PK) Analysis Plan details the pharmacokinetic analysis.

The PD data analyses will be based on the subjects in the Safety Population who have sufficient blood samples to conduct the intended analyses.

Exploratory efficacy analysis will be conducted on all DX-2930 treated subjects administered 300 mg or above with a historical baseline attack rate of at least 2 attacks over the past 3 months prior to enrollment and any placebo treated subject with a historical baseline attack rate of at least 2 attacks over the past 3 months.

7.3 Protocol Deviations

Information on protocol deviations, including visit, date and reason for deviations, will be listed for all subjects in the Safety Population. The deviations will be classified as major or minor by Dyax before the unblinding of the subjects.

7.4 Subgroups

There are no planned subgroup analyses for this study.

8 STATISTICAL ANALYSIS

Statistical analysis and programming of tables and listings will be conducted by Aptiv Solutions, using SAS® Release 9.3 or higher (SAS Institute Inc., Cary, North Carolina, USA). After the TFLs are approved as final, SAS programs used to perform statistical analyses and generate analysis datasets and TFLs will be archived; the analysis SAS Datasets will be archived in XPT format created using SAS PROC COPY. All SAS datasets and code to produce the analysis datasets will be provided to Dyax Corp.
8.1 General/Types of Analyses

Continuous data will be summarized with the following descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical data will be summarized with frequencies (number of subjects in category) and percentages. Percentages will be computed using the number of subjects with available data as the denominator, except for AEs, for which the denominator will be the number of subjects in each dose cohort, across all DX-2930 dose cohorts and for all subjects in the Safety Population.

8.2 Handling of Dropouts or Missing Data

All attempts will be made to prevent any missing values. Missing or invalid data will be treated as missing and will not be imputed.

8.3 Interim Analysis

Overall, there will be administrative interim analyses of the accumulating data, and these analyses will be performed without any intention to stop the trial. There will be no adjustment to significance level. The analyses will be made purely for the purpose of monitoring the (overall) progress of the trial, such as safety, PK, PD, anti-drug antibodies, and exploratory assessment data.

One such analysis will be conducted after at least 6 subjects have reached day 36 in the 300 mg cohort unless the highest dose level in the study is lower than 300 mg in which case the analysis will be conducted after at least 6 subjects at the highest dose cohort have reached the Day 36 time point. All available subject safety, PK, anti-drug antibody and exploratory biomarker data for visits conducted through Day 36 of the 300 mg cohort (or highest cohort as indicated above) will be included. Unblinded aggregate data will be reviewed across all dosing cohorts and by individual cohort by sponsor to identify any safety signals and to assess PK and exploratory biomarker results. The output generated for the initial interim analysis will be limited to summary tables 14.1.1 through 14.1.6 and 14.3.1.1 through 14.3.7. No efficacy analyses will be included in these analyses (Tables 14.2.X). No individual by subject listing listings will be generated unless the sponsor determines that additional information is required to fully evaluate a potential safety signal or the other findings.

Additional interim analyses may be conducted following the initial interim analysis. Available PK, PD, anti-drug antibodies, safety data, and results of exploratory analyses may be evaluated to guide selection of dose levels for the Phase 2 study, and if additional cohorts may be added.

A blinded medical monitor will be retained to assess safety for the remainder of the study.
8.4 Pooling Strategy for Study Sites

There is no plan for pooling study sites.

8.5 Visit Windows/Unscheduled Visits

The following visit windows apply to each visit: Day 1, Day 2 ± 2 hours, Day 4 ± 4 hours, Day 8 ± 6 hours, Day 15, Day 16 ± 2 hours, Day 18 ± 4 hours, Day 22 ± 6 hours, Day 29 ± 1 day, Day 36 ± 1 day, Day 50 ± 2 days, Day 64 ± 2 days, Day 92 ± 3 days, and Day 120 ± 3 Days. Visits will be displayed as captured in the eCRF database and there will be no derivation of visit windows.

Unscheduled visits will only be displayed in the listings, except that HAE attacks that happened during unscheduled visits will be summarized in the relevant tables.

8.6 Other Issues

If any screening safety data are repeated, the measurement taken closest to dosing will be used in the analysis. Baseline will be defined as the last non-missing result, including results from repeated and unscheduled measurements, before dosing. If there are repeated measurements at a time point after dosing, the most extreme value at that time point will be used in the summary tables. The value representing the greatest absolute change from baseline will be considered the most extreme. If the absolute change from baseline is the same for multiple values, the most extreme value will be considered to be the value that is farthest from the midpoint of the range of normal values used in the edit ground rules (edit checks) for database setup. In the situation where multiple laboratory data provide contradictory or ambiguous results, medical judgment will be used prior to unblinding to determine which is worse.

9 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject demographics (sex, age, ethnicity and race, baseline height, baseline weight and baseline BMI) will be listed for the All Subjects Population and summarized for the Safety Population by each dose level, combined DX-2930 cohorts and overall in tabular format using descriptive statistics for continuous variables and frequency and percentages for discrete variables. Historic C1-INH functional, antigenic and C4 results will be presented by subject listing and summarized in tabular format for the safety population.

BMI will be calculated as: weight (kg) / [height (m)]^2.

Medical history and HAE attack history will be listed for the All Subjects Population and summarized by each dose level in tabular format for the Safety Population.
The inclusion and exclusion status and waiver information will be listed for the All Subjects Population.

10 ANALYSIS OF PHARMACOKINETICS AND PHARMACODYNAMICS

10.1 Pharmacokinetic Analysis

Refer to the PK Analysis Plan for more information about the PK analyses.

The plasma concentrations and the derived PK endpoints will be listed for each subject included in the PK Population.

The plasma concentrations will be summarized (including also coefficient of variation) by treatment and time points. The PK parameters will be also summarized (including also coefficient of variation, geometric mean and geometric coefficient of variation) by treatment.

10.2 Exploratory Biomarkers

Exploratory biomarker analyses will be conducted to evaluate the pharmacodynamic effects of DX-2930. The cleavage of kininogen, the native substrate of plasma kallikrein from which bradykinin is generated, will be measured through a Western blot assay. Other exploratory biomarker assays may also be conducted.

11 TREATMENT COMPLIANCE AND EXPOSURE

The study drug administration information (visit, injection ID, start date/time, administration location and volume) will be listed for subjects in the Safety Population.

12 SAFETY ANALYSIS

Safety measures include AEs, clinical laboratory tests, physical examinations, ECG determinations, and vital signs. The Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 coding system will be used for System Organ Class (SOC) and preferred term classification of AEs. All safety data will be listed by subject and summarized in tabular format using descriptive statistics for continuous variables and frequency and percentages for discrete variables for each dose level, total DX-2930 and overall in the Safety Population.

AEs will be summarized by SOC and preferred term for each dose cohort. Vital sign assessments, 12-lead ECGs, clinical laboratory tests, and change from baseline will be summarized by assessment name, visit, and, when appropriate, point of time of sample collection for each dose cohort. Descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum) will be calculated for quantitative safety data as well as
for changes from baseline, when appropriate. In addition, clinical laboratory and ECG shift tables will be provided.

12.1 Adverse Events

All AEs will be listed by subject, including non-treatment emergent (i.e., pre-dosing) AEs, if applicable. On listings, onset day of an AE will be calculated as (onset date – dosing date + 1) when onset date is on or after dosing date, and (onset date – dosing date) when onset date is before dosing date.

An overall summary of adverse events will be provided. The total number of events and proportion of subjects experiencing any of the following will be computed by dose received, combined DX-2930 cohorts and overall:

- Any treatment emergent adverse events (TEAE)
- Grade 3 or higher TEAEs
- Related Grade 3 or higher TEAEs
- Mild TEAEs
- Moderate TEAEs
- Severe TEAEs
- Life threatening TEAEs
- Related TEAEs
- Severe related TEAEs
- Life threatening related TEAEs
- Serious adverse events (SAEs)
- Related serious adverse events
- Adverse events leading to death
- Adverse events leading to early termination from the study

Treatment emergent AEs will be summarized by SOC and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA® version 17.1). The tables will summarize treatment emergent adverse events alphabetically by SOC, and within each SOC, alphabetically by preferred term for each dose level, combined DX-2930 and overall, using frequency and percentage. A subject having the same TEAE more than once will be counted once for each preferred term and once within each SOC.

Additional summary tables will be presented for study drug related TEAEs and for grade 3 or higher TEAEs by SOC and preferred term for each dose cohort, combined DX-2930 cohorts and for all subjects in the Safety Population.
Separate tables will summarize all SAE data, AEs leading to early termination from the study, and AEs leading to death. Separate by-subject listings will also be provided for these AEs.

12.2 Laboratory Tests

Individual data listings of laboratory results will be presented for each subject. Values outside of the laboratory’s reference limits will be flagged and the Investigator’s assessment will be provided. Clinically significant worsening from baseline or new clinically significant laboratory test abnormalities that were considered AEs by the Investigator will be presented in the AE analyses. Clinical laboratory tests will be summarized descriptively in tabular format. Observed values and change from baseline for numeric clinical laboratory data will be summarized using descriptive statistics. Shift tables will be presented for hematology, coagulation, and chemistry laboratory results only.

Listings of all laboratory results and abnormal laboratory results containing all laboratory categories (e.g., hematology, coagulation, serum chemistries, and urinalysis) will be produced, showing normal ranges and out-of-range flags.

Laboratory tests from unscheduled visits will only be displayed in the listings. Laboratory listings will be shown by subject, parameter, and time point.

Pregnancy test data will be listed for each subject in the Safety Population.

12.3 Anti-drug Antibody Testing

For DX-2930 plasma anti-drug antibody testing, by-subject results will be listed by time point. A shift table by time point for each dose level, total DX-2930 and overall will be presented for confirmed results and for neutralized antibody results.

12.4 Vital Signs

Vital sign measurements will be summarized using descriptive statistics for each visit/time point for the Safety Population. Change from baseline in vital sign measurements will be calculated and summarized descriptively.

Clinically significant worsening from baseline or new clinically significant vital sign findings that were considered AEs by the investigator will be presented in the AE analyses.

A by-subject listing of all vital sign measurements will be displayed. Values outside the normal values will be flagged as either lower (L) or higher (H) than the normal range. The following normal ranges will be used to identify abnormal vital signs:
• Systolic blood pressure: 90-140 mm Hg
• Diastolic blood pressure 60-90 mm Hg
• Heart rate: 60-100 bpm
• Respiration rate: 12-20 beats/min
• Temperature: 35-38 ºC

Unscheduled visits will only be displayed in the listings.

12.5 Physical Examinations

Abnormal physical examination findings will be listed for each subject and time point. Clinically significant worsening from baseline or new clinically significant physical examination abnormalities that were considered AEs by the Investigator will be presented in the AE analyses. Physical examination will be summarized descriptively by body systems and time points in tabular format.

12.6 Electrocardiogram

Twelve-lead ECG data (observed and change from baseline) will be listed for each subject and time point. Observed values as well as change from baseline at each time point will be summarized descriptively in tabular format. An ECG shift table will be presented. Clinically significant worsening from baseline or new clinically significant ECG abnormalities that were considered AEs by the Investigator will be presented in the AE analyses.

12.7 Prior and Concomitant Therapies

The use of prior and concomitant therapies taken will be documented throughout the study. Prior and concomitant therapies will be coded to a World Health Organization Drug Dictionary term per the March 1, 2014 release of WHODD. A listing of prior and concomitant medication use, sorted by subject, and a table summary by the medication class and preferred term will be generated for the Safety Population.

Prior medications are all therapies taken prior to the first dose of study medication. Concomitant therapies are all therapies taken after the first dose of study medication. If any therapies were started prior to dosing and were continued after dosing, they will be shown in the listings as prior and concomitant therapies.
13 OTHER ANALYSES

13.1 C1-INH Results

On-study C1-INH functional data will be listed and summarized in tabular format using descriptive statistics for each dose level, total DX-2930 and overall in the Safety Population. Observed values as well as change from baseline will be summarized descriptively in tabular format. A shift table by dose group and time point will be presented.

13.2 C4 Results

On-study C4 data will be listed and summarized in tabular format using descriptive statistics for each dose level, total DX-2930 and overall in the Safety Population. Observed values as well as change from baseline will be summarized descriptively in tabular format. A shift table by dose group and time point will be presented.

13.3 Efficacy Analysis

The exploratory efficacy analyses will be conducted for the endpoints defined in Section 6.5.3.4 based on the HAE Attack Analysis Populations defined in Section 7.2. The Last-Observation-Carried-Forward method and imputation of missing data will not be used in this analysis.

Generalized Estimating Equation (GEE) approach with Poisson distribution assumption will be applied to the repeated measures mixed model with independence working correlation structure. The treatment group will be a fixed effect and the number of baseline HAE attacks per week will be included as a covariate in the GEE. Subject will be considered as a random effect. The baseline attack rate will be calculated by dividing the number of HAE attacks within the past 3 months by 13 weeks.

The baseline attack rate will be used as a covariate, but there may be a small number of large potential outliers among reported baseline attack rates. To avoid any possible undue influence of a baseline attack rate outlier, we will test any potential outliers using the Dixon Gap test (with alpha=0.05), prior to performing any efficacy analyses. If an outlier is present by the Dixon Gap test, it will be given the value of mean + 2 SD, where mean and SD are computed without the presence of the Dixon outlier.

The least square mean lsmean (log of the mean event rate) for each dose level and its corresponding standard error (SE) can be directly estimated from the GEE model. The mean event rate can be estimated by transforming the above lsmeans by the exponential function.

The lsmean difference of the natural logarithms of attack rates between each dose level and placebo, which is also the regression coefficient for each treatment group effect, and its 95%
confidence interval can also be directly estimated from the GEE model. The ratio of the mean event rate per week for each dose level vs. placebo and its 95% CI can be estimated by transforming the above lsmean difference and its 95% confidence interval by the exponential function.

The percentage change in mean attack rate of each active treatment group from the attack rate of placebo defined as 100%*(treatment attack rate – placebo attack rate)/placebo attack rate will also be displayed. The 95% CI for the percentage change in mean attack rate will also be displayed.

Sample code for the above analysis is:

```
PROC GENMOD data= ;

CLASS trta (ref='Placebo') usubject;

MODEL attack=trta base / dist=poisson;

REPEATED subject=usubject / corr=ind;

LSMEANS trta/diff cl ilink;

ODS OUTPUT diffs=meandiff lsmeans= means;

RUN;
```

In addition, the following will also be summarized by descriptive statistics.

- Number and proportion of subjects in each treatment arm with no HAE attacks. Use Fisher’s exact test to compare these proportions.
- Number of attack-free days per the entire length of the observation period (Day 1 to Day 50, Day 8 to Day 50, Day 8 to 64, or Day 8 to Day 92).
- Proportion of attack-free days per the entire length of the observation period (Day 1 to Day 50, Day 8 to Day 50, Day 8 to 64, or Day 8 to Day 92).

### 13.4 HAE Attacks

Characteristics of historic HAE attacks and ones experienced in the study, including frequency, severity, duration and acute HAE attack therapies will be listed and summarized in tabular format using descriptive statistics for each dose level, total DX-2930 and overall in the safety population. The frequency and duration of HAE attacks will be summarized as continuous variables (mean, median, SD, minimum and maximum). The attack severity (Mild, Moderate and Severe), attack duration category (<12 hours, 12-24 hours, 24-48 hours
and >48 hours), and the type of acute HAE attack therapies will be summarized by count and percentages. The summary will be presented at both the event and subject level. For the subject level analysis, the total frequency of HAE attacks, maximum attack severity, and average attack duration hours will be obtained for each subject and then summarized.

A listing of subject, dose group, baseline attack rate, number of attacks during study, and attack characteristics will be provided.

14 SUMMARY OF CHANGES FROM PROTOCOL SPECIFIED ANALYSIS

The shift table for coagulation lab parameters is added. There are no further changes from the protocol specified analysis.

15 REPORTING CONVENTIONS

- Section 14 tables and Section 16 listings should be in landscape format with Courier New 8 pt. font. Output should adhere to margins of: top - 1.5 in, bottom - 1.0 in, right - 1.0 in, and left - 1.0 in). For section 14 tables, a blank row will separate the header from the content of the table listing. For tables that have “n (%)”, the placement should be centered below “N=xx” in the column header. Frequency tables will be center justified. Descriptive statistics will be decimal aligned.
- The heading should consist of four lines. Line 1: Sponsor identifier. Line 2: Protocol identifier. Line 3: blank line. Line 4: Table/Appendix number Table Title – Population.
- A solid line should appear both above and below the column headings of a table. A solid line should appear at the end of the table or at the bottom of each page if the table extends to more than one page. Footnotes should start after the bottom solid line.
- The mean and median will be displayed to one decimal place greater than the original value, and the standard deviation (SD) will be displayed to two decimal places greater than the original value. For blood pressure, heart rate and respiratory rate, the mean and median will be displayed as whole number and the standard deviation (SD) will also be displayed as whole number with no decimal place.
- Unless specified otherwise, “%” should reflect the total population of the treatment groups. Any deviation from that should be part of the footnote. For 0 counts, the corresponding percentage should be indicated as 0 as should 0/0.
- “N” will represent the entire treatment (dose) group for the population group being analyzed, while “n” will represent count of non-missing values for variables analyzed.
- All data listings will be sorted by cohort, subject number and parameter or time point (as applicable).
- The date format for all dates is DDMMMYYYYY.
- If no data are collected for use in the tables and listings, then a table and/or listing will be created stating that no data are available.
16 LIST OF TABLES, FIGURES AND LISTINGS

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<th>Day 1 Dosing</th>
<th>Day 1 Post Dosing</th>
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<th>Day 4</th>
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<th>Day 22</th>
<th>Days 29±1, 36±1, 50±2, 64±2, &amp; 92±3 *</th>
<th>Final Visit Day 120±3 or ET Visit</th>
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Confidential Page 30 of 32 Dyax Corp
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<td>*Note: During this outlined period (Day 29 through Day 92), physical examination, vital signs, and safety laboratory tests (hematology, coagulation, serum chemistry, and urinalysis) will occur on Days 29±1, 36±1, 64±2, and 92±3. During this period laboratory test for C1-INH Function will occur on Days 29±1, 36±1, 64±2 and 92±3. During this period, anti-drug antibody testing will be conducted on samples obtained on Days 36±1, 64±2, and 92±3. 12-lead ECG will be performed at Day 36±1 during this outlined period.</td>
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EGC = electrocardiogram; PK = pharmacokinetic; ET = early termination

<sup>1</sup>Height, weight and calculation of BMI will be additional assessments conducted at this time point.
This physical examination will be abbreviated and include General, Skin, Cardiovascular, Pulmonary, Abdomen, and Extremities. (For Day 1 post-dosing and Day 15 post-dosing, this examination will occur at 4 hours ±15 minutes).

Documentation of vital signs including oral body temperature, HR, BP, and RR. On Day 1 post-dosing and Day 15 post-dosing, oral body temperature will not be collected.

Documentation of vital signs; HR, BP, and RR only at 1, 2, and 4 hours ±15 minutes

CBC with differential

Includes INR, aPTT and PT

Includes total protein, albumin, glucose, alkaline phosphatase, bilirubin (total and direct), AST, ALT, GGT, LDH, uric acid, BUN, creatinine, calcium, sodium, potassium, chloride, CO2, phosphate, magnesium, cholesterol, triglycerides, CPK

Includes pH, glucose, ketones, blood, specific gravity, nitrite, protein, bilirubin and microscopy

C1 inhibitor (C1-INH) antigen or functional level < 40% of the normal level is required for entry into the study. Subjects with antigen or functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range and a family history consistent with HAE Type I or II. Test results must have been obtained within 5 years of enrollment. Following enrollment into the study, C1-INH functional levels will be collected at the outlined time points.

Serum or urine pregnancy test to be obtained at screening, prior to first dosing, and at Day 120 final visit or ET

Prior concomitant medications and procedures will be documented before dose administration. Concomitant medications and procedures will be assessed on a continual basis throughout the study

Pre-existing signs and symptoms will be captured prior to dosing. AEs will be assessed on a continual basis from the signing of the consent form and throughout the study

Clinical information related to historical HAE attacks will be obtained prior to dosing on Day 1. Clinical information related to any HAE attacks as well as any acute attack treatments occurring during the study will be obtained throughout the study

If the subject presents to the study site for an acute HAE attack during the study and it coincides with a scheduled study visit, the additional exploratory assessments and procedures (including blood draws), beyond what is already scheduled will not be necessary for that visit.